Autorità Garante della Concorrenza e del Mercato

THE ITALIAN COMPETITION AUTHORITY

AT THE MEETING of 17 May 2022;

HAVING HEARD the rapporteur, Professor Michele Ainis;

HAVING REGARD TO Article 102 of the Treaty on the Functioning of the European Union (TFEU);

HAVING REGARD TO Council Regulation (EC) no. 1/2003 of 16 December 2002 on the implementation of the rules on competition laid down in Articles 81 and 82 of the Treaty (now Articles 101 and 102 of the TFEU);

HAVING REGARD TO the Commission Communication on cooperation within the Network of Competition Authorities of 27 April 2004;

HAVING REGARD TO Law no. 287 of 10 October 1990;

HAVING REGARD TO Presidential Decree no. 217 of 30 April 1998;

HAVING REGARD TO its decision no. 27940 of 8 October 2019, initiating proceedings to establish a breach of Article 102 of the TFEU against the companies Essetifin S.p.A., Leadiant Biosciences S.p.A., Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation;

HAVING REGARD TO its decision no. 28325 of 4 August 2020, rejecting the commitments presented by the companies Essetifin SpA, Leadiant Biosciences SpA, Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation;

HAVING REGARD TO its decisions no. 28377 of 13 October 2020, no. 29704 of 8 June 2021, no. 29855 of 19 October 2021 and no. 29982 of 8 February 2022, whereby the deadline for completion of the investigation proceedings was extended, most recently until 20 May 2022, to grant to the Parties the widest possible exercise of the right of defence and to fully guarantee their right to be heard;

HAVING REGARD TO the Statement of Objections, sent to the Parties on 22 September 2021, pursuant to Article 14 of Italian Presidential Decree no. 217 of 30 April 1998;

HAVING REGARD TO the final submissions of the companies Essetifin S.p.A., Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation, and Altroconsumo, received on 28 January 2022;

HAVING HEARD in a final hearing the representatives of Essetifin S.p.A., Leadiant Biosciences Ltd., Leadiant GmbH and Sigma-Tau Arzneimittel GmbH in liquidation, and Altroconsumo, on 14 February 2022;

HAVING REGARD TO the documents of the proceedings and the evidence acquired during the investigation;

IN CONSIDERATION of the following

I. THE PARTIES

I.1 The undertaking concerned

1. Essetifin S.p.A. (formerly Sigma Tau Finanziaria S.p.A.), holding of the Leadiant group, is a company that controls 100% of the shares of Leadiant Biosciences Ltd., incorporated under British law, and Leadiant Biosciences Inc., incorporated under US law[1].

[1] The investigation proceedings were also initiated against Leadiant Biosciences S.p.A., a company established on 30 January 2017 by Essetifin S.p.A., which wholly controlled it. Leadiant Biosciences S.p.A. in turn wholly controls Leadiant Biosciences Ltd. and Leadiant Biosciences Inc. However, on 22 July 2021, Leadiant Biosciences S.p.A. merged into Essetifin S.p.A. As a result of this transaction, therefore, Essetifin S.p.A. directly, and no longer indirectly, controls the two British and US companies.

2. Leadiant Biosciences Ltd. is a company active in the market for the production and sale of orphan drugs. Leadiant Biosciences Ltd. is the new company name adopted in December 2016 by Sigma Tau Rare Disease Ltd. As a result of a more complex sale of the group's companies and assets[2], the business branches relating to the orphan drug activities of Sigma Tau Pharmaceuticals Ltd., belonging to the former Sigma Tau Group, were conferred on this company in May 2015[3].

3. Leadiant GmbH is a company incorporated under German law, active in the market for the production and sale of medicines, 100% controlled by Leadiant Biosciences Ltd.[4]

4. Sigma Tau Arzneimittel GmbH in liquidation is a company incorporated under German law wholly owned by Essetifin S.p.A.[5], previously active in the market for the production and sale of drugs.

5. Essetifin S.p.A., Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation are therefore part of the same corporate group[6] and will subsequently, if necessary, also be jointly referred to as "Leadiant" or the "Party", except where the precise corporate identity of each of them, or of the companies of the former Sigma Tau group of which they are successors, is necessary for understanding the facts being ascertained. fThe turnover of the Leadiant group in 2021 was *[100-200]** million euro.

I.2 The complainant

6. Altroconsumo is a consumer association registered in the list of the most representative associations in Italy kept by the Ministry of Economic Development.

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[2] See the Authority's decision of 25 March 2015 in case C11988 – Marino Golinelli & co./Sigma Tau Finanziaria and other enterprises and parts of enterprises.
[3] See doc. 78.388. Previously, in December 2013, Sigma Tau Pharmaceutical Ltd. had, in turn, acquired the business unit relating to orphan drugs as a result of a merger by incorporation of Sigma Tau Rare Disease S.A., a company incorporated under Portuguese law, established in 2011 and belonging to the former Sigma Tau group.
[4] See doc. 110.4B.
[5] See doc. 110.4B.
[6] See Court of Justice, 24 October 1996, in Case C-73/95, *Viho v European Commission*; Court of First Instance, 12 December 2007, Case T-112/05, *Akzo Nobel NV et al. v European Commission*.
* Some data are omitted in this version, as they contain confidential or secret information.

II. THE PROCEEDINGS

II.1 The opening of the investigation file and the subsequent complaint

7. Between the end of August 2018 and the beginning of September 2018, news was circulated in the press, both nationally and internationally, about certain events concerning the production and sale of the orphan drug named *Chenodeoxycholic Acid Leadiant*® for the treatment of an ultra-rare disease called cerebrotendinous xanthomatosis (CTX) in the Dutch and Italian markets[7].

8. In August 2018, the *Dutch Pharmaceutical Accountability Foundation* filed a complaint with the Dutch Competition Authority concerning Leadiant Biosciences Ltd.'s request to the health insurers for payment of a price for the sale of this product equal to approximately €15,300 for a pack of 100 capsules of 250 mg. This price was considered absolutely unjustified, especially due to the fact that, until that point, Dutch patients affected by CTX had been treated in the Netherlands with a drug from the same Leadiant Biosciences Ltd. containing the same active substance, authorised for the treatment of gallstones and used off label for the treatment of the rare disease, sold at a price of about €30 per pack, but then withdrawn from the market.

9. *Chenodeoxycholic Acid Leadiant*® was introduced into the Italian market in June 2017. However, in the absence of a price agreement between the company and the Italian Medicines Agency (AIFA), it was marketed according to the rules of the class 'C non-negotiated' (Cnn), or at a price freely set by the company, which in the aforementioned article was indicated as equal to €169,000 per year, charged to patients[8].

10. Prior to the marketing authorisation of *Chenodeoxycholic Acid Leadiant*®, Italian patients affected by CTX were also treated with the drug owned by Leadiant Biosciences Ltd. based on registered chenodeoxycholic acid for the treatment of gallstones but administered off label for the treatment of the rare disease[9]. And even before that, the Oncology and Clinical Pharmacy (hereinafter, the "Pharmacy") of the Azienda Ospedaliera

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[7] See *Appeal against the former Sigma Tau,* in *Milano Finanza,* 4 September 2018. See also *Dutch doctors fight pharma company's 500-fold drug price rise,* in *Financial Times,* 2 September 2018; *Dutch doctors resist pharma firms' 500-fold price hike,* in*www.pharmafile.com,* 3 September 2018; *New Dutch Foundation to Address High Medicines Pricing Announces Plan to File Complaint with Competition Authority,* in www.medicineslawandpolicy.org of 25 August 2018. See doc. 1.

[8] See doc. 1.

[9] See doc. 10, annex 2.

Universitaria Senese di Santa Maria alle Scotte (hereinafter, the " University Hospital of Siena") had produced the drug in galenic form, with the aim of administering it free of charge to all patients with CTX[10].

11. On the basis of this information, on 25 September 2018, investigation file no. A524 was opened *ex officio*.

12. Subsequently, on 31 July 2019, a complaint was received from Altroconsumo, where the association complained that Leadiant Biosciences Ltd. had put in place an unlawful conduct from an antitrust perspective, likely to constitute an exploitative abuse *sub specie* of unfairly excessive prices under Article 102(a) of the TFEU.

II.2 The preliminary investigation and the inquiry

13. In order to acquire elements useful to understand the market context of reference for the orphan drug under investigation and to know the status and/or the outcome of the negotiation of the price of *Chenodeoxycholic Acid Leadiant*®, a request for information was sent to AIFA on 26 September 2018, with the Agency replying on 22 October 2018[11].

14. Since September 2018, moreover, the competent investigation units of other national competition authorities, such as the *Authority for Consumers & Markets* (ACM) of the Netherlands, which had already initiated an investigation proceedings in the case in relation to the Dutch market, and the *Comisión Nacional de los Mercados y la Competencia* (CNMC) of Spain, which was assessing the existence of the requirements necessary to open the proceedings in relation to the Spanish market, have been contacted several times within the ECN network established by Regulation (EC) no. 1/2003[12].

15. In particular, following the numerous interactions with the ACM, pursuant to Article 12 of Regulation (EC) no. 1/2003, a copy of the contract for the exclusive supply of chenoxycholic acid entered into on 16 November 2016 by Sigma Tau Rare Disease Ltd. (now Leadiant Biosciences Ltd.) and the Italian chemical company, Prodotti Chimici e Alimentari S.p.A., was acquired on 9 May 2019[13], followed by a copy of some specific documents contained in the file of the proceedings opened by the ACM itself, acquired

[10] See doc. 6.
[11] See docs. 2 and 3.
[12] See *https://www.acm.nl/en/publications/acm-extends-its-investigation-orphan-drug-cdca-leadiant* and *https://www.cnmc.es/pr*ensa/*inocacion-leadiant-20201222*.
[13] See docs. 5, 5.1 and 5.2.

on 5 June 2019[14].

16. In addition, in order to analyse the various phases that have characterised the many decades of clinical experience developed by the University Hospital of Siena in relation to the treatment of the rare disease, a specialist and some pharmacists from the Pharmacy of the Hospital were contacted several times between March and May 2019[15]. On 10 May 2019, the Pharmacy's representatives were formally heard[16].

17. Subsequently, as anticipated, Altroconsumo filed a complaint on 31 July 2019[17].

18. Finally, on 7 September 2019, in order to obtain more up-to-date information on the developments of the negotiation procedure on the price of the orphan drug, a second request for information was sent to AIFA, with the Agency replying on 4 October 2019[18].

19. On 8 October 2019, the Italian Competition Authority initiated, pursuant to Article 102 of the TFEU and Article 14 of Law no. 287/1990, investigation proceedings against the companies Essetifin S.p.A., Leadiant Biosciences S.p.A., Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation, in order to verify the existence of any conduct contrary to competition law carried out by the aforementioned companies.

20. On 15 October 2019, inspections were carried out at the Rome premises of Essetifin S.p.A. and Leadiant Biosciences S.p.A.[19], at the premises of Industria Chimica Emiliana S.p.A. (in Reggio Emilia)[20] and its subsidiary Prodotti Chimici e Alimentari S.p.A. (in Basaluzzo)[21], as well as at the premises of Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation in Munich[22]. Finally, on 15-17 October 2019, inspections were carried out at the headquarters of Leadiant Biosciences Ltd. in Windsor. Inspections at the premises of the foreign companies Leadiant Biosciences Ltd., Leadiant GmbH and Sigma Tau Arzneimittel GmbH in liquidation were carried out, respectively, by the British Competition and Markets Authority and by the

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[14] See docs. 7 and 7.1.
[15] See doc. 6.13.
[16] See docs. 4 and 6.
[17] See doc. 8.
[18] See docs. 9 and 11. This update follows a series of informal contacts with the relevant AIFA departments between February and June 2019.
[19] See docs. 18, 21 and 22.
[20] See docs. 24 and 25.
[21] See docs. 27 and 28.
[22] See docs. 83.1 and 83.2.

German Competition Authority (*Bundeskartellamt*), in execution of two requests for cooperation pursuant to Article 22 of Regulation (EC) no. 1/2003[23].

21. The documents collected in the inspection carried out by the Competition and Markets Authority were sent to the Italian Competition Authority on 4 December 2019 pursuant to Article 12 of Regulation (EC) no. 1/2003 and were acquired on the same date in the investigation file[24]. The documents acquired in the inspection carried out by the *Bundeskartellamt* were sent to the Italian Competition Authority on 30 June 2020 pursuant to Article 12 of Regulation (EC) no. 1/2003 and were acquired on the same date in the investigation file[25].

22. On 8 July 2020, following the extension of the deadline for the presentation of commitments, as requested by the Party[26], and the automatic suspension of the terms of the administrative proceedings first provided for by Article 103 of Decree Law no. 18/2020 and then by Article 37 of Decree Law no. 23/2020[27], Leadiant presented commitments pursuant to Article 14-*ter* of Law no. 287/1990[28]. The Italian Competition Authority rejected the commitments' proposal by means of a decision dated 6 August 2020, based on the Authority's legitimate interest in proceeding with the investigation of the infringement[29].

23. During the investigation, the Directorate sent requests for information to the company in relation, among other things, to the costs incurred by the company for the launch of *Chenodeoxycholic Acid Leadiant*® on the European market[30].

24. In addition, in order to obtain information relevant to the proceedings, AIFA and the companies Industria Chimica Emiliana S.p.A. (hereinafter referred to as "ICE") and Prodotti Chimici Alimentari S.p.A. (hereinafter referred to as "PCA") were heard twice[31].

25. During the investigation, Leadiant repeatedly accessed the

[23] See docs. 81 and 82.
[24] See doc. 42 and annexes.
[25] See doc. 83.
[26] See docs. 52, 60, 62 and 63.
[27] See doc. 76.
[28] See docs. 84.1 and 87.1.
[29] See docs. 88 and 89.
[30] See docs. 99, 105, 107 and 110.
[31] See docs. 72 and 108 and 69 and 120.1.

documents[32], filed two written pleadings[33] and were heard on 7 May 2021[34].

26. The investigation proceedings were extended four times, first on 13 October 2020[35], then on 8 June 2021[36], 19 October 2021[37] and, finally, on 8 February 2022[38].

27. On 22 September 2021, the Statement of Objections (SO) was sent to the Parties[39].

28. The Parties replied to SO on 28 January 2022[40] and were heard at the final hearing before the Board on 14 February 2022[41].

III. DESCRIPTION OF THE INVESTIGATED FACTS

III.1 The regulatory framework

29. The *Chenodeoxycholic Acid Leadiant*® is the 'hybrid' version of an existing drug, named *Xenbilox*®, also owned by Leadiant until the drug was present on the market. Therefore, the set of European rules relating to the marketing authorisation (MA) of 'hybrid' medicines first comes into play[42].

As the *Chenodeoxycholic Acid Leadiant*® is also an 'orphan' drug, the case must also be examined in light of the provisions of Regulation (EC) no. 141/2000 and of the subsequent acts adopted by the European Commission in this regard.

Finally, in light of the decades of experience of Italian hospitals in the production of galenic products based on chenodeoxycholic acid, the rules governing the 'galenic formulations' will be illustrated.

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[32] See docs. 66, 67, 78, 79, 96, 98, 100, 101 and 116, 168-bis, 168-ter, 168-quater, 170, 180, 188 and 189.
[33] See docs. 84 and 140.
[34] See doc. 122.
[35] See docs. 90, 91 and 93.
[36] See docs. 134-137.
[37] See docs. 171-173.
[38] See docs. 199-200.
[39] See docs. 159-160.
[40] See docs. 185, 186 and 187.
[41] See docs. 201, 201-bis, 202 and 202-bis.
[42] See Directive 83/2001/EC, as amended by Directive 2004/27/EC.

III.1.1 The European framework for the marketing authorisation of hybrid drugs

30. The request for a MA for medicines different from originator drugs is regulated by Article 10 of Directive 83/2001/EC, which provides for procedures that are simpler and faster than the full-fledged ones (governed by Article 8(3)(i) of the same Directive) applicable to the MA applications for originator drugs, and that for this reason are referred to as 'abbreviated'.

31. The greater simplicity and speed of the 'abbreviated' authorisation procedures lies in the possibility for the applicants not to repeat the clinical trials already carried out to prove the safety, effectiveness and quality of the originator drug, but to just prove the bioequivalence[43] between the drug for which the authorisation is requested and the originator drug, which thus represents the 'reference' drug.

32. Within the 'abbreviated' procedures, the European legislator has provided for both a 'simple' (Article 10(1) of Directive 83/2001/EC) and a 'hybrid' (Article 10(3) of the same Directive) procedure. The first one applies to drugs that fall within the legal definition of "generic medicinal product" referred to in Article 10(2)(b), or that meet "*the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent*"[44] with respect to the 'reference' drug, whereas the second one applies to drugs that have some differences with respect to the 'reference' drug[45].

33. Such differences may lie either *a)* in the different therapeutic indication or *b)* in the different means of administration or in the different dosage.

34. In both cases, the "hybrid authorisation procedure" referred to in Article 10(3) of the Directive makes it possible to refer to the clinical data of the 'reference' medicinal product, provided that these are necessarily

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[43] Two drugs are considered bioequivalent when, with the same dose, they have the same bioavailability, or when the amount of active substance made available in the systemic circulation and the time it takes to reach its maximum concentration in the blood after administration of the drug, are so similar that they do not involve significant differences in terms of efficacy and safety. There is assumed to be bioequivalence between two drugs when they are pharmaceutical equivalents, or contain the same active substance, in the same dosage, and have the same pharmaceutical form. See EMA, *Guidelines on the Investigation of Bioequivalence*, 2010, available at *https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf*.

[44] See CJEU, 3 December 1998, Case C-368/96, *Generics (Captopril, Aciclovir and Ranitidine)*, [1988] ECR I-7967, paragraph 36, confirmed by CJEU, 29 April 2004, Case C-106/01, *SangStat v. Novartis Pharmaceuticals (Sandimmun)*, unpublished but available on the Court's website, paragraph 33.

[45] See CJEU, *SangStat*, paragraphs 52 and 55.

supplemented to address the mentioned differences. In particular, in the case in point *a)*, the submission of clinical data certifying the safety and efficacy of the drug for the different therapeutic use is also required.

35. The present case falls within the hypothesis under point *a)*: *Chenodeoxycholic Acid Leadiant*® is, in fact, as anticipated above, a hybrid drug of the 'reference' drug *Xenbilox*®, to which it is identical from a chemical and pharmaceutical perspective, but from which it differs as regards the therapeutic indication. Therefore, for the purposes of requesting the authorisation for the orphan drug, Sigma Tau used part of the dossier of *Xenbilox*®, supplementing it with additional data (see paragraph 144 below for more details).

36. The requirement for the submission of additional clinical evidence may be waived, as in this case, in exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) no. 726/2004. In the event that it is impossible to provide comprehensive information on the efficacy and safety of the medicinal product under normal conditions of use, the grant of the MA is conditional on compliance with certain requirements, including stricter pharmacovigilance and the completion of missing clinical studies within a given deadline.

37. The additional documents produced by Sigma Tau as part of the MA application procedure for *Chenodeoxycholic Acid Leadiant*® did not contain the clinical data necessary to provide a complete proof of the efficacy and safety of the new therapeutic indication and the orphan drug was therefore authorised under "exceptional circumstances" (see paragraph 155 below).

III.1.2 The European regulatory framework for orphan drugs

38. "Orphan" drugs are medicinal products used to treat rare diseases, designated as such when they meet the requirements of Article 3(1) of Regulation (EC) no. 141/2000, i.e. when *a)* they are intended for the treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union (prevalence criterion), *or* the treatment of a life-threatening or chronically debilitating condition and it is unlikely that, without incentives, the marketing of the medicinal products in the EU would generate sufficient return to justify the necessary investment (return on investment criterion); and when *b)* there exists no satisfactory method of treatment authorised in the European Union or, if such method exists, the medicinal products in question will be of "significant benefit" to

those affected by that condition (significant benefit criterion)[46].

39. The European Commission can therefore assign the orphan designation to a drug – subject to a favourable opinion from the *Committee for Orphan Medicinal Products* (COMP) of the EMA - where the applicant company is able to prove one of the two requirements indicated under *a)* and the requirement under *b)*, provided for by the aforementioned legislative provision.

40. Subsequently, if the conditions are met, the European Commission may grant the authorisation to the orphan drug, following a favourable opinion from the *Committee for Medicinal Products for Human Use* (CHMP) of the EMA. At the same time, the COMP of the EMA verifies the permanence of the requirements for the orphan designation, through a comparative examination of the therapies that may already be authorised for the treatment of the rare disease[47].

41. Only where this scrutiny leads to a positive outcome, according to the provisions of Article 8(1) of Regulation (EC) no. 141/2000, companies holding marketing authorisation for an orphan drug shall enjoy market exclusivity for ten years (starting from when the authorisation is granted), by virtue of a prohibition on the European Union and the Member States to grant other authorisations for 'similar' medicines[48] with the same therapeutic indications. According to the provisions of Article 8(3)(c) of Regulation (EC) no. 141/2000, this market exclusivity is subject to some exceptions and does not prevent the marketing authorisation of a similar medicinal product with the same therapeutic indications as the already authorised orphan drug, *inter*

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[46] Article 3(2) of Commission Regulation (EC) no. 847/2000 of 27 April 2000 states that: "*For the purposes of the implementation of Article 3 of Regulation (EC) no. 141/2000 on orphan medicinal products, the following definition shall apply: - "significant benefit" means a clinically relevant advantage or a major contribution to patient care"*. The Communication on the application of Articles 3, 5 and 7 of Regulation (EC) no. 141/2000 on the orphan medicinal products of 18 November 2016 in point B.5 states that significant beneficial effect means a "*clinically relevant advantage*", or improved efficacy, better safety profile or better tolerability of the drug; while "*a major contribution to patient care*" can be based on the ease of self-administration, or on better adherence to therapy thanks to a change in the pharmaceutical form.

[47] See EU Court, 9 September 2010, in Case T-74/08, *Now Pharm v European Commission*, paragraph 43; Court of Justice, 3 March 2016, in Case C-138/15, *Teva Pharma and Teva Pharmaceuticals Europe v EMA*, paragraph 64; EU Court, 22 March 2018, in Case T-80/16 *Shire Pharmaceuticals Ireland Ltd. v EMA*, paragraph 68. See also the Communication on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products of 18 November 2016 in point B.5.

[48] Article 3(3)(b) of Commission Regulation (EC) no. 847/2000 of 27 April 2000 states that "'*similar medicinal product' means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication; […] 'similar active substance' means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism*".

alia, when the applicant company can demonstrate that its drug is safer, more effective or anyway clinically superior[49]. The commercial exclusivity also does not apply when the request for marketing authorisation concerns drugs that are 'not similar' to the already authorised orphan medicinal product (even if the therapeutic indications are the same).

III.1.3 The national legislation on galenic preparations

42. According to article 3(1)(a) and b) of Legislative Decree no. 219/2006, the following are considered as galenic drugs:

a) medicinal products prepared in pharmacies on the basis of a medical prescription intended for a specific patient, called "*magistral formulae*", as described in further detail by Article 5 of Legislative Decree no. 23 of 17 February 1998, converted, with amendments, into Law no. 94/98;

b) medicinal products prepared in pharmacies according to the indications of the European Pharmacopoeia or of the national Pharmacopoeias in force in the Member States of the European Union, called "*officinal formulae*", and intended for direct supply to undifferentiated patients that are customers of the said pharmacy.

43. According to Article 5(2) of Legislative Decree no. 23 of 17 February 1998, converted, with amendments, into Law no. 94/98, if there is a medicinal product on the market based on a certain active substance authorised for the treatment of a given disease, physicians are not allowed to prescribe a patient a formula (or "preparation") based on the same active substance, unless the prescription, for the specific purpose of customising the therapy, provides for a different dosage or different excipients[50].

III.2 Chenodeoxycholic acid (CDCA)

44. Chenodeoxycholic acid (CDCA) is a primary bile acid, produced by

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[49] Article 3(3) of Regulation (EC) no. 847/2000 states that a "clinically superior" medicinal product is one that is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:
1) greater efficacy, 2) greater safety, or 3) in exceptional cases, a major contribution, by other means, to diagnosis or to patient care.

[50] The patient could be allergic to the excipients of the medicinal product on the market or respond better to therapy when administered with a dosage different from the one on the market. Such therapeutic requirements would therefore justify the exception to the prohibition of the production of magistral preparations based on certain active substances where medicinal products containing them are authorised.

the liver and derived from cholesterol. Together with cholic acid, CDCA is the main constituent of the bile and plays a leading role in the digestion and absorption of lipids.

45. The CDCA was first isolated in 1924, first from domestic goose bile and then from human bile, and its chemical configuration was precisely defined in the 1930s[51]. The process of synthesising the active substance is currently not covered by industrial property rights.

III.2.1 The process of producing CDCA as a pharmaceutical grade active substance

46. CDCA as a pharmaceutical-grade active substance is a naturally derived substance, which cannot be produced in the laboratory from synthetic material[52]. The main raw material from which this active substance originates is bovine bile, but it can also be obtained from the bile of poultry or pigs[53].

47. The production of CDCA from bovine bile is structured as follows: cholic acid, i.e. the other primary bile acid, is extracted from the animal bile; it is then purified to obtain, through various chemical synthesis steps, ursodeoxycholic acid, a secondary bile acid[54]. CDCA is an intermediate product in the process of synthesizing ursodeoxycholic acid from cholic acid[55].

48. For production purposes, the uninterrupted availability of raw material in sufficient quantities is necessary; therefore, especially as regards bovine bile, CDCA producers must keep stable commercial relations with the operators active on the market for the extraction and collection of the raw material (or with the cattle slaughterhouses) in order for them to obtain suitable supplies[56].

49. The CDCA production also undergoes strict manufacturing processes to achieve the purity standards required by the industry (pharmaceutical grade). In particular, in the European Union (but also in the United States), the

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[51] See MAXWELL, ECKHARDT, *Drug Discovery: A Casebook and Analysis*, Springer Science and Business Media, 1990, p. 383; SNEADER, *Drug Discovery: A History*, John Wiley & Sons, 2005, p. 273.

[52] See doc. 78.416: "[...] *the product cannot be synthesised in a laboratory* [...]".

[53] See docs. 25.3.8, 28.2.182, 78.303 and 120.1.

[54] See doc. 28.2.33, annex. "*documentation for pre-NDA meeting 15 07 2014.pdf*".

[55] See doc. 120.1.

[56] See doc. 78.416: "[…] *the product [...] is beholden to the API producers being able to contract with enough global meat producers to ensure that a sufficient level of bile is available for the bile acid products they produce"*. The fact that the animals from which the active substance is extracted are referred to as "cattle" indicates that these considerations apply to bovine bile.

sector is subject to the regulatory standards established by the Good Manufacturing Practices (GMP)[57], which require manufacturing companies to comply, also for the purpose of guaranteeing traceability, with certain quality and safety requirements that are among the highest in the chemical industry, from the raw materials to the finished products[58]. These standards are more stringent than those imposed in other countries, such as, for example, India and China.

50. The CDCA production process is not complex[59]. This applies also after that the purity standard required in the European Union for the synthesis of the CDCA from the raw material was made more stringent with the definition of a new test in 2019, following a review of the monograph of the European Pharmacopoeia carried out by the *European Directorate for the Quality of Medicines* of the Council of Europe (EDQM)[60] (see paragraph 53 below for more details).

III.2.2 Companies active in the supply of CDCA

51. In view of the most common method of extracting CDCA (i.e. from bovine bile), in consideration of the stringent production standards required in the European Union for the production of pharmaceutical active substances and of the small size of the market (see paragraph 63 below), only a small number of companies have been, and still are, active in the supply of CDCA for pharmaceutical use.

52. The evidence mentioned above shows, in fact, that, in the view of Sigma Tau, there were only two operators able to obtain adequate quantities of raw material[61]. One of them was, and remains, the Italian company PCA,

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[57] See, for example, Article 46 (F) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004.

[58] See doc. 28.2.33, annex. "*documentation for pre-NDA meeting 15 07 2014*", which shows that the quality standards imposed by the European regulation for the production of CDCA derived from bovine bile require, *inter alia*, that slaughterhouses be certified and located in countries where there is no risk that livestock will contract TSE/BSE. The fact that PCA possesses this certification emerges from doc. 25.3.12.

[59] See doc. 120.1.

[60] See doc. 78.320: *"The active principle use[d] to manufacture CDCA Leadiant undergoes extensive testing, including determination of the correct form of CDCA in pharmaceutical grade and production according to the latest GMP and Quality control. This is relevant due to the fact that CDCA is a polymorph and testing ensures usage of the active molecule in industrial product, whilst not testing the active principle might result in usage of a form of the molecule that could be inactive*". See also docs. 78.194 and 78.195.

[61] See doc. 78.416: "[...] *there are two global API providers relevant for this product*" and doc. 78.133, Annex "AIFA Sigma Tau MEETING REPORT 24 June" ("[...] *Product of bovine derivation. 2-3 producers around the world*").

which, in addition to being a world leader in the production of ursodeoxycholic acid[62], has also been the main producer of CDCA at European level for many years. Since 2008, in fact, the chemical company has been part of a corporate group, headed by ICE (with which PCA has also recently merged[63]), which controls a series of companies active in the sector of extraction, collection and processing of bovine bile in the areas of greatest production, namely Mexico, Costa Rica, Colombia, Brazil, Argentina, Uruguay, Paraguay, South Africa, India, Australia and the USA[64].

53. The evidence shows that PCA has long been recognised as an operator with significant know-how, a high level of regulatory compliance, reflected in its ability to adhere to the GMP and to obtain and maintain a regulatory dossier (i.e. the Drug Master File or DMF), and has an excellent commercial reputation, in general in the production of pharmaceutical-grade active substances derived from bile acids, as well as in the production of this specific compound[65]. In fact, at the end of 2011, the EDQM turned to PCA as the only manufacturer of the active substance within the European Union to act as a point of reference to improve the CDCA synthesis process in relation to the permitted level of impurities[66]. From that point until 2019, the chemical company, involving Sigma Tau (later Leadiant), which had in the meantime developed a new CDCA purity test[67], subsequently transferred to and implemented by PCA[68] (see paragraph 127 below), worked closely with the EDQM, for the purposes of preparing the new test, relying largely on the contribution of PCA[69].

54. The other company that has similar characteristics is mentioned explicitly in a document dated February 2016 and implicitly in other documents of 2017[70]: this is New Zealand Pharmaceuticals Ltd. (hereinafter,

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[62] See docs. 25.3.12 and 28.2.181.
[63] See doc. 120.1.
[64] See docs. 25.3.2 and 28.2.181.
[65] The Annex to doc. 28.2.16 shows that PCA has produced CDCA since at least 1998, supplying Dr. Falk Pharma GmbH. See also docs. 28.2.54 and 78.102 (“*CDCA Sigma-Tau is obtained through a complex extraction procedure and its production undergoes the most current GMP standards (reference). The production process of the CDCA has been standardized and optimized during the 30 years of production…*”). See, finally, doc. 120.1.
[66] See doc. 78.6 (“[…] *I could not identify another manufacturer and I have therefore only information from your part*”). See doc. 28.2.31 (“*[…] they are waiting for our data and support. The finalization is depending on us*”).
[67] See docs. 28.2.32, 28.2.34, 28.2.39, 28.2.47, 28.2.53, 28.2.73, 28.2.84, 78.54.
[68] See doc. 28.2.77.
[69] See docs. 28.2.31, 78.6, 78.15, 78.21-78.25, 78.189, 78.194, 78.195.
[70] See docs. 78.323, 78.416 and 78.133, Annex "AIFA Sigma Tau MEETING REPORT, 24 June".

"NZP"), subsequently acquired by ICE in August 2020[71].

55. This company was considered by Sigma Tau when, in 2016, it carried out a search to identify sources of supply of CDCA other than PCA (with which it had an exclusive supply contract since June 2008 - see paragraph 96 below). However, as far as Sigma Tau was aware, NZP was at that time engaged commercially with another pharmaceutical company, the US firm Retrophin Inc. [now Travere Therapeutics Inc., ed.][72]. Furthermore, research carried out in July 2016 showed that there were, at least in abstract terms, 13 CDCA suppliers, located inside and outside the European Union, including PCA and ICE, two German companies, one American, one Mexican and several Chinese. However, the quality of the raw material (apart from that produced by PCA and ICE) was not known[73]. For these reasons, in August 2016 Sigma Tau believed that it had no sources of supply other than PCA[74].

56. The evidence, in fact, highlights the sporadic existence of non-EU sources of production of CDCA, especially in China[75]. However, for some time, these sources have been unable to adhere to the specific regulations required by European legislation and to pass the quality controls established by the GMP to access European markets.

57. Some documents indicate, in fact, that PCA itself in 2017 believed that non-EU suppliers of CDCA, especially Chinese provides, would not have represented "*a problem*" for Sigma Tau[76].

58. The lower quality of the raw material coming from non-EU markets, in particular the Asian ones, is in fact proven by several documents acquired in inspection that illustrate the (unsuccessful) attempt, by some Spanish pharmacies[77], by the hospital of Amsterdam[78] and by that of Antwerp[79], to

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[71] See the press release available on *https://www.iceitaly.com/news/ICE-acquires-New-Zealand-Pharmaceuticals*.

[72] See docs. 78.323 and 22.7.114.

[73] See doc. 78.7. See also docs. 84, 185 and 187 which contain a historical extract from the Thomson Reuters Newport Global database, which, according to Leadiant, highlighted, as early as 2015, the presence on the market of (at least) 15 alternative providers of APIs for CDCA. As a minimum, the suppliers indicated shall match those indicated in the list contained in doc. 78.7.

[74] See doc. 78.5.

[75] See docs. 25.3.5, 78.190, 78.303.

[76] See doc. 78.262: "*Compounding and foreign/exotic API supply of CDCA will not represent a problem*". See also docs. 28.2.132 ("[...] *a Chinese source will not represent an issue for you*").

[77] See docs. 22.7.40 and 78.257 ("*We have just received confirmation that the pharmacy was closed and forced to withdraw all compounded CDCA from the hospitals. The inspectors have collected samples of the product that is being tested and the pharmacy will receive a fine and likely lose the license to operate*").

[78] See doc. 78.93.

[79] See doc. 78.297, which states that, in December 2017, the Antwerp hospital "*bought their CDCA raw material at Eurochemicals in the Netherlands and compound capsules themselves […] The raw material has been produced in China and took them off a while before it arrived. They have re-analysed it in order to*

produce the CDCA in a galenic version from the end of 2017 and during 2018 on the basis of raw material imported from China by a wholesaler of pharmaceutical-grade active substances[80]. In particular, the checks carried out by the competent Dutch authorities in August 2018, at the request of Leadiant, showed the presence of excessive levels of impurities in the magistral preparations produced by the Amsterdam hospital compared to those provided for by the monograph from the European Pharmacopoeia, with the consequent interruption of the production[81]. This indicates that, as PCA also confirmed at the hearing, the only alternative source of production of CDCA whose existence is proven during those years *"was then unable to produce an active substance compliant with the purity standards required by the European Pharmacopoeia*"[82].

59. As a result of this, in October 2018, the said wholesaler went back to PCA after two years, as a certified producer in Europe[83], the only one with this feature, according to what Leadiant itself stated in an internal document dated April 2018[84].

60. The quality level of the raw material from Asian producers has only recently improved. Some documents on file, including the minutes of the PCA's hearing, indicate, in fact, that in February 2020 the Amsterdam hospital resumed the galenic production of the CDCA thanks to the use of raw material from another source of Asian origin that has so far been found to adhere to the European regulatory specifications, also in the new version resulting from the amendments to the European Pharmacopoeia[85]. At present, this supplier is therefore one of the sources of production of CDCA capable of supplying the markets of the European Union[86], exclusively to support a production of

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assure that it is pharmaceutical grade". After the withdrawal of the galenic products from the Dutch market, they were also withdrawn from the Belgian market.

[80] See docs. 22.7.64, annex "Theophylline – CDCA", 78.297 and 138.4.9, which indicate that this intermediary, Eurochemicals B.V., in October 2017, had managed to conclude a contract with a CDCA producer other than PCA and to import the raw material into the European Union by supplying several hospitals in some Member States.

[81] See docs. 22.5.8, 78.93 and 78.326.

[82] See doc. 120.1.

[83] See docs. 28.2.183 and see with doc. 22.7.64.

[84] See doc. 138.4.9 ("*Furthermore, there is only one approved EU certified supplier of pharmaceutical grade CDCA…"*).

[85] See docs. 75, 75.1 and 120.1. In particular, the latter document shows, in the opinion of PCA, *"[t]he need for the hospital in Amsterdam to set up galenic production [...] may have stimulated the investment necessary for such production of CDCA to be able to pass the checks of the European regulatory authorities"*.

[86] According to the chemical company, therefore, the "*Chinese source of CDCA today seems to be able to comply with the purification standards required in Europe and recently to have reached the high quality standards that PCA has always respected*" (see doc. 120.1).

galenic nature.

III.3 Pharmaceutical uses of CDCA: the treatment of CTX

61. Since their introduction on the market in the early 1970s, chenoxycholic acid-based drugs have been authorised for sale by the individual national regulatory authorities of the European Union only for the treatment of gallstones[87]. However, since the early 1990s (and in the literature even in the 1980s), CDCA has no longer been considered adequate to the international standards established for the dissolution of gallstones and has been superseded by other treatments that have proved more effective for this therapeutic indication[88].

62. As documented by numerous scientific studies published in the early 1980s[89], however, the medical/scientific community has found that the active substance has a therapeutic utility in another medical domain: in fact, it proved immediately effective in the treatment of cerebrotendinous xanthomatosis (or CTX).

63. CTX is a disease caused by a congenital defect in the synthesis of primary bile acids. Patients with this condition are unable to produce enough chenodeoxycholic acid due to mutations in the CYP27A1 gene, which cause a lack of the liver enzyme sterol 27-hydroxylase. The enzyme defect causes the accumulation of cholestanol and cholesterol in many tissues, including the tendons and the central nervous system, generating tendon and/or brain xanthomas, which cause neurological, cognitive and systemic dysfunctions[90]. It is therefore a very serious progressive pathology, preventing a patient's normal development and generally leading to loss of autonomy and early death. It affects a very small proportion of the European population (250

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[87] See DANZIGER, HOFMANN, SCHOENFIELD, THISTLE, *Dissolution of cholesterol gallstones by chenodeoxycholic acid,* in *N. Eng. J. Med.*, 1972, no. 286, pp. 1-8; CAREY, *Editorial: Cheno and urso: what the goose and the bear have in common,* in *N. Engl. J. Med.*, 1975, no. 293 (24), pp. 1255–7.

[88] See *https://www.farmaterverantwoording.nl/*wp-*content/uploads/2021/04/2018.*09.*07-Handhavingsverzoek-CDCA_En*glish-*unofficial-translation.pdf*. In the medical literature see, *ex multis*, RUPPIN, DOWLING, *Is recurrence inevitable after gallstone dissolution by bile acid treatment?*, in *Lancet*, 1982, no. I, pp. 181 *et seq.*; PODDA, ZUIN, BATTEZZATI, GHEZZI, FAZIO, DIOGUARDI, *Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstones dissolution: a comparison with ursodeoxycholic acid alone,* in *Gastroenterology*, 1989, no. 96, pp. 222 *et seq.*

[89] See, *ex multis*, BERGINER, SALEN, SHEFER, *Long-Term Treatment of Cerebrotendinous Xanthomatosis with Chenodeoxycholic Acid,* in *N. Engl. J. Med.*, 1984, no. 311, pp. 1649-1652. Even in the EMA/650359/2016 *Assessment report. Chenodeoxycholic acid Sigma Tau* of 15 September 2016, p. 33: there are at least 70 scientific studies that testify to the oral administration of CDCA in at least 200 patients since 1975.

[90] See doc. 133.

patients have been diagnosed in Europe[91]) and is therefore an ultra-rare disease. The countries in which it is most widespread are Italy, the Netherlands, Belgium, Spain, France, the United Kingdom and, to a lesser extent, Germany. The number of patients who have been diagnosed with CTX is not precisely known as there are several conflicting sources. The information acquired and the documents acquired in inspection show that there are about 45 patients in Italy (41 in 2020)[92], 50 in Spain[93], around 60 in the Netherlands[94] and about 24 in the United Kingdom[95]. It is therefore a very small market[96].

64. Since the discovery of this new therapeutic use, CDCA-based drugs have been used for the treatment of CTX and, until the introduction of the orphan drug Leadiant, were prescribed off-label.

65. In fact, Sigma Tau had commissioned market research in September 2014, which showed that the CDCA, from a medical prescription pattern perspective, had long been the "*standard of care*" for CTX in most EU Member States (France, the United Kingdom, Italy, Germany, Spain, Sweden, the Netherlands and Austria)[97].

66. One of the leading experts of CTX in the world, defined as a "*world key opinion leader*" by Sigma Tau[98] - a specialist doctor from the University Hospital of Siena who, with his team, carried out a retrospective study for Sigma Tau to support the marketing application for the orphan drug (see paragraphs 145-147 below) – in the procedure for approving the framework agreement concerning the conducting of this study, declared to the Ethics Committee of the Tuscany Region, in October 2014, that "*[...] its use* [of the CDCA ed.] *in the treatment of cerebrotendinous xanthomatosis (rare disease) is well established and has been scientifically recognised for many years. Prescribing the drug in question is part of normal clinical practice"*[99].

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[91] See doc. 187.
[92] See doc. 122.
[93] See doc. 138.4.1.
[94] See the complaint from the *Dutch Pharmaceutical Accountability Foundation*. See also *https://www.biocentury.com/bc-week-review/company-news/deals/2009-02-09/sigma-tau-spa-solvay-deal*.See also doc. 122.
[95] See NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE), *Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis*, 2018, p. 11.
[96] See doc. 22.7.17 (*"I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years……it's a too small pathology… it's an orphan who nobody wants to adopt!"*).
[97] See doc. 22.7.17.
[98] See docs. 95 and 138.4.7.
[99] See doc. 6.4.

67. This assessment is also confirmed by documents relating to subsequent years. In fact, further market research commissioned between the end of 2015 and the first months of 2016 showed that, for the specialist doctors interviewed, CDCA was the treatment of choice in most cases (15 out of 16 doctors) in France, Spain, Germany, Italy, the Netherlands, Belgium and the United Kingdom[100]. Documents from 2016 also show that another expert of this pathology renowned in Europe, who carried out a second retrospective study for Sigma Tau to support the MA for the orphan drug (see paragraph 149 below), believed that the CDCA was a therapy "*worldwide accepted (literature), applied (treating physicians), and effective (open-label, single arm study)*"[101].

68. The same scientific literature collated by the company and presented in support of its request for the orphan designation and for the MA for CDCA as a treatment for CTX indicates that the active substance is the "*treatment of choice*"[102] and that its effectiveness in the treatment of rare disease has been specifically found with the administration to patients of 250 mg of CDCA three times a day[103].

69. Even some qualified institutional sources have recently indicated that, despite the absence of prospective clinical trials, the "*first-line treatment*" for CTX is CDCA[104]. This is particularly the case in Italy, where this active substance has always been the drug of choice for the treatment of rare disease because, when taken regularly in the dose indicated above, it slows the

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[100] See doc. 78.105, Annex "Market Research_clinical-FINAL" ("*All respondents in all countries, except for one respondent in the UK, stated they use CDCA to treat CTX*"; "*Xenbilox is the only CDCA treatment right now. And the key opinion leader on biliary acid diseases, Professor Peter Clayton in the UK, thinks it's the best option*"; "*We have demonstrated that CDCA improves not only biochemical, but also clinical and instrumental parameters in our patients, and also other colleagues have proven it, but in these years I have published many data on CDCA treatment, and we for example, have shown that CDCA intake improves conduction of myelinated fibers of both central and nervous system, and peripheral nervous system. Also it increases mineral density -it stabilises the brain magnetic resonance imaging patterns, and in our experience we have never had side effects, neither in children nor adults with this drug*"; "*CDCA is the standard of care, and the neurological symptoms are the most difficult to live with, so we chose to use the product that offers the best results at the neurological level, to prevent neurological issues*"; "*Due to the biochemical pathway, there is really only one effective treatment, that is with chenodeoxycholic acid*").

[101] See doc. 78.417 of March 2016. See also doc. 78.17, annex "*ST-CDCA_Slidesmeeting12092016.pptx"* of September 2016, which shows that, in France, CDCA was considered the therapy chosen for the treatment of CTX at the time.

[102] See docs. 22.7.8, annex, 22.5.17 ("*CDCA is unanimously recognized as the therapy of choice for CTX*"), 78.30, annex "Annex 1 – Overview of product development", 78.385.

[103] See docs. 78.237, 78.385.

[104] See *https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=605&Disease_Disease_Search_diseaseType=ORPHA&Disease_Disease_Search_diseaseGroup=909&Ziekte(n)/ziektegroep=CTX&title=CTX&search=Disease_Search_Simple* and NICE, *Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis*, p. 12.

spontaneous evolution of the disease in most patients, by stabilising neurological and psychiatric manifestations and slowing the increase in the size of tendon xanthomas[105].

70. Finally, the aforementioned specialist doctor of the University Hospital of Siena stated at the hearing that, based on his forty-year experience, the CDCA is "*to be preferred in the treatment of the rare disease in question*" and that "*there is a clear consensus in the medical/scientific community at the international level that CDCA is the therapy of choice for CTX*"[106].

71. The doctor also stated that there is no treatment other than CDCA at present, not even in the experimental phase. The only current lines of research – aimed at the future development of gene therapy – are at an embryonic stage. In addition, given the lack of funding, research into this therapy is proceeding very slowly and even if it were to be effective, it would not be introduced on the market until ten years from now[107].

III.3.1 CDCA-based drugs

72. The information available in the case files showed that, since the 1970s, CDCA-based drugs were sold in some European countries under different trade names (*Quenobilan*® and *Quenocol*® in Spain, *Chenodex*® in France, *Xebyl*® in Portugal, and *Chenofalk*® in the Netherlands, Belgium and Germany[108]). The following four CDCA products were available in Italy: *Chenossil*®, *Chenofalk*®, *Fluibil*® and *Chenocol*®[109]. *Quenobilan*®, *Quenocol*® and *Chenofalk*® were produced using the raw material provided by PCA and ICE[110]. Among the various products mentioned, *Chenofalk*® in particular was administered off-label by Italian doctors to treat patients with CTX.

73. *Chenofalk*® became unavailable on the Italian market in 1996. Moreover, the other chenodeoxycholic acid-based drugs on the domestic market at that time have been found over time to be less and less available before marketing ceased definitively between the late 1990s and the early

[105] See doc. 133. See also https://malattierare.toscana.it/percorso/scheda/xantomatosi-cerebrotendinea.
[106] See doc. 133.
[107] See doc. 133.
[108] *Chenofalk* was approved in Germany for the first time in 1976, with Dr. Falk GmbH as the MA holder. See doc. 96.75.
[109] See docs. 3 and 8.1.
[110] See docs. 138.1 and 138.2.

2000s[111].

74. Faced with the difficulty of supplying CDCA-based drugs, during the second half of the '90s and in response to a request from specialists at the University Hospital of Siena who were treating several patients with CTX[112], the Hospital decided to guarantee the continuity of treatment to the said patients by producing the drug in galenic form[113].

75. The galenic production of CDCA began in 1997. Since then, the Pharmacy has always purchased the active substance from ICE through an intermediary[114] and has supplied the magistral preparations to the pharmacies of other Italian hospitals[115].

76. The cost of the raw material was €0.083 per capsule, plus the professional fees applied according to the rates in force at the time, for a total production cost of €0.67 per capsule. The price for 100 capsules of 250 mg thus equalled €67, leading to an annual treatment price of €733.65 per patient[116].

77. However, ICE informed the Pharmacy in 2005 that it no longer intended to produce the active substance in question. In 2007, the Pharmacy then purchased from PCA the last 75 kg of stock of the active substance, which was used for galenic production until November 2015, when the stocks of raw material ran out[117].

78. In other European Union national markets, doctors continued to administer the aforementioned CDCA-based drugs to patients with CTX off-label, at least as long as they were available. In particular, the information obtained shows that *Chenofalk*® became unavailable in the Belgian market in 2005 and that the drug has been imported since then from Germany, where it has been marketed since the mid-1970s[118], first under the same trade name[119]

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[111] See docs. 3.3 and 6.13. The scarcity of the active substance has also been documented in the scientific literature. See A. FEDERICO, M.T. DOTTI, *Cerebrotendinous xanthomatosis,* in *Neurology,* 2001, 57(9), pg. 1743; P. SAMENUK, B.M. KOFFMAN, *Chenodeoxycholic treatment of cerebrotendinous xanthomatosis,* 2001, 56(5), pg. 695.

[112] See doc. 133.

[113] See doc. 6.13.

[114] See doc. 25.1 and docs. 25.3.17-25.3.31 and 120.1.

[115] See docs. 6, 6.13, 10 and 120.1. This includes, for example, the R. Margherita Children's Hospital and the S. Anna Obstetrics and Gynaecology Hospital in Turin.

[116] See docs. 6 and 22.7.17. See doc. 10, annex 1.

[117] See doc. 6.9.

[118] See docs. 96.75 and 96.165.

[119] See *Réponse de la ministre des Affaires sociales et de la Santé publique du 14 décembre 2015, à la question n. 554 de monsieur le député Olivier Chaster du novembre 2015*, pag. 054, available at *https://www.dekamer.be/QRVA/pdf/54/54K0054.pdf*. See also *https://geneesmiddelendatabank.fagg-afmps.be/#/query/human/*.

and then under the trade name of *Xenbilox*®; in the Netherlands, the drug was marketed under the name of *Chenofalk*® until the end of 2009 (imported from Germany from the middle of 2008) and then as *Xenbilox*® (see paragraphs 97 and 106 below)[120]. Likewise, *Quenobilan*® and *Quenocol*® were removed from the Spanish market between the second half of 2008 and the beginning of 2009, and *Xenbilox*® has been imported from Germany since then[121]. *Chenodex*® has not been sold on the French market since 1999, and its MA was withdrawn at the beginning of 2005. *Xenbilox*® took its place in the French market[122]. *Xebyl*® has not been marketed in Portugal since 2011[123].

79. The evidence indicates that from 2011 (and from the beginning of 2016 with regard to Italy) and until the introduction of the Leadiant orphan drug on the market, the only CDCA-based drug actually available in Europe was *Xenbilox*®, owned by Sigma Tau[124].

80. Likewise, from June 2017, patients taking *Xenbilox*® were administered *Chenodeoxycholic Acid Leadiant*, the only CDCA-based product registered for the treatment of CTX currently available in the domestic market[125], as well as other national markets in the European Union[126].

81. The aforementioned specialist from the University Hospital of Siena stated at the hearing that, in his opinion, there is no difference at the therapeutic level between the Pharmacy's CDCA-based magistral formulations, *Xenbilox*® and *Chenodeoxycholic Acid Leadiant*® (hereinafter also "*CDCA Leadiant*®"), which he has administered over time to his patients[127].

III.4 Other drugs used to treat CTX

82. Although CDCA-based drugs are the predominant therapy chosen by doctors for the treatment of CTX, the documents on file show that there are also other therapies that doctors have sometimes used for the treatment of this disease: cholic acid, ursodeoxycholic acid and statins (in particular,

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[120] See docs. 8 and 138.4.1.
[121] See docs. 138.1 and 138.2.
[122] See *https://www.has-sante.fr/upload/docs/application/pdf/2014-07/orphacol_ct13339.pdf*.
[123] See *https://app.infarmed.pt/sgrt/detalherstock.aspx?id=2503*.
[124] See doc. 8.
[125] See doc. 3.
[126] See docs. 78.249 (where, in a presentation from November 2015, there is express mention of "*switching*" and a "*plan of transitioning*" from *Xenbilox*® to *CDCA Leadiant*®), 78.12, 78.225 ("*Move all patients currently on compounding and Xenbilox to CDCA Leadiant*").
[127] See doc. 133.

simvastatin, lovastatin and pravastatin).

83. Ursodeoxycholic acid and statins have, however, been used on a very limited basis in clinical practice, which from the outset demonstrated barely detectable effects in the correction of the metabolic changes associated with CTX. This has therefore led specialists, especially in Italy[128], to consider them ineffective on the rare disease, and therefore not a replacement for CDCA[129].

84. With regard to cholic acid, the aforementioned market research commissioned by Sigma Tau in September 2014 showed that this substance was only used sporadically in some cases as a therapy for the treatment of the rare disease[130] and that, according to most clinical studies and medical specialists, in non-naïve patients CDCA should not have been replaced with cholic acid for the treatment of CTX[131].

85. According to the mentioned research, one explanation for this was that cholic acid was considered to be less effective than the CDCA in treating CTX by doctors in several EU Member States[132]. This was, and remains, true for Italy, where the leading experts displayed strong scepticism about the use of cholic acid for the treatment of the rare disease[133]; it is potentially usable for paediatric patients[134], and the individuals interviewed (defined as "payers") believed that an increase in the price of the CDCA-based drug would not lead to the replacement of this active substance with cholic acid, precisely because

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[128] See *https://malattierare.toscana.it//percorso/scheda/xantomatosi-cerebrotendinea*.

[129] See docs. 22.7.17, 78.59, annex "CDCA Launch Plan", 78.348, 78.369 and 96.23. With regard specifically to bile acids, some investigation documents indicate a precise hierarchy based on efficacy in the treatment of the rare disease: within this classification, ursodeoxycholic acid is in last place, preceded by cholic acid and CDCA, which is in first place. See docs. 96.5, 96.12, 96.17, 96.23 and 96.189.

[130] See doc. 22.7.17 ("*used infrequently and most consensus is [that] it is inferior to CDCA*"; "*Little or no use now*"). In France, the United Kingdom and Spain, this active substance was used, albeit at a minimum. In particular, cholic acid was seen by some French doctors as a potential alternative to CDCA, but, aware of its lesser efficacy, they considered it preferable not to replace CDCA with cholic acid (*"Should not be used in CTX if the patient can receive CDCA"*) and to prescribe it only in cases of liver toxicity detected after the administration of CDCA ("*2 of 3 doctors prefer not to use it, 1 suggested could be used where liver problems*"). This means that, as the consultants themselves stated, even in France "*[i]t is now well accepted in the physician community that CDCA is the SoC* [Standard of Care. Editor's note]".

[131] See doc. 22.7.17 ("*many physicians thought it would be damaging to patients to replace CDCA with CA*!").

[132] See doc. 22.7.17: "[…] *considered less effective in CTX than CDCA and is not supported by very strong data in CTX. NOT interchangeable*" (France); "*I would not consider both (CDCA and CA) as equal. I have not experience with cholic acid but I know some studies comparing both and they do not consider them equal. Cholic acid has not demonstrated to be effective in these studies*" (Spain).

[133] See doc. 22.7.17: "*We don't believe in the effectiveness of Cholic acid (in CTX) and it's not true that it has a better safety profile. […] We don't believe in the specificity of the cholic acid, the scientific literature doesn't confirm it and at the mean time we don't believe in the asserted safety of this molecule […] I know that the expectations about the use of cholic acid in the treatment of CTX have been disappointing*". See *https://malattierare.toscana.it//percorso/scheda/xantomatosi-cerebrotendinea*.

[134] See doc. 96.23.

of its lower effectiveness on CTX[135].

86. Not even the European Commission's authorisation of *Kolbam®*, which is cholic acid based, as an on-label drug for the treatment of CTX in 2014[136] and its introduction to the French market (which in principle could have constituted a potential factor in overturning this therapeutic hierarchy)[137] have appreciably changed doctors' preferences. In fact, the acquired evidence indicates that even before obtaining these administrative titles, CDCA, despite being an off-label medicinal product, continued to remain, even in France, the therapy of choice for the treatment of CTX[138].

87. Obtaining the orphan designation and the MA (see paragraphs 152-154 below) also definitively enshrined the therapeutic superiority of CDCA at the regulatory level and reduced competition with cholic acid to a marginal level, as the company itself had recommended in November 2016 ("*[m]arginal competition by Cholic Acid in Europe*")[139], and as confirmed by other more recent documents dating back to 2019[140].

88. Lastly, the specialist from the University Hospital of Siena during the hearing (see paragraph 70 above) in relation to this issue said that the "*level of cholic acid in bile plays a smaller role in the development of the rare disease compared to CDCA. [...] there are only two publications that describe the results of the administration of cholic acid in patients with the rare disease [...]. Based on these two studies, cholic acid has a certain efficacy on the disease, but this remains much less documented than the efficacy of CDCA*"[141].

89. As regards the presence and/or use of cholic acid-based drugs in the Italian market, it should be noted that *Kolbam®,* although available in some national markets of the European Union, has never been authorised in Italy[142].

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[135] See doc. 22.7.17: "*[…] the cholic acid doesn't have any scientific credibility in the cure of CTX and also the declared greater safety is considered as a "bluff" not adequately supported by clinical evidences*".

[136] The medicinal product *Kolbam®*, owned by Retrophin Inc., classified as an orphan drug on 29 October 2009 after a long judicial dispute, was authorised by the European Commission on 24 November 2015 (the MA was initially issued on 4 April 2014) for three therapeutic indications: in addition to two congenital defects in the synthesis of primary bile acids, it was also authorised for the treatment of CTX.

[137] See doc. 22.7.17.

[138] See doc. 78.343, which highlights that in 2015 French neurologists attempted to convince the competent national authorities that it would be better to continue prescribing CDCA to patients with CTX, and not redirect them towards cholic acid. See doc. 78.105, Annex "*Market Research_clinician-FINAL*" which shows that the French doctor interviewed during market research commissioned by Sigma Tau between the end of 2015 and the beginning of 2016 said: "*...wants to use CDCA instead [and] so was happy to hear that Kolbam's MA had been annulled...*".

[139] See doc. 78.236.

[140] See docs. 22.5.17 and 78.165.

[141] See doc. 133.

[142] See doc 3.

However, currently the drug is no longer marketed in any Member State since the MA was revoked by the European Commission on 13 July 2020 at the request of the manufacturer[143].

90. There is also another cholic acid-based drug, *Orphacol*®, which was authorised in 2013 for the treatment of congenital defects of primary bile acid synthesis other than those that cause CTX[144]. *Orphacol*® is registered and marketed in Italy[145], but the filings do not show any evidence that this drug is used off-label on the national market for the treatment of the rare disease referenced under this decision, since, based on the statements of the specialist from the University Hospital of Siena during the hearing, it appears that CDCA is the only therapy to have been ever used in Italy for the treatment of CTX[146]. Moreover, the said company considered the off-label use of cholic acid after registration of the orphan drug unlikely[147].

III.5 The investigated facts

III.5.1 The design of the project to register an orphan drug for the treatment of CTX (2007-2014)

91. Sigma Tau began the project of registering CDCA as an orphan drug for the treatment of CTX in 2006 in the United States[148]. In that year, the US branch of the former Sigma Tau group requested the orphan designation for CDCA, obtaining it in February 2007[149].

92. Immediately after, in April 2007, Sigma Tau began working with a consultancy firm to assess the possibility of registering CDCA as an orphan drug for the treatment of CTX in Europe, as well. At that time, Sigma Tau already planned to sell the future orphan drug at a price higher than what was

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[143] See *https://www.ema.europa.eu/en/documents/public-statement/public-statement-kolbam-withdrawal-marketing-authorisation-european-union_en.pdf.*

[144] The drug received the orphan designation on 18 December 2002. After a equally lengthy judicial dispute, the European Commission issued the MA for the drug in a decision dated 12 September 2013. On the other therapeutic indication for which *Orphacol* was authorised, see also doc. 3.2.

[145] *Orphacol*® has been authorised for sale in Italy since 20 January 2017 and is classified as a class H medicinal product under national law.

[146] See doc. 133.

[147] See doc. 78.104, where Leadiant itself states that "*it will be likely that once registered, an off-label use will be more difficult*".

[148] See docs. 22.7.156, Annex "CTX FDA meeting 08-31-2007, Annex "CTX February 2008", 28.2.3 and 28.2.4.

[149] See docs. 22.7.156, Annex "CTX FDA meeting 08-31-2007, 78.31, Annex "*ODD Sigma Tau Section A to E. 10Sep2014_Final"*.

applied at that time to a CDCA-based drug registered for the treatment of gallstones but administered off-label to treat CTX, which the company was intending to purchase. To achieve this aim, the company was considering gradually increasing the price of this product (step price increase[150]).

93. The company identified *Chenofalk*®, owned by the pharmaceutical company Dr. Falk Pharma GmbH[151], as the drug to be acquired, in order to obtain the availability of the dossier and the administrative rights related to CDCA with a view to request the registration of the drug for the treatment of CTX[152].

94. In May 2007, the company contacted the EMA to lay out and prepare its orphan designation application. However, following discussions with the Agency, it realised that it was unable to provide all the clinical information requested by the Institution, and therefore temporarily set aside the registration project[153].

95. Nevertheless, the company decided to continue at least the initial part of the project, and on 19 June 2008 Sigma Tau Pharmaceuticals Inc. purchased from Dr. Falk Pharma GmbH the entire dossier relating to *Chenofalk*®, including the MA for the German market[154], taking over the product's distribution[155].

96. Following the purchase of the distribution rights to *Chenofalk*®, in order to guarantee a safe source of raw material for the future production of the drug, Sigma Tau Pharmaceuticals Inc. and PCA, after initial discussions between the second half of 2007 and the first half of 2008[156], signed an exclusive supply agreement on 24 June 2008[157].

97. The *Chenofalk*® MA valid for the German market was then awarded

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[150] See doc. 96.213 and 22.7.3 annex "121 06 Draft Report 250307" ("*step price increase should be possible. Step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current pack (to evaluate best option requires further analysis). Precedent in Germany for novelty being recognised of old product in new indication. Clear rationale and KOL* [Editor's Note: Key Opinion Leader] *support will be needed to facilitate reimbursement of CDC after a step price increase*").

[151] See docs. 96.223, 96.213, 22.7.3, Annex "121 06 Draft Report 250307", 22.7.156, Annex "CTX Decision Analysis v3", "CTX FDA meeting 08-31-2007" and "CTX February 2008", 28.2.3 and 28.2.4.

[152] See doc. 96.54.

[153] See docs. 138.4.1 and 138.4.6.

[154] The dossier included all rights relating to *Chenofalk*, including the MA for Germany, know-how, technology, production data, registration dossiers, clinical and preclinical data and any trade secrets relating to the production, development, registration, marketing and exploitation of the drug. The MA for the German market was issued by the *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM) to Dr. Falk Pharma GmbH on 13 September 1999. See docs. 28.2.19 and 127. See *https://www.pharmaceutical-business-review.com/news/16498sigmatau_acquires_chenofalk_from_dr_falk_p/*.

[155] See doc. 78.300.

[156] See docs. 28.2.3, 28.2.4-11, 28.2.13-16, 28.2.28-28.2.30.

[157] See docs. 28.2.27 (incorporating the text of the Agreement) and 28.2.25.

to Sigma Tau Arzneimittel GmbH on 14 October 2008[158]. From then on, the German company distributed the drug in Germany at an ex-factory price of €37.75 (excluding VAT) and at a retail price of €58.69 (including VAT) for a pack of 100 capsules of 250 mg[159]. The medicinal product was also exported from Germany to a number of Member States, including the Netherlands[160], France and Belgium[161].

98. Several documents dating from the period between mid-2008 and mid-2009 confirm that Sigma Tau intended to pursue its commercial strategy through a gradual increase in the price of the product sold in Germany[162], to be applied even before the registration of the orphan drug, so as to prepare not only the German market, but also the other European markets, for the higher price of the orphan drug[163].

99. In particular, the company was aware of the fact that, only if it had held a monopoly in the sale of CDCA-based drugs throughout Europe[164] could it have applied a "*premium price*" for the drug sold off-label for the treatment of CTX, pending the obtaining of the orphan designation[165]. During the first half of 2007 and then in early 2008, some consultancy firms therefore suggested that the company check how to prevent other entities from producing CDCA-based drugs[166]. Sigma Tau then identified some "*competing*

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[158] See docs. 78.300, 96.165 and 127.

[159] See doc. 96.75.

[160] See doc. 96.75.

[161] See doc. 96.99.

[162] See docs. 22.7.3, Annex "*006060_2 Report*", 96.165, 96.99 and 96.75, which reflect the exact wording already used by the consulting company in 2007: "[...] *step price increase should be possible*" (see doc. 96.213 and doc. 22.7.3, annex "*121 06 Draft Report 250307*").

[163] See doc. 22.7.3, Annex "*006060_2 Report*": "[...] *therefore getting an increase in the German price is necessary (or removing this product as a price benchmark) if a higher level of price is the ambition for Chenorm* [Editor's note: trade name that the company initially intended to give to the orphan drug] *across Europe. […] Options are a step price increase or product withdrawal, if the German price is not to limit the price achievable for Chenorm elsewhere*" and 22.7.3, Annex "*121 06 Report Draft 250307*" ("*Price should ideally be at level desired post-approval. Desired step price increase can happen pre-or post CTX MA approval*").

[164] See doc. 96.99, which states: "*Acquisition of competing MAs:*
Estedi (Quenobilan) -Spain
Zambon (Quenocol) - Spain
Basi (Xebyl) – Portugal
[…] Acquisitions would give us market exclusivity in the EU (based on current regulatory and sales data").

[165] See doc. 96.99 ("*Sell product on a named patient basis as an unlicensed medicine at premium price […]*
CDCA currently worth $160,000 in Germany (based on approximately 3,000 units sold per year)
If product can be sold as a premium priced unlicensed medicine in Germany, market could be worth between $3-4 million").

[166] See doc. 96.213, 22.7.3, Annex "*121 06 Report Draft 250307*" ("*Current and future suppliers/manufacturers of CDC*
Ease of manufacture?
Can pharmacists compound it?

MAs"[167], namely those for the only CDCA-based drugs other than Sigma Tau's *Chenofalk*® that still exist in the European Union, *Quenobilan*®, *Quenocol*® in Spain and *Xebyl*® in Portugal (see paragraph 78 above), which it planned to purchase, as well as the *Chenofalk*® MA valid for the Netherlands owned by another company and in relation to which Sigma Tau was debating "*how to proceed*"[168].

100. A document in the filings shows that, after the spontaneous exit from the market of *Quenobilan®/Quenocol®*, the German branch of the former Sigma Tau group acquired ownership of the *Chenofalk*® marketing authorisation valid for the Netherlands in September 2009[169]. However, the company never used it, although it considered maintaining its formal validity strategic[170]. The revocation request was finally submitted on 9 September 2015[171].

101. The company expected a significant increase in turnover generated by the application of a Europe-wide price that, through the application of the projected premium price, could extend from a minimum of €1,327 to a maximum of €3,318 per pack, with an annual per-patient therapy cost ranging from €14,600 to €36,500[172].

102. These price assessments reflected the indications expressed as early as April 2007 by the consulting company referenced above, which, on the basis of market research, indicated that demand would accept an annual per-patient price corridor of €10,000–€40,000 and, in particular, considered an annual price of €14,600 (and therefore a price of €1,327 per pack) within this corridor

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Can ST stop others from making it?
Can ST stop others from supplying it to pharmacists?
Can ST prevent rival suppliers' CDC from being used in CTX?
If so, for how long and in which territories?"); doc. 22.7.3, Annex "006060_2 Report" ("*Check availability of other supplies of CDC*
e.g. Estedi and Zambon product in Iberia
Other products/brands/generics?
Other countries?
Scale of operation, commercial/regulatory status?
Prices levels? Are they official, published prices?
Interchangeability with Chenorm for use in CDX?
Main current uses?").

[167] See doc. 96.99 ("*competing Mas*").

[168] See doc. 96.99 ("*Valid MA in Netherlands (TRAMEDICO) - How to proceed?*").

[169] See doc. 78.300.

[170] See doc. 22.7.17 ("*If the current licence is withdrawn in NL, off-label use for CTX would no longer be possible which would be disastrous. However when the CTX EMA approval is imminent, it may make sense to withdraw the old indication in NL as this may create an opportunity to rebrand the product (and price it differently and higher compared to the old product)*").

[171] See doc. 96.151.

[172] See doc. 96.99.

as "*reasonable*". The consultancy firm also believed that the highest anticipated price could be obtained in some markets, but that this might not be in line with the company's ethics[173].

103. In order to justify the application of this price even before the registration of the orphan drug, Sigma Tau (as suggested by the consulting company) intended to leverage the *de facto* status of the product as an orphan drug (after a dedicated awareness campaign with all relevant stakeholders) and proceed to make "personalised" sales of the drug administered (initially) off-label[174]. In any case, it was essential to obtain the orphan designation for the drug and the MA for the new indication and the associated ten-year exclusivity that would have ensured the company significant expected profitability.

104. Two of the aforementioned documents in particular highlight the company's awareness of the complexity of the implementation of a strategy aimed at applying the indicated premium price in Germany, where pharmaceutical regulation could have fixed the reimbursement price of the future orphan drug to be administered for the treatment of CTX (whether administered off-label or registered for this therapeutic indication) at the reimbursement price in force for *Chenofalk*® at the time[175].

105. In order to minimise this, the company envisaged two hypotheses: an outright increase in the price of *Chenofalk*®, or its withdrawal from the market and reintroduction at a higher price[176].

106. Not having acquired the 'Falk' trademark together with the regulatory dossier, on 15 December 2009 Sigma Tau changed the trade name of *Chenofalk*® to *Xenbilox*®[177] and, in February 2010[178], increased the ex-factory price of the drug to €660 per pack (which was then also applied to sales made in the other Member States of the European Union)[179]. This business move was not welcomed by the competent German authorities, but they could not prevent it[180].

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[173] See doc. 96.213.
[174] See doc. 96.213 ("*CTX patients will be managed through named patient supplies up until CDC indication is licensed*"), docs. 96.75, 96.99 and 96.165, 22.7.3 (both annexes).
[175] See docs. 96.213 and 96.99.
[176] See doc. 22.7.3, Annex "006060_2 Report", 96.99 and 96.165.
[177] See doc. 127.
[178] See doc. 127.
[179] See docs. 96.141 and 96.143.
[180] See doc. 22.7.17: "*Regarding price the history of CDCA, price activity may be very controversial. It was sold as Chenofalk by Dr Falk Pharma at €58.69 for 100 capsules of 250 mg. Chenofalk went off the market and Xenbilox was introduced by Sigma Tau at €861.14 for 100 capsules of 250 mg. Since it was a new product, no rebate was applicable. The system could not do anything against this price increase, but it was commented on negatively*".

III.5.2 The price increase of Xenbilox® in 2014

107. The second part of the project, consisting of the introduction to the market of the CDCA-based orphan drug registered for the treatment of CTX at a higher price, which had been planned for some time, only occurred in 2014 for reasons that will be set out below in paragraphs 145 *et seq.*[181].

108. Between March and April 2014, the company therefore began to plan how to implement a new increase in the price of *Xenbilox*®, not only for the German market, but for the whole of Europe[182]. It was aware that an increase in the ex-factory price of the product in Germany to €860 per pack – the first time it assessed a price increase as per the evidence – would have been neutralized by the price moratorium introduced by German law a few years priori[183], which would still have required that the reimbursement price remain at €660. However, given the lack of profit growth in Germany, the company would have seen its profits grow abroad, where sales were not subject to the reimbursement price constraint. For foreign sales, the company expected to avail itself of a German wholesaler, Juers Pharma Import Export GmbH (hereinafter referred to as "Juers Pharma"), which would have been charged a sales price very close to €860 per pack, *[omitted]*. The wholesaler would have assumed responsibility for commercial relations with distributors in the importing countries, thus assuming responsibility for the price increase[184] to

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[181] See docs. 96.83 dated April 2014 ("*For Xenbilox we have no intention to touch the current MA. The plan is to submit an ODD and later a CTX file in ST UK name. After approval we withdraw German product MA. Still this is not yet a plan just an intention chart (before implementation we need to check a few things namely if there are other active MAs in EU that could easily jeopardize our future pricing)*").

[182] See doc. 96.141 ("*You remember that we spoke about a price increase for Xenbilox. Last week I have met […] the Managing Director of "Juers Imports/Exports" and we have developed an idea how we can keep the price in Germany but increase it for foreign markets (by rationing German wholesalers and have Juers as our wholesaler and point of sale for Xenbilox – who would sell the product to (foreign) customers at a higher price*"). See docs. 22.7.32 and 78.49 ("*we are planning to implement a significant price increase for international shipments outside Germany (where no price increase is possible due to local MA and price reimbursement). We aim to a max price equal to 4,000 euro x unit outside Germany, with and weighted average selling price of 3,500 euro x unit including Germany*").

[183] The *price moratorium* was introduced for the first time in 2010 in the German legal system and was reformed in May 2017 through the law on the strengthening of pharmaceutical supply ("*Gesetz zur Stärkung der Arzneimittelversorgung*", or AMVSG for short). The *price moratorium* prevents increases in the reimbursement price of drugs already on the market, requiring manufacturers to grant health insurance providers a discount equal to any price increases over the prices applied on August 1, 2009. The 2017 reform extended the validity of the *price moratorium* until 31 December 2022, after updating the reimbursement prices for inflation in 2018.

[184] As far back as the beginning of 2008, the company had been informed of the price freedom enjoyed in most European countries by pharmaceutical distributors in a system in which drugs, especially those without an MA for a given therapeutic indication, are imported and administered off label to individual patients at the specific request of a doctor ("*Named Patient Supplies*" referred to in docs. 96.99 and 96.213). See in particular

be set at €860 plus transport costs[185].

109. In April 2014, the company assessed for a second time an increase in the ex-factory price of *Xenbilox*® to €950 per pack[186]. Subsequently, a third price increase was evaluated: in the minutes of the *Rare Diseases Operational Team* of Sigma Tau meeting held in Munich on 6 May 2014, the short-term and medium/long-term objectives of the *Xenbilox*® project were highlighted, defined in the said report as the "2014 Very Important Project". The short-term objective was to

"*price increase [sic] (in 2 steps)*
=> 1st step, 1st of July 2014: €2400/pack
=> 2nd step, Jan, 1st 2014 [Editor's note: 2015]*: €4000/pack*"[187].

The medium to long-term objective was "*registration process… to get the ODD*"[188] for the therapeutic indication of CTX. The submission to the EMA was planned for the following month of September.

110. This significant increase in the price of *Xenbilox*® was, therefore, identified by the company as the first operational step in the project to obtain the orphan designation and registration of CDCA with the new therapeutic indication. Similar indications are also seen in the presentation of the *Strategic Plan* of the *Global Rare Disease Business Unit*, dated August 2014, where possible increases in turnover resulting from the "*Xenbilox price increase and*

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doc. 22.7.3, Annex "006060_2 Report" ("*[…] In most cases, distributors are free to set the price they want. exceptions are Spain (a state pricing committee evaluates) and France (where a formal national process is adhered to, though there is pricing flexibility). […] In terms of price-setting, this will mostly be at the distributor's discretion, though in some countries price will be negotiated with the state authorities (e.g. Spain)*").

[185] See doc. 96.141 ("[…] *how we can increase our profit without being stuck by the price moratorium. Here is the idea:*
Xenbilox units sold in 2013: 3.125 units (all sold at 660 Euro per unit = 2.06m Euro)
Units sold to German wholesaler: 614 (we have to assume these packs stay in the German market, however I strongly believe that ca. 300 packs are still being sold to foreign markets)
Units sold to distributors with high likelihood of being send to a foreign market: 1.627
Units sold directly to a foreign market: 884
Idea to discuss: increase the price to 860 Euros per unit to ALL customers (incl. German market). Everything that ends up in Germany will be reimbursed with 660 Euros and we have to refund the German sick funds with the price difference of 200 Euros.
All units that are being sold to foreign markets will not have to be refunded -> 2,511 packs x 200 Euro = ca. 500,000 Euro increase in sales (+ ca. 300 units x 200 Euros = 60,000 Euros) -> all additional sales are profit.
We will only supply the German wholesalers. All other customers will be referred to JUERS who manage the distributors for us. Our price to JUERS will be similar to the 860 [omitted]*. We will have to agree that JUERS will only charge the 860 Euros plus a little surcharge for delivery*").

[186] See doc. 96.45.

[187] See doc. 96.228.

[188] See doc. 96.228.

global registration" project were estimated[189].

111. The evidence shows that, from 1 July 2014, Sigma Tau, as a short-term objective, ultimately increased the ex-factory price *of Xenbilox*®, which was sold in Germany at €2,900 per pack[190].

112. From 2 July 2014 until October 2016, sales of *Xenbilox*® in EEA and non-EEA countries were mainly made by Juers Pharma, who purchased the drug from Sigma Tau Arzneimittel GmbH, and, except in some countries, including Italy, to a lesser extent also by the latter[191].

113. In response to the protests of some patients who complained that it was impossible for them or their insurance providers to support this price, the company, in a letter dated July 2014, justified this increase by the need to finance the development of the orphan drug indication ("*In order to be able to maintain and further develop CDCA for this rare disease indication, Sigma Tau has to revise the price in accordance with an orphan indication (CTX)*")[192].

114. An internal company document from September 2015 shows how the price increase introduced in July 2014 allowed Sigma Tau to greatly increase the turnover from *Xenbilox*®, which grew from some €2 million in 2013[193] to over €7 million in 2015[194].

115. This price increase did not immediately affect Italy, where patients were treated until November 2015 through the administration of the CDCA-based magistral preparations produced by the Pharmacy of the University Hospital of Siena.

116. With the end of the Pharmacy's galenic production and until the introduction of *Chenodeoxycholic Acid Leadiant*® in Italy in June 2017, the Italian Local Health Authorities (ASLs), including the University Hospital of Siena, were no longer able to use the Pharmacy's magistral preparations and had to import *Xenbilox*® from Germany pursuant to Ministerial Decree 11

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[189] See doc. 95.5.

[190] See doc. 96.39, 96.43, 96.143 and 96.157. The company decided not to carry out the second price increase initially planned for January 2015, given the negative demand seen in response to the first increase in July 2014 (see doc. 96.175).

[191] See docs. 84, 105, 110.1, 138.4.1 and 147.

[192] See docs. 96.43 and 96.217. This document was a response to the negative reaction with which this price increase had been received by patients and doctors in various EU countries, especially France, Belgium, Portugal and the Netherlands, where patients taking *Xenbilox*® were no longer in a position to be able to buy the drug, which had become too expensive. See docs. 96.87, 96.139, 96.147, 96.175 and 96.177.

[193] See doc. 96.155.

[194] See docs. 96.149 and 78.27.

February 1997, as subsequently amended[195], in order to guarantee continuity of treatment to their patients (see paragraphs 130, 133 and 134 below). For example, in 2016 the Oristano ASL purchased *Xenbilox*® at a final cost, including the margin of the wholesaler and other intermediaries involved in the distribution, which ranged from €3,400 to €3,600 per pack[196].

III.5.3 The obtainment of the preliminary orphan designation in 2014

117. On 28 August 2014, Sigma Tau Pharmaceuticals Ltd. requested the recognition of *Chenodeoxycholic Acid Sigma Tau* as an orphan drug for the treatment of CTX based on the criteria of prevalence and significant beneficial effects (see paragraph 38 above)[197].

118. The orphan designation was obtained by Sigma Tau Pharmaceuticals Ltd. on 16 December 2014 on a preliminary basis[198] (and was then transferred to Sigma Tau Arzneimittel GmbH on 7 May 2015[199]). In particular, the EMA's *Committee for Orphan Medicinal Products* (COMP) conferred the orphan designation on the basis of an examination of the scientific literature that highlighted the effectiveness on the main symptoms of CTX of CDCA, as produced by Sigma Tau and used by the company to demonstrate the existence of "significant beneficial effects" of CDCA compared to existing therapies (in particular with respect to the cholic acid contained in *Kolbam*® and *Orphacol*®)[200].

119. The importance of the orphan designation within the project is highlighted by the evidence, which shows that it was the company's intention to continue the application for the MA for the new therapeutic indication only

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[195] The Decree, published in Official Gazette of the Italian Republic no. 72 of 27 March 1997, lays down measures for the arrangements for importing proprietary medicinal products registered abroad.

[196] See doc. 10, Annex 2, 22.7.25 and 28.2.100. See also doc. 78.124 ("*All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3.7€ k/pack became available. Until then they were treated at 4 €/pack*").

[197] See European Commission Decision (2014)10054 of 16 December 2014. See the preparatory documents for the application for orphan designation in docs. 78.32 and 78.398.

[198] See European Commission Decision (2014)10054 of 16 December 2014 available at *http://ec.europa.eu/health/documents/community-register/html/o1406.htm*.

[199] See European Commission Decision (2015)3246 of 7 May 2015 available at *http://ec.europa.eu/health/documents/community-register/html/o1406.htm*. See also EMA/COMP/744266/2014 Rev.1 Committee for Orphan Medicinal Products *Public summary of opinion on orphan designation Chenodeoxycholic acid for the treatment of inborn errors in primary bile acid synthesis*, of 21 May 2015, available at *https://www.ema.europa.eu/documents/orphan-designation/eu/3/14/1406-public-summary-opinion-orphan-designation-chenodeoxycholic-acid-treatment-inborn-errors-primary_en.pdf*.

[200] See EMA, *Public summary of opinion.*

in the event it ultimately obtained the said administrative title, possession of which would only have allowed it to request higher reimbursement prices[201].

III.5.4 Price assumptions for the orphan drug

120. Once the ex-factory price of *Xenbilox*® increased to €2,900 per pack on the German market (on 1 July 2014), Sigma Tau began planning the next price increase, to be applied as soon as the drug had obtained final orphan designation. A document from July 2014 contains the assessments carried out by Sigma Tau with regard to the European market, assuming that the orphan designation would be obtained at the end of 2015 and that the orphan drug would be launched in the first quarter of 2016; on this occasion, the Net Present Value (NPV) analysis for the project to register and market CDCA as an orphan drug for the treatment of CTX was estimated under two possible scenarios: a 'base case' and 'best case' scenario (see section III.6.2.i below). These estimates used €5,000 (i.e. €55,000 per patient per year) as the assumed price per pack for the future drug, which showed extremely high profitability[202].

121. These price assumptions were well above the values that later emerged from the aforementioned market research commissioned in September 2014 by Sigma Tau to obtain assessments from doctors and patients requiring the drug regarding the price level of a CDCA-based drug registered for CTX. The research showed that in France, for example, the price deemed appropriate for therapy was around €25-35,000 per year, in Italy around €15-20,000 per year [203] and in Spain between €20-30,000 per year. In contrast, in the United Kingdom it rose to £50,000 per year, although some respondents had indicated

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[201] See docs. 22.7.105, Annex, 22.7.129 ("*in case of negative response, STRD will definitively withdraw the EMA authorization filing and will continue to sell Xenbilox under current procedures without any room for sales expansion*"; "*In case of negative response to the appeal to COMP opinion: - With no ODD, request for approval withdrawn; - Xenbilox sold off-label; - No price increase vs current; - No volume increase*"), 22.7.49, 78.8, 78.236, 78.239, 96.104.

[202] See doc. 95.6.

[203] See doc. 22.7.17 ("*Given the current very-low price that CDCA is available for, it was unsurprising that when pricing was discussed, responses were constrained by the peculiarity of the situation in Italy*
'The actual cost of the CDCA internally produced is very cheap, maybe too cheap! I am not sure but I think that the cost of a capsule is lower than 1€'
'If the cost of an industrially-manufactured CDCA will be too far from the actual cost calculated through the value based system (14€ for a capsule) probably the National and the Regional Health Authorities will consider it too expensive'
If CDCA were supplied conventionally, annual costs of €15-20,000 were considered appropriate, but we also heard;
'a very old molecule very easy to be manufactured is never too cheap!'").

that, for an effective but old drug, the annual price of therapy should be between £4-6,000[204].

122. A document dated December 2014, however, highlights Sigma Tau's awareness of the possibility that applying a high price to the orphan drug might be negatively perceived by the medical community: "*Sigma Tau want to increase the monthly treatment cost of Xenbilox® and have already introduced some price increases but there are some concerns regarding a potential back-lash from treating clinicians*"[205].

123. From a document dated October 2015, it appears that new market research commissioned by Sigma Tau showed the existence of four risk factors relating to competition that might have prejudiced the application of the price policy planned by the company. These factors were identified the case of *Xenbilox*® in some national markets, in the production of magistral preparations in Italy, in the need to justify this price request in the light of the investments made, and, lastly, in the price of drugs registered for other ultra-rare diseases, including *Orphacol*®[206]. In particular, the research carried out showed the extreme reluctance of the interviewees (health economists, doctors and pharmacists/consultants from the national regulatory authorities) to make a price comparison between CDCA and the other drugs mentioned above[207].

124. A presentation containing the guidelines for the 2016-2020 *Long Range Plan* of Sigma Tau's *Global Rare Disease business unit*[208] is attached to a subsequent internal email dated January 2016. In view of a revised internal plan, which assumed the approval of the designation of orphan drug by the EMA for the month of August 2016 and the consequent launch of the product in October, three new price hypotheses for the orphan drug were developed: 1) the first, defined as "realistic", amounted to €6,000 per pack; 2) the second amounted to €7,500 per pack ("higher price"); 3) the third, the most optimistic, was €10,000 per pack ("significantly higher price"). The presentation

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[204] See doc. 22.7.17.
[205] See doc. 78.71.
[206] See doc. 78.80 ("*Based on discussions with Sigma Tau there were 4 price "points" that could be relevant to the project. Price of compounded CDCA (Italy). Price of off-label Xenbilox (Netherlands and Spain but price may not be visible). Premium price required by Sigma Tau to justify the investment. Prices of other ultra-orphan products that have a similar clinical impact. […] Expectation that prices 2-3x the Xenbilox price was feasible with an ideal upper limit of approx. €100,000/annum. Key risks were seen as follows: Presence of compounded CDCA: Lower threat. Withdrawal of Xenbilox: Needs to be well managed. Potential indication restriction: Probably only an issue if CDCA perceived to be "very" high price*").
[207] See doc. 78.80 ("*None of the respondents wanted to use benchmark or analogue products produced for the pricing exercise. […] In some cases respondents were slightly affronted that and attempt was being made to make pricing decisions by this approach*").
[208] See doc. 95.4.

concluded that "Xenbilox*/CDCA approval and launch in Europe and possibly in the US represents a unique and exciting opportunity to grow and further develop the business*". These three hypothetical prices were used in the subsequent documents found referring to the period prior to the launch of the orphan drug on the market. In no case was there a hypothetical price greater than €10,000 per pack[209].

III.5.5 The signing of a new exclusive CDCA supply agreement with PCA in 2016

125. Documents in the evidence show that, as early as 2008, the pharmaceutical company became aware of the fact that if it had charged particularly high prices for the orphan drug, pharmacists would have been able to set up galenic production[210]. However, as mentioned above, in June 2008 Sigma Tau secured the exclusive supply of the raw material from the only existing supplier in Europe (see paragraphs 52, 53, 59 and 96 above). As a result, several Italian ASLs wishing to introduce their own galenic production were unable to access the raw material PCA that they had planned to use[211]. In at least two cases, the requesting physicians were redirected to purchase *Chenofalk*®[212]. But this demand for CDCA was finally met by the Pharmacy of the University Hospital of Siena, which also supplied its own CDCA-based galenic drugs to other Italian hospitals using a stock of the raw material accumulated in 2007 (see paragraph 75 above).

126. Subsequently, in September 2014, a consultancy firm emphasised to the company that, especially for an "*old drug*", the production of magistral preparations, as was the case in Italy, might be a risk to the success of the price strategy that Sigma Tau intended to apply[213]. From here arose the need for the pharmaceutical company to have the exclusivity over the raw material, as suggested in 2015,[214] and, specifically for Italy, to try to put a stop to the

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[209] In particular, doc. 78.27 (email entitled "Xenbilox 5 years plan + PY sales") dated September 2016 – the closest to the launch of *CDCA Leadiant*® on the market – refers to the base scenario, i.e. €6,000.

[210] See doc. 22.7.3, Annex "006060_2 Report" ("*If ST charges prices significantly higher than currently available product, pharmacists will seek to supply using this lower-priced product instead of branded Chenorm if the two are interchangeable*").

[211] See docs. 25.3.10, 25.3.32, 28.2.17, 28.2.18, 28.2.21, 28.2.26, 28.2.168, 28.2.169, 28.2.170, 28.2.171.

[212] See docs. 28.2.17, 28.2.18, 28.2.26, 28.2.173.

[213] See doc. 22.7.17: "*Strategies to get around paying very high prices for old drugs include import from other countries and suggesting small batch manufacturing by pharmacies. CDCA seems to be available to be bought for compounding so this will remain a risk in Germany (as it is already done in Italy)*".

[214] See doc. 78.34: "*how can ST minimise the risk from compounded product availability in each country? How are compounding companies obtaining the API for CDCA? (High minimum order quantities and low*

galenic production of the University Hospital and replace it with *Xenbilox*®[215].

127. In order to confirm its exclusivity over the supply of the raw material, at the beginning of 2015 Sigma Tau Pharmaceuticals Inc. then contacted PCA with a proposal to enter into a new exclusive supply agreement for the active substance[216]. In view of this, the pharmaceutical company first asked PCA to begin preparations for drafting the DMF and to improve the production of the active substance by implementing the new purity test developed by Sigma Tau (see paragraph 53 above)[217]. The chemical firm carried out these tasks for a total fee of *[€300,000-€400,000]*[218].

128. The conclusion of the new exclusive supply agreement was preceded by long negotiations[219] during which the parties were opposed on several issues, including, in particular, the extent and reciprocity of the exclusivity[220].

129. In relation to this clause, some documents from March 2016 show that, during the course of the negotiations, the parties considered it necessary to find a legal justification for this clause, which pertained to the market exclusivity resulting from the orphan designation[221]. Subsequent documents from October 2016, however, confirm that the pharmaceutical company's concern was actually to prevent pharmacies from setting up galenic production using the raw material from PCA ("*the concern is that a compounding pharmacy could look to buy API from you on the grounds that it was to be used for a bile acid disorder other than CTX and then use some it for CTX patients*")[222].

130. Pending the signing of the new agreement, in November 2015 the Pharmacy of the University Hospital of Siena stopped producing galenic

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prescribed volumes mean that API likely to be out of date). ST should have exclusive use for all API destined for use in CTX patients".

[215] See doc. 22.7.17: "[…] *need to establish if will help Xenbilox supply* […] *Discussions in Italy to understand if any possibility to replace self-compounded CDCA with Xenbilox*"; "*understand what, if anything, it would take to stop the hospital making its own CDCA and instead purchase imported CDCA*", doc. 78.44 ("*The idea of buying their product was just to eliminate it*"), doc. 78.52 ("*stop them selling CDCA*").

[216] See doc. 78.203.

[217] See docs. 28.2.32-28.2.42, 28.2.67 and 78.203.

[218] See docs. 28.2.79, 28.2.81, 28.2.92, 28.2.102, 28.2.128, 28.2.134, 78.13, 78.199, 110.4B.

[219] See docs. 22.7.43, 28.2.31, 28.2.32, 28.2.55, 28.2.66, 78.192, 78.198, 78.202, 78.220, 78.228 and 78.230.

[220] See docs. 22.7.92, 22.7.113, 22.7.116, 28.2.68, 70.31, 70.33, 70.35, 70.39, 78.4, 78.209.

[221] See doc. 28.2.66 ("*S-T for the reasons widely explained during our last meeting on November, 11th at PCA and in our e-mail exchanges, S-T requires PCA to grant exclusivity on CDCA supply (at least 10 years) for the production of any FF use to treat any biliary acid disorders. PCA-S-T will work together with their legal advisors in order to find a way to legally justify exclusivity, e.g. by linking to EU and US orphan drug designation of CDCA*").

[222] See doc. 78.9.

CDCA-based drugs because it had run out of raw material stocks (see paragraph 77 above). In January 2016, the Pharmacy communicated the lack of raw material to Sigma Tau. However, in a meeting, Sigma Tau declared itself unwilling to provide additional raw material, but proposed that the orphan drug produced by the company be provided directly to the patients of the Hospital[223]. On the other hand, there was the possibility that the University Hospital would make use of the early access set out under Law no. 648/1996 for drugs not registered in Italy and still in the trial phase[224] [225].

131. The request for authorisation to AIFA was carefully monitored and guided by Sigma Tau, who considered the issue "*delicate*", as it could have significant implications both inside and outside the confines of Europe on the price strategy that it intended to implement[226]. This would be especially true if such a request had pertained to *Xenbilox*®[227], as it could not have pertained to the orphan drug, which at the time was not yet in production. The company intended to avoid this circumstance at all costs[228]. The company, therefore, took its time, even if it was aware of the potential negative consequences that it would have on patients[229], and in the meantime decided to redirect the

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[223] See docs. 6.10, 6.11 and 6.13.

[224] Law no. 648/1996 allows the Italian National Health Service to cover a drug, subject to an opinion from AIFA's Technical/Scientific Committee (CTS) when there is no valid therapeutic alternative; this applies to innovative medicinal products authorised in other States, but not in Italy; to medicinal products not yet authorised, but in clinical trials; and to medicinal products to be used for a therapeutic indication other than the indication for which it is authorised. If there is a valid therapeutic alternative, medicinal products may be used for a therapeutic indication other than the indication for which it is authorised.

[225] See doc. 78.251.

[226] See docs. 78.270 and 78.290 "*The 648 application for Siena is very a "delicate" issue and I want to be sure to move properly. […] we agree this is a "delicate", but crucial topic that needs to handled carefully. Especially given the potential implications this might have across EU and beyond, under the International Reference Pricing Scheme".*

[227] See docs. 78.154 and 78.288 ("[…] *we are waiting for a pending decision from the NRG committee to have a commercial brand name. Until we do have one, 648 is on hold. […] What I meant is that, in the current circumstances, given that we still have Xenbilox on the market, if any of the stakeholders you listed requests for a 648, it will be under the commercial brand name of Xenbilox. Please take into account that part of the procedure to request for a 648 is to mention commercial brand name and active principle*".

[228] 78.110 ("*My current understanding is that a 648 submission for the new product can't be done under the price of Xenbilox. That would mean this 648 is for Xenbilox, and not for the new product. […] Agree. 648 has to be for CDCA and not for Xenbilox."*). See doc. 78.270 ("*Please note that the document (which Sue has already seen even though in a previous version) deals with CDCA, as that being the object of the request (and not Xenbilox)*"). See doc. 78.287 ("*The request and the report is based on CDCA (no mention of Xenbilox whatsoever). At some point, when we address the therapeutic plan, the name of the drug and the producer/supplier must be indicated. At that point the new brand name and the MAH or MA applicant, that I understand at the moment is still ST GmbH, will have to be included"*.).

[229] See doc. 78.270: "*An ethical issue. There are patients that sooner or later will need the drug that Siena cannot provide. I know they can get it from Germany but it may not be so easy. […] Understand the ethical concern, but quite honestly from ST-RD perspective the patients in Italy are in the exact same conditions of all other patients across the world, with the exception of Germany and the US. [...] I'm not worried about playing for time and managing Siena. I hope, however, that this will be done in good time. The March CTS*

University Hospital of Siena to purchase *Xenbilox*® from Juers Pharma[230].

132. In mid-February 2016, however, the University Hospital of Siena urged the company to provide what was needed to start the AIFA application procedure for early access pursuant to Law no. 648/1996 as the[231] stock of ready-made magistral preparations would only allow it to provide the medicine to three patients for the next two or three months[232]. The serious problem of supply and the difficulty in guaranteeing to patients the continuity of their therapy, however, was still an issue in mid-March, generating major concern and disappointment among doctors in Siena ("*Unfortunately the information we had, not from AIFA but from Dr* [N.] *who, as you will remember, should have sent us all the documents to forward the procedure to AIFA, indicated that we should have waited until April, the period necessary for them to complete something that I no longer remember... contrary to all the declarations of principle made and repeated that patients would not suffer any inconvenience resulting from the 'industrial process', they will suffer and how* [Editor's note: indeed], *and we along with them...*")[233].

133. Based on the evidence, it appears that the request had not yet been completed by the end of March 2016 because, contrary to the initial forecasts (which envisaged the start of production for April 2016), the product was not yet in production and did not have a trade name[234]. Patients with CTX monitored by the University Hospital of Siena were therefore treated with *Xenbilox*® imported from Germany[235].

134. With the end of galenic production by the Pharmacy of the University Hospital of Siena, other public Italian medical centres also encountered great difficulties in supplying the drug to continue the therapy administered to their patients until that point. Because of this, they again turned to PCA (or Sigma Tau itself) to obtain the active substance and thus proceed with galenic production. They were unsuccessful, given the exclusivity agreement to which

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meeting could be a target. The reference to the ethical aspect of Italian patients was a way to raise awareness of the time frames".

[230] See docs. 78.145 and 78.154.

[231] See doc. 78.154 ("*Dear Dr.* [N.], *since I have not yet received the necessary documentation to start the process of providing CDCA to CTX patients, I urge you to provide it in view of the practical difficulties related to the drug's unavailability, which we will encounter soon*").

[232] See docs. 6.10 and 6.11.

[233] See docs. 6.9, 6.10, 6.11, 22.7.146.

[234] See docs. 78.287 and 78.288.

[235] See docs. 6 and 78.124 ("*All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3.7€ k/pack became available*").

the chemical company was bound since 2008[236].

135. In June 2016, concerned about the growing and pressing demand for CDCA from Italian hospitals, who were complaining about the serious shortage of the active substance and the risk to their patients, PCA reported the problem to the pharmaceutical company, proposing a derogation from the exclusivity clause contained in the supply contract with Sigma Tau. Sigma Tau considered these requests potential threats to the introduction of the orphan drug at the desired price in the Italian market, and especially to its future reimbursement by the Italian National Health Service, and therefore countered them by spreading the message on the market that the only source that hospitals should have used was Sigma Tau itself (with the purchase of *Xenbilox*®)[237].

136. The new exclusive CDCA supply agreement was concluded between Sigma Tau Rare Disease Ltd. and PCA on 11 November 2016, fully replacing the agreement between Sigma Tau Pharmaceuticals Inc. and the same PCA dated 24 June 2008, which was terminated by mutual consent[238].

137. The new agreement has a term of 7 years, which can be automatically renewed for another two, and is valid globally. Among other things, it states that the pharmaceutical company can purchase CDCA exclusively from PCA and use this active substance solely for the production and marketing of *Chenodeoxycholic Acid Sigma Tau*® for the treatment of CTX (Article 2.2); similarly, and binding the chemical company even more than in the past, the agreement states that PCA shall sell CDCA exclusively to the pharmaceutical company for the production and marketing of the aforementioned product (Article 2.3)[239]. The exclusivity that binds the chemical company does not prevent it from supplying the raw material to third parties if the CDCA is used to produce other medicines for different treatments. Article 5.1 of the agreement also provides for a fee for PCA equal to *[€1,000-€5,000]* per kg (while under the 2008 agreement, PCA initially received a fee equal to *[€1-€500]* per kg for the years 2008 and 2009, subsequently increased to *[€500-*

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[236] See docs. 28.2.58-28.2.61, 28.2.86, 78.197, 78.243. Doc. 22.7.64, Annex "*Theophylline – CDCA*" also shows that, in October 2016, hospitals in other Member States were also trying to find the active substance on the market. The pharmaceutical company was also aware of the unavailability of CDCA on the market, given the exclusivity agreement (see doc. 78.104: "*Differently from us, CA API can be acquired*").

[237] See docs. 78.19 and 78.241 ("*They perfectly know how and where to buy. They are trying to get it from PCA at a cheap price to create a precedent that will kill our future reimbursability and price*.").

[238] See docs. 28.2.99 (containing the text of the agreement), 28.3B, 78.191 and 78.192, 78.198, 78.231.

[239] To this end, see clause 2.1 of the 2008 agreement along with clause 2.3 of the 2016 agreement.

€1,000] per kg[240]) and two royalty payments to PCA, each equal to *[€200,000-€300,000]*, upon Sigma Tau's obtainment of the MA from the EMA and from the FDA (Article 7.2) [241].

138. Several pieces of evidence show that, in compliance with the exclusivity clause contained in the November 2016 agreement, over the years PCA has rejected multiple requests to supply CDCA to fuel the production of galenic medicines.

139. Between 2017 and 2019, PCA was, in fact, contacted by various operators providing pharmaceutical-grade active substances to hospital pharmacies in some European countries – which might have included Italy, according to the assessments of the pharmaceutical company – that intended to produce galenic preparations[242], and, during this same period, by two Italian doctors who were treating patients with CTX and who, in at least one case, deeming the price at which the orphan drug was sold "*extremely expensive"* and "*unacceptable*", also required the active substance to prepare the drug by themselves[243]. Another Italian doctor expressed similar disappointment; aware of the previously existing galenic production and believing that the price of *Xenbilox*® was already high, he gave a highly negative assessment of the price at which Leadiant intended to introduce (and then did introduce) *CDCA Leadiant*® on the Italian market and stressed its unfairness in light of the investments made[244]. Furthermore, the company was aware of the fact that this position would be shared not only by the medical/scientific community, but also by AIFA[245].

140. In response to these requests, PCA always refused to provide CDCA (sometimes citing stockouts[246]) and promptly referred all requests received to

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[240] See docs. 28.2.27, 28.2.68 and 22.7.92.

[241] See docs. 25.3.9, 28.2.99, 28.2.111, 28.2.112, 28.2.115.

[242] See docs. 28.2.117, 28.2.119, 28.2.123, 28.2.131, 28.2.132, 28.2.156-28.2.159, 28.2.161-28.2.165, 28.2.183, 28.2.184, 78.201, 78.204-78.208 and 78.210.

[243] See docs. 22.7.68, 22.7.69, 28.2.121, 28.2.136, 28.2.140, 28.2.141, 28.2.189, 28.2.191, 78.89, 78.98, 78.122, 78.158, 78.213, 78.286, 78.347, 78.350, 78.367.

[244] See doc. 78.124 ("- *All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3.7€ k/pack became available. Until then they were treated at 4 €/pack - Given that all companies need to make money (no doubt on that), the x 1k increment is not perceived as "fair" toward the investments (retrospective study in Siena and production upgrade, that he wasn't even aware of) - A second increment with change to Leadiant will sound even more inappropriate*"). See doc. 78.159, where the company's internal correspondence comments on the article entitled *Ricorso contro la ex Sigma Tau (*Appeal against the former Sigma Tau*),* in *Milano Finanza,* 4 September 2018, expressing concern regarding the fact that a doctor stated that the price of the orphan drug should have been 10 times lower.

[245] See doc. 78.124 ("*His position will probably be common in Italy, both among clinicians and AIFA commission members (especially now that EPAR is clear on the hybrid medicine of Xenbilox)*").

[246] See docs. 28.2.158 and 28.2.162.

Leadiant. For its part, Leadiant always carefully monitored the PCA's behaviour, verifying that it had not provided the active substance to companies that could serve hospital pharmacies, including those in Italy, especially during the first six months of 2017[247].

III.5.6 Obtaining the final orphan designation and the MA in 2017

141. After Sigma Tau Arzneimittel GmbH transferred the German MA for *Xenbilox*® to Sigma Tau Rare Disease Ltd. in August 2015[248], on 29 October 2015 the German subsidiary of the group submitted the MA application for *Sigma Tau Chenodeoxycholic Acid*, through the aforementioned authorisation procedure via the abbreviated hybrid form (see paragraphs 32-35 above)[249].

142. The dossier submitted by Sigma Tau Arzneimittel GmbH for the orphan drug marketing authorisation application took some of the data from the *Xenbilox*® dossier (which, as mentioned in paragraph 35 above, is the reference drug for the orphan drug[250]), and in particular from Module 4 relating to the pre-clinical, pharmacological, pharmacokinetic and toxicological studies of the drug[251]. The other parts of the dossier – the product quality profiles (Module 3) and the clinical drug trial (Module 5) – were developed by the company.

143. In Module 3, the company presented the results of the tests carried out to improve the quality of the product. The evidence shows that Sigma Tau did not carry out bioequivalence studies, given that the two compounds were identical from a pharmaceutical standpoint, in terms of composition (active substance and excipients) and dosage, in addition to being produced using the

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[247] See docs. 22.7.104, 78.206, 78.207 ("*We continue with our investigation and I am confident that any threat to our commercial position will be quashed. I would ask that you continue to be vigilant and let me know if you see anything else suspicious coming to you from the Netherlands"*) and docs. 28.2.149, 78.219, 78.312,78.313 ("*Anyway it would really help if PCA would close the tap on all of this for the coming months. I am sure it is also not in their best interest to have compounding around. They have a nice contract*") and 78.314.

[248] See docs. 96.151, 96.83 and 138.4.1.

[249] See doc. 78.68. See European Commission decision of 10 April 2017 C(2017)2488 (final), available at *https://ec.europa.eu/health/documents/community-register/2017/20170410136235/dec_136235_it.pdf*.

[250] See EMA, *Assessment report*, p. 5.g

[251] The content of the dossier is specified in Annex I to Directive 2001/83/EC, which contains "analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products". The first of the four parts into which Annex I is divided (entitled "requirements relating to the standardised marketing authorisation dossier") contains 5 modules. Of those relevant here, one is dedicated to the chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances (Module 3); one is dedicated to non-clinical reports (Module 4), containing a request to produce evidence of pharmacological, pharmacokinetic and toxicological studies carried out on the medicinal product under application; and one on clinical studies (Module 5). See doc. 138.4.13.

raw material from the same chemical company, PCA[252].

144. In Module 5, which concerns the "additional information" required by the applicable regulations to test the efficacy and safety of hybrid drugs under the new therapeutic indication (see paragraph 34 above), the company submitted two retrospective studies based on the administration of two similar CDCA-based drugs (*Xenbilox,* in one case, and the galenic preparations of the Pharmacy of the University Hospital of Siena, in the other[253]) to patients with CTX monitored by the two main centres specialized in the treatment of the rare disease in Europe[254], thereby replacing prospective placebo-controlled trials, the main clinical trial method. The company decided not to carry out prospective clinical trials, in view of the fact that to do so a control group, i.e. a group of patients to whom the drug is not administered, would have to be created, which would have posed ethical problems since patients included in this group are in fact denied access to therapy, and since in any case the rarity of the disease would not have allowed the creation of a statistically significant sample of patients on which to carry out the clinical trials[255].

145. Towards the middle of 2014, Sigma Tau Pharmaceuticals Inc. had begun to collaborate directly with the specialist at the University Hospital of Siena to determine his willingness to carry out a retrospective study on the 25 patients suffering from the rare disease, under treatment for decades with CDCA in galenic form at the Hospital[256].

146. Sigma Tau was not the only company to contact the University of

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[252] See docs. 95.5, 95.6, 78.30, Annex 1, p. 28 ("*This product does not meet the definition of a generic, nor are there changes to the bioavailability as the reference and proposed product are the same"*), 78.60, 78.211, 78.352, annex entitled "Chenodeoxycholic acid – 2nd LoOI", 78.357 ("[…] *the retrospective data that will be collected have been obtained with a galenic formulation of chenodeoxycholic acid and the retrospective protocol is purposely focused on chenodeoxycholic acid and not Xenbilox. The Univ of Siena will prepare a technical report that will in some way "validate" it and will highlight overlapping features with Xenbilox indicating the same API.* […] *the galenic formulation manufactured in house at the pharmacy can be considered pharmaceutically equivalent and this means at least in the EU no bioequivalence studies are required. The API comes from the same manufacturer and the excipients and composition are according to the Ph.Eur monograph for CDCA*"). See EMA, *Assessment report,* p. 8.

[253] To bolster consistency between the two retrospective studies (carried out on the basis of the administration of the galenic drug and *Xenbilox*®) presented in support of its MA application, Sigma Tau conducted a comparison between the capsules produced by the Pharmacy of the University Hospital of Siena and *Xenbilox*®. See doc. 78.44. See also EMA, *Assessment Report,* p. 35: "*Results of studies of dissolution comparing the two products demonstrated that, despite minor differences in excipients contained in the compounded and reference formulations, both products can be considered similar*".

[254] See doc. 72.1, p. 18.

[255] See docs. 78.30, "Annex 1 – Overview of product development", 78.45, 78.60, 78.66, 78.68, 78.69, 78.70, 78.346, 78.351, Annex "CDCA reg strategyEU_21.01.16.pptx", 78.405.

[256] This means the collection and organisation of the material related to the clinical observation of patients treated with a given drug. See docs. 6.1, 22.7.56, 22.7.62, 22.7.67, 22.7.71, 22.7.119, 22.7.121, 78.36, 78.37, 78.41, 78.55.

Siena to conduct the said study. Indeed, Retrophin Inc. (hereinafter also "Retrophin") has owned since 2014 a CDCA-based orphan drug authorised for the treatment of gallstones in the United States but administered for the treatment of CTX, *Chenodal*[257], and had also made a similar attempt, but it proved unsuccessful[258]. The exclusive cooperation between the University of Siena and Sigma Tau began at least as early as May 2014 and continued in the months preceding the submission of the request for orphan designation of CDCA[259].

147. The collaboration was then formalised. In October 2014, Sigma Tau Research Switzerland S.A. and the University Hospital of Siena entered into an agreement covering one of the two aforementioned retrospective studies[260], which was then merged in December 2014 into a framework agreement between Sigma Tau Pharmaceuticals Inc. and the Company that disciplines not only the execution of the study, but also the transfer of all the data, knowledge and results it achieves[261]. In particular, Article 7 of the agreement states that the scientific results obtained are the property of Sigma Tau (now Leadiant). Similarly, letter c) of the framework agreement provides for the obligation for the University Hospital of Siena to transfer to Sigma Tau all data, knowledge and results achieved/obtained during the retrospective study and the prohibition to transfer, sell or license or otherwise assign the relative data and/or rights to third parties. In addition, Sigma Tau Research Switzerland S.A. entered into a protocol with the hospital which, among other things, provides in Article 12.4 for the binding transfer of data obtained in retrospective studies to Sigma Tau[262].

148. All this, namely the company's exclusive right over the data and the

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[257] *Chenodal* obtained orphan designation in 2010 (see https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=300510 and *https://ww*w.sec.gov/Archives/edgar/data/1438533/000162828016011857/rtrx-201510k.htm). Retrophin Inc. acquired the ownership of *Chenodal* with the acquisition of Manchester Pharm Inc. in early 2014 (seehttps://www.thepharmaletter.com/article/retrophin-to-acquire-manchester-pharma-in-62-5-million-deal). *Chenodal* is in phase 3 of clinical trials investigating the efficacy of CDCA for the treatment of CTX (see https://clinicaltrials.gov/ct2/show/NCT04270682 and https://www.globenewswire.com/en/news-release/2020/02/24/1989511/0/en/Retrophin-Reports-Fourth-Quarter-and-Full-Year-2019-Financial-Results.html).

[258] See docs. 95, 133 and 138.4.7.

[259] See docs. 6.1, 6.2, 22.7.71, 95 and 138.4.7 ("*We need to take this relation with Prof* [F.] *directly on board (STRD), get the clinical data on the CTX study asap and eventually involve him in a new study. We need to engage him and soon*").

[260] See docs. 6.6 and 6.7.

[261] See docs. 6.3 and 6.8. This agreement is attached to University Hospital of Siena Resolution no. 84 of 20 February 2015, which approved the framework agreement. See also doc. 22.7.141.

[262] See doc. 78.41.

results of the study implemented at the end of 2014, as well as Sigma Tau's simultaneous obtainment of the preliminary orphan designation[263], was considered by the company to be sufficient to prevent the US company from having access to the European market[264].

149. In addition, in early 2015, Sigma Tau Pharmaceuticals Ltd. entered into a similar agreement with the Dutch hospital Casinius Wilhelmina in Nijmegen to conduct another retrospective study based on the off-label administration of *Xenbilox*® to 35 patients since 1981. Similar contractual obligations regarding Sigma Tau's exclusive ownership of the data underpinning the retrospective study and the related results are contained in article 4 of the agreement and in article 12.4 of a second protocol also concluded with Sigma Tau Pharmaceuticals Ltd.[265]

150. According to the information that the company included in its regulatory dossier submitted to AIFA for the purpose of requesting reimbursement for *Chenodeoxycholic Acid Leadiant*®, information that was also confirmed at the hearing with the specialist of the University Hospital of Siena[266], the two retrospective studies are the largest ever carried out globally, not only in terms of the sample size of patients involved, but above all in terms of the length of the observation period of the results of the administration of CDCA to these patients[267].

151. The retrospective studies of the University Hospital of Siena and the Dutch hospital Casinius Wilhelmina in Nijmegen cost Sigma Tau, *[€100,000-€200,000]*[268] and *[€100,000-€200,000]*[269], respectively, for a total of

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[263] See doc. 95.15, which shows that at the end of 2014 the company believed that "*ODD protects against other CDCA products*". This circumstance then evidently convinced Sigma Tau that Retrophin Inc. would not enter the European market, to the point that it believed it held a market share of 100%. See docs. 22.7.129 and 95.15 ("*Retrophin will not enter RoW market*"). See also doc. 78.249 which shows that Sigma Tau stated in July 2015 that the US competitor "*is thought to have pulled out of Europe (in terms of plans to launch there) since ST obtained the Orphan designation for CDCA so Retrophin's CDCA is not expected to be a competitor in Europe*".

[264] In July 2015, the company discussed internally the potential effects that the registration of *Chenodal* would have on the European market, concluding that if Retrophin Inc. had also wanted to seek orphan designation in Europe, it would not have been able to use the data from the Italian or Dutch centres, due to the exclusivity enjoyed by Sigma Tau over such data ("*Require EU case studies to support EU filing and ST has exclusive agreement with* [F.] *and potentially* [V.] *to have access to their case studies so Retrophin could not use these major centres*" (see doc. 78.249).

[265] See docs. 22.7.117, 78.41, 78.224, 78.227 and 78.237.

[266] See doc. 133.

[267] See doc. 72.1, which shows that, in terms of the sample size of patients, the two retrospective studies are the largest; in the reimbursement dossier, a Spanish study is also cited with a sample size of patients comparable to those of the two Dutch and Italian studies, but still smaller (23 patients). Samples sizes from the other studies are much smaller. See also doc. 140.3.

[268] See doc. 6.8.

[269] See docs. 78.222, 78.223, 78.237 and 78.387.

[€300,000-€400,000], which might be supplemented by *[€200,000-€300,000]*, corresponding to the royalties provided for in the contract stipulated between Sigma Tau Research Switzerland S.A. and the University Hospital of Siena[270].

152. The company submitted the MA application on 14 September 2015[271]. The documents on file shows that, in the context of the authorisation procedure, in September 2016 the EMA's *Committee for Medicinal Products for Human Use* (CHMP), in issuing a positive opinion on the authorisation application, believed that *CDCA Sigma Tau* was not "similar" to *Kolbam® or Orphacol®*[272] pursuant to Article 8(1) of Regulation (EC) No 141/2000[273], given the structural diversity between CDCA and cholic acid, their different mode of action and the consequently different biochemical action, as highlighted by Sigma Tau during the procedure[274]. This finding therefore enabled the company to avoid the foreclosing effects linked to the *market exclusivity* already enjoyed by *Kolbam®* and *Orphacol®* (see paragraph 41 above).

153. Furthermore, after an initial negative opinion in October 2016[275], following the appeal filed by Sigma Tau (which had already become Leadiant at that point) in February 2017 the EMA's *Committee for Orphan Medicinal Products* (COMP) finally ruled that the requirements for orphan designation were satisfied and confirmed the orphan status for CDCA[276]. The decision was based on the clinical evidence adopted by the said company regarding

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[270] See doc. 141.

[271] See EMA, *Assessment Report.*

[272] See EMA, *Assessment Report.*

[273] For the notion of similarity, see paragraph 41 below in the text and its footnote.

[274] See docs. 78.176 ("*structurally they differ in terms of the number of hydroxyl group substituents of the nuclear steroid backbone. CA is a trihydroxylated while CDCA is dihydroxylated. It is indeed known that even small structural differences in structural features, such as is the case between can chenodeoxycholic acid and cholic acid can lead to major differences in biochemical activity*"), 78.352, 78.53 e 78.351. Note that in April 2016 the EMA's CHMP was moving in the opposite direction, towards a judgment of similarity between CDCA and cholic acid (see doc. 78.176). It was reversed due to the arguments put forward by Sigma Tau based on the differences between the two compounds discussed in the text.

[275] At the meeting that took place from 4-6 October 2016, the EMA COMP issued a negative opinion on the maintenance of the orphan designation, believing that the superiority of CDCA over cholic acid had not been sufficiently demonstrated by Sigma Tau. In particular, according to the EMA, Sigma Tau did not demonstrate through comparative scientific studies that CDCA actually offered a "*significant benefit*" compared to cholic acid. Sigma Tau appealed this opinion in January 2017, citing the superiority of CDCA over cholic acid through a qualitative comparative analysis of the effects of the two compounds. See docs. 22.7.8, 22.7.49, 22.7.105, 78.235, 78.366, 78.391, 78.392, 78.405, 78.407. See also www.ema.europa.eu/documents/minutes/minutes-comp-meeting-4-6-october-2016 *_en.pdf* and *www.ema.europa.eu/*d*ocuments/minutes/minutes-comp-meeting-17-19-january-2017_en.pdf*.

[276] See https://www.ema.europa.eu/en/documents/orphan-review/recommendation-maintenance-orphan-designation-time-marketing-authorisation-chenodeoxycholic-acid_en.pdf and doc. *Timelines for publishing of EPAR for CDCA.*

CDCA's "significant beneficial effects", especially neurological effects, compared to cholic acid as contained in *Kolbam*® and *Orphacol*®[277].

154. The MA for *Chenodeoxycholic Acid Sigma Tau*® was released to Sigma Tau Arzneimittel GmbH on 10 April 2017. Therefore, as reported in the Community Register, the 10 years of market exclusivity will expire on 12 April 2027.

155. Given the difficulty of comprehensively demonstrating the safety and efficacy of the drug[278] for the above reasons, the MA for the orphan drug was granted by the European Commission "under exceptional circumstances"[279], i.e., subject to the obligation placed on the company to collect data on the safety and efficacy of long-term treatment of patients with CTX and to send the results by 2022 (and every 5 years thereafter). This conditional release makes up for the lack of complete clinical data in support of the applicant's MA application.

156. On 12 May 2017, the orphan drug was renamed *Chenodeoxycholic Acid Leadiant*®. On 31 May 2017, the relevant MA was transferred from Sigma Tau Arzneimittel GmbH to Leadiant GmbH, a newly established company of the former Sigma Tau group (for more details, see section III.5.7.ii below)[280].

157. On 12 June 2017, the final orphan designation for *Chenodeoxycholic Acid Leadiant*® was also transferred from Sigma Tau Arzneimittel GmbH to Leadiant GmbH[281].

III.5.7 The strategy of differentiation of CDCA Leadiant® *from* Xenbilox®

158. The evidence shows that in order to launch the new orphan drug on the

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[277] See docs. 78.405, 78.373 and 22.7.105. See COMP decision EMA/39662/2017 Rev. 1 of 22 June 2017, available athttps://www.ema.europa.eu/en/documents/orphan-review/recommendation-maintenance-orphan-designation-time-marketing-authorisation-chenodeoxycholic-acid_en.pdf, to maintain orphan status where, in fact, it is stated: "*that the claim of a significant benefit of Chenodeoxycholic acid sigma-tau in inborn errors in primary bile acid synthesis is justified because data show that patients with a type of inborn error in primary bile acid synthesis called cerebrotendinous xanthomatosis (CTX) show neurological improvements when treated with this medicine which have not been seen with cholic acid in the treatment of this disease. […] Therefore, although other methods for the treatment of this condition have been authorised in the EU, the COMP concluded that Chenodeoxycholic acid sigma-tau is of significant benefit to patients affected by inborn errors in primary bile acid synthesis*".

[278] As confirmed by the expert consulted by Leadiant, whose opinion is contained in doc. 138.4.13.

[279] Pursuant to Article 14, paragraph 8 of Regulation (EC) No 726/2004. See EMA, *Assessment report,* pp. 35 and 39. See European Commission Decision C(2017)2488 (final) of 10 April 2017.

[280] See European Commission Decision C(2017)3894 of 31 May 2017.

[281] See European Commission Decision C(2017)4087 (final) of 8 June 2017 available on *https://ec.europa.eu/health/documents/community-register/html/o1406.htm*.

market and support the anticipated pricing policy (see sect. III.5.4 above), Sigma Tau implemented a strategy to differentiate it from *Xenbilox*®[282] that it rolled out through two closely linked lines of action: the withdrawal of *Xenbilox*® from the German market before the launch of *CDCA Leadiant*®, and the creation of a new company, different from Sigma Tau Arzneimittel GmbH, or Leadiant GmbH, to which the orphan drug's MA is attributed.

i) *The withdrawal of Xenbilox® from the German market and other national markets*

159. The decision to withdraw *Xenbilox*® from the German market was evaluated in early 2014[283], and then considered more seriously in September 2014 immediately after the company had requested preliminary orphan designation for CDCA (see paragraph 117 above), as the information provided by the consultant clearly indicated that the desired price increase would not have been possible without the withdrawal of *Xenbilox*® from the market[284]. In this case too, the identical nature of the active substance of the orphan drug and the off-label drug would in fact have triggered the price moratorium and forced the company to reimburse German health insurance providers for the difference between the currently approved reimbursement price of *Xenbilox*® and the price of the future orphan drug (in the form of a price discount), thus hindering the revenue maximisation targets the company had set for itself[285]. A price increase, and more generally the freedom to set it, would have been feasible in Germany only if the orphan drug had been qualified as a product that, from a commercial and regulatory point of view, could be considered new compared to *Xenbilox*®[286].

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[282] See doc. 78.57, dating back to 2015, where reference is made to the "*brand differentiation*" between the two products.

[283] See doc. 96.83 ("*For Xenbilox we have no intention to touch the current MA. The plan is to submit an ODD and later a CTX file in ST UK name. After approval we withdraw German product MA. Still this is not yet a plan just an intention chart (before implementation we need to check a few things namely if there are other active MAs in EU that could easily jeopardize our future pricing)*").

[284] See doc. 22.7.17 (: "*[…] In some countries a further price increase may only be possible with combination of current licence withdrawal, approval in CTX and rebranding"*).

[285] See doc. 22.7.17 ("*[…] Xenbilox currently costs 36€ per tablet, 3 capsules per day would cost less than treatment with cholic acid. In Germany there is a de facto price freeze. The statutory sickness funds will charge the net price increase back from the manufacturer, Sigma Tau GmbH in Germany (the PZN of the drug is 5484764). Thus Sigma Tau will not benefit from any price increase (including the last one) to Xenbilox*").

[286] See doc. 22.7.17 ("*An (effective) price rise may be possible as follows. With a new approval for a new indication, a new brand name and a new PZN* [Editor's note: the number of MAs in Germany.] *there would*

160. Given the multiple implications of this strategy, the company carried out the withdrawal operation carefully[287]. On the one hand, in fact, the withdrawal of *Xenbilox*® from the market seemed to indicate that the orphan drug was considered new and thus to prevent its reimbursement price from being anchored to that of the off-label drug[288]; on the other hand, however, if the orphan drug had been new, it would have been subject to evaluation[289] by the German regulatory authorities for the added therapeutic value[290], which the company initially wanted to avoid[291].

161. Subsequently, the company evaluated the hypothesis of subjecting the orphan drug to the said evaluation procedure of the therapeutic added value, since it realised that even in the event that *Xenbilox*® were withdrawn from the market, the rules on the price of newly introduced drugs on the market and owned by companies that have previously marketed drugs with the same active substance with a comparable pharmaceutical form[292] would still have tied the reimbursement price of the orphan drug to that of the old off-label drug[293]. If, on the other hand, it had been able to demonstrate that the orphan drug had an added therapeutic value over *Xenbilox*®, it could have dissociated itself from the reimbursement price of the latter drug and not been forced to grant the discount to the health insurance providers[294].

162. Nevertheless, according to an external consultant, the outcome of this procedure remained uncertain, among other things, given the absence of prospective studies to be put forward in support. In particular, the consultant

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be free pricing. Since the drug substance/active pharmaceutical ingredient is not new, there would not be an automatic mandatory requirement to submit a benefit dossier and have it evaluated (AMNOG)").

[287] See docs. 78.80, 78.92 and 78.244, Annex "AP1122 CDCA Pricing Study Results 22nd Oct 2015 V3F updated 27 November 2015" ("*Withdrawal of Xenbilox: Needs to be well managed*").

[288] See doc. 96.171.

[289] See docs. 78.379 and 96.171.

[290] Under the Drug Market Reform Act ("Arzneimittelmarkt-Neuordnungsgesetz", or AMNOG), in force since 1 January 2011, the retail prices of drugs are freely defined by companies at launch. However, for the purposes of defining the reimbursement price, which, in contrast, is negotiated, the Federal Committee ("*Gemeinsamer* Bundesausschus" or G-BA) and the Institute for Quality and Efficiency in Health Care ("*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*" or IQWiG) have the task of assessing the additional therapeutic value of all newly authorised medicinal products, namely those introduced on the German market since 2011. If there is proven to be added value, the Central Federal Association of Health Insurance Funds and the pharmaceutical company negotiate the reimbursement price of the new drug to be paid by the health insurance funds. This takes the form of a discount on the retail price originally set by the company. See docs. 96.41 and 96.167.

[291] See docs. 96.41 and 96.167.

[292] See paragraph 130a (1a) SGB V.

[293] See doc. 78.80 ("[…] *central negotiation with insurers not required, although individual insurers may request separate negotiations. Anti-Avoidance Regulation will tie price to latest Xenbilox price, and possibly to that prior to the latest price freeze (effective date 1 August 2009)*").

[294] See docs. 78.379, 96.171 and 96.183.

suggested that the company request the evaluation procedure only if it was actually convinced that it could demonstrate a significant added therapeutic value that justified the projected price increase that the company intended to apply to the orphan drug (at the time, €10,000 per pack)[295]. If not, he suggested that formal confirmation be sought from the competent authority that the evaluation procedure was not applicable to the orphan medicinal product[296].

163. In December 2015 the responsible German authorities communicated that the procedure for assessing the therapeutic added value of the orphan drug was not mandatory, after that Sigma Tau had sent them a request for clarification at the end of October 2015[297]. This was specifically because the drug was not new and contained the same active substance as an existing drug. Consequently, despite the planned withdrawal of *Xenbilox*®, the orphan drug would fall within the purview of the price moratorium and would force Sigma Tau to reimburse the health insurance funds for the difference between the launch price of the orphan drug and the reimbursement price of *Xenbilox*®[298].

164. However, the price moratorium would not have been applicable if, at the time of the launch of the orphan drug on the German market, in addition to the absence of *Xenbilox*® from the official price list, the MA holder for the new orphan drug had been a company other than the one holding the distribution rights of *Xenbilox*®[299] (for more information, see the following section).

165. Therefore, the planning process for the withdrawal of *Xenbilox*® from the German market continued over the following months,[300] and in May 2016 the company decided that *Xenbilox*® would be withdrawn when the launch of the new product was completed, which in turn depended on when the company would obtain the MA for the orphan drug[301].

166. In September 2016, after obtaining a positive opinion of the EMA's COMP on the request for an MA for the orphan drug, Sigma Tau began to outline a more concrete withdrawal strategy, identifying for the first time a precise, although not definitive, timeline. The company decided to start the withdrawal procedure for *Xenbilox*® at the end of September 2016, fulfilling final orders in October 2016, and to conclude it between April and May 2017,

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[295] See doc. 78.379.
[296] See docs. 78.379.
[297] See docs. 78.379, 96.171 and 96.183.
[298] See docs. 96.187 and 78.379.
[299] See doc. 96.187.
[300] See docs. 96.73 and 96.107.
[301] See docs. 78.374 and 96.131.

withdrawing any packs still on the market[302]. In mid-October 2016, Sigma Tau sold the existing stock of *Xenbilox*® to the wholesaler Juers Pharma, who continued to sell the product to end customers until the drug was definitively withdrawn from the market[303].

167. In the documents already mentioned, reference is also made to the previously identified reasons that supported the decision to withdraw *Xenbilox*® from the German market[304]. These reasons are based on a document dating back to September 2015, in which it is established that withdrawal would have been justified by the fact that the original therapeutic indication, the treatment of gallstones, no longer had a market, with much more effective therapies having become established[305]. However, internal company correspondence from the second half of May 2017 reveals that the real reason for the withdrawal *of Xenbilox*® from the market was strategic ("*I confirm that Xenbilox is only recalled locally in Germany. It is recalled only for strategic reasons, not for a quality or a safety reason*"[306]), meaning aimed to prevent the competent authorities from referring to *Xenbilox*® during the negotiation of the price of the orphan drug, as had been feared several times as per the evidence mentioned above.

168. Between March and April 2017, the company also decided to request the removal of *Xenbilox*® from the official list after the conclusion of the procedure to withdraw *Xenbilox*® from the market, i.e. during the first half of May 2017, with it being removed between the end of May and the beginning of June 2017[307]. Immediately afterwards, a request was made for the orphan drug's inclusion in the official price list[308]. This prevented the two products, *Xenbilox*® and the orphan drug, from formally coexisting on the market[309].

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[302] See docs. 78.10, 78.12, annex, 78.161, 96.185, 96.49 and 96.227.
[303] See docs. 105 and 138.4.1.
[304] See docs. 96.49 and 96.227.
[305] See docs. 96.145, 96.41, 96.167 and 96.85 ("*It would be important to had that the number of CTX patients in Germany is very low – estimated to be less than 20 patients, currently. Therefore, it is no longer viable to have Xenbilox commercially available for such a small patients population. Basically, making the case that we are operating at a financial loss and we cannot continue to supply the drug, hence the need for a centralized procedure and launching a new product.*")
[306] See doc. 96.57.
[307] See docs. 78.81 and 78.161.
[308] See docs. 96.49 and 96.227.
[309] See docs. 78.244, Annex "*Pricing Strategy for CDCA*_15FEB2017" and Annex "AP1122 *CDCA Pricing Study Results 22nd Oct V3F updated 27 November 2015.pdf*", 78.249, which shows that the consulting company used by the company suggested keeping *Xenbilox*® on the market until the introduction of the orphan drug; however, the company did not agree ("*Xenbilox could remain on the market until a number of EU launches in order to maintain patient supply However, ST does not want Xenbilox to co-exist on the market with CDCA and intends to remove Xenbilox from the German market prior to first CDCA launch*"), 78.262 ("*Xenbilox and the new CDCA Leadiant will not co-exist in the market"*) and 96.185.

169. Conversely, Sigma Tau (now Leadiant) also did not request the revocation of the *Xenbilox*® MA[310]. The definitive revocation of the *Xenbilox*® MA was only requested from the German regulatory authorities in June 2019[311].

170. The documents on file indicates that the strategy to prevent the presence on the market of *Xenbilox*® and *CDCA Leadiant*® at the same time played a role in the negotiations initiated with the other national regulatory authorities[312], including AIFA (see paragraphs 197, 199 and 203 below).[313]

ii) *The creation of a new company under German law to take ownership of the orphan drug MA*

171. Some documents from the beginning of 2016 show that the company had decided to create a new company in Germany (Leadiant GmbH). In a presentation from that time, the company assessed the advantages and disadvantages of this choice, concluding that there were several positive aspects resulting from this. These included the possibility of obtaining the desired price for the future orphan drug[314].

172. The aforementioned document from March 2016 explains the link between the creation of the new company and the effects of this decision on the price of the future orphan drug: according to the company, neither Sigma Tau Rare Disease Ltd., the holder of the MA for *Xenbilox*® at that time, nor Sigma Tau Arzneimittel GmbH, the previous holder of the *Xenbilox*® MA, could have been the holder of the MA for the new orphan drug, without the competent authorities referring to the reimbursement price of the first drug in

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[310] See docs. 96.49, 96.227 and 138.4.1. Based on the sunset clause, the company in fact decided to wait until the *Xenbilox* MA automatically expired three years from the end of the sale of the medicine (October 2019). The *sunset clause* is defined in Article 14 of Regulation (EC) No 726/2004 and Article 24 of Directive 2001/83/EC. It stipulates that the marketing authorisation for a centrally authorised medicinal product shall cease to be valid if: *i)* the medicinal product is not placed on the market within three years of the date of the authorisation granted; or *ii)* a medicinal product previously placed on the market is no longer actually on the market for three consecutive years. The equivalent regulatory provision applicable in German law is Article 31 (1) No. 1 AMG.

[311] See doc. 138.4.1.

[312] See doc. 78.329 ("*If a rebranding process is implemented in Germany, and the manufacturer of both drugs remains the same (Sigma Tau), Spanish authorities will try to use the previous price of Xenbilox as an external reference price instead of the new branded product's price. However, Xenbilox has not received a formal price from the Spanish authorities, thereby avoiding a formal ability to act as a reference. Sigma Tau can argue the product is different because it has a new indication unrelated to the previous one, and that research activities have been conducted to prove the efficacy and safety of this new orphan indication*").

[313] See doc. 108.

[314] See docs. 22.7.50.

the definition of the reimbursement price of the second. Hence arose the need to create a new entity, controlled by Sigma Tau Rare Disease Ltd. ("*As we discussed before we will need a newco in Germany because neither ST GmbH nor STRDL can be MA holders and/or distributors of the new CDCA without an immediate reference to the old Xenbilox® price. A name change is not enough. This must be a new pharmaceutical entrepreneur (new numbers, register, etc). However the newco can be fully owned by STRDL*"[315]).

173. In November 2016, when Sigma Tau Rare Disease Ltd. was about to change its name to Leadiant Biosciences Ltd. (in December 2016)[316], doubts arose internally in relation as to the appropriateness of *Xenbilox*® also being owned by a company of the Leadiant group, albeit another one than the German subsidiary itself. In other words, it was feared that notifying the British regulatory authorities of the change in the name of the MA holder of *Xenbilox*® from Sigma Tau Rare Disease Ltd. to Leadiant Biosciences Ltd. would have brought the two products, *Xenbilox*® and the orphan drug, back under the umbrella of the same company group and would have led the German regulatory authorities to associate them as part of the procedure for allocating the reimbursement price to the orphan drug. In this way, the efforts to create a new company under German law, which was necessary to realise the profits deriving from the introduction of the orphan drug in Germany at a higher price than what was used for *Xenbilox*®, would have been frustrated[317].

174. However, the internal discussion concluded in March 2017 that the existence of a controlling relationship between Leadiant Biosciences Ltd. and Leadiant GmbH would not have jeopardised the latter's autonomy under German law[318].

175. In August 2017, the German health insurance providers association sent a communication to Leadiant GmbH stating that the provisions of the price moratorium for newly introduced medicines owned by companies that previously marketed drugs with the same active substance and with a comparable pharmaceutical form, were applicable to the present case, and

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[315] See doc. 96.79.

[316] See doc. 28.2.96.

[317] See doc. 96.153 ("*I'm not quite sure whether it is a good idea to transfer Xenbilox to Leadiant. As far as I did understand the situation around the pricing issue with CDCA we should not mix up the MAH for Xenbilox with the MAH of CDCA. As the German Leadiant and the UK Leadiant are a so-called group of companies I assume if we transfer the Xenbilox license to a Leadiant company that we then jeopardize all our effort to set up a new company to get a high price for CDCA*").

[318] See doc. 96.117 ("*And remember in the UK we are not creating a new company but simply changing the name of the current one so there is no transfer but a change in name of the MAH*"). See also docs. 96.49, 96.153 and 96.185.

asking for a price discount equal to the difference between this price and the reimbursement price of the previously marketed drug, *Xenbilox*®, equal to €660 per pack[319].

176. Between August and September 2017, Sigma Tau and the association exchanged correspondence in which the company stressed that Leadiant GmbH was a new company and not a spin-off or successor of Sigma Tau Arzneimittel GmbH, from which it had not acquired any assets, rights or obligations. Therefore, the two companies should have been considered different and independent. It also stated that the orphan drug was a new drug and not *Xenbilox*® with a new trade name[320].

177. The evidence shows that the company managed to convince the association of health insurance providers of the accuracy of its thesis and to prevent it from asking for a discount when determining the reimbursement price of the orphan drug, referring to the lowest price of *Xenbilox*®[321].

III.5.8 Market reactions to the price of the orphan drug in Germany and other European countries

178. Certain internal company documents reveal Leadiant's awareness of the German regulator's opposition to the price at which the orphan drug had been launched on the market[322], equal to about *[€20,000-€30,000]* per pack[323], especially in view of the perception of the commercial operation as a mere 'repurposing' activity[324].

179. The negative reaction with which the orphan drug's launch price was met in Germany could also be found in the press, to whose requests for explanation Sigma Tau responded by stressing the difference between *CDCA Leadiant*® and *Xenbilox*®, which was registered for the treatment of a different disease affecting many more patients, and the fact that Leadiant had had to bear significant costs of research, development and registration for the

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[319] See doc. 96.65.

[320] See doc. 96.65, 96.196, 96.113 and 96.169. The company prepared similar arguments in a document dated September 2017, which contained the answers to be given to the potential questions of the German press about the reasons for the high price at which the orphan drug had been introduced in Germany. See doc. 22.7.16, Annex "170908_EN_QA Leadiant V5".

[321] See docs. 22.7.63 and 78.144.

[322] See doc. 96.19.

[323] See docs. 78.244, Annex "Pricing Strategy for CDCA_15FEB2017", 78.91 and 96.121.

[324] See doc. 78.225 ("*Stakeholder perception of transition from Xenbilox to CDCA Leadiant. […] Payers could take CDCA Leadiant as an example of repurposing not being acceptable, even under ODD*").

orphan drug[325].

180. Despite this complicated institutional context, the company considered it useful to keep the orphan drug on the German market at a high price, as at least for the first year in which the company was free to choose its level, this price would have constituted a benchmark for negotiation in other European countries[326].

181. Other evidence reflects the equally negative reaction of some stakeholders to the prices proposed by Leadiant in various European Union countries for the launch of the *CDCA Leadiant®*, an expression of the demand for the drug.

182. A document dated October 2017, in particular, shows the negative reaction of Austrian doctors to the price of the orphan drug[327].

183. Likewise, a letter dated April 2018 sent by the Dutch Ministry of Health to the President of the House of Representatives of the States General contains a negative assessment of the price of the orphan drug, in light of the relative investment made in innovation. In particular, the Minister considered that the annual price of €160,000-€220,000 proposed by Leadiant to the Dutch insurance providers was inappropriate given the company's efforts to obtain the orphan designation, based on the mere collection of the scientific literature and on having commissioned two retrospective studies that showed the effects of the drug on the disease, activities considered useful but not 'revolutionary' and not deserving the economic remuneration requested by the company[328].

III.5.9 The introduction of Chenodeoxycholic Acid Leadiant in Italy and price negotiation with AIFA

184. In relation to the introduction of the orphan drug into the Italian market, the evidence shows that during the first half of 2016, the company was preparing for a preliminary meeting with AIFA to be held in June 2016, in view of the start of the price negotiation procedure in Italy. One document in particular shows that the company had given instructions to a consulting firm that was assisting it during the negotiations regarding the information to be indicated in the orphan drug reimbursement dossier. It should have been described not as a drug based on a known active substance with a new

[325] See docs. 96.31 and 22.7.16, Annex "170908_EN_QA Leadiant V5".
[326] See doc. 96.19.
[327] See doc. 96.24.
[328] See doc. 96.77.

therapeutic indication, but as a completely new drug for the Italian market[329]. Similarly, another document from the same period (June 2016) indicates that the company intended to move "*in Italy, carefully avoiding the creation [...] of connections with the name Sigma-Tau*"[330].

185. For this reason, the company's concern was to ensure, for example, that hospitals did not ask the Agency for access to the Fondo Nazionale AIFA 5% (AIFA 5% National Fund)[331] for the purchase of *Xenbilox*® close to the start of the orphan drug price negotiation procedure with AIFA, requesting it instead for the new orphan drug that would soon be placed on the market[332].

186. In March 2017, the company began to collect the information necessary for the reimbursement dossier to be submitted to AIFA, including not only the data relating to the investments in research and development carried out in Italy in the three-year period from 2014-2016, but also those relating to other medicines, different from and unrelated to CDCA[333]. As part of all of the investments, the research led to the identification of the total project costs for registering the orphan drug in Italy, which – with the exception of the price paid to the University of Siena for the retrospective study – amounted to approximately *[€100,000-€200,000]*[334].

187. At the end of May 2017, the company's Chief Financial Officer (CFO) also indicated that the total investments in research and development made in

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[329] See docs. 78.172 and 78.291 ("*new indication of a known compound. OK? No, not ok. I understand your comment about this being strange, but in fact this is a 1st registration of a new pharmaceutical product in Italy. Let us keep it like that, because this is something we can argue from a Legal standpoint. We should state it as is and not mention the compounding if we do not have to*").

[330] See doc. 78.95.

[331] AIFA's foundational legislation provides for a national fund for the use of orphan drugs for rare diseases and medicinal products that represent a hope of treatment, pending marketing, for particular and serious diseases (Article 48(19)(a) of Legislative Decree no. 269 of 30 September 2003, converted into Law no. 326 of 24 November 2003). This fund is financed by 5% of annual expenses for the promotion activities of pharmaceutical companies. Requests for access to the fund are forwarded to AIFA through the regions by the reference centres treating the patients, or by specialist facilities identified by the regions, with a definition of the diagnosis and the therapeutic plan.

[332] See doc. 22.7.150, which shows that an Italian hospital, BESTA, intended to purchase *Xenbilox*® in March 2017 and request access to the AIFA 5% National Fund. The company thus planned to provide the orphan drug to the hospital free of charge to prevent it from requesting access to the Fund for *Xenbilox*® and to prepare the reports that would have allowed the sale of *CDCA Leadiant*® in the future or, in any case, to request access to the Fund for the price proposed to AIFA; and doc. 78.90. Similarly, the University Hospital of Siena intended to submit the same application (see doc. 78.86).

[333] See docs. 78.420 ("*The P&R dossier that Dario and Lucia are assembling for AIFA must include the R&D investments that the "Company or Group" has sustained in the last three years in Italy and asked me some support on this. R&D costs independently of the specific product (CDCA in this case) and of the Applicant (e.g. Germany) can be indicated. They refer generically to the Leadiant Group and to R&D projects and for this reason we can also include costs sustained in Italy for example on Heparanase (which I have) or other projects*") and 78.168.

[334] See docs. 78.420 and 78.421.

Italy by Sigma Tau/Leadiant between 2014 and 2017 also for products other than CDCA amounted to approximately *[€2-€3]* million, (of which *[€100,000-€200,000]* were for CDCA)[335].

188. In the meantime, expecting difficult discussions with the national authorities regarding the price it intended to ask for the orphan drug compared to the investments made for its development[336], in view of the negotiation procedure set to begin with AIFA, the company also verified the amount of the external costs incurred until that point for the CDCA Project at a global level, thus managing to establish in detail (item by item) that such costs amounted to approximately *[€10-€20]* million for the years 2014-2017[337]. Of these, only a small part can actually be classified as investment in research and development[338]. Other internal company documents found in the evidence dating back to the years 2014-2017 indicate the estimated (and not particularly significant) research and development costs that the company had incurred or expected to incur for the launch of the orphan drug on the European market[339].

189. Leadiant submitted the request for reimbursement and classification of *Chenodeoxycholic Acid Leadiant*® to AIFA on 15 June 2017. With this request, the company proposed a retail price of €25,592.64 (and an ex-factory price of €15,506.93) for a pack of 100 capsules of 250 mg[340]; given that patients take three 250 mg capsules per day, i.e. 1095 capsules per year, the annual cost of therapy per patient would therefore be €280,239.41 (less the regulatory discounts of 5%+5%).

190. The request was examined by AIFA's Technical Scientific Committee (CTS)[341]. Through its decision dated 4 August 2017, AIFA included the drug in the Cnn class (i.e., the class where drugs with pending price negotiations are automatically included, pursuant to Article 12(5) of Law no. 189/2012) at

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[335] See docs. 78.449, 78.463, 78.172, 78.173.

[336] See doc. 78.438 ("*In the spirit of expecting very difficult discussions concerning our proposed price vs R&D investment...*"). Moreover, there was some awareness of this even in March 2016: "[...] *it would seem inevitable that at some point we will have to offer to 'open our books' in order to assist with the justification of price for CDCA* [...]" (see doc. 78.441).

[337] See docs. 78.419, 78.433, 78.438, 78.439, 78.443, 78.149, 78.458, 78.442, 78.459, 22.7.5, 78.460.

[338] See docs. 22.7.5, 78.459, Annex "STRD CDCA RD cost final v2 with only external costs" and Annex "LB Inc 2014-Feb ytd 2017 CDCA Expenses". It should be noted that, in the documents mentioned, the company has classified as research and development costs cost items that are not attributable to this category (see, for example, the cost items entitled "*fee for service*", "*promo trade show exhibits*", "*promo sales material development*" and "*advertising*" contained in the sheet "Raw Data Bdg 17" of Annex "STRD CDCA RD cost final v2 with only external costs").

[339] See doc. 78.62, Annex "GRD Strategic Plan 2015-2019 (FINAL selection) 20OCT2014", 95.4, 95.5, 78.434, 78.447.

[340] See docs. 3.2, 72.1, 78.72.

[341] See documents 78.72, 78.78, 78.83 and 78.84 for the application.

the price proposed by the company in the reimbursement request[342].

191. Therefore, pending an agreement on price, *CDCA Leadiant*® was sold at an unrestricted price to the Italian ASL, which purchased it using the import procedure referred to in the aforementioned Ministerial Decree of 11 February 1997[343] at the ex-factory price of €15,506.93 per pack of 100 capsules of 250 mg[344].

192. In December 2017, Leadiant received a request from a hospital for the free supply of the orphan drug based on 'compassionate use', but decided to reject this request because it would have involved achieving zero profits in Italy until the end of the negotiation procedure with AIFA[345].

193. Over the following months, the *Health Technology Assessment* (HTA) and the AIFA CTS carried out their own investigation on the drug, noting that the evidence supporting the effectiveness of the treatment was obtained mainly in an academic setting, in one case using the drug's active substance in galenic form, which was no longer available during the registration process of the orphan drug, effectively discontinuing the treatment of a segment of patients[346].

194. As a result of this investigation, in its meeting on 19 March 2018 AIFA's Price and Refunds Committee (CPR) held that the ex-factory price of €15,506.93 per pack requested by the company, equal to five times the price of the product previously used, *Xenbilox*®, could not be accepted without additional elements to justify it in view of the activities carried out for the introduction of the drug to the market (the presentation of retrospective studies and the review of the literature). Therefore, the Committee asked the company in writing to provide a cost-based justification[347]. Similarly, the CPR held that the number of CTX patients in Italy in three years' time would be higher (90) than the company's estimate (49)[348].

195. Some documents on file indicate that, between March and April 2018, the company had internal discussions on how to respond to the Agency and prepared a draft letter indicating the number of patients served at that point

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[342] See doc. 78.152. The determination was published in Official Gazette no. 203 of 31 August 2017.
[343] This channel is managed by the Ministry of Health through the Border Offices (USMAF).
[344] See docs. 8.2, 8.3, 8.4 and 10, Annex 3. See also *https://www.aslroma1.it/uploads/files/32_56_2357_del_16.08.2017.pdf*.
[345] See doc. 78.157 ("*This is a can of worms we really do not want to open if we can avoid. You agree to one you agree to all and then no sales in Italy until reimbursement which will happen god knows when*").
[346] See doc. 3.1.
[347] See docs. 3.2 and 11.1.
[348] See docs. 3.2., 11.1. 78.113, 22.7.142, 22.7.148, 78.85, 78.114, 78.132, 78.136-78.140, 78.142, 78.170, 78.171, 78.178, 78.179 and 78.441.

(37) and the amounts of the investments in research and development made in Italy (see paragraph 187 above). At the same time, it decided to avoid as much as possible any reference to *Xenbilox*® in order to exclude the existence of any commercial ties to the drug[349].

196. This response to AIFA arrived on 10 April 2018. Through it, the company also asked to be summoned to a new meeting, informing the Agency that it was willing to reach an agreement to repay the ASLs the difference between the negotiated price and the price they paid to purchase the orphan drug[350].

197. At the meeting held on 29 May 2018, the AIFA CPR noted that the only drug that had been used for the treatment of CTX in Italy following import from abroad, *Xenbilox*®, was not available on the national market[351]. In this regard, during the hearing AIFA stated that it perceived the withdrawal of this drug from the Italian market as a major obstacle to the price negotiation procedure for *CDCA Leadiant*® and as one of the instruments of artificial differentiation between the two products, together with the change of ownership of the new orphan drug[352].

198. On 14 June 2018, AIFA's CPR sent a communication summoning the company for a meeting on 26 June 2018 and, in response to the counterclaims, stated what had already been expressed in the meetings on 19 March and 29 May 2018: "*In view of the fact that the authorisation procedure was based exclusively on retrospective studies and data from the literature, it reiterates that it cannot accept a price five times higher than the price of the previously authorised product XENBILOX (...)*"[353].

199. The company intended to reply that the only existing correlation with *Xenbilox*® stemmed from the fact that the latter drug is the "reference drug" for *CDCA Leadiant*®. There was no correlation for the rest, since Leadiant had never marketed any CDCA-based drugs in Italy, nor did it ever have anything to do with the price at which *Xenbilox*® had been marketed in Italy. In this way, the company felt that it was avoiding entering into the merits of

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[349] See docs. 78.99, 22.7.143 ("*I would prefer avoid discussing direct relations with Xenbilox. Especially because Leadiant Biosciences or the ST companies never sold Xenbilox in Italy, the commercialization of Xenbilox in Italy was always done by a 3rd party and hence outside our control*") and 78.111, Annex "CPR *Letter*" and "*CPR eng Letter*".

[350] See docs. 3.2 and 11.1.

[351] See docs. 3.2 and 11.1.

[352] See doc. 108.

[353] See docs. 78.77, Annex and 78.79, Annex

any discussion related to *Xenbilox*®[354]. However, this line of argument was not unanimously supported within the company or by external consultants, because it was considered risky and ineffective[355]. The company then contemplated stating that at least the off-label drug was only authorised in Germany and that it was imported into Italy by third parties[356]. However, since this route was also considered dangerous, the company finally decided to limit itself to stating that *Xenbilox*®, approved in Germany for the treatment of gallstones and used as a reference drug in the hybrid authorisation procedure for the orphan drug, was a separate product[357].

200. In the days prior to the meeting with AIFA, Leadiant also developed price/volume agreement scenarios to propose to the Agency, anticipating a compromise price which, in the worst-case scenario (which it had expressly decided to reserve for the subsequent negotiation rounds), could have totalled around €9,000[358].

201. During the meeting on 26 June 2018, it emerged first that, as already noted by the HTA Sector in September 2017, there was no on-label medicine on the domestic market that could be considered as a therapeutic alternative, since *Kolbam*® was not authorised in Italy and *Orphacol*® was registered for other therapeutic uses[359].

202. At the same meeting, the company explained the characteristics of the product, the authorisation process, the sales data and the prices applied in other EU countries. For its part, the CPR repeated its doubts to the company about

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[354] See docs. 78.141 ("*1. There is no "previously authorised product" in Italy not for CTX not for any other indication in what concerns Leadiant products; 2. Leadiant has never commercialised/sold any other Chenodeoxycholic acid in Italy. 3. The only relation between the products is that Xenbilox was referenced in the CMC part since CDCA is an Hybrid drug; 4. For the above reasons we reject the notion of "5 fold price increase"; 5. The company is willing to negotiate a sustainable solution based on CDCA Leadiant added value for patients but cannot and will not be referred to a drug it never commercialised in Italy for a completely different indication; 6. The framing should be other EU countries price. Price for drugs with similar epidemiology etc.; 7. XENBILOX discussion is a lost one. Will not enter lost d[i]scussions*"), 78.77, Annex (*slide* 5): "*Xenbilox was a drug approved exclusively in Germany for Gallstone dissolution. It was to the best of our knowledge imported into Italy through wholesalers, international pharmacies and other similar distributors as an unlicensed medicine and used off-label in CTX patients. Leadiant has never engaged the Italian authorities for funding or for price negotiations regarding Xenbilox as an unlicensed off-label medicine […] The reference medicine for CDCA Leadiant was Xenbilox. However CDCA Leadiant is not the same medicine as Xenbilox*"), 22.7.149. Annex 78.79, Annex 78.116 ("*The point is that we had nothing to do with the selling of this drug in Italy. This is not a price increase in any way sort or form*"; "*I want to avoid a discussion and price comparison with Xenbilox as center of the conversation. I do not believe we can get out with the best outcome if we do not avoid it at all cost*").

[355] See docs. 78.112 ("*we must be very careful in saying that LB has never sold Xenbilox etc etc.*") and 78.116.

[356] See doc. 78.77.

[357] See docs. 78.118 and 78.119.

[358] See docs. 22.7.136 and 78.75.

[359] See docs. 3.2 and 11.1.

the price level requested, referring once again to the fact that the orphan drug's base compound was dated and had been present on the Italian market at a price five times lower than that requested by the company[360]. In response, Leadiant illustrated the cost items that made up the financial investment made by the company to keep the orphan drug on the market. However, this was not considered sufficient by the CPR, which requested the submission of evidence to substantiate these costs.

203. In addition, the CPR requested clarifications as to why the compound was unavailable not only on the Italian market, but also on other national EU markets, for other therapeutic indications after the approval of the orphan drug by the EMA. In response to this question, Leadiant replied that there was market exclusivity linked to the orphan designation[361].

204. Leadiant also stated that it was not able to document in detail the production costs of the drug and proposed to the Agency two different price/volume agreements (quantity discounts) with three price brackets[362]. For its part, the AIFA CPR replied to both proposals that the starting price requested by the company was too high, asking that a new proposal be formulated that aligned the price with *Xenbilox®'s* price that would therefore make the cost of therapy sustainable for the Italian National Health Service. At Leadiant's request, negotiations were then suspended pending the company's sending of a new proposal within 15 days[363].

205. Subsequently, in July 2018, despite AIFA's request the company considered it preferable not to continue quantifying research and development costs[364].

206. In the absence of any feedback from Leadiant, on 9 November 2018 AIFA's competent HTA Sector sent a reminder to the company. Leadiant did not reply to the said reminder. On 15 February 2019, AIFA's CPR then sent a second reminder, giving the company a period of thirty days to respond[365].

207. Following these reminders, the company sent a new reimbursement

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[360] See docs. 3.2 and 11.1.
[361] See docs. 3.2 and 11.1.
[362] See doc. 3.2. The company first proposed a 15% discount on the price of packs for 0 to 37 patients, 30% for 38 to 47 patients and 60% for more than 47 patients. Following the CPR's rejection, it then proposed a 20% discount on the price for 0 to 37 patients, 30% for 38 to 47 patients and 80% for more than 47 patients. See docs. 22.7.136 (78.75), 22.7.137 (78.76) and 78.113. for additional bid scenarios.
[363] See docs. 3.2 and 11.1.
[364] See doc. 78.150 ("*Pierre in fact pulled the number together for me a while ago and after seeing it I thought it best not to take it any further*"). Doc. 78.113 shows that the company had decided to move negotiations in a different direction ("*We should set the turnover that we want to secure and move from there*").
[365] See doc. 11.

dossier on 11 March 2019, announcing a new price proposal[366] that was effectively detailed on 1 April 2019. It provided for a new price/volume agreement with three new brackets based on three different discounts applicable to the same initially proposed ex-factory price of €15,506.93 per pack[367]. On 15 April 2019, the CPR decided not to accept the proposal and in turn submitted a counter-proposal[368]. After several exchanges of correspondence aimed at finding an agreement[369], the parties met again on 22-25 July 2019. However, they were not able to reach a compromise on that occasion either. Negotiations were thus interrupted once again, and the procedure was again suspended until a date that was to be determined. The CPR also stated that it was still awaiting precise data on the costs of production for the drug, and in particular on the investment in research and development made by Leadiant, as well as information on the reimbursement prices charged in the other Member States mentioned by the company during the meeting[370].

208. In September 2019, AIFA again asked Leadiant to send information about the cost data, together with an indication of the refund price used in other European Union Member States[371]. The information requested by the Agency was sent by Leadiant with in two communications, dated 11 October 2019[372] and 26 November 2019[373], respectively. In particular, in the first communication the company provided information on the prices charged for *CDCA Leadiant*® in Germany (as mentioned, approximately *[€20,000-€30,000]*) and the United Kingdom (approximately *[£10,000-£20,000]*)[374]; in the second communication (therefore sent after notification of the Italian Competition Authority's opening of proceedings), it provided information on the costs incurred for the launch of the orphan drug.

209. More specifically, based on the study carried out by the consultancy company *Copenhagen Economics* after the initiation of the investigation

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[366] See docs. 11 and 72.1. The new proposal was based on the annual movement of packages: the first bracket concerned packages from 0 to 370, the second from 371 to 490 and the third from 490 onwards. This final bracket would have been "*free of charge*".

[367] See docs. 11.1 and 78.121, where it is indicated that the discounts applied to the three brackets referenced in the previous footnote were 25%, 50% and 100%.

[368] See doc. 11.1, which shows that the CPR had proposed a 50% discount on the price from 0 to 370 packs, 80% from 371 to 490 packs and from 490th pack, the spending cap of €2.9 million would have applied.

[369] See doc. 70.6. On 13 May 2019, the company first sent a communication proposing a 30% discount on the first bracket, then, for the July 2019 session, a 36% discount on the first bracket and a spending cap of €3.3 million. At the meeting on 21 May 2019, the CPR expressed an opinion in which it was decided to convene the company and to reiterate at that meeting the request for a 50% discount for the first bracket. See doc. 72.1.

[370] See docs. 11, Annex 1, and 70.6.

[371] See doc. 78.127, 78.128 and 78.156.

[372] See docs. 49.3 and 72.2.

[373] See doc. 72.1.

[374] See docs. 49.1 and 72.4.

proceedings pursuant to Article 102(a) of the TFEU by the Dutch ACM[375], in the second communication Leadiant stated that it had spent almost *[€30-€40]* million between 2014 and 2017 – a figure that represents the total direct and indirect costs incurred in bringing the CDCA product to the market, including the development of the new test for the production of the updated active substance, the pharmaceutical product and the development of the dossier for the European MA – and that it expected to spend *[€100-€200]* million from 2017 to 2023 (for a total of about *[€100-€200]* million), due to the activities imposed by the EMA for the maintenance of the MA (patient register and compliance with the requirements imposed by national laws for placing the product on the respective markets).

210. The figures from the consultancy firm's study were revised downwards by Leadiant in February 2020 during discussions with the Dutch Competition Authority[376]. In particular, it appears that the costs initially provided by Leadiant contained significant intercompany items that should not have been included. The costs thus adjusted (which in principle correspond to the costs communicated by the company during the course of the proceedings, see section III.6.2.ii below for more information) amount to approximately *[€70-€80]* million, i.e. less than half of the costs provided in discussions with AIFA, for the period of 2014-2023. However, according to the information acquired during the investigation, Leadiant did not provide AIFA with information on additional and different costs compared to those offered in November 2019[377].

III.5.10 The final outcome of the CDCA Leadiant® price negotiation with AIFA

211. Following the receipt by AIFA of the aforementioned information in October and November 2019, a new meeting was held on 18 December 2019 between Leadiant and the CPR, during which the parties reached an agreement on the price of *CDCA Leadiant®*, valid from March 2020 for a period of 24 months[378].

212. The information obtained during the investigation showed that, for the purposes of reaching the agreement, the cost data provided by the company did not play an effective role, as they did not have the degree of detail required

[375] See docs. 70.7, 70.9 and 70.11.
[376] See docs. 95, 95.16 and 95.17.
[377] See doc. 108.
[378] See docs. 72 and 72.1.

by the CPR nor were they sufficiently documented. Therefore, in accepting the new proposed Leadiant agreement the AIFA CPR adopted an approach based chiefly on the therapeutic value of the drug[379].

213. In relation to the content of the agreement, AIFA stated that it provides for the application of a confidential discount of *[50-60%]* on the price requested by the company, the establishment of a maximum cost ceiling of €2.8 million per year and the use of payback measures in the event this ceiling is surpassed. These parameters were set by taking into account a number of *[40-50]* patients, i.e., closer to the company's estimates (see paragraph 196 above), and the expected purchase of approximately *[400-500]* packs in one year. Under these conditions, the Italian National Health Service pays *[€5,000-€7,000]* per pack of *CDCA Leadiant*®[380]. At present, the spending ceiling has never been exceeded and the number of packages necessary to do so exceeds Leadiant's sales forecasts for Italy until 2023[381].

214. In addition, the payback clause contained in the agreement states that Leadiant shall pay back the difference between the price negotiated with AIFA and the price that Leadiant previously charged the ASLs and the regions for the sale of the orphan drug, when it fell under class Cnn (i.e., when it had not yet been classified and could only be purchased at a price freely set by the company). According to the company's estimates, included in the negotiation agreement signed with the Agency, this difference was quantified as a total of *[€6-€7]* million[382].

215. At the two hearings, the Agency's representatives stated that the agreement entered into, although sufficiently satisfactory, given the starting bargaining positions – the price initially proposed by Leadiant, equal to 5 times that of *Xenbilox*®, and the discount requested by AIFA, equal to 80% of the price proposed by Leadiant[383] – must be assessed in light of the context in which the negotiation took place.

216. In particular, according to AIFA, it is necessary to consider certain elements that negatively influenced the progress of the negotiation of the price of the *CDCA Leadiant*® and its outcome. Firstly, the drug had, in fact, already been on the market for about two and a half years and the ASLs, who were making significant payouts, had been using the Cnn-class orphan drug as therapy for patients with CTX for a long time, and therapeutic continuity

[379] See docs. 72 and 72.1.
[380] See docs. 72 and 72.1.
[381] See doc. 110.1.
[382] See docs. 72 and 72.1.
[383] See docs. 72 and 72.1.

needed to be guaranteed for them. Secondly, the negotiation procedure, which had been interrupted several times due to lack of agreement on price, had been underway for a long time, and this showed a substantial lack of interest on the part of the company to reach a compromise, making it more likely that the negotiations would end with a lack of agreement and that *CDCA Leadiant*® would fall definitively under class C[384]. Lastly, the Agency had no therapeutic alternatives. Therefore, in the light of the difficult context in which the negotiation procedure took place, the Agency considered that the ex-factory price of the orphan drug of *[€5,000-€7,000]* per pack was the best result that it could have achieved at that time to avoid the scenario of the drug's definitive inclusion in class C at the ex-factory price of €15,506.93 per pack.

217. Without these elements of context, the Agency would have considered it appropriate to grant the company a price increase equal to a few percentage points (less than 10%) compared to the price paid by the ASLs for the import of *Xenbilox*® between 2016 and 2017. This is because, compared to *Xenbilox*®, the orphan drug has a sole added value, given by the registration for the treatment of the rare disease that until then was treated with off-label drugs[385].

III.6 Analysis of prices charged by Leadiant in Italy

III.6.1 Introduction

218. In this section, the elements necessary for the analysis of the prices applied by Leadiant to the drug *CDCA Leadiant*® in Italy from June 2017, will be identified. In particular, based on the evidence, Leadiant has implemented the following prices:

– the per-pack ex-factory price of €15,506.93, applied from the start of marketing of the drug in Italy (June 2017) until the agreement reached with AIFA, which went into effect in March 2020 after the start of the investigation proceedings;

– the per-pack ex-factory price of *[€5,000-€7,000]* (net of regulatory discounts), the subject of the agreement with AIFA, was introduced in March 2020 and is still in force. In order to apply the negotiated price retroactively to all purchases made by the Italian National Health Service since *CDCA Leadiant*® was placed on the market, Leadiant committed, as already

[384] Doc. 22.7.12 indicates that this was a real scenario that Leadiant considered in September 2018, not only for Italy, but more generally for all the countries where the company was conducting the price negotiations.
[385] See doc. 108.

illustrated, to pay back to hospitals *[€6-€7]* million of the turnover generated through sales of the orphan drug while it fell under the Cnn class[386]. As of 7 May 2021, this amount had not been fully refunded, with around *[€300,000-€400,000]* in the process of being paid to the Italian National Health Service[387].

219. These prices will be compared to the costs incurred by Leadiant for the registration of CDCA as an orphan drug and its subsequent production, marketing and maintenance.

220. In order to assess the profitability of *CDCA Leadiant*® and, therefore, whether there is a disproportion between the price and the costs incurred, two different methods of analysis will be used in the case in question: the first consists of measuring the project's internal rate of return (IRR) for registering and marketing the orphan drug for the treatment of CTX (hereinafter also the "CDCA Project"), while the second measures the difference between the revenues deriving from the sales of *CDCA Leadiant*® and the cost plus, i.e., the costs incurred for the creation of the product plus a reasonable profit for the business activities.

221. Note that the first of the two methods described above is the same as the one adopted by Sigma Tau in July 2014 in order to evaluate the profitability of the CDCA Project[388].

222. In the following section, the two methods will be illustrated and the profitability analysis of *CDCA Leadiant*® performed by the company during the project launch phases will be presented based on the first of the two methodologies, as indicated above. This assessment was carried out globally, separately for the United States and the rest of the world[389], with Europe included in the latter category.

223. Based on the same method and with the final and forecast data provided by the company during the proceedings, we will proceed to analyse the excessive price of *CDCA Leadiant*® for Italy. Subsequently, the price that Leadiant applied will be analysed using the second method, i.e., cost plus.

III.6.2 The IRR analysis

224. The first excessive pricing analysis method employed here makes use

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[386] See doc. 72.1.
[387] See doc. 122.
[388] Generally, companies choose which projects to develop and which to abandon on the basis of their prospective profitability, adjusted for the risk factor.
[389] This wording reflects what the company used. See doc. 95.6, indifferently defined as "*Rest of the World*", "*RoW*" or "*EU & Other Markets*", as opposed to "*US Market*".

of one of the tools used in corporate finance to support business investment decisions, namely the internal rate of return (IRR)[390].

225. In corporate finance, the analysis of investment projects (capital budgeting analysis) is aimed at identifying which projects to undertake with a view to maximising value for shareholders. To this end, with the methodology in question, the expected internal rate of return of the project is determined and compared with the cost of capital that the company must bear to carry out the project. If the expected rate of return exceeds the cost of capital, the project is profitable, and the company is therefore encouraged to undertake the project. Otherwise (i.e., if the cost of capital is higher than the expected rate of return), there will be no benefit for the company when the project is launched.

226. It should be noted that the use of the Weighted Average Cost of Capital (WACC) as a discount factor makes it possible to assess the profitability of the investment, while also taking into account the relative degree of specific risk. The riskier the project, the higher the cost of capital required to finance the project and, consequently, the higher the rate of return needed to compensate the undertaken risk. Furthermore, based on the discounting of cash flows, the methodology in question takes into account the factor of time – the most recent cash flows (normally negative, as they reflect the project's initial outlays) have a greater weight than those more distant in time (normally positive as the project begins to generate revenue after a certain period).

227. The IRR analysis is normally used *ex ante*, when a company must decide whether or not to undertake a project. As it will be seen, at the start of the CDCA Project Sigma Tau carried out a financial analysis of its net present value at European level. In an *ex-ante* analysis, by definition, the cash flows taken into account are based on the company's expectations regarding costs and revenues (i.e., expected costs and revenues). The same methodology can, however, also be applied *ex-post* to assess the actual profitability of the project, using the final data relating to effectively realised costs and revenues.

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[390] The IRR of an investment project is the discount rate that makes the sum of the current cash flows values (negative and positive) generated by the project equal to zero. The formula used to calculate IRR (indicated by *i* in the formula) is as follows:

$\sum_{t=0}^{n} \frac{CF_t}{(1+i)^t} = 0$ where:

t= time limits;

CFt= cash flow (positive or negative) at time t.

An investment project analysis method substantially equivalent to the IRR is Net Present Value (NPV), calculated as the sum of the present value of the cash flows generated by the project net of the initial outlay – if the NPV is positive, the project is profitable. The IRR is the discount rate that brings the value of the NPV to zero.

i. Leadiant's analysis

228. In July 2014, in an internal document called "*Xenbilox – Deciding the strategic path...*", Sigma Tau evaluated the different options available in relation to the marketing of the future orphan drug (which the company continued to call *Xenbilox*®) in the USA and the 'Rest of the World', which essentially coincided with Europe[391]. At the time, the company had already obtained orphan designation in the USA and was in the process of applying for it for Europe.

229. As regards the Rest of the World (and therefore Europe), the economic analysis carried out by Sigma Tau shows a very strong incentive to proceed with the request for orphan designation of CDCA and for the MA of the future orphan drug for the new therapeutic indication. This is mainly due to the high profitability expected from the production and sale of the orphan drug, which, according to Sigma Tau's calculations, had a gross operating margin of 99%. This level of operating margin resulted from the large difference in production costs (€4 per package, as indicated under the item "*COGS Euros/unit*" in Figure 1 and Figure 2) and the price at which it was assumed the drug would be sold. In particular, as shown in the "*Assumptions*" section of the document, an initial increase in the ex-factory price to €2,900 was expected in mid-2014 (which did actually occur), a second increase to €4,100 at the beginning of 2015 and a final increase to €5,000 per package during the second half of 2015 in conjunction with the obtaining of the orphan designation; these increases would have gone into effect in all the 'Rest of the World' countries except for Germany (where sales were estimated at 10% of the total), where, in consideration of the price moratorium (see paragraph 108 above), it was assumed that the price would not increase until 2017 when it would reach the level of €5,000, as previously implemented in the other European countries[392]. Note that in the scenarios set out in the document, Sigma Tau always assumes a monopoly position in Europe ("*market share 100%*" in Figure 1 and Figure 2).

230. In particular, in applying the NPV model, the company (which envisaged the marketing of the orphan drug from 2016) considered two scenarios: a more cautious baseline scenario, in which, in the absence of changes to the company's operating model, it assumed modest growth (from

[391] See doc. 95.6 ("*A top level assessment has been carried out to understand the value associated with different future options*").

[392] The "Average Selling Prices" shown in the two Figures and relating to the years 2014-2016 represent weighted averages of the subsequent price increases applied in the fractions of the year and assume that sales in Germany did not suffer such increases.

1.7% to 2.5%) in the rate of diagnosis of the disease on the affected population (Figure 1); and a more optimistic scenario, in which, in the face of higher costs incurred by the company aimed at improving the diagnosis of the disease, it would have been diagnosed in 10% of cases (Figure 2).

231. In the first (base case) scenario, discounting the expected cash flows over the 2015-2024 period[393] through a project WACC of 12%, Sigma Tau obtained an NPV of over €58 million. In the second (best case) scenario, the NPV exceeded €107 million, even discounting the expected cash flows through a project WACC of 15%, which is higher than in the previous scenario, in order to take account of the additional risk deriving from the higher costs to be incurred to improve the diagnosis of the disease (and thus obtain higher sales volumes). The IRR calculated on the basis of these data appears to assume infinite value in both scenarios, as Sigma Tau expected to generate positive cash flows in each year of the project and, mathematically, the only value of the IRR that can bring the NPV to zero is equal to infinite.

232. These results derive from the fact that Sigma Tau planned to increase the ex-factory price of *Xenbilox*® from €660 to €2,900 per pack (and actually did so in July 2014) at the very beginning of the project, before the start of the application for registration of the orphan drug, as already illustrated, to finance the relative costs (essentially the registration costs estimated for the years 2014, 2015 and 2016). The project revenues considered by Sigma Tau in the estimate of cash flows take account of the sales of *Xenbilox*® at the increased price, as well as the sales of the orphan drug once confirmation of the orphan designation was obtained, at the assumed price of €5,000 per pack.

[393] This can be seen from the analysis of the document, where the cash flows taken into account in the calculation of the NPV are those indicated with numbers from 1 to 9.

Figure 1 - Baseline scenario [394]

XENBILOX

EU & Other Markets

currency: euro		2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	
						EMA approval (Q1)									
Potential n. of patients based on extrapolated prevalen				10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	
% of patients dignose				1.7%	1.7%	2.2%	2.3%	2.4%	2.5%	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	
market share				100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
n. of patients treatec		211	279	171	171	222	232	242	242	252	252	252	252	252	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*5%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
Units (bottles of 100 tab:		2,316	3,071	1,885	1,885	2,439	2,550	2,661	2,661	2,772	2,772	2,772	2,772	2,772	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*5%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
Average Selling Price (euro/unit		641.1	649.2	1,663	4,160	4,783	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	
growth vs. P			*1%*	*156%*	*150%*	*15%*	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	
Annual Treatment cost x patient (euro'00(		7	7	18	46	53	55	55	55	55	55	55	55	55	
Net Sales (euro'000		**1,485**	**1,994**	**3,134**	**7,841**	**11,666**	**12,751**	**13,306**	**13,306**	**13,860**	**13,860**	**13,860**	**13,860**	**13,860**	
growth vs. P			*34%*	*57%*	*150%*	*49%*	*9%*	*4%*	*0%*	*4%*	*0%*	*0%*	*0%*	*0%*	
COGS (euro/unit)	4.0														
COGS (euro'000)		9	12	8	8	10	10	11	11	11	11	11	11	11	
% on sale		*0.6%*	*0.6%*	*0.2%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	
Gross Margi		**1,476**	**1,981**	**3,126**	**7,834**	**11,656**	**12,741**	**13,295**	**13,295**	**13,849**	**13,849**	**13,849**	**13,849**	**13,849**	
% on sale		*99.4%*	*99.4%*	*99.8%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	
Distributior	0.3%	4	6	9	24	35	38	40	40	42	42	42	42	42	
Registration exp				100	300	200									
Other OPEX	3.5%						446	466	466	485	485	485	485	485	
Total OPE		**4**	**6**	**109**	**324**	**235**	**485**	**506**	**506**	**527**	**527**	**527**	**527**	**527**	
				3%	4%	2%	4%	4%	4%	4%	4%	4%	4%	4%	
EBIT		**1,471**	**1,975**	**3,017**	**7,510**	**11,421**	**12,256**	**12,789**	**12,789**	**13,322**	**13,322**	**13,322**	**13,322**	**13,322**	
Tax	20.0%	294	395	603	1,502	2,284	2,451	2,558	2,558	2,664	2,664	2,664	2,664	2,664	
Net Income		**1,177**	**1,580**	**2,413**	**6,008**	**9,137**	**9,805**	**10,231**	**10,231**	**10,658**	**10,658**	**10,658**	**10,658**	**10,658**	
	days														
A/R	60	247	332	522	1,307	1,944	2,125	2,218	2,218	2,310	2,310	2,310	2,310	2,310	
Inventory	360	9	12	8	8	10	10	11	11	11	11	11	11	11	
A/P	30	1	2	10	28	20	41	43	43	45	45	45	45	45	
NWC (euro'000		**256**	**343**	**520**	**1,287**	**1,934**	**2,094**	**2,185**	**2,185**	**2,276**	**2,276**	**2,276**	**2,276**	**2,276**	
NWC change (euro'000			**-87**	**-177**	**-767**	**-647**	**-160**	**-91**	**0**	**-91**	**0**	**0**	**0**	**0**	
Free Cash Flov		**1,177**	**1,493**	**2,236**	**5,242**	**8,490**	**9,645**	**10,140**	**10,231**	**10,567**	**10,658**	**10,658**	**10,658**	**10,658**	**59,558**
					0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**9**
					5,242	**7,581**	**7,689**	**7,218**	**6,502**	**5,996**	**5,400**	**4,821**	**4,305**	**3,843**	**21,477**
WACC	12%														
NPV Auto	58,595														
NPV Manua	58,595														
TV	21,477														

[394] See doc. 95.6, p. 19.

Figure 2 - Best case scenario[395]

XENBILOX

EU & Other Markets

Best Case Scenario

EMA approval (Q1)

currency: euro		2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	
Potential n. of patients based on extrapolated prevalen				10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	10,080	
% of patients dignose				1.7%	1.7%	2.2%	2.5%	4.0%	6.5%	8.0%	10.0%	10.0%	10.0%	10.0%	
market share				100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	
n. of patients treatec		211	279	171	171	222	252	403	655	806	1,008	1,008	1,008	1,008	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*14%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
Units (bottles of 100 tab:		2,316	3,071	1,885	1,885	2,439	2,772	4,435	7,207	8,870	11,088	11,088	11,088	11,088	
growth vs. P			*33%*	*-39%*	*0%*	*29%*	*14%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
Average Selling Price (euro/unit		641.1	649.2	1,663	4,160	4,783	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	
growth vs. P			*1%*	*156%*	*150%*	*15%*	*5%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	
Annual Treatment cost x patient (euro'00(		7	7	18	46	53	55	55	55	55	55	55	55	55	
Net Sales (euro'000		**1,485**	**1,994**	**3,134**	**7,841**	**11,666**	**13,860**	**22,176**	**36,036**	**44,352**	**55,440**	**55,440**	**55,440**	**55,440**	
growth vs. P			*34%*	*57%*	*150%*	*49%*	*19%*	*60%*	*63%*	*23%*	*25%*	*0%*	*0%*	*0%*	
COGS (euro/unit)	4.0														
COGS (euro'000)		9	12	8	8	10	11	18	29	35	44	44	44	44	
% on sale		*0.6%*	*0.6%*	*0.2%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	*0.1%*	
Gross Margi		**1,476**	**1,981**	**3,126**	**7,834**	**11,656**	**13,849**	**22,158**	**36,007**	**44,317**	**55,396**	**55,396**	**55,396**	**55,396**	
% on sale		*99.4%*	*99.4%*	*99.8%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	*99.9%*	
Distributior	0.3%	4	6	9	24	35	42	67	108	133	166	166	166	166	
Registration exp:				100	300	200									
Other OPEX	15.0%					875	2,079	3,326	5,405	6,653	8,316	8,316	8,316	8,316	
Total OPE		**4**	**6**	**109**	**324**	**1,110**	**2,121**	**3,393**	**5,514**	**6,786**	**8,482**	**8,482**	**8,482**	**8,482**	
				3%	4%	10%	15%	15%	15%	15%	15%	15%	15%	15%	
EBIT		**1,471**	**1,975**	**3,017**	**7,510**	**10,547**	**11,728**	**18,765**	**30,494**	**37,531**	**46,913**	**46,913**	**46,913**	**46,913**	
Tax	20.0%	294	395	603	1,502	2,109	2,346	3,753	6,099	7,506	9,383	9,383	9,383	9,383	
Net Income		**1,177**	**1,580**	**2,413**	**6,008**	**8,437**	**9,383**	**15,012**	**24,395**	**30,025**	**37,531**	**37,531**	**37,531**	**37,531**	
	days														
A/R	60	247	332	522	1,307	1,944	2,310	3,696	6,006	7,392	9,240	9,240	9,240	9,240	
Inventory	360	9	12	8	8	10	11	18	29	35	44	44	44	44	
A/P	30	1	2	10	28	93	178	284	462	568	711	711	711	711	
NWC (euro'000		**256**	**343**	**520**	**1,287**	**1,861**	**2,143**	**3,430**	**5,573**	**6,859**	**8,574**	**8,574**	**8,574**	**8,574**	
NWC change (euro'000			**-87**	**-177**	**-767**	**-574**	**-283**	**-1,286**	**-2,143**	**-1,286**	**-1,715**	**0**	**0**	**0**	
Free Cash Flov				**2,236**	**5,242**	**7,863**	**9,100**	**13,726**	**22,251**	**28,738**	**35,816**	**37,531**	**37,531**	**37,531**	**209,099**
					0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**9**
					5,242	**6,838**	**6,881**	**9,025**	**12,722**	**14,288**	**15,484**	**14,109**	**12,269**	**10,669**	**59,439**
WACC	15%														
NPV Auto	107,526														
NPV Manua	107,526														
TV	59,439														

233. Note that the profitability of the project in question was particularly high for Sigma Tau, even considering a sale price for the drug no greater than €5,000 per pack, so that it decided to proceed with the application for orphan designation and marketing authorisation for the orphan drug in Europe. This implies that setting a higher price (as was actually the case) could only have resulted in a further widening of the difference between prices and costs.

ii. The economic analysis carried out during the proceedings

234. Based on the analysis described above, which Sigma Tau carried out prospectively for the 'Rest of the World', an excessive price analysis of *CDCA Leadiant*® pricing in Italy was carried out using the same methodology adopted by the company. To this end, the profitability of the project for the registration and marketing of the orphan drug was calculated on the basis of

[395] See doc. 95.6, p. 22.

the final data (2014-2020) and the forecast data provided by the said company regarding the Italian market. As will be clarified below at the appropriate moments, the assumptions adopted in carrying out the analysis are all favourable to the Party.

235. According to financial theory, the costs and revenues to be considered in the calculation of the cash flows for the analysis of the IRR are 'incremental', i.e., those deriving from the comparison of the situation that takes into account the project with the situation that would have occurred if there were no project. However, in its *ex-ante* analysis Leadiant seems to consider the total cash flows and not only the incremental cash flows. Therefore, in the following calculations, the analysis was carried out by taking account of both the total cash flows and only the incremental flows.

236. With regard to Italy, there were no sales of *Xenbilox*® during the years 2014-2015. In 2016 and early 2017, *Xenbilox*® was imported into Italy through the wholesaler Juers Pharma, to which Sigma Tau sold the product at an ex-factory price of €2,900 per pack. Finally, from June 2017, once *Xenbilox*® had been withdrawn from the market (see sect. III.5.7.i above), the company began marketing *CDCA Leadiant*® in Italy, which, in the absence of a negotiated price, was sold to the ASLs at the ex-factory price of €15,506.93 per pack, a price that was still in place when the proceedings began. From March 2020, the date of entry into force of the negotiation agreement with AIFA dated 19 December 2019, the product was sold at the ex-factory negotiated price of *[€5,000-€7,000]*, net of regulatory discounts, and the difference between the price paid and the negotiated price, as stated above, was reimbursed by the company to the ASLs after the agreement came into force. The following sections assume, favourably to the Party, that the ex-factory price of *[€5,000-€7,000]* was applied to all sales in Italy from the beginning of 2020 and that *[€6-€7]* million were reimbursed by the company to the Italian National Health Service, mostly (*[€6-€7]* million) in 2020, with the remainder (*[€300,000-€400,000]*) fully paid in 2021[396].

237. Using the actual and forecast data of the sales of *Xenbilox*® and *CDCA Leadiant*® provided by the Party for the years 2014-2023[397], and assuming,

[396] More specifically, it is assumed: *i)* that the agreement was implemented from 1 January 2020 instead of the day after its publication in the Official Gazette (3 March 2020), applying the negotiated price to all sales in 2020; *ii)* that the *[€6-€7]* million that had already been reimbursed to the Italian National Health Service on 7 May 2021 (see doc. 122) had been fully paid during the year of entry into force of the agreement (2020) and that the remaining *[€300,000-€400,000]* were fully paid during 2021.

[397] See doc. 110.1.

again favourably to the Party, that the sales of *CDCA Leadiant*® for the years between 2024 and 2027[398] will not increase compared to 2023's sales, the revenues from sales in Italy of *Xenbilox*® and *CDCA Leadiant*® were calculated and are shown in Table 1.

Table 1 – Revenues from the CDCA Project in Italy (in euros)

Year	Xenbilox® Quantity (Q^X)	Xenbilox® Price (P^X)	CDCA Leadiant® Quantity (Q^{CDCA})	CDCA Leadiant® Price (P^{CDCA})	CDCA Italy project revenues * (R^P Italy=Q^X*P^X + $Q^{CDCA}*P^{CDCA}$)
2016	*[100-200]*	*2,900*			*[300,000-400,000]*
2017	*[50-100]*	*2,900*	*[100-200]*	*15,506.93*	*[2-3m]*
2018			*[300-400]*	*15,506.93*	*[5-6m]*
2019			*[300-400]*	*15,506.93*	*[5-6m]*
2020			*[300-400]*	*[5,000-7,000]*	*[2-3m]*
2021			*[300-400]*	*[5,000-7,000]*	*[2-3m]*
2022			*[400-500]*	*[5,000-7,000]*	*[2-3m]*
2023			*[400-500]*	*[5,000-7,000]*	*[2-3m]*
2024			*[400-500]*	*[5,000-7,000]*	*[2-3m]*
2025			*[400-500]*	*[5,000-7,000]*	*[2-3m]*
2026			*[400-500]*	*[5,000-7,000]*	*[2-3m]*
2027			*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*

* Before refunds to the NHS.

238. With regard to project costs as made available by Leadiant in aggregated form at European level[399], it should be noted that they are composed of the direct costs of production and distribution of *Xenbilox*® for the years 2014-2017, as well as the (final and forecast) direct and shared costs incurred for the registration, marketing and maintenance of *CDCA Leadiant*® from 2014 to 2027[400]. Net of intercompany items (including inter-company royalties[401]) and financial charges, they are shown in Table 2 .

239. With regard to these costs, it should be noted that, for the entire 2014-2027 period, only *[40-50%]* of them are costs directly attributable to the product, while the remaining *[50-60%]* is the result of the allocation made by

[398] For the year 2027, only one third of the annual sales was considered, given that market exclusivity ends in April.

[399] The Party reported that its accounting system is not structured in such a way as to be able to differentiate costs by individual country or only for countries belonging to the EEA. The costs provided therefore refer to all the countries (except the USA) where *CDCA Leadiant*® is marketed, although almost all activities and related costs have been incurred for EEA countries. See docs. 105 and 110.3.

[400] Also with regard to costs, given the fact that market exclusivity expires in April, a value equal to one third of annual costs was considered for 2027.

[401] It is believed that the intercompany royalties paid in 2016 by Leadiant UK to Leadiant US under a license agreement for the marketing of *Xenbilox*® outside the United States should not be considered in this analysis, similar to the other intragroup items already excluded by the Party in the cost calculation. These are amounts paid by one group company to another group company that do not constitute significant costs for the purposes of this analysis and have therefore been excluded.

the Party to *CDCA Leadiant*® of the shared costs incurred by the company for most of the products in its portfolio. In addition, of the *[40-50%]* of direct costs, about *[10-20%]* relates to the costs of production and distribution of the product and *[30-40%]* to regulatory, market access[402], marketing, legal and (less than 1%) research and development costs[403] (including the costs incurred for the improvement of the quality of the API recorded by Leadiant itself under a different cost category).

240. With regard to the legal costs included in the direct costs for *CDCA Leadiant*®, they also include significant costs incurred by the company in the years 2019 and 2020 for consulting as part of antitrust proceedings lodged by several national competition authorities in Europe, pursuant to Article 102(a) of the TFEU in relation to the company's pricing policy for the marketing of the orphan drug. Costs of this type, albeit to a lesser extent, are also expected for each year from 2021 to 2027. In principle, these costs should not be considered in the context of examining the price abuse at issue here, as they were incurred because of the conduct at issue. However, these costs were taken into account in the analysis conducted here, conservatively and in favour of the Party.

241. Furthermore, with reference to the criterion of shared cost allocation for *CDCA Leadiant*® used by the company, i.e., the estimate of the working time spent by its employees on the various products in its portfolio (also on the basis of an ex-post estimate made by the Party), leading to the allocation of as much as *[30-40%]* of the total shared costs incurred by the company over the period 2014-2027 to the orphan drug (and more than 60% for the period of 2016-2020), it should be observed how this criterion can also be flawed by the fact that the time spent on this product was so high precisely because it required a significant amount of work for regulatory, medical and market access activities aimed at supporting the demand for a potentially excessive price. With the criterion used by the Party, the indirect costs allocated to *CDCA Leadiant*® constitute more than 50% of the total costs of the product that the Party declared for the 2014-2027 period. However, also in this case, using an extremely concessive approach, no corrections have been made to the shared cost allocation criterion identified by the Party.

242. The project costs for Italy were obtained on the basis of the share of

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[402] Among these, the costs attributable to scientific information (disease awareness) total approximately *[€100,000-€200,000]*. See doc. 110.3.

[403] Of these, approximately *[€100,000-€200,000]* are attributable to the development of the 'easy to swallow formulation' - see doc. 110.3.

sales in Italy compared to total sales[404] (for the years 2014-2016, adopting an approach favourable to the Party, for the sole purpose of attributing the costs of the CDCA Project to Italy, the average share of sales volumes in Italy for the years 2017-2027 equal to *[10-15%]* was used, with sales volumes of *Xenbilox*® in Italy equal to zero for the years 2014-2015 and low for the year 2016[405]).

Table 2 – Costs of the CDCA Project for Italy (in euros)

Year	Costs Xenbilox® (C^X)	CDCA Leadiant® Costs (C^{CDCA})	CDCA Project costs ($C^P=C^X+C^{CDCA}$)	Italy volumes out of total volumes (%)	CDCA Italy project costs (C^P Italy = C^P*% volumes Italy)
2014	*[200,000-300,000]*	*[1-2m]*	*[2-3m]*	*[10-15]*	*[200,000-300,000]*
2015	*[300,000-400,000]*	*[6-7m]*	*[7-8m]*	*[10-15]*	*[800,000-900,000]*
2016	*[50,000-100,000]*	*[7-8m]*	*[7-8m]*	*[10-15]*	*[900,000-1m]*
2017	*[1-50,000]*	*[7-8m]*	*[7-8m]*	*[10-15]*	*[900,000-1m]*
2018		*[7-8m]*	*[7-8m]*	*[10-15]*	*[900,000-1m]*
2019		*[10-20m]*	*[10-20m]*	*[10-15]*	*[1-2m]*
2020		*[10-20m]*	*[10-20m]*	*[5-10]*	*[1-2m]*
2021		*[9-10m]*	*[9-10m]*	*[10-15]*	*[1-2m]*
2022		*[7-8m]*	*[7-8m]*	*[10-15]*	*[900,000-1m]*
2023		*[6-7m]*	*[6-7m]*	*[10-15]*	*[800,000-900,000]*
2024		*[6-7m]*	*[6-7m]*	*[10-15]*	*[800,000-900,000]*
2025		*[6-7m]*	*[6-7m]*	*[10-15]*	*[800,000-900,000]*
2026		*[6-7m]*	*[6-7m]*	*[10-15]*	*[800,000-900,000]*
2027		*[1-2m]*	*[1-2m]*	*[10-15]*	*[200,000 - 300,000]*

243. To calculate the IRR of the CDCA Project, based on the costs and revenues represented above, it is necessary to determine the cash flows (i.e., the difference between monetary income and expenses that have occurred over a period) actually achieved for the period 2014-2020 and the expected cash flows for the period 2021-2027, i.e., until the end of the exclusive ten-year market period.

244. To this end, in Table 3, the annual profits for Italy relating to the CDCA Project were calculated as the difference between the revenues and

[404] From 2021, sales of *CDCA Leadiant*® in the Netherlands were considered zero, in consideration of the regulatory change that since 2019 has allowed the setting up of galenic production, even with the availability of an orphan drug. For details of the calculations made, see the Economic Appendix.

[405] This cost allocation criterion is favourable to the Party because it enables the taking into account of a part of the costs incurred for *Xenbilox*® and for *CDCA Leadiant*® even when there are no (years 2014-2015) or few (year 2016) sales in Italy.

costs of the project; the reimbursements to the Italian National Health Service made by the Party in execution of the agreement with AIFA and relating to the difference between the price paid and the negotiated price, were subtracted from the profit for the years 2020 and 2021. The average tax rate that Sigma Tau/Leadiant paid during the period 2014-2019 was also applied to the profits thus calculated, as shown in the financial statements filed by Leadiant Biosciences Ltd. and by the companies of the Sigma Tau group of whom Leadiant Biosciences Ltd. is a successor[406]. In particular, it equals 21%[407]. It should be noted that the rate used here is the highest (and therefore more favourable to the Party) both compared to the one used by Sigma Tau in the ex-ante analysis described above (equal to 20%)[408] and the average tax rate recorded in Europe in the pharmaceutical sector during the same period (equal to 19%)[409]. The change in net working capital (NWC) compared to the previous period was also deducted for each year[410]. The change in the NWC was calculated using the methods adopted by Sigma Tau in its *ex-ante* evaluation model[411].

Table 3 – Cash flows for the CDCA Leadiant® project for Italy (in euros)

Year	CDCA Italy project profit (U^P Italy=R^P Italy – C^P Italy)	Profit from CDCA Italy project, net of taxes	NWC change	CDCA Italy project cash flow
2014	*-[200,000-300,000]*	*-[200,000-300,000]*	*0*	*-[200,000-300,000]*
2015	*-[800,000-900,000]*	*-[800,000-900,000]*	*-[1-50,000]*	*-[800,000-900,000]*
2016	*-[500,000-600,000]*	*-[500,000-600,000]*	*[1-50,000]*	*-[500,000-600,000]*
2017	*[1-2m]*	*[1-2m]*	*[300,000-400,000]*	*[1-2m]*
2018	*[4-5m]*	*[3-4m]*	*[500,000-600,000]*	*[3-4m]*
2019	*[4-5m]*	*[3-4m]*	*[1-50,000]*	*[3-4m]*
2020	*-[5-6m]**	*-[5-6m]*	*-[1-2m]*	*-[4-5m]*

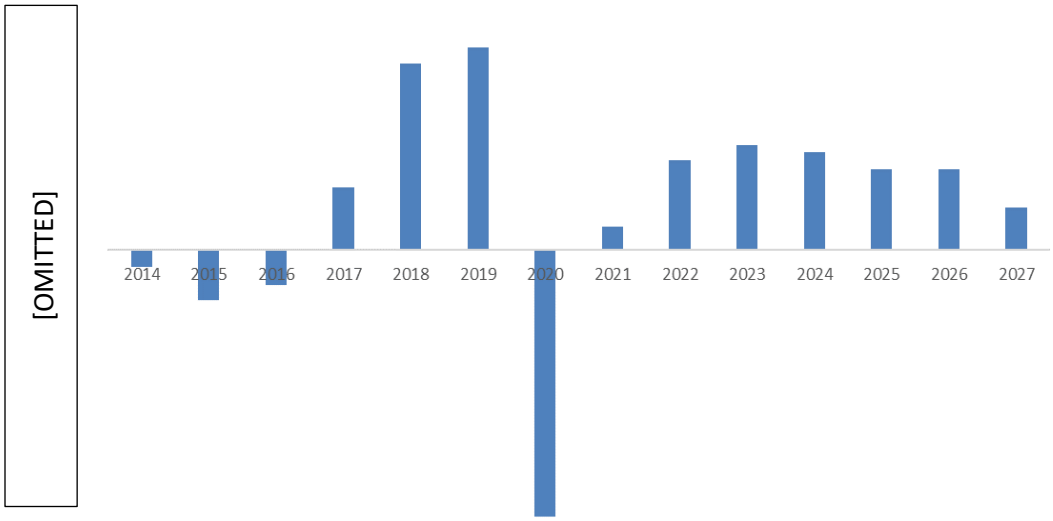
[406] See docs. 129 and 131 and their annexes.
[407] In calculating the tax effect, a mechanism for carrying forward tax losses was assumed, i.e., that any tax losses incurred in one year can be carried forward to a decrease in income in subsequent years. For details of the calculations made, see the Economic Appendix.
[408] See doc. 95.6.
[409] *Dataset Damodaran online, Effective tax rate by industry – Europe* – average years 2014-2019 of the data "*Average across only money-making companies*" relating to the "Drugs (Pharmaceutical)" sector (http://people.stern.nyu.edu/adamodar/New_Home_Page/dataarchived.html).
[410] A company's net working capital (NWC) is the difference between its short-term assets (trade receivables, inventory, other short-term assets) and its short-term liabilities (trade payables, other short-term liabilities). A reduction in NWC generates a positive cash flow, while an increase in NWC generates a negative cash flow. Given the extremely small value, depreciation was not taken into account, although, in principle, it should also have been added to the profit to obtain the cash flow. Since it would have increased the value of the cash flows, albeit marginally, this choice is still favourable to the Party. Given the extremely small value, depreciation was not taken into account, although, in principle, it should also have been added to the profit to obtain the cash flow. Since it would have increased the value of the cash flows, albeit marginally, this choice is still favourable to the Party
[411] See doc. 95.6. For details of the calculations made, see the Economic Appendix.

Year	CDCA Italy project profit (U^P Italy=R^P Italy – C^P Italy)	Profit from CDCA Italy project, net of taxes	NWC change	CDCA Italy project cash flow
2021	*[900,000-1m]***	*[900,000-1m]*	*[500,000-600,000]*	*[300,000-400,000]*
2022	*[1-2m]*	*[1-2m]*	*[50,000-100,000]*	*[1-2m]*
2023	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2024	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2025	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2026	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2027	*[600,000-700,000]*	*[400,000-500,000]*	*-[200,000-300,000]*	*[700,000-800,000]*

*Based on the assumed reimbursement to the Italian National Health Service of the difference between the negotiated price and the price paid, in 2020, *[€6-€7]* million were returned to hospitals.
** It is assumed that the remaining *[€300,000-€400,000]* will be fully reimbursed in 2021.

245. Figure 3 shows the trend of project cash flows for Italy for the period 2014-2027. The negative flows for the years 2014-2016 reflect the costs associated with the activities in preparation for obtaining the orphan designation for CDCA and the registration of *CDCA Leadiant*® as an orphan drug for the treatment of CTX and were only partially offset by the sales of *Xenbilox*® at the increased price in Italy. Since 2017 the project has begun to generate largely positive cash flows, with the exception of 2020, when almost the entire agreed upon sum was reimbursed, as per the AIFA agreement.

Figure 3 - Cash flows for the CDCA Leadiant® project for Italy (thousands of euros)



246. The calculated internal rate of return for the period 2014-2027, i.e., the entire time frame of the project, gives a value of *[50-60%]*. This value must be compared to the cost of capital (the WACC) to determine the profitability of the project.

247. In this case, it is considered appropriate to use the WACC value used

by Sigma Tau in its *ex-ante* analysis. Once again, in the favour of the Party, the highest value, meaning the best-case scenario value, will be considered, therefore incorporating a higher risk component of 15%. This value is considered to be significantly concessive, given that the average WACC observed for companies in the pharmaceutical sector in Western Europe in 2014 amounts to 10%[412].

248. Therefore, based on the above analysis, the sale price of *CDCA Leadiant*® in Italy generates a rate of return on the project equal to *[three/four]* times the cost of capital.

249. Again favourably to the Party, the analysis of the IRR was also carried out taking as a reference only the incremental cash flows, i.e., those attributable to the project and which, in the absence thereof, would not have occurred. In this case, since the project under examination consists of the launch of a new product (*CDCA Leadiant*®) replacing an existing product (*Xenbilox*®), only the incremental revenues and costs were taken into account in the calculation of the relevant cash flows, i.e., the difference between the revenues (costs) attributable to the new product and the revenues (costs) relating to the replaced product that would have been generated (incurred) without the project.

250. In addition to the aforementioned documents, which show that the increase in the ex-factory price of *Xenbilox*® from €660 to €2,900 in mid-2014 was an integral part of the CDCA Project (see paragraphs 109 and 113 above), other documents show that, if the registration of the orphan drug had not been successful, Sigma Tau would have continued to sell *Xenbilox*® administered off-label for the treatment of CTX[413] and that, in the absence of the project, no price increases were expected for *Xenbilox*®[414] during the subsequent years. In particular, a document dated August 2014 states that, without the project in question, *Xenbilox*®'s revenues would have remained in line with those of previous years ("*Base case 2015-19 forecast is conservative and includes 2 Mln€ flat sales in EU only, consistent with historical trend*")[415]. In the same document, the incremental revenues deriving from the CDCA Project are indicated and quantified separately ("*What-if: Xenbilox price increase and global registration… Based on a preliminary*

[412] See Dataset Damodaran online, *Cost of Capital by industry – Europe* – year 2014, "*Cost of Capital*" data relating to the "*Drugs (Pharmaceutical)*" sector, available at *http://www.stern.nyu.edu/~adamodar/pc/archives/waccEurope14.xls*.
[413] See, *inter alia*, doc. 22.7.129.
[414] Doc. 95.5, p. 41.
[415] Doc. 95.5.

analysis driven by assumptions on price increase, prevalence and diagnosis rate, Xenbilox shows a great potential. A global registration (EMA+FDA) with a significant price increase (€110k annual treatment per patient in EU and about €140k in US) may lead up to 29 Mln sales increase in 2019 (best case +80Mln) and 31 Mln in EBITDA (best case +69 Mln)"). Assuming a price per pack of approximately €10,000, Leadiant therefore believed it could increase its turnover by €29 million per year, indicated in the document as "*Xenbilox Incremental sales*"[416], compared to the no-project scenario, where revenues are quantified at €2 million, in line with the revenues from previous years when *Xenbilox*® was sold at a price of €660 per pack.

251. For this reason, the incremental cash flows attributable to the CDCA Project to be considered are the differential ones, compared to the no-project scenario, i.e., the continuation of the off-label sale of *Xenbilox*® at the price of €660 per pack in force before the project[417]. Consequently, the incremental revenues were calculated by subtracting those that would still have been generated by selling *Xenbilox*® at €660 from the revenues generated or expected by the Party.

252. The Party has provided an estimate for the incremental costs, i.e., those that would not have been incurred in the absence of the CDCA Project (but by continuing to sell *Xenbilox*® administered off label), which does not appear realistic for the following reasons. Firstly, in the estimate of the incremental costs provided[418], the Party considered all the direct costs of *CDCA Leadiant*® as incremental. This is far-fetched, given that the *CDCA Leadiant*® production process does not differ significantly from the *Xenbilox*® production process, and therefore a large part of these costs would still have been incurred even without the project.

253. Secondly, it should be noted that the Party has provided the value of the incremental shared costs not by separating from the shared costs attributed to *CDCA Leadiant*® the costs that would have been incurred in any case without the project, as would be expected; on the contrary, the company made this estimate based on the total common costs, i.e. those incurred by the company for the production and marketing of all the products in its portfolio. This method leads to the paradox that for some years – and especially the

[416] The incremental sales of *Xenbilox*® are even quantified at 80 million in the best case scenario, which assumes a significant increase in the rate of diagnosis of the disease and, therefore, in the quantities sold.
[417] Again with a view to favouring the Party, no account was taken of the fact that, in the absence of the CDCA Project and the related activities aimed at encouraging the diagnosis of the disease, off-label sales of *Xenbilox*® from 2017 could have been lower than those achieved or expected for *CDCA Leadiant*®.
[418] See docs. 110, 110.5 and 127.

initial and final ones of the project – the incremental costs of *CDCA Leadiant*® would be higher than the total costs that Leadiant itself attributes to the same product, while, throughout the project period, the incremental costs and the total costs of *CDCA Leadiant*® would essentially coincide. In other words, according to the Party, all the shared costs attributed to *CDCA Leadiant*®, which, as already noted (see paragraph 239 above), represent more than half of the total costs of the product over the project period, would be incremental.

254. In addition, according to the Party, for the first 8 years of the project (2014-2021), more than 50% of the total shared costs, i.e., those incurred for all products in its portfolio, would be incremental to *CDCA Leadiant*®. This is because if CDCA had not obtained orphan drug designation, the company, while continuing to market the other products in its portfolio (including off-label *Xenbilox*®) would have significantly reduced its corporate structure in Europe, *[omitted]*.

255. On this point, it should be noted that the scenario of drastically reducing the European corporate structure of Leadiant in the event of a negative outcome of the CDCA Project does not appear to be supported by any concrete proof. The evidence submitted shows, on the contrary, how the company expected to continue with the off-label sale of *Xenbilox*® in this case, without being able to expand its sales, but never assuming a drastic restructuring of its European premises[419].

256. It should also be noted that the Party has provided an estimate of the multi-year incremental costs (*[50-60%]* of the total shared costs for the years 2014-2021 and *[20-30%]* for the years 2022-2027), stating that "*the per-year estimate of the incremental shared costs... would not provide added informative value*"[420] and that the most granular allocation of the per-year shared costs was carried out (in defining the data for *CDCA Leadiant*® total costs) using the allocation key of the time worked.

257. In view of the above, it is considered more prudent to consider the total costs for *CDCA Leadiant*® provided by the Party in further analysis of the incremental cash flows. Note that this choice is extremely favourable to the Party, since incremental costs are, by definition, a subset of total costs.

258. Table 4 shows the incremental profits for the CDCA Project obtained using the incremental revenues (i.e., net of the revenues deriving from the sales of *Xenbilox*® that would have occurred anyway) minus the incremental costs (which, in this case, with an extremely favourable approach to the Party,

[419] See doc. 22.7.129.
[420] See doc. 127.

are considered to match total costs for the reasons illustrated above). The profit net of taxes and of the change in the Net Working Capital, in order to determine the incremental cash flows, were calculated in accordance with what had already been done for the calculation of the total cash flows[421].

Table 4 – Incremental cash flows for the CDCA Leadiant® project for Italy (in euros)

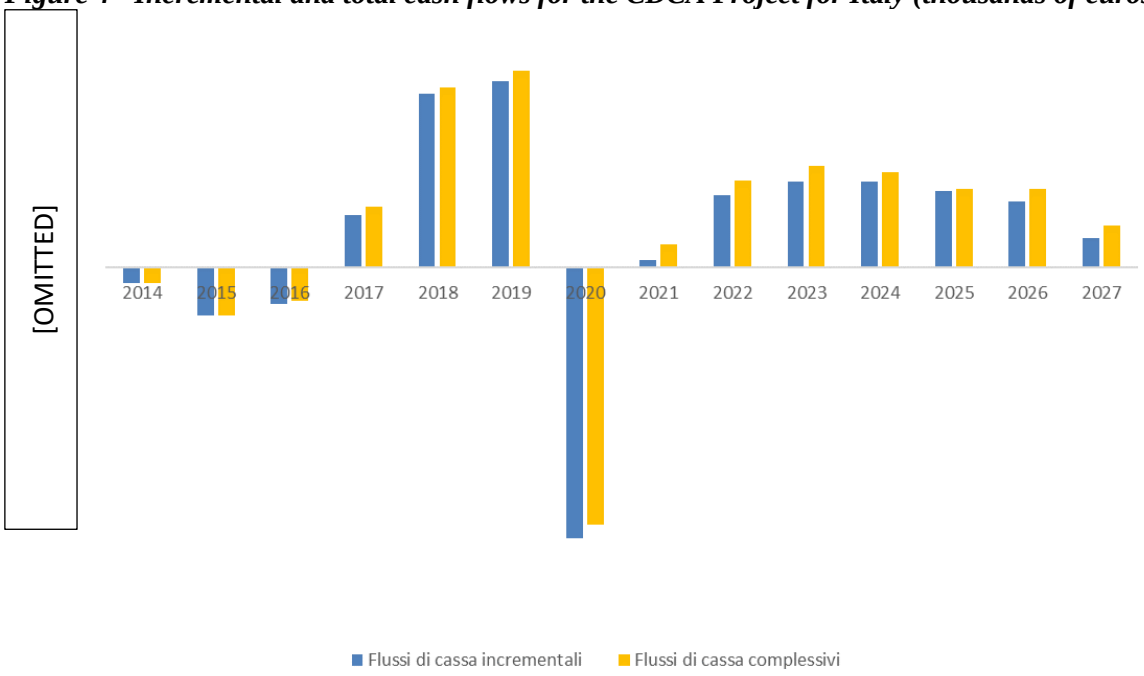
Year	CDCA Italy project incremental profit (Incremental R^P Italy – Incremental C^P Italy)	Incremental profit for CDCA Italy project, net of taxes	NWC change	CDCA Italy project incremental cash flow
2014	*-[200,000-300,000]*	*-[200,000-300,000]*	*0*	*-[200,000-300,000]*
2015	*-[800,000-900,000]*	*-[800,000-900,000]*	*-[1-50,000]*	*-[800,000-900,000]*
2016	*-[600,000-700,000]*	*-[600,000-700,000]*	*[1-50,000]*	*-[600,000-700,000]*
2017	*[1-2m]*	*[1-2m]*	*[300,000-400,000]*	*[800,000-900,000]*
2018	*[4-5m]*	*[3-4m]*	*[500,000-600,000]*	*[2-3m]*
2019	*[4-5m]*	*[3-4m]*	*[1-50,000]*	*[3-4m]*
2020	*-[5-6m]**	*-[5-6m]*	*-[1-2m]*	*-[4-5m]*
2021	*[600,000-700,000]***	*[600,000-700,000]*	*[500,000-600,000]*	*[100,000-200,000]*
2022	*[1-2m]*	*[1-2m]*	*[50,000-100,000]*	*[1-2m]*
2023	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2024	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2025	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2026	*[1-2m]*	*[1-2m]*	*[1-50,000]*	*[1-2m]*
2027	*[300,000-400,000]*	*[200,000-300,000]*	*-[200,000-300,000]*	*[400,000-500,000]*

*Based on the assumed reimbursement to the Italian National Health Service of the difference between the negotiated price and the price paid, in 2020, *[€6-€7]* million were returned to hospitals.
** It is assumed that the remaining *[€300,000-€400,000]* will be fully reimbursed in 2021.

259. Figure 4 shows the incremental cash flows for the CDCA Project, obtained as described above and compared to total cash flows (shown above in Figure 3). Incremental flows are more contained than non-incremental flows, as the sales of *Xenbilox*® (that would have taken place even without the project) have not been deducted from the latter. The use of incremental cash flows is, therefore, favourable to the Party.

[421] For the detailed calculation, see the Economic Appendix.

Figure 4 - Incremental and total cash flows for the CDCA Project for Italy (thousands of euros)



Flussi di cassa incrementali	Incremental cash flows
Flussi di cassa complessivi	Total cash flows

260. The result of the calculation of the internal rate of return on incremental cash flows for the period 2014-2027, corresponding to the entire project period, gives a value of *[40-50%]*. Also in this case, still using a cost of capital of 15% in benefit to the Party, the prices applied by Leadiant generate a project profitability three times that of the cost of capital.

III.6.3 The cost plus analysis

261. The second methodology used to analyse the price's excessiveness is to examine the disproportion between the prices charged and the costs incurred by Leadiant for the *CDCA Leadiant®*, according to the following relationship: PQ – (C + ROS) = EXC.

262. The value in brackets represents the cost plus (C^+) and is obtained from the sum of the costs (indicated by C and composed of both the costs directly attributable to the product as well as the share of indirect costs attributed to it) and a measurement of the reasonable profitability of the company (Return on Sales – ROS).

263. The difference between revenues (PQ) and cost plus represents the excess (EXC), whose potential disproportion must be assessed. The measure

of the excess thus obtained will be compared to the cost plus in order to obtain a percentage value (EXC%), which does not change with the sales volumes and is comparable with the results achieved in other cases of unjustifiably excessive prices.

264. In this case, the excess was calculated starting from June 2017, the year in which the marketing of *CDCA Leadiant*® in Italy began, and considered until 2020, the last full year for which sales of *CDCA Leadiant*® actually occurred, as well as until the end of market exclusivity, i.e. April 2027, based on the data relating to costs and revenues provided by the Party.

265. For the purpose of calculating revenues, the quantities sold in Italy from June 2017 (effective until 2020 and estimated from 2021 onwards) were multiplied by the unit price of *[€5,000-€7,000]* for each year. This is because the price negotiated in the agreement with AIFA, net of regulatory discounts, was applied retroactively to Cnn-class sales made to hospitals through a mechanism that provides for the refund of the difference between the paid and negotiated price. In the following analysis, since the monetary manifestation of revenues is not relevant, while the related economic competence is, it will be considered as if the negotiated price was applied *ab origine*[422].

266. As regards costs, both direct and indirect, the data already considered in the IRR methodology were taken into account (see Table 2).

267. With regard to the measure of company profitability, which ensures a reasonable return on its activity, in continuity with the previous excessive prices cases in the pharmaceutical sector[423], it was decided to use a balance sheet index that measures the profitability of sales, the ROS (based on the relationship between operating result and sales). The choice of this indicator seems appropriate since the CDCA Project consists essentially of the repurposing of *Xenbilox*®, a product already present in the company's portfolio, and is not characterised by high levels of investment or risk. In order to identify an appropriate value of ROS that could represent a reasonable profitability margin for the business, the average ROS for companies in the pharmaceutical sector in Western Europe in the period 2014-2019 was

[422] From the information provided by the company, the differential between what was paid by the ASLs in the years 2017-2019 and what was due if it had been applied *ab origine*, the negotiated price is higher than the *[€6-€7]* million agreed upon in the agreement with AIFA. It follows that actual revenue was higher than that which would have been achieved by applying the negotiated price to all sales. However, to the benefit of the Party, the negotiated price will be applied to all sales of *CDCA Leadiant*® to calculate revenues.

[423] See AGCM Measure no. 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*.

considered, amounting to 20.54%[424] (hereinafter rounded up to 21%). This profitability benchmark is significantly higher than the one used in the Italian Competition Authority's previous cases[425]. Given that the investigation is aimed at verifying the possible application of excessive prices, it is considered inappropriate to calculate the ROS from the turnover achieved by applying these prices. Consequently, the reasonable return for the company will be calculated by applying an appropriate mark up on costs (cost uplift) based on the ROS identified above[426].

Table 5 – Calculation of cost plus and excess in percentages (in euros)

Year	**CDCA Leadiant® Quantity (Q^{CDCA})**	**CDCA Leadiant® Price (P^{CDCA})**	**CDCA Leadiant® Revenues ($R^{CDCA}= P^{CDCA}*Q^{CDCA}$)**	**CDCA Leadiant® Costs (C^{CDCA})**	**C^{+} ($C/^{CDCA}$ (1-ROS))**	**EXC % (($R^{CDCA} – C^{+})/C^{+}$)**
Jun-Dec 2017	*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*	*[500,000-600,000]**	*[600,000-700,000]*	*[20-30%]*
2018	*[300-400]*	*[5,000-7,000]*	*[2-3m]*	*[900,000-1m]*	*[1-2m]*	*[80-90%]*
2019	*[300-400]*	*[5,000-7,000]*	*[2-3m]*	*[1-2m]*	*[1-2m]*	*[60-70%]*
2020	*[300-400]*	*[5,000-7,000]*	*[2-3m]*	*[1-2m]*	*[1-2m]*	*[60-70%]*
2021	*[300-400]*	*[5,000-7,000]*	*[2-3m]*	*[1-2m]*	*[1-2m]*	*[50-60%]*
2022	*[400-500]*	*[5,000-7,000]*	*[2-3m]*	*[900,000-1m]*	*[1-2m]*	*[100-150%]*
2023	*[400-500]*	*[5,000-7,000]*	*[2-3m]*	*[800,000-900,000]*	*[1-2m]*	*[100-150%]*
2024	*[400-500]*	*[5,000-7,000]*	*[2-3m]*	*[800,000-900,000]*	*[1-2m]*	*[100-150%]*
2025	*[400-500]*	*[5,000-7,000]*	*[2-3m]*	*[800,000-900,000]*	*[1-2m]*	*[100-150%]*
2026	*[400-500]*	*[5,000-7,000]*	*[2-3m]*	*[800,000-900,000]*	*[1-2m]*	*[100-150%]*
2027	*[100-200]*	*[5,000-7,000]*	*[800,000-900,000]*	*[200,000-300,000]*	*[300,000-400,000]*	*[150-200%]*
Jun 2017-Dec 2020	*[1,000-2,000]*	*[5,000-7,000]*	*[7-8m]*	*[3-4m]*	*[4-5m]*	***[60-70%]***
Jun 2017-Apr 2027	*[3,000-4,000]*	*[5,000-7,000]*	*[20-30m]*	*[10-20m]*	*[10-20m]*	***[90-100%]***

* Considering that sales of *CDCA Leadiant*® in Italy started in June 2017, the costs incurred in 2017 by the company were reproportioned to an equivalent period of the year.

[424] See Dataset Damodaran online, *Operating and Net Margins by Industry – Europe* – average for 2014-2019 of the "*Pre-tax Unadjusted Operating Margin*" data relating to the "*Drugs (Pharmaceutical)*" sector, available at *http://people.stern.nyu.edu/adamodar/New_Home_Page/dataarchived.html*.
[425] See *A480 – Price Increase of Aspen's Drugs*, paragraphs 174, 182, 319, in which a ROS of 13% was used.
[426] See Decision *CMA Pfizer/Flynn*, point III.C.5.56. The coefficient to be applied to the costs to obtain the cost plus is 1/(1-ROS).

268. As of June 2017, as shown in Table 5, the Party reported excess cost revenues (including a reasonable margin of return); this excess, as a percentage of the *cost plus*, in the period 2017-2020 ranges between *[20-30%]* and *[80-90%]*, with an excess for the entire period of *[60-70%]*. Considering the entire period of market exclusivity, i.e., until April 2027, the excess percentage amounts to *[90-100%]*.

IV. THE ARGUMENTS OF THE PARTIES

IV.1 Procedural exceptions

269. As a preliminary matter, Leadiant alleged that the principle of 'equality of arms' between the prosecution and the defence was breached as a result of the postponement of the date of the hearing after it had already filed its submissions. The company believes that the fairness of the adversarial proceedings between the Party and the Investigating Offices before the Board during the final hearing was altered by the fact that, due to the postponement of the final hearing, the Investigating Offices were able to benefit from more than three times (17 days) the period of time provided for in the aforementioned Presidential Decree (5 days) for the analysis of the reply to the Statement of Objections. Therefore, in view of the postponement of the final hearing, the Italian Competition Authority should have identified appropriate ways to ensure equality of arms in the case in question.

IV.2 The existence of a dominant position to the benefit of Leadiant

270. With regard to the attribution to Leadiant of a dominant position on the national market of CDCA-based drugs for the treatment of CTX – the definition of which has not been the subject of any counter-arguments by the Party – since January 2016, the company considers that this position of pre-eminence did not exist before the obtainment of the marketing authorisation for the orphan drug. Since *Xenbilox*®, which was authorised in Germany for the treatment of gallstones but without an MA in Italy, was imported into the domestic market by independent wholesalers (totally independently, in very limited quantities and only for a few months between 2016 and 2017[427]),

[427] See doc. 84.

Leadiant was not directly active in the national market. Therefore, it would not be possible to assign it a real market position in Italy[428].

271. In any case, according to the Party the market position of Leadiant could be challenged by several parties able to place CDCA-based products, of both a galenic and industrial nature, on the market.

272. As regards the former, Leadiant believes that PCA neither was, nor is, the only credible operator in the CDCA market as a pharmaceutical-grade active substance capable of providing CDCA to hospital pharmacies wishing to produce the drug in galenic form. This was allegedly demonstrated by: *i)* an historical excerpt from the *Thomson Reuters Newport Global database*, highlighting the presence on the market of (at least) 15 alternative CDCA suppliers as early as 2015; *ii)* the supply offer of CDCA to PCA by a wholesaler of pharmaceutical-grade active substances, which in all likelihood was supplied in turn by a Chinese manufacturer, in 2017; *iii)* the offer of CDCA presented by Pierre Fabre directly to Leadiant in 2019; *iv)* the confirmed existence from the beginning of 2020 of a Chinese source of CDCA that was operational in Europe through the sale of the active substance to the Amsterdam hospital, which set up galenic production in February 2020 capable of adhering to the specifications of the European Pharmacopoeia; and, finally, *v)* the existence of at least two operators with MAs for CDCA-based pharmaceutical products (*Chenodal*, marketed in the United States by Retrophin, and *Chino*, marketed in Japan by Fujimoto Pharmaceutical Corporation), which purchased the active substance from suppliers other than PCA[429]. It should also be noted, according to Leadiant, that the production of CDCA is not a complex activity and that there are also other parties able to enter the market at any time, especially companies that, as emerged during the course of the proceedings, produce ursodeoxycholic acid, allowing them to also produce CDCA as an intermediate product of the former.

273. Based on these factual elements, Leadiant believes that, after the stocks of CDCA from the University Hospital of Siena ran out, Italian hospitals could have easily obtained stocks from these sources alternative to PCA and that, therefore, the lack of access to the active substance is not attributable to the exclusive supply contract of CDCA, also in view of the fact that since 2005 PCA had interrupted the supply of CDCA to the Pharmacy of the University Hospital of Siena[430], and that the sole purpose of this contract

[428] See docs. 185 and 187.
[429] See docs. 84, 126, 185 and 187.
[430] See docs. 185 and 187.

was to protect the investments made by both parties.

274. In relation to the competitive threats posed by other industrial CDCA-based drugs able to compete with Leadiant on the market before obtaining the authorisation for the orphan drug, the company generally observes that *Xenbilox*® did not enjoy any regulatory protection, since the dossier protection had expired, nor did it enjoy patent protection, since the drug was off patent, so that any other company could have entered the market with a CDCA-based drug. In addition, it identifies in particular two alleged potential competitors for CDCA: the aforementioned *Chenodal*, of which Retrophin was, and remains, the owner, and *Kolbam*®[431].

275. As for the market position held by the company after obtaining the orphan designation and the MA for the orphan drug, the company merely states that Leadiant's ability to exercise market power could in the future be limited by the competitive dynamics in other EU Member States that can influence the Italian market, as well as the very sustainability of Leadiant's presence on this market, given the extremely reduced patient base at the EU level.

276. Lastly, the company believes that the significant bargaining power held by AIFA, as shown by the fact that the agreement entered into by the company with the Agency in December 2019 led to the application of a negotiated price that is the lowest in Europe, precludes the attribution of a dominant position to Leadiant on the relevant market.

IV.3 The rise in the price of **Xenbilox®**

277. The company considers that its behaviour, as shown by the findings of the investigation, is normal, to be expected and merely aimed at the development of the CDCA Project.

278. On a preliminary basis, the Party disputes the relevance of events dating back to 2007 for the purposes of verifying the infringement, which could only have started from 15 June 2017[432].

279. In any case, Leadiant affirms that all the documents that refer to an increase in the price of the product ("*step price increase*"), and more generally to the future sale price of the medicine, are nothing more than mere economic

[431] See docs. 185 and 187.

[432] In this regard, the Party cites the Regional Administrative Court of Lazio, judgment no. 8239/2021, which considered that a series of investigation documents could not be used as evidence as they fell outside the time frame of the alleged anti-competitive practice, or referred to facts prior to the period of performance of the alleged agreement.

assessments reflecting the drastic fall in sales resulting from a contraction in demand, in turn linked to the obsolescence of CDCA for the treatment of CTX, the instability of the market at that particular time and the profitability of the project, especially in the light of the achievement of the orphan designation.

IV.4 The artificial differentiation between **Xenbilox®** *and the orphan drug*

280. Firstly, Leadiant contests the Italian Competition Authority's competence to examine the events relating to the withdrawal of *Xenbilox*® from the German market and the establishment of Leadiant GmbH, since this would lead to assess facts that would not be covered by the subject-matter of the proceedings from a geographical perspective.
281. Furthermore, in particular, the withdrawal of *Xenbilox*® was allegedly not dictated by the intention to influence either the German regulator or those of other Member States, but was merely the result of the fact that the original therapeutic indication, the treatment of gallstones, no longer had a market. It would therefore have been financially unsustainable to keep both medicines on the market in the face of the small number of rare disease patients in Germany. In this sense, this should be understood as the document stating that the reasons for the withdrawal of the off-label drug are "strategic", to be interpreted as a synonym of "commercial".
282. Likewise, the establishment of Leadiant GmbH would not have had any anti-competitive purpose, since this would not have prevented health insurers from referring to the reimbursement price of *Xenbilox*®, but rather from benefiting from an automatic discount on the price of *CDCA Leadiant*® equal to the difference between the price of this drug and the reimbursement price of *Xenbilox*® in Germany, which would be irrelevant in this case.

IV.5 The orphan drug price negotiations with AIFA

283. Leadiant also denies having been obstructive towards AIFA. From this point of view, in fact, the case differs significantly from the previous Aspen case of the Italian Competition Authority. It is submitted that Leadiant did not, in fact, exert any pressure on the Agency during the negotiations, either through the reiteration of the request to transfer the drug to class C, nor did it threaten the withdrawal of the drug from the domestic market, nor finally instrumentalise the unavailability of the product within the national territory.

On the contrary, the company always adopted a cooperative attitude towards AIFA, so much so that the company declared to the Agency in April 2018 that the difference between the purchase price at that time and the price negotiated with AIFA would be returned to the health facilities. Secondly, the company never intended to cause and has never actually caused any harm to the Italian National Health Service or patients, both in light of the negligible size of the drug budget and given the absence of any evidence about cases of interruption of treatment attributable to Leadiant.

284. In addition, the company states that the duration of the price negotiations for the orphan drug, although articulated and complex, due to, *inter alia*, uncertainties about the impact of the disease, were not particularly long compared to the average. The average time between the EMA authorisation and the AIFA determination for eligibility for reimbursement in the 2017-2020 period would, in fact, be 24 months, with maximum values of 89 months. In the case of *CDCA Leadiant*®, approximately 32 months passed between the EMA authorisation (April 2017) and the resolution approving the price agreement (December 2019), 2 of which were used for the submission of the reimbursement dossier and 12 of which elapsed pending the convocation of the company by the AIFA's CPR (which took place in June 2018), so that the actual negotiation on the price (taking into account the periods of consensual suspension) took place over a total of 18 months. It would therefore be impossible to find Leadiant guilty of a delaying and obstructive conduct.

285. The company also denies that it was late in providing the cost data requested by the Agency during the negotiations. Quite to the contrary, it would have submitted in a timely manner, or when drafting the reimbursement dossier, the information required by CIPE Resolution no. 3/2001 and the attached dossier outline, which require an indication of the total amount of investments in research and development and productive investments made by the proposing company in Italy over the last three years. The request by AIFA to know the amount of the production costs of the orphan drug would thus be irrelevant because it does not meet the criterion adopted by the CIPE Resolution, which is totally and exclusively focused on the cost-effectiveness attributable to a drug, or on a value-based and non-cost-based approach.

286. AIFA also failed to comply with the provisions of the applicable regulatory framework insofar as it claimed to have brought the price of *CDCA Leadiant*® in line with that of *Xenbilox*®, whereas instead Article 48(5)(d) of Legislative Decree no. 269/2003 requires AIFA to take "*as terms of*

comparison the reference price for the relevant homogeneous therapeutic category and the comparative daily cost in the context of drugs with the same therapeutic indications". From this it would also follow that AIFA could not in any case use *Xenbilox*® as a comparator drug of reference for negotiating the price of *CDCA Leadiant*®, with comparison with drugs without an MA in Italy and authorised for different indications legally precluded. For this reason, the artificial differentiation between *Xenbilox*® and *CDCA Leadiant*®, the implementation of which is in any case denied by the company, would have had no effect on AIFA.

287. On this subject, Leadiant concludes by stating that the negotiation did not take place under unfavourable conditions for AIFA, so much so that it ended with a result much closer to the Agency's position than to the company's and that the negotiated price is the lowest among those applied in the other EU Member States, that the drug budget is absolutely negligible and that the Agency itself declared itself sufficiently satisfied with the outcome of the negotiations.

IV.6 The excessiveness of the price of CDCA Leadiant®

IV.6.1 The analysis of the IRR

288. According to the Party, the IRR analysis carried out during the course of the proceedings to demonstrate the excessive disproportion between the price of *CDCA Leadiant*® and the costs incurred is based on an inappropriate model that fails to take proper account of the risks faced by the company in the project in question and/or relies on incorrect assumptions that do not reflect the facts.

289. From the perspective of the risks which the company has faced, and will continue to face, Leadiant noted firstly that obtaining and maintaining the orphan designation was not certain, especially considering the fact that the European Commission had already authorised two other drugs indicated for the treatment of congenital errors in the synthesis of primary bile acids (including CTX), *Kolbam*® and *Orphacol*®[433].

290. Secondly, Leadiant recalled that the authorisation for the orphan drug was issued "under exceptional circumstances" and that the existence of the conditions under which the marketing authorisation was granted is examined

[433] See docs. 84 and 122.

annually. To this end, the company must collect data on the long-term safety and efficacy of the therapy in patients treated with *CDCA Leadiant*® through a register of CTX patients that serves to assemble such data and submit to the EMA, based on the said register, on the results and findings of a study (involving children, adolescents and adults)[434].

291. In addition, Leadiant mentioned the risks associated with negotiating the conditions for reimbursement. The determination of the market price depends on the success of the negotiations to be conducted on the basis of the individual national reimbursement regimes with bodies endowed with strong bargaining powers.

292. In addition, the risks associated with market coverage/quantity should be considered, as they are particularly marked for drugs used to treat extremely rare diseases such as CTX and further exacerbated by the fact that the market exclusivity deriving from the orphan designation, in addition to being shortened to six years, is likely to be overcome in the presence of 'similar' drugs considered safer, more effective or in any case clinically superior[435].

293. To better reflect the risk information, Leadiant believes that it would be more efficient to use a risk-adjusted NPV model. This approach, unlike the model used during the proceedings, where the risk component is incorporated into the WACC, uses multiple parameters to take account of the risk (probability of success and discount rate). These parameters are estimated not from the perspective of Leadiant but from that of an *ex-ante* investor, something that would guarantee an objective and non-subjective assessment of the risk. In the model proposed by the Party, the choice of the probabilities of success in the various steps is based on the research of the literature relating to the average probabilities of success of orphan drug development projects, tailored to the specifics of the case in question. The discount rate was instead estimated through a survey conducted in 2020 on over 400 evaluation experts in the pharmaceutical sector. Using this methodology, in the opinion of the Party, the price of *CDCA Leadiant*® would not be excessive; the Minimum Viable Price, that is the minimum price that the Party believes an investor would require to decide to invest in the project, would in fact total approximately *[€5,000-€7,000]* per pack.

294. With specific regard to the value of the WACC used in the investigation, Leadiant argues that it would not be appropriate, since it was derived from an internal Leadiant document, *[omitted]*, and would therefore

[434] See docs. 84 and 122.
[435] See doc. 84.

tend to underestimate this value. In addition, this would constitute a corporate WACC and would not be related to the specific CDCA Project, which would be characterised by a higher WACC value.

295. The Party also argues that the investigative analysis was based on some erroneous assumptions. In particular, Leadiant argues that in the scenario without a project, which was used in the IRR analysis procedure on incremental cash flows, even if the CDCA Project had not been undertaken, the fact that the price of *Xenbilox*® would still have increased would not have been considered. This is because the company would have had similar incentives to increase the price of *Xenbilox*® in both scenarios (i.e., whether or not the project was implemented).

296. Finally, the fact that the price of *CDCA Leadiant*® is destined to decrease progressively even during the exclusivity period, given that the supply conditions are subject to periodic renegotiation with the regulator, would not have been taken into account.

IV.6.2 The analysis of the cost plus method

297. Leadiant considers it insufficient to verify the unfair burden of the price of the orphan drug through the cost plus method, as was the case with the precedent set by the Italian Competition Authority[436], *Aspen*, and with that of the British Competition Authority, *Pfizer/Flynn*[437]. In fact, unlike in the case at hand, these cases concerned already existing products, the initial investments for which had been recovered and in relation to which no contribution had been made in the scientific field. This case, on the other hand, is first and foremost characterised by the above-mentioned significant regulatory and commercial risks at all stages of its development. After all, Leadiant notes, AIFA also decided not to apply a "value-based" approach to the drug instead of a "cost-based" approach[438] in determining the reimbursement price of *CDCA Leadiant*®[439].

298. In addition to the inadequacy linked to the nature of the product, Leadiant feels the cost plus method would not take into account the time value of money and, therefore, the dynamic evolution of a project for the development of a new drug such as *CDCA Leadiant*®.

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[436]See AGCM Measure no. 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*.
[437] See *Competition & Markets Authority* decision of 7 December 2016, *Unfair pricing in respect of the supply of phenytoin sodium capsules in the UK* (Case EC/9742-13).
[438] See doc. 72.
[439] See doc. 105.

299. Furthermore, the calculation of the cost plus from 2017 did not take account of the initial investment incurred by Leadiant in the years 2014-2016 to bring the product to the market.
300. Finally, the industry average ROS used as a benchmark to assess excessive pricing would not be appropriate, since it would not reflect the specific risk of the CDCA Project.

IV.7 The unfairness of the price of CDCA Leadiant®

301. According to the Party, the second phase of the United Brands test developed by the Court of Justice, aimed at determining price unfairness, in this case should have assessed the economic value of the drug (including the non-cost related factors, such as the benefits for patients and society) and the price of the same drug in other European countries or the price of comparable pharmaceutical products[440].
302. Indeed, Leadiant criticises the choice of considering only the first of the two criteria indicated in the *United Brands* text, which looks at inequality in the absolute sense. This criterion, in fact, according to the Party would only apply to those cases in which the unfairness of prices can be determined without the need for any comparison with similar or competing products. Such cases should only be identified in relation to prices for which consumers do not receive any product in return[441]. Leadiant's misconduct would not fall under these cases[442].
303. The correctly applied unfairness test should, on the contrary, have verified whether or not there was a rational economic explanation to the price applied by the company[443], which should have been combined with a necessary and fundamental 'security check'[444] carried out through an assessment of the unfairness of the price compared to the price of other comparable products that do not necessarily belong to the same relevant market[445].

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[440] See docs. 185 and 187.
[441] In support of these statements, the Party cites paragraphs 122-123 of Advocate General Wahl's opinion in Case C-177*/16, AKKA v LAA*.
[442] See docs. 185 and 187.
[443] In support of these claims, the Party cites paragraph 131 of Advocate General Wahl's opinion in Case C-177*/16 AKKA v LAA*.
[444] In this regard, the Party employs an expression used in paragraph 124 of Advocate General Wahl's opinion in Case C-177*/16 AKKA v LAA*.
[445] In this regard, the Party cites the European Commission, COMP/A.36568/D3, *Port of Helsingborg*, paragraph 171 and Court of Justice, 4 May 1998, in Case C-30/87 *Bodson v. Pompes funèbres libérées*, paragraph 31.

304. On the basis of these observations, Leadiant argues that the unfairness test is incorrect and that a comparative assessment of the price of *CDCA Leadiant*® would actually have indicated that the price was not unfair.

305. According to the Party, in fact, several pharmaceutical products are found in the case in question, which, for the purposes of assessing fairness, can be considered close comparators of *CDCA Leadiant*®. One of these would be *Orphacol*, an orphan drug marketed in Italy that is absolutely comparable to *CDCA Leadiant*®, as it is also repurposed, authorised in exceptional circumstances with a comparable patient population and cost levels for marketing and maintenance, and has a value for patients similar to that of the Leadiant orphan drug. The Party points out that the annual price of *CDCA Leadiant*® (equal to *[€60,000-€70,000]*) would be lower than the annual price of *Orphacol* (equal to *[€100,000-€200,000]*) by almost *[50-60%]*[446].

306. The company also states that *CDCA Leadiant*® is less expensive than the average Italian price of orphan drugs contained in a sample of 75 medicines by around *[40-50%]* and less expensive than the average price of orphan drugs in therapeutic areas similar to that of CTX by about *[50-60%]*[447].

307. In addition, a comparison with the data on the actual expenditure on orphan drugs in Italy found in two reports by AIFA and the Orphan Drugs Observatory shows that the total annual expenditure on *CDCA Leadiant*® (equal to approximately *[€2-€3]* million) is *[80-90%]* lower than the average total annual expenditure for an orphan drug in Italy (equal to approximately €14.98 million), and is essentially negligible in terms of both values and consumption, equal to approximately *[0-1%]* and *[0-1%]*, respectively, of the total of orphan drugs[448].

308. Finally, the company states that the Italian price of *CDCA Leadiant*® is lower than the French, British and German prices by *[30-40%]*, *[40-50%]* and *[70-80%]*, respectively. Leadiant denies that these differences are due to the strategy that supported the abuse and states that, conversely, they are the result of negotiations with the national regulatory authorities. According to the company, the British and French prices are particularly relevant, as the former was considered a "valid reference" by AIFA and the latter reflects the competitive relationship between CDCA and cholic acid[449].

309. In any case, according to the Party, the test of the inherent unfairness

[446] See docs. 185, 186 and 187.
[447] See docs. 185, 186 and 187.
[448] See docs. 185, 186 and 187.
[449] See docs. 185, 186 and 187.

of the price of *CDCA Leadiant*® is incorrect – the qualitative factors used for the test allegedly do not take account of the added value that the orphan drug brings to patients and the Italian National Health Service, nor of the significant costs and risks incurred by Leadiant for its development[450].

IV.7.1 Differences between Xenbilox® *and* CDCA Leadiant®

310. Leadiant claims that there are large differences between *Xenbilox*® and *CDCA Leadiant*®. The latter is an orphan drug specifically developed for the treatment of an ultra-rare disease, while the former was merely used as a reference drug in the MA application procedure to the European Commission and was, according to the Party, only one of several CDCA-based products authorised for a different therapeutic indication, namely the treatment of gallstones[451].

311. In addition, with respect to *Xenbilox*®, but also with respect to the galenic formulations prepared by hospital pharmacies, the orphan drug developed by the company had substantial differences, due to *i)* the improvement of the drug's production method; *ii)* the systematic demonstration, for the first time, of the efficacy, safety and quality of the treatment; *iii)* the certainty of the supply of and access to the drug, thanks to the obtainment of an authorisation in Italy; as well as *iv)* the guarantees and post-registration obligations, including those deriving from enhanced pharmacovigilance[452].

312. In this regard, Altroconsumo underlines the connections between *Xenbilox*® and *CDCA Leadiant*® that prevent it from being considered comparable to a newly introduced drug. Moreover, Altroconsumo states that, in this case, there might also be some doubt as to whether Leadiant has put in place a genuine repurposing activity, since the compound was already being used exclusively for the treatment of the rare disease, albeit in an off-label arrangement.

IV.7.2 Costs and risks associated with the project

313. Leadiant stated that the project, despite relating to repurposing, has entailed and continues to entail highly significant costs and risks, not solely

[450] See docs. 185 and 187.
[451] See docs. 84, 122 and 140.3.
[452] See docs. 84, 122, 126, 185 and 187.

pertaining to research and development costs and the 'living' costs of production of the drug.

314. The price of the *CDCA Leadiant*® therefore covers, *inter alia*, the implementation of a wide range of new synthesis and purification tests of the active substance that are the basis of the orphan drug production process, the autonomous development of part of the DMF and the regulatory dossier for *CDCA Leadiant*®, distribution and logistics activities and the fulfilment of stringent regulatory obligations relating to obtaining the orphan designation, the MA (and its maintenance), marketing, scientific information[453].

315. In addition, according to the company, it is important to recognize the value that the CDCA project has brought to patients and the Italian National Health Service, since, in general, this represents an incentive for further investments. This would be in line with the EMA's evaluation, which recognised the importance of the company's investments and the project by positively evaluating both the application for orphan designation and for an MA.

316. Finally, the company considers that the appropriate consideration of the non-economic benefits that *CDCA Leadiant*® brings to the Italian National Health Service and to the demand – which would not have suffered any inconvenience or damage in terms of lack of supply and/or health risk – would alone be sufficient to conclude that the price of the orphan drug is not unfair.

317. On the other hand, Altroconsumo considers that, given that the price of a drug must reflect its social and therapeutic value (and therefore also the activity carried out by the pharmaceutical company in relation to the drug) and that such value must not be measured in an absolute way, opting instead for an incremental measurement, the price thus requested by Leadiant for the orphan drug is disproportionate to the social value created by the company.

V. ASSESSMENTS

V.1 Introduction

V.1.1 Procedural exceptions

318. In relation to the alleged breach of equality of arms, it should be noted

[453] See docs. 84 and 122 and 140.3.

that Leadiant had a very long period to produce its defence arguments in response to the Statement of Objections. The SO was, in fact, notified on 22 September 2021 and, as a result of the extension of the deadline for the acquisition of evidence, which was approved by the Board on 22 October 2021 at the request of these same companies, the deadline to file the reply was set for 19 January 2022. This deadline was further postponed to 28 January 2022, following an initial postponement of the final hearing to 2 February 2022, communicated to the companies on 29 December 2021.

319. The Party therefore had 128 days, i.e., more than four times the 30 days provided for by Article 14(2) of Presidential Decree no. 217 of 30 April 1998, to submit its own reply. This deadline was further extended by 9 days with the communication dated 31 January 2022, which provided for a second deferral of the deadline for the acquisition of evidence and the date of the final hearing to 14 February 2022, with a new deadline for the drafting of additional statements of defence by the companies set for 9 February 2022.

320. Given the above, it is believed that the postponement of the deadline for the acquisition of evidence and the date of the final hearing to 14 February 2022 did not result in any violation of the principle of equality of arms between the prosecution and the defence.

V.1.2 The abuse and the strategy that enabled it

321. The investigation conducted firstly made it possible to ascertain that Leadiant has held, since early 2016, a dominant position (or rather, a monopoly) on the Italian market of CDCA-based drugs used for the treatment of a rare disease, called CTX.

322. Furthermore, the evidence clearly indicates that Leadiant abused this market position since June 2017 through a conduct adopted *vis-à-vis* AIFA during the price negotiation procedure that allowed it to charge unfairly excessive prices to the Italian National Health Service for the sale of *CDCA Leadiant*®. Such abuse is the result of a very complex strategy that the dominant company conceived long ago and intentionally cultivated over several years, with the aim of creating the right context to allow it to apply its abusive pricing policy effectively.

323. Below it will be summarised what will then be fully illustrated in the following sections: the constituent elements of the strategy that allowed Leadiant to acquire a dominant position and pave the way for the pricing abuse, firstly outside Italy and then on the domestic market; the application of

the price of *CDCA Leadiant*® obtained through the negotiation levers adopted during the negotiations with AIFA; and the economic analysis that led to ascertaining the illegality of this price pursuant to Article 102(a) of the TFEU.

324. In mid-2008, the dominant company purchased a CDCA-based drug registered for the treatment of gallstones but then almost exclusively used off label for the treatment of CTX, thus becoming the only operator active at the European level in the marketing of this drug. The ultimate purpose of Leadiant was to secure the orphan designation and register the drug for the treatment of CTX. Crucial for the achievement of this purpose was the conclusion reached in mid-2008 of a supply agreement that allowed it to obtain exclusive control of the drug's active substance by contracting the only credible supplier of CDCA in Europe, the Italian chemical company PCA.

325. Once Leadiant obtained a leading position on the national markets (except in Italy) of the European Union in the marketing of the CDCA-based drug used off label for the treatment of CTX, it prepared these markets for the future price at which it intended to sell the orphan drug by significantly increasing the price of *Xenbilox*® (as the aforementioned drug was then called) in mid-2014 from €660 to €2,900 per pack.

326. This price increase, which significantly boosted the revenues of the dominant company, served to finance the concomitant regulatory activities aimed at obtaining the orphan designation (December 2014) and the MA for the orphan drug (April 2017).

327. *Xenbilox*® entered the Italian market only in January 2016, immediately after the Pharmacy of the University Hospital of Siena ceased the galenic production it had carried out since 1997. In particular, thanks to the aforementioned exclusive CDCA supply contract entered into with PCA, Leadiant prevented Italian hospitals from finding the active substance and continuing the galenic preparation hitherto managed by the Pharmacy, causing patients suffering from the rare disease considerable inconvenience and forcing hospitals to import *Xenbilox*®, the only CDCA-based medicinal product available, at the highest price at which it had been marketed since 2014. This has allowed Leadiant to extend its dominant position to the domestic market of CDCA-based drugs, becoming the only operator in Italy, as well. With the signing of a new agreement with PCA in November 2016, Leadiant further strengthened its position on the Italian market, ensuring that, through an even stricter exclusivity clause, the production of CDCA-based galenic drugs was definitively prevented.

328. Furthermore, again close to the completion of the orphan drug

registration project, which heralded to its rapid introduction on national markets, including the Italian one, between the end of 2016 and the beginning of 2017 Leadiant implemented a strategy to artificially differentiate *CDCA Leadiant*® from *Xenbilox*®. Such differentiation consisted of the withdrawal of *Xenbilox*® from the German market and the establishment of a new company incorporated under German law, which would become the orphan drug's MA holder. This was to ensure that the owner of the orphan drug was formally distinguished from the owner of *Xenbilox*® and that the two medicines were not linked when the reimbursement price was determined by the competent authorities, not only those in Germany, but also those in other Member States, including Italy.

329. When *CDCA Leadiant*® was introduced on the domestic market in June 2017, the dominant company started negotiating the price of the orphan drug with AIFA, proposing a fee of €15,506.97 per pack. AIFA considered the price unjustified, neither in the light of the costs, which the company did not provide in the details requested by the Agency, nor in the light of the activities carried out to obtain the registration of the orphan drug, nor, lastly, in the light of the therapeutic value of the drug.

330. The Agency considered, on the other hand, that the adequate price of the orphan drug should not exceed that of *Xenbilox*® by more than 10%, the maximum value attributable to the benefit associated with the registration of the orphan therapeutic indication.

331. However, the dominant company adopted a dilatory and obstructive behaviour that prolonged the length of the process, which lasted about two and a half years. This put the Agency in a disadvantaged position, which already existed due to the need for the Italian National Health Service to provide patients with an essential, irreplaceable and life-saving medicine within a reasonable time frame and at an economically sustainable price.

332. By intentionally exploiting this weak bargaining position, the dominant company was able to obtain an ex-factory price for the orphan drug of *[€5,000-€7,000]* per pack, which, although much lower than the initially proposed price, was found to be unjustifiably excessive on the basis of the analyses carried out during the investigation, since: *a)* it is disproportionate to the total costs incurred and *b)* unfair in light of the nature of the product, the investments made in research and development, the risks faced in the registration project and the added therapeutic value that AIFA, in addition to the demand expressed by the doctors, attributes to *CDCA Leadiant*®. Moreover, it is believed that, without the Italian Competition Authority's

intervention, this negotiated price would have been higher, thus more disproportionate, and even less justified in light of the aforementioned parameters.

333. This behaviour required the Italian National Health Service to incur a significantly higher expense for the purchase of the drug.

334. In summary, therefore, for the reasons that will be better and more thoroughly argued in the following sections, it is believed that as of 15 June 2017, Leadiant has engaged in unlawful conduct pursuant to Article 102(a) of the TFEU, thereby abusively exploiting its dominant position to apply unjustifiably excessive prices for the sale of the orphan drug called *CDCA Leadiant*® to the Italian National Health Service.

V.2 The relevant market

335. The established practice at the European Commission and the jurisprudence of the Court of Justice[454], both constantly applied by the Italian Competition Authority[455], indicate that the definition of the relevant product market in the pharmaceutical sector is based on the notion of therapeutic substitutability of medicines.

336. This relationship of interchangeability is based firstly on the therapeutic classes identified by the *Anatomical Therapeutic Chemical classification system* (ATC), which divides drugs according to an alpha-numeric classification that is articulated into five hierarchical levels. The third level of this classification, ATC3, identifies a therapeutic-pharmacological subgroup encompassing medicines normally intended for the treatment of the same diseases, with such medicines being generally interchangeable but not with those belonging to other classes on the first and second levels. Therefore, ATC3 is the starting point for identifying mutually replaceable pharmaceutical products for the purposes of defining the relevant market[456].

337. Often, however, considerations relating to doctors' prescribing trends,

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[454] See European Commission decision of 15 June 2005 COMP/A. 37.507/F3 – *AstraZeneca*, paragraphs 380 *et seq*. With reference to this case, it should be noted that both the EU Court of First Instance (judgment of 1 July 2010, case T321/05, paragraphs 154-155) and the Court of Justice of the European Union (judgment of 6 December 2012, case C457/10) confirmed the European Commission's decision on the definition of the relevant market. See also European Commission decision of 10 February 2021 AT.40394 – *Aspen*, par. 26 *et seq*.

[455] See AGCM Measure no. 15175 of 8 February 2006, case A363 - Glaxo-Principi Attivi, in Bulletin no. 6/2006; AGCM Measure no. 16597 of 21 March 2007, case A364 - Merck-Principi Attivi, in Bulletin no. 11/2007.

[456] See European Commission, *AstraZeneca*, par. 371 *et seq*.

the relative institutional organisation for supply and demand (pricing, reimbursement methods, existence of an insurance system, etc.) and the greater or lesser effectiveness of a drug in the treatment of the disease, require a more specific substitution analysis allowing for the identification of interchangeability relationships between drugs at a different level of the ATC classification (ATC4 or ATC5[457]) or between drugs belonging to other classes.

338. With reference to the geographic market, the practice is to consider the competitive environment on a national level, due to the institutional differences that characterise the health systems and pharmaceutical policies of the individual Member States (meaning the regulation of prices, reimbursement methods, classification of medicines, distribution channels), the different access regimes (i.e., the patenting and marketing authorisation regimes), as well as in consideration of the possibly different routes of epidemiological spread of a certain disease and the various types of economic availability of the Member States, although an accentuated harmonisation process is taking place at the EU level, which has introduced significant legislative innovations, especially in the field of market access regimes[458].

V.2.1 The market for CTX drugs

339. The market affected by this decision is the market for the production and sale of medicines for the treatment of an ultra-rare disease, CTX.

i) The demand for CTX drugs

340. The demand for drugs that treat CTX tends to originate from specialists who treat patients in the hospitals where they operate and, therefore, by ASLs which, at the request of the said doctors, purchase these medicines, which are therefore marketed through the hospital channel.

341. The investigation carried out shows that there are, or have been, different therapies used by doctors for the treatment of this disease: CDCA-based drugs, and in limited cases, medicines based on cholic acid, ursodeoxycholic acid and statins (in particular, simvastatin, lovastatin and pravastatin), in combination with CDCA (see section III.4 above).

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[457] The definition of the relevant product market was made to coincide with level 4 of ATC classification, both in the EU-level AstraZeneca case and in the Merck and Glaxo cases in Italy, while the Commission went so far as to limit the relevant market to the single active substance in certain merger cases.

[458] See European Commission, *AstraZeneca*; AGCM Measure no. 25186 of 19 November 2014, *A480 – Price Increase of Aspen's Drugs*.

342. *Chenodeoxycholic acid Leadiant* is a drug used to treat bile diseases (ATC3 code, A05A), and in particular it belongs to the class of bile acids and their derivatives (ATC4 code, A05AA), since it contains one of the primary bile acids, chenodeoxycholic acid (ATC5 code, A05AA01).
343. In the therapeutic subgroup of bile acids and their derivatives, there are two other active substances that in some cases have been administered, also off label, for the treatment of CTX. These include cholic acid (code ATC5, A05AA03) and ursodeoxycholic acid (code ATC5, A05AA02).
344. Simvastatin (ATC5 class, C10AA01), lovastatin (ATC5 class, C10AA02) and pravastatin (ATC5 class, C10AA03) belong to the therapeutic class of HMG-CoA reductase inhibitors (ATC4 class, C10AA), which in turn are part of the class of lipid agents (ATC3 class, C10).

ii) Supply of CTX medicines

345. The findings of the investigation show that CDCA-based drugs other than the orphan drug marketed by Leadiant have not been available on the Italian market for some time.
346. The obsolescence of chenodeoxycholic acid in the treatment of gallstones and the small size of the market for the treatment of CTX since the second half of the 1990s have led to the exit from the domestic market of companies that marketed these drugs (see paragraphs 61, 72, 73 and 78 above).
347. From 1997 to 2016, CDCA-based galenic drugs were present on the Italian market, which were produced to address the aforementioned shortage in industrial production of drugs containing this active substance and to guarantee therapeutic continuity to patients with CTX. However, the galenic production ceased in November 2015 due to the lack of availability of raw material on the Italian market (see paragraphs 73-77 above).
348. From that moment, and until the introduction of the orphan drug *CDCA Leadiant®*, *Xenbilox®*, which was the only CDCA-based drug at the time available in Europe and owned by the company, was used off label for the treatment of the rare disease CTX in Italy (see paragraph 79 above).
349. In June 2017, *Chenodeoxycholic Acid Leadiant®* was introduced on the domestic market and has since become the only CDCA-based CTX treatment product currently available (as well as in other national markets in the European Union) (see paragraph 80 above).
350. During the procedure, it was also established that *Kolbam®,* a cholic acid-based medicine, was never authorised in Italy. In any case, the MA

granted by the European Commission was revoked in July 2020 (see paragraphs 86 and 89 above). Therefore, it cannot be imported from abroad either.

351. The other cholic acid-based drug, *Orphacol*®, was authorised for the treatment of congenital defects of the synthesis of primary bile acids other than those that cause CTX and was marketed as such in Italy, as well (see paragraph 90 above).

352. There are no drugs based on ursodeoxycholic acid or statins marketed in Italy for the treatment of CTX.

iii) Conclusions on the relevant market

353. The evidence acquired during the investigation clearly indicates that there is no therapeutic interchangeability between the aforementioned drugs. This emerges both from doctors' prescribing trends observed over a period of time that extends at least from 2014 to today, and from the assessments expressed by the doctors themselves on the effectiveness of the aforementioned drugs in the treatment of CTX.

354. From the point of view of the prescribing pattern adopted by doctors, CDCA has always represented the therapy of choice for CTX in all European Union Member States where the disease is present (see paragraphs 65-70 above). The effectiveness of CDCA in the treatment of the rare disease is, in fact, recognised *i)* at the scientific level in the literature; *ii)* at an empirical level in clinical practice ("*worldwide accepted (literature), applied (treating physicians), and effective (open-label, single arm study)*")[459]; and *iii)* at the institutional level ("*first-line treatment*")[460].

355. In this regard, one of the leading experts in the world of CTX confirmed that CDCA is "*to be privileged in the treatment of the rare disease in question*" and that "*there is a clear consensus in the medical/scientific community at the international level on the fact that CDCA is the therapy of choice for CTX*"[461].

356. The evidence collected during the investigation indicates that this applies in particular to Italy, where the active substance has been used for

[459] See doc. 78.417 dated March 2016. See also doc. 78.17, annex "*ST-CDCA_Slidesmeeting12092016.pptx"* of September 2016, which shows that, in France, CDCA was considered the therapy chosen for the treatment of CTX at the time.

[460] See https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=909 and NICE, *Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis*, p. 12.

[461] See doc. 133.

about forty years, essentially exclusively in the treatment of the rare disease (see paragraph 70 above).

357. Numerous elements of the investigation also show that CDCA is considered superior to cholic acid in terms of its efficacy in the treatment of CTX, with cholic acid in turn considered superior to ursodeoxycholic acid (see paragraphs 83-84 above).

358. Cholic acid is only seldom used in rare cases where CDCA has side effects. In particular, physicians, especially those in Italy[462], do not prescribe cholic acid for the treatment of the rare disease, nor do they substitute cholic acid for CDCA in non-naive patients, since the active substance, while lowering bile acid levels, does not have an appreciable effect on the clinical picture of patients (see paragraphs 84, 85, 88 above).

359. This is first confirmed by the absence of any information in the evidence that indicates that *Orphacol*®, although available on the market (foreign and domestic) before *Chenodeoxycholic Acid Leadiant*®, has never been prescribed (off label) for the treatment of the rare disease covered by this decision[463]. The physicians' preference for CDCA over cholic acid continued over the period (about 3 years) during which *Kolbam*® was the only drug authorised for CTX. In other words, they preferred to prescribe an off-label drug instead of an on-label drug, precisely because of the therapeutic superiority of the former, even if this was not formally recognised at regulatory level (see paragraph 86 above).

360. The non-equivalence in therapeutic terms between CDCA and cholic acid, moreover, was affirmed by the EMA itself, using the evidence produced by the same pharmaceutical company with the purpose of demonstrating the existence of "significant beneficial effects" of CDCA compared to cholic acid (see paragraphs 87 and 153 above)[464] at the conclusion of the process that first led to the issuance of the orphan designation for *CDCA Sigma Tau* in 2014 and then to the confirmation of maintaining the orphan status in 2017.

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[462] See doc. 22.7.17 ("*We don't believe in the effectiveness of Cholic acid (in CTX) and it's not true that it has a better safety profile. […] We don't believe in the specificity of the cholic acid, the scientific literature doesn't confirm it and at the mean time we don't believe in the asserted safety of this molecule […] I know that the expectations about the use of cholic acid in the treatment of CTX have been disappointing*" *[…] the cholic acid doesn't have any scientific credibility in the cure of CTX and also the declared greater safety is considered as a "bluff" not adequately supported by clinical evidences*"). See also doc. 96.23.

[463] See doc. 133.

[464] See the COMP decision to maintain orphan status where, in fact, it is stated: "*Therefore, although other methods for the treatment of this condition have been authorised in the EU, the COMP concluded that Chenodeoxycholic acid sigma-tau is of significant benefit to patients affected by inborn errors in primary bile acid synthesis"*.

361. Ultimately, given the minimal possibility of therapeutic substitution of CDCA with cholic acid for the treatment of CTX, it should be considered that the latter compound is unable to exert a sufficient competitive constraint on the former in order to consider both as belonging to the same relevant market[465].

362. Therefore, *Orphacol*® cannot be considered an effective and reliable competitor of *Chenodeoxycholic Acid Leadiant*®, and therefore cannot be included in the same relevant market.

363. Similar considerations can be made for ursodeoxycholic acid and statins, in relation to which there is a very limited clinical practice that in any case reveals, especially according to Italian doctors, the absence of an appreciable effect in the correction of metabolic alterations present in CTX (see paragraph 83 above).

364. Therefore, in the light of the established legal principles on the definition of the relevant market in the pharmaceutical field, as lastly reiterated in the ruling of the Council of State on the *Aspen* case[466], it is considered appropriate in this case to limit the relevant market at the level of the individual active substance (ATC5 level) and to define it, from a product perspective, as inclusive only of CDCA-based drugs (ATC5 code, A05AA01).

365. Furthermore, for the reasons already mentioned, relating to the specific characteristics of the Italian National Health Service, the level of epidemiological spread of the disease in the Italian territory and the different willingness to pay of Italy compared to the other Member States, it is considered that, even in the case in question, the market for the product identified above has a limited extension to the national territory.

V.3 Leadiant's dominant position

366. Several pieces of evidence help to attribute to Leadiant a dominant position in the relevant market as defined above, with it being the only company active therein since the beginning of 2016.

367. First of all, the exclusive CDCA supply agreement concluded in 2008 between Sigma Tau and PCA, the only credible producer of this input in Europe (see sect. V.3.2.i.a below), gave the pharmaceutical company control

[465] This is also confirmed by a document that indicates how the same company had recommended that, once it obtained the MA for its CDCA-based orphan drug, cholic acid would exert marginal competitive pressure. See doc. 78.236 ("*[m]arginal competition by Cholic Acid in Europe*").

[466] See Council of State, judgment no. 1823 of 13 March 2020, paragraphs 6.1 and 6.2.

over the raw material, representing a contractual barrier that has allowed it to protect itself from competition from producers of CDCA-based medicines, and in particular from producers of galenic drugs based on the same compound. This closed the domestic market to the magistral preparations from January 2016, when galenic production at the Pharmacy of the University Hospital of Siena was terminated, thus allowing the company to become, from that moment on, the sole operator on the Italian market through the sale of *Xenbilox*® (a position strengthened through the new exclusive supply agreement of November 2016).

368. In addition, starting from April 2017, i.e., after obtaining the orphan drug MA, in addition to the aforementioned contractual barrier, Leadiant was also able to count on a double regulatory barrier, valid both against rival producers of CDCA-based medicines of an industrial nature used for the treatment of CTX, and against rival producers of magistral preparations based on the same compound. In fact, the obtainment of the MA for the orphan drug allowed Leadiant to firstly acquire the ten-year market exclusivity that, pursuant to Article 8(3) of Regulation (EC) No 141/2000, prevents the registration of other products similar to the *CDCA Leadiant*® for the treatment of the rare disease in question (see paragraph 41 above). Secondly, Article 5 of Italian Legislative Decree no. 23 of 17 February 1998 prohibits, except in very limited cases, the production of galenic drugs when an industrial product is registered for a specific therapeutic indication on the domestic market, namely, in this case, from June 2017, when the orphan drug was introduced into Italy (see paragraph 189 above). This has meant that since then, patients with CTX in Italy have only been treated with Leadiant's orphan medicinal product (see paragraph 80 above).

369. Several pieces of evidence, however, indicate that this will also happen in the coming years, reasonably at least until Leadiant's exclusivity right expires in April 2027.

370. Leadiant disputes this reconstruction, first of all because it believes that the exclusive agreements stipulated by Sigma Tau with PCA did not close the market to the magistral preparations, and in any case because the sales of *Xenbilox*® in Italy between 2016 and 2017 were managed by a third party, while Sigma Tau has never been directly operational on the domestic market.

371. In addition, the Party asserts that, even after obtaining orphan designation and the MA for *CDCA Leadiant*®, its ability to exercise market power would have been limited, and could be even in the future, by the competitive dynamics of other EU Member States, which can influence the

Italian market and the very sustainability of Leadiant's presence on this market, given the extremely small patient base at the EU level.

372. These claims are not supported. As will be illustrated below, the investigation showed that, at the beginning of 2016, the company extended to Italy the dominant position it already enjoyed in the other national markets of the European Union, thanks to the sale of the only existing CDCA-based drug, *Xenbilox*®, and that it consolidated this market position by obtaining the MA for the orphan drug for the national territory.

V.3.1 Sigma Tau's acquisition of a dominant position outside Italy

373. The evidence indicates that in June 2008, Sigma Tau Pharmaceuticals Inc. acquired the entire dossier for *Chenofalk*®, a CDCA-based drug owned by Dr. Falk Pharma GmbH used off label for the treatment of the rare disease and then, in October 2008, transferred the ownership of the marketing authorisation of this medicinal product valid for Germany to Sigma Tau Arzneimittel GmbH (now in liquidation), which was thus replaced by Dr. Falk Pharma GmbH (see paragraphs 91-95 above).

374. At a time when there was no longer any interest in the marketing of CDCA-based drugs for the treatment of gallstones in Europe, since the active substance had been replaced by other treatments, and companies were gradually leaving the market (see paragraph 346 above), the only valid economic reason for entering was to access another niche market that was extremely small, but potentially very profitable thanks to the significantly high prices generally granted to orphan drugs – namely, the market for CTX, a disease that had been treated with CDCA for decades. This was, in fact, Sigma Tau's stated goal [467].

375. However, the objective pursued by the company assumed that there were no other companies on the European market that marketed CDCA-based drugs, meaning that the company had obtained a monopoly on the market for the sale of CDCA-based drugs in Europe (see paragraph 99 above).

376. Therefore, in mid-2008, the company considered purchasing the four MAs relating to the few CDCA-based drugs registered for the treatment of gallstones still present on the national EU markets owned by other companies,

[467] See the following press releaseshttps://www.pharmaceutical-business-review.com/news/16498sigmatau_acquires_chenofalk_from_dr_falk_p/;https://www.biocentury.com/bc-week-review/company-news/deals/2009-02-09/sigma-tau-spa-solvay-deal; https://www.pharmaceutical-business-review.com/news/16498sigmatau_acquires_chenofalk_from_dr_falk_p/.

which were *Quenobilan*® and *Quenocol*® in Spain, *Xebyl*® in Portugal, and the *Chenofalk*® MA valid for the Netherlands (the "*competing MAs*"[468]), to eliminate them from the market. However, at the time when Sigma Tau was making these assessments, the structure of the national markets for CDCA-based medicinal products naturally underwent further changes that rendered such acquisitions unnecessary (except in one case – see below) and that helped Sigma Tau achieve its objective. In fact, the aforementioned Spanish products exited the market between the end of 2008 and the beginning of 2009, and the associated authorisations were consequently revoked. Therefore, only the "*competing*" Dutch marketing authorisation for *Chenofalk*®, which Sigma Tau purchased in September 2009 and strategically kept valid[469] without ever using it[470], remained valid until it expressly cancelled it on 9 September 2015. Likewise, the *Xebyl*® MA remained inactive since the drug had not been marketed as of early 2011 (see paragraphs 78 and 99 above).

377. Essentially, therefore, the evidence clearly indicates that, since the beginning of 2011 there was only one CDCA-based drug available on the market in Europe: *Xenbilox*®, owned by Sigma Tau.

378. In this regard, it should be noted that when the company claims that its market position in Europe was at the time absolutely competitive, since *Xenbilox*® did not enjoy any protection of a regulatory nature, with the protection dossier having expired, nor patent protection, with the drug being off-patent, the Party fails to consider that Sigma Tau's signing, as early as 2008, of an exclusive supply agreement of CDCA with PCA, who, as already mentioned, was the only credible supplier of the raw material present on the European market, as well as the only manufacturer of the active substance in question with adequate access to the raw material, possessing adequate technological capabilities and the necessary administrative requirements in terms of regulatory compliance in existence at the European level at the time (see paragraphs 52-53 above), constituted a significant obstacle for any company wishing to enter the market. Indeed, any company that wanted to

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[468] See doc. 96.99.

[469] See doc. 96.75, which shows that the Netherlands was one of the markets to which Sigma Tau Arzneimittel GmbH would have exported *Chenofalk*® from the second half of 2009. It follows that, even though it had an authorisation valid for the Netherlands, which would have allowed it to distribute the medicine directly on the Dutch market while remaining subject to national price regulations, the company resorted to exporting the drug from Germany, which, being based on the "*Named Patient Supplies*" mechanism, was not subject to price restrictions (see footnote on p. 238).

[470] See doc. 22.7.17 ("*If the current licence is withdrawn in NL, off-label use for CTX would no longer be possible which would be disastrous. However when the CTX EMA approval is imminent, it may make sense to withdraw the old indication in NL as this may create an opportunity to rebrand the product (and price it differently and higher compared to the old product)*").

produce a CDCA-based drug would have faced the difficulty of finding a source of production of this raw material.

379. Likewise, Leadiant deliberately chooses not to give any importance to the crucial element of the extremely small size of the market, which would in any case have discouraged the entry of new operators, even in the unlikely event that they were able to find another source of production of CDCA (see again section V.3.2.i.a below). This appears to be laconically confirmed by Leadiant's own statements found in the documents on file, where the company considered it highly unlikely that new drugs would enter the market precisely because of its small size[471]. It should be noted that the aforementioned document dates back to September 2014, i.e. at a time following the increase in the price of *Xenbilox*® to €2,900 per pack in July 2014, which made the drug very profitable for Sigma Tau (see paragraph 114 above) and, therefore, also for any other potential entrants. Therefore, if the incentive for other operators to enter the market was, in the opinion of the company itself, non-existent, tough the market for CDCA-based medicines had become profitable, even more so there was no potential competitive threat before that time, when the market was much less profitable, given the much lower price at which the drug was previously sold (€660 per pack). And this despite the absence of patent and regulatory protection.

380. The only company producing CDCA-based drugs that did not suffer from the obstacles posed by the small size of the market and the exclusivity agreement was Retrophin Inc., who had access to the raw material through the only other supplier considered credible outside Europe, the aforementioned NZP (see paragraph 54 above); it already produced and marketed (in the United States) a CDCA-based drug and therefore did not need to make new investments in the production and marketing of the drug.

381. However, the Party's assessments regarding Retrophin's ability to challenge Sigma Tau's market position are not acceptable because they completely fail to consider what emerged during the investigation about the real possibility for the US company to enter the European market. The evidence shows unequivocally that the two conditions already enjoyed by Retrophin were not remotely sufficient for a competitive entry into the market with a CDCA-based drug for the treatment of CTX. In order to represent a real

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[471] See doc. 22.7.17 (*"I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years.…..it's a too small pathology… it's an orphan who nobody wants to adopt!"*).

competitive threat, in fact, Retrophin would have needed to obtain orphan designation. To this end, it was also necessary to have supporting clinical trials[472].

382. The way in which Sigma Tau carried out its project is a clear confirmation of this: the first attempt to apply for the orphan designation, presented on a preliminary basis by the company to the EMA in May 2007, foundered precisely because it was presented without any support of a clinical nature (see paragraph 94 above). Sigma Tau concretely resumed the project in mid-2014 when it began to collaborate directly with the specialist from the University Hospital of Siena to start collecting clinical data primarily useful for the application for orphan designation (see paragraph 145 above). This collaboration accelerated in May 2014 when Sigma Tau, as the Party itself states, learned of the news that Retrophin intended to enter the European market ("*We need to take this relation with Prof [F.] directly on board (STRD), get the clinical data on the CTX study asap and eventually involve him in a new study. We need to engage him and soon*")[473]. The ongoing collaboration made Sigma Tau feel confident enough to submit the preliminary orphan designation request in August 2014, which was later obtained in December of the same year (see paras. 117-118 above). The clinical support received by Sigma Tau was further strengthened thanks to the scientific cooperation initiated in early 2015 with the other treatment centre, the Dutch hospital Casinius Wilhelmina in Nijmegen (see paragraph 149 above).

383. The evidence, therefore, clearly shows the decisive role that these scientific collaborations have had in the concrete implementation of the second phase of the project and in its success (obtaining the MA and the definitive orphan designation). If Retrophin wanted to request the registration of its own CDCA-based orphan drug for the treatment of CTX in the European Union, it would therefore have had to submit its own equally valid studies to support the request, and thus would have had to enjoy clinical support similar to that received by Sigma Tau.

384. Towards the middle of 2014, Retrophin indeed tried to establish a collaboration with the University Hospital of Siena, without success (see paragraph 146 above). Moreover, the possibilities of collaborating both with

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[472] See doc. 78.249 ("*Require EU case studies to support EU filing and ST has exclusive agreement with* [F.] *and potentially* [V.] *to have access to their case studies so Retrophin could not use these major centres*"). See doc. 133.

[473] See Docs. 6.1, 6.2, 22.7.71 and 138.4.7.

this treatment centre and with the Dutch hospital Casinius Wilhelmina in Nijmegen subsequently dissolved completely, due to the exclusivity agreements stipulated by Sigma Tau with them (see paragraphs 147 and 149 above). This represented a significant obstacle to the entry of Retrophin into the European market.

385. The Party's argument that the US company could have found clinical support from other specialists is disproven by the investigation, which clearly showed that there were no other treatment centres and/or other specialists that could have offered similar clinical support. First of all, it should be noted that, as stated by the same company, the specialist at the University Hospital of Siena – one of the few experts in Europe with decades of experience in the treatment of the rare disease with CDCA – was at that time the "*world opinion leader*"[474]. In addition, the two European centres with which Sigma Tau collaborated exclusively are those that globally had, and still have, the largest database ever collected, in terms of the sample of patients involved, but above all in terms of the length of the observation period of the results of the administration of CDCA to these patients (see paragraph 150 above). The Party's assertions, therefore, are not capable of casting doubt on the fact that the impossibility of relying on the clinical experience gained by the world's leading expert and the doctors of the second most important treatment centre in Europe constituted a significant barrier to entry for Retrophin.

386. Confirmation of the existence and effect of the barrier built by Sigma Tau between 2014 and 2015, which prevented, and still prevents, the US company from even attempting to access the European market, can also be found in the assessments expressed by the same company in relation to the US competitor. ("*ODD protects against other CDCA products*"; "*pulled out of Europe (in terms of plans to launch there) since ST obtained the Orphan designation for CDCA so Retrophin's CDCA is not expected to be a competitor in Europe*")[475].

387. In conclusion, therefore, Retrophin has never been able, nor for the same reasons will it be able, to pose a competitive threat to Sigma Tau before obtaining the MA for the orphan drug.

388. All this indicates that, contrary to what Leadiant claims, *Xenbilox*® was not merely one of several CDCA-based products authorised for the treatment of gallstones, nor could any company have entered the market using *Xenbilox*® as a reference drug in a project similar to the Sigma Tau project.

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[474] See docs. 95 and 138.4.7.
[475] See docs. 95.15 and 78.249.

On the contrary, as early as 2011 *Xenbilox*® was in fact the only CDCA-based medicine in circulation in Europe, and since 2014 the company has built specific entry barriers to ensure it remains so.

389. As for the competitive threat allegedly posed by *Kolbam,* which existed on the market before *CDCA Leadiant*®, the considerations expressed above regarding the therapeutic inadequacy of cholic acid for the treatment of CTX based on the evaluations of specialists who were treating patients with the rare disease (see paragraphs 357-359 above), preferring to treat them in any case with an off-label drug because it was more effective, are valid here.

390. In conclusion, therefore, for several years before obtaining the authorisation for the orphan drug, Sigma Tau enjoyed an undisputed market position in almost all the national markets of the European Union. This was then extended to the Italian market, starting in January 2016, for the reasons set out below.

V.3.2 The extension of Leadiant's dominant position to the Italian market in 2016

i) The foreclosure of the market to galenic CDCA-based preparations

391. The evidence indicates that, as early as 2007, Leadiant felt the need to have control of the raw material and avoid the possibility of other competitors' producing CDCA-based drugs[476]. In particular, it was concerned that the possible presence of galenic preparations on national markets might hinder the CDCA Project. Since the compound is very old, it was also produced and/or producible by hospital pharmacies, as was the case especially in Italy, where galenic production by the Pharmacy of the University Hospital of Siena enjoyed a strong, long-standing operation (see paragraph 75 above).

392. In order to acquire control of the raw material, Leadiant entered into the aforementioned contract in June 2008 for the supply of CDCA exclusively with PCA (see paragraph 96 above). However, the exclusivity clause in this contract did not prevent, until January 2016, CDCA-based galenic products used for the treatment of CTX from appearing on the Italian market. In 2007,

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[476] See doc. 22.7.3, Annex "121 06 Draft Report 250307" ("*Current and future suppliers/manufacturers of CDC*
Ease of manufacture?
Can pharmacists compound it?
Can ST stop others from making it?
Can ST stop others from supplying it to pharmacists?
Can ST prevent rival suppliers' CDC from being used in CTX?
If so, for how long and in which territories?");

the Pharmacy of the University Hospital of Siena then purchased stock of the active substance from PCA, which was used for that production until November 2015, when such stock ran out (see paragraph 77 above).

393. The Pharmacy's production activity, therefore, had hitherto prevented Leadiant from entering the Italian market, the only one of the European markets concerned in which it was not present with *Xenbilox*®. This explains why between 2014 and 2015 the company tried to understand how to stop galenic production in Italy and replace it with *Xenbilox*® ("[...] *replace self-compounded CDCA with* Xenbilox"[477]; "[...] *stop the hospital making its own CDCA and instead purchase imported CDCA*"[478]; "*stop them selling CDCA*"[479]).

394. However, the company failed and had to wait for galenic production at the Pharmacy of the University Hospital of Siena to end in November 2015. In January 2016, the Pharmacy communicated the lack of raw material to Sigma Tau and, unable to find it on the market precisely because of the aforementioned exclusive contract, asked Sigma Tau directly to obtain it, receiving a clear refusal. Similarly, the other Italian hospitals that were previously supplied from the Pharmacy tried, unsuccessfully, to obtain the active substance from PCA or Sigma Tau during the first half of 2016 (see paragraphs 130 and 134 above).

395. What is more, is that through constant and intense monitoring of PCA, Sigma Tau carefully verified that the chemical company had effectively fulfilled its contractual obligations and did not transfer the active substance, especially to those who could use it to produce galenic drugs. Sigma Tau did not change its behaviour even when PCA proposed derogating from the exclusive contract to meet the needs of the hospitals that were complaining about the serious shortage of raw material and the risk it posed for their patients. Conversely, it took advantage of the situation of necessity to redirect hospitals towards the purchase of *Xenbilox*®, with a view to introducing the orphan drug on the Italian market[480] (see paragraph 135 above).

396. Sigma Tau's strategy achieved its goals. Indeed, since the beginning of 2016, the magistral preparations have disappeared from the Italian market and the ASLs, forced by the pharmaceutical company, have begun to import *Xenbilox*® from Germany, which has thus become the only product present

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[477] See doc. 22.7.17.
[478] See doc. 22.7.17.
[479] See doc. 78.52.
[480] See docs. 78.19 and 78.241 ("*They perfectly know how and where to buy. They are trying to get it from PCA at a cheap price to create a precedent that will kill our future reimbursability and price*").

on the domestic market (see paragraph 116 above).

397. The position thus obtained by Sigma Tau on the Italian market was greatly strengthened with the signing of the second supply contract with PCA in November 2016, which contains an even more stringent exclusivity clause. Article 2.3 of the November 2016 exclusivity contract, in fact, places an additional obligation on PCA, who is required to verify that any third party to which it sells CDCA does not use it to produce drugs aimed at treating CTX (see paragraph 137 above)[481]. It is no coincidence, in fact, that this contract was concluded in November 2016, i.e., two months after Sigma Tau had received a positive opinion from the *Committee for Medicinal Products for Human Use* (CHMP) in response to its request for authorisation for the orphan drug. At this crucial moment of the project[482] it was, in fact, even more necessary to have absolute control over the raw material to eliminate any element of disturbance, such as cheap magistral preparations, to the market position that Leadiant had acquired in Italy.

398. The evidence acquired thus contradicts Leadiant's comments about the uniqueness of the function of the agreement stipulated with PCA, which allegedly lies in the need to protect the mutually indispensable investments made by both parties and to avoid free riding on such investments, elements that should set the contract within the scope of the research and development agreements. The main purpose of the exclusivity clause contained in the agreement is, instead, to give Sigma Tau control over the primary source of CDCA present in Europe in order to continue, and indeed strengthen, its obstruction to prevent the entry of magistral preparations to national markets, and in particular the Italian one, which had already had effects since January 2016 ("*the concern is that a compounding pharmacy could look to buy API from you on the grounds that it was to be used for a bile acid disorder other than CTX and then use some it for CTX patients*"[483]).

399. In fact, the refusal to supply opposed by PCA and the monitoring activity carried out by Sigma Tau continued even after the conclusion of the second exclusive CDCA supply contract with PCA (see paragraphs 138-140

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[481] See, to this end, clause 2.1 of the June 2008 Agreement with clause 2.3. of the November 2016 Agreement.
[482] It should be noted that, at the time, Sigma Tau believed that it would have the MA from the European Commission in November 2016.
[483] See doc. 78.9. See also doc. 78.34 ("*how can ST minimise the risk from compounded product availability in each country? How are compounding companies obtaining the API for CDCA? […] ST should have exclusive use for all API destined for use in CTX patients*"); doc. 28.2.66 ("*S-T for the reasons widely explained during our last meeting on November, 11th at PCA and in our e-mail exchanges, S-T requires PCA to grant exclusivity on CDCA supply (at least 10 years) for the production of any FF use to treat any biliary acid disorders. PCA-S-T will work together with their legal advisors in order to find a way to legally justify exclusivity, e.g. by linking to EU and US orphan drug designation of CDCA*").

above), and in particular during the first few months of 2017, relating to an even more delicate phase of the project of registration of the orphan drug, namely the phase that led Sigma Tau to obtain the MA and the confirmation of the orphan status of CDCA before the introduction of *CDCA Leadiant*® to the market and the subsequent price negotiation with AIFA.

400. Ultimately, the evidence described above clearly shows that, after the end of production by the University Hospital of Siena, i.e., well before the regulatory barrier could be erected deriving from Article 5 of Legislative Decree no. 23 of 17 February 1998 (specifically, a year and a half before), the legitimate attempts made by Italian hospitals from the beginning of 2016 to find the raw material to fuel galenic production were intentionally prevented by the dominant company, invoking in the relations with PCA the exclusivity clause contained firstly in the agreement stipulated with the chemical company in June 2008 and then in the subsequent agreement of November 2016. In this way, from January 2016 and until the orphan drug received an MA valid at the national level (in June 2017), Leadiant closed the Italian market to galenic production and reserved it for itself.

a. The irreplaceability of PCA as a credible supplier of CDCA in Europe

401. The contractual barrier erected by Leadiant came into effect because both contracts with PCA enabled the establishment of a commercial link between the only credible supplier in Europe at the time and the pharmaceutical company.

402. The pre-eminence of PCA's position on the European market is attested by several documents on file. Some of the most suggestive include those that show that the EDQM turned to PCA in 2011 as the only manufacturer of the active substance in the territory of the European Union ("[...] *I could not identify another manufacturer*"[484]) to be used as a reference to improve the purity test of CDCA; that, for the purposes of revising the CDCA monograph, the contribution of the chemical company, although supported by Sigma Tau, was essential; and that the Directorate finally established a test that is largely based on the test developed by Sigma Tau and owned by PCA[485] (see paragraph 53 above).

403. The market position that PCA enjoyed, and still enjoys, was also

[484] See docs. 28.2.53 and 78.6.
[485] See doc. 28.2.31 ("*[...] they are waiting for our data and support*").

recognised by Sigma Tau both in 2016 and 2017, in terms of privileged access to bovine bile, the main input from which CDCA is derived, and of adherence to the GMP[486], as well as in 2018, when Sigma Tau defined it as the only certified operator in Europe[487].

404. However, Leadiant today denies that PCA enjoyed such a market position and disputes the existence of such a contractual barrier on the basis of the alleged existence of multiple sources of CDCA production other than PCA that could have easily fuelled galenic production between January 2016 and June 2017, if hospitals had acted promptly to search for them and establish commercial relationships with them, as for example the Amsterdam hospital did between 2019 and 2020.

405. These statements are unacceptable because they are widely contradicted by the same evidence produced by the Party. Before reviewing it, however, it is necessary to note that the time period during which the existence of alternative sources to PCA must be checked is about 18 months, between the end of the CDCA stocks of the Pharmacy of the University Hospital of Siena (end 2015/beginning 2016) and the introduction of *CDCA Leadiant*® in the Italian market (June 2017), an event which, as already illustrated, led to the exacerbation of a regulatory barrier that prevents, apart from exceptional cases, the production of CDCA-based magistral preparations on the domestic market. The existence of any sources of production of the active substance alternative to PCA subsequent to the period referenced above is therefore, irrelevant since it could not in any case be legitimately used for any galenic production capable of satisfying all the demand for CDCA-based drugs in Italy.

406. From this point of view, therefore, the evidence produced by the Party concerning the supply of CDCA to PCA by a wholesaler of pharmaceutical-grade active substances, in turn probably supplied by a Chinese manufacturer, is completely irrelevant, as it dates back to October 2017, when the Italian pharmacies were already prevented from setting up galenic production of CDCA. The same is true for the documents proving *i)* that *Pierre Fabre* offered the supply of CDCA directly to Leadiant in 2019; *ii)* that there is a Chinese source of CDCA capable of supplying the galenic production of

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[486] See doc. 78.416 ("[...] *there are two global API providers relevant for this product*"), one being PCA and the other NZP, 78.133, Annex "AIFA Sigma Tau MEETING REPORT 24 June" ("[...] *Product of bovine derivation. 2-3 manufacturers worldwide*") and 78.323 ("[…] *there are truly only 2 GMP, FDA approved suppliers globally*").

[487] See doc. 138.4.9 ("*Furthermore, there is only one approved EU certified supplier of pharmaceutical-grade CDCA...*").

CDCA of the Amsterdam hospital from at least February 2020; and *iii)* that there are other European companies which, as producers of ursodeoxycholic acid, could enter the market for the production and sale of CDCA as a pharmaceutical-grade active substance.

407. However, even if one considers such evidence as an indication that sources other than PCA existed before the points in time to which the said documents date, as the Party states, the following should be noted. Firstly, the document proving that a wholesaler of pharmaceutical-grade active substances offered CDCA to PCA in October 2017 contains another document, an e-mail exchange, from exactly one year earlier (October 2016, which is a significant point in time for the purposes of this evaluation), in which it was instead the wholesaler who asked PCA to provide CDCA on behalf of a hospital[488]. In 2016, therefore, the roles were reversed. And this was also the case a year later (October 2018), when the same wholesaler again asked PCA to supply CDCA.

408. These events are highly indicative not only of the fact that in 2016, i.e. when Italian hospitals asked PCA to supply CDCA, the source indicated by Leadiant as an alternative to PCA was not actually available because it did not have access to the raw material (so much so that it itself turned to PCA), but they also explain certain other elements that are crucial for assessing the existence of a dominant position held by Sigma Tau in the period prior to the obtainment of the MA for the orphan drug.

409. First of all, it is clear that the source of production of CDCA to which the wholesaler turned at least from October 2017 was not a reliable and stable source. In this regard, it should be noted that, given the severity of the disease and the life-saving nature of the drug, even galenic production requires a stable and lasting procurement source that guarantees continuity of supply. Evidently this source, which was identified by Leadiant in its own defence arguments (as well as *Pierre Fabre*, whose offer is completely sporadic), did not possess these characteristics and therefore could not be considered as a valid alternative to PCA by Italian hospitals, not even in 2016.

410. In addition, the evidence regarding the relationships between PCA and the wholesaler of pharmaceutical-grade active substances must be read together with the documents on file that indicate the (unsuccessful) attempt by several hospitals and pharmacies located in other Member States, in particular the Amsterdam hospital, to set up a galenic production between 2017 and 2018

[488] See docs. 28.2.183 and see with doc. 22.7.64.

using the raw material from an Asian source through the imports of the said wholesaler. This evidence shows that in August 2018 it became clear that the above-mentioned galenic production was not compliant with the technical specifications imposed by the European Pharmacopoeia, as it contained too many impurities. It was immediately after this event that the aforementioned wholesaler of raw materials again contacted PCA, stating that it had confidence only in the quality of the CDCA produced by European operators[489], and in particular in PCA. This shows that the Asian sources, described by Leadiant in its own defence arguments as having long been available on the market, were not only unstable, but also not yet adequate to support galenic production of CDCA as of the end of 2018. Thus, they would not have been able to in 2016, either, when Italian hospitals had attempted to resume production.

411. In particular, the document that supposedly highlights that 15 suppliers of CDCA alternative to PCA were effectively active inside and outside the European Union (at least) as early as 2015, is largely devoid of probative value, not only due to the events mentioned above, but also due to a plethora of documents on file that indicate that these production sources were not concretely available on the market, neither before 2015 nor after.

412. Indeed, as per the evidence it appears that the sporadic sources of CDCA production outside of Europe, especially in China, have long been unable to access the European market, precisely because of their inability to adhere to the GMPs imposed by European authorities, which require stricter standards than those imposed in other countries, such as India, China and other Asian countries[490]. PCA itself recognised this, and in October 2016 – i.e., during the period relevant for this evaluation – it stated that non-EU CDCA suppliers, in particular those from China, would not pose "*a problem*" for Sigma Tau, in the sense that at the time these production sources could not in general be considered valid alternatives by anyone wanting to produce CDCA-based drugs[491]. The events that occurred from 2017 to 2018 proved this to be correct.

413. Indeed, Sigma Tau itself clashed with this reality in 2016 when, before entering into a new exclusive supply contract with PCA, it set out to find alternative producers; it first obtained a list of potential operators who,

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[489] See doc. 28.2.183.

[490] See docs. 25.3.5, 78.190, 78.303.

[491] See doc. 78.262: "*Compounding and foreign/exotic API supply of CDCA will not represent a problem*". See also docs. 28.2.132 ("[...] *a Chinese source will not represent an issue for you*").

however, were not able to replace or support PCA, precisely because the quality of the raw material they produced was uncertain, and then, on the eve of the conclusion of the contract with PCA, it concluded that there were no valid alternatives to the Italian chemical company (see paragraph 55 above). Indeed, at the end of the above market research, Sigma Tau resolved in November 2016 to again choose PCA as its exclusive CDCA supplier.

414. The only other operator seriously considered by Sigma Tau, because it was able to obtain sufficient quantities of bovine bile, the main input from which the raw material is obtained, and adhere to GMPs in a similar way to PCA – NZP – could not be considered an effective alternative to PCA in 2016 because at that time, it was commercially engaged with Retrophin to produce *Chenodal*, which was marketed in the United States (see paragraphs 54-55 above). Moreover, the same documentary evidence serves to dismiss the Party's other arguments concerning the concrete availability of operators supplying other manufacturers of industrial CDCA-based drugs (such as *Chino*). Lastly, the aforementioned evidence clearly reveals that in 2018 the pharmaceutical company itself believed that there was only one certified operator in Europe, namely PCA. This indicates that it had excluded other European companies, such as PharmaZell GmbH and Dipharma Francis Srl, now indicated, though without any supporting evidence capable of refuting the aforementioned investigation documents, as operators possessing the potential and skills to enter the market to produce and sell CDCA as a pharmaceutical-grade active substance, given that they produced ursodeoxycholic acid from non-bovine bile, with respect to which chenodeoxycholic acid is an intermediate product.

415. All the observations made thus far on the effective operation of sources of production of CDCA other than PCA also contradict the Party's arguments regarding the ease of supply of CDCA by a hospital. The aforementioned events at the Amsterdam hospital, who since 2018 has been trying to set up galenic production of CDCA by turning to non-EU sources (only managing to succeed in February 2020), show how it is anything but easy for a hospital pharmacy to find a reliable, stable source of a raw material able to comply with the European Pharmacopoeia. The Amsterdam hospital took 18 months to find a supplier with these characteristics, i.e., exactly the amount of time that elapsed between the moment in which the stocks of CDCA from the Pharmacy of the University Hospital of Siena ran out and the introduction of *CDCA Leadiant*® to the Italian market. In any case, it was not possible for a hospital to wait for this long of a period before resuming the administration of

the therapy to its patients without causing serious damage to them. Faced with the urgent need of having to continuously administer the therapy to their patients, hospitals therefore had no alternative but to contact Sigma Tau to purchase *Xenbilox*®.

416. All this shows that, at least between January 2016 and June 2017, PCA was the only source of CDCA production from which hospital pharmacies could obtain the raw material to fuel galenic production pending the entry of the orphan drug on the domestic market. This was however impossible due to the commercial exclusivity that bound the chemical company to Sigma Tau and which the latter leveraged to prevent the continuation of the production of magistral preparations after January 2016.

ii) The entry to the Italian market with the sale of Xenbilox® from January 2016

417. The company's arguments to justify the impossibility of assigning a dominant position to it on the relevant market from January 2016 also appear to be without merit in claiming that *Xenbilox*® did not have an MA in Italy, nor was it marketed directly by Leadiant on the Italian market, instead being marketed by a third-party wholesaler, Juers Pharma, said to be acting in total autonomy.

418. In this regard, it should be noted first of all that Leadiant's alleged non-involvement in the marketing of *Xenbilox*® in Italy is disproven by the evidence referenced hitherto, which shows that the company wished to eliminate the production at the Pharmacy of the University Hospital of Siena to force the Hospital, and consequently other Italian hospitals, to purchase *Xenbilox*® (see paragraph 126 above), and that it was the company itself that redirected the University Hospital of Siena, as well as all Italian hospitals that requested the supply of raw material after the cessation of the Pharmacy's galenic production, to purchase *Xenbilox*® from Juers Pharma (see paragraph 135 above).

419. The evidence acquired also shows, as already illustrated, that a distribution system based on custom sales made by a third party in markets other than Germany was the model specifically chosen by Leadiant (at the time Sigma Tau) precisely to invoke the formal lack of connection between the company and the price applied in these markets. The party behind the commercial policy applied by independent distributors in Italy for the sale of

Xenbilox® was Juers Pharma, and therefore Leadiant[492]. In fact, since mid-2014, when the company implemented the ex-factory price increase of *Xenbilox*® to €2,900, Juers Pharma had been implementing its commercial policy in national markets other than Germany, including Italy, on the basis of precise indications from Leadiant (see paragraph 108 above).

420. The argument that Leadiant was commercially unrelated to the sales of *Xenbilox*® is also refuted by certain pieces of evidence, which indicate that some company employees as well as external consultants, as part of the negotiation procedure with AIFA, advised against its use ("*we must be very careful in saying that LB has never sold Xenbilox etc.*"[493]).

421. This means that sales of *Xenbilox*® in Italy, since the beginning of 2016, when the drug began to be imported by the Italian ASLs from Germany, are obviously attributable to Leadiant, even without a valid MA for the drug in Italy.

422. It should be noted, moreover, that, contrary to what the Party claims, the closure of the Italian market to the CDCA-based galenic productions and the entry of Sigma Tau to the Italian market with the sale of *Xenbilox*® did not take place without significant inconvenience to Italian patients and the centres that were treating them.

423. Some pieces of evidence, in particular, show that several Italian hospitals have complained about how the lack of access to the raw material created a shortage of supply and risk for patients. An example of the risk faced by patients can be seen in the evidence that shows that the stock of magistral preparations already produced at the end of 2015 would have allowed the University Hospital of Siena to provide the medicine to only three patients and only for the subsequent two or three months (see paragraph 132 above).

424. The enormous difficulty that this has caused patients and the centres that were treating them is clearly shown by the complaints from a doctor who, four months after the raw material stocks ran out, decried the failure to initiate the procedure to request the early access to the orphan drug pursuant to Law no. 648/1996, proposed by the same dominant company, instead of granting the access to PCA's raw material requested by the hospital to continue galenic production: "*Unfortunately the information we had, not from AIFA but from Dr* [N.] *who, as you will remember, should have sent us all the documents to*

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[492] The fact that Leadiant was perfectly aware of the economic and commercial conditions under which Xenbilox® was sold in Italy can be found in doc. 78.124 ("*All CTX patients were treated in Siena until 2015 - Since 2016 they were sent back to the hospital of the place they live for treatment. This is when only Xenbilox at about 3,7€ k/pack became available*").

[493] See doc. 78.112.

forward the procedure to AIFA, indicated that we should have waited until April, the period necessary for them to complete something that I no longer remember... contrary to all the declarations of principle made and repeated that patients would not suffer any inconvenience resulting from the 'industrial process', they will suffer and how [Editor's note: indeed], *and we along with them...*"[494]. This risk-filled situation was only remedied with the import of *Xenbilox*® from Germany.

425. The difficulties, at least for the University Hospital of Siena are, moreover, made evident by the Party's defence arguments, which state that early access to the orphan drug pursuant to Law no. 648/1996, in place of the purchase of *Xenbilox*®, would in any case have had only a redistributive effect in the sense that, pending the negotiation of the reimbursement price of *CDCA Leadiant*®, the resources necessary for the purchase of therapy for patients with CTX would not have come from the Italian National Health Service but would remain the responsibility of the University Hospital of Siena (with the purchase of *Xenbilox*®).

426. In fact, more precisely, once the stocks of CDCA from the University Hospital of Siena ran out, given the presence of the exclusivity clause contained in the contract with PCA, the supply shortage problem could be solved through the early access pursuant to Law no. 648/1996, as initially hypothesised, or with the import of *Xenbilox*®, which is what effectively happened. However, from a financial point of view, the two solutions were not equivalent, precisely because, as Leadiant itself states, in the first case the public facilities could have guaranteed therapy free of charge, while in the second case they had to sustain significant outlays (a pack of *Xenbilox*® containing 100 capsules of 250 mg costed about €3,400-€3,600), much more than the cost incurred until the creation of the galenic production (a pack of 100 magisterially produced capsules of 250 mg amounted to €67). Therefore, since it was impossible to provide the orphan drug under the early access regime, a derogation from the exclusivity clause contained in the supply contract stipulated with PCA could have represented a valid solution. This was proposed by the chemical company itself, but Leadiant was unwilling to consent (see paragraph 135 above). This undoubtedly caused difficulties for the public health facilities involved and confirms Sigma Tau's obtainment of a position of absolute prominence on the domestic market.

V.3.3 The stability of the dominant position acquired in Italy

427. The Party's argument concerning the obstacles to maintaining the dominant position acquired in Italy in the future through obtaining the MA for the orphan drug in the national territory is shaky, since it fails to precisely identify the potential competitive forces able to effectively regulate its market power.

428. In terms of potential competition, it is necessary to reiterate once again that the Italian market for the production and sale of CDCA-based drugs used for the treatment of CTX is extremely small (as are the national markets in other EU Member States), given the rarity of the disease in question (see paragraph 63 above). This means that the number of companies that can reasonably be expected to have a real economic interest in entering this market is, as the company itself has acknowledged, extremely small[495].

429. It should also be borne in mind that, in the context of this restricted group of operators, any undertaking intending to introduce a new pharmacological therapy for the treatment of CTX, must currently demonstrate, first of all, that pursuant to Article 3(1)(b) of Regulation (EC) no. 141/2000, the orphan candidate drug is of "significant benefit" for people affected by this disease, compared to existing therapies[496]. In addition, the applicant must demonstrate that the candidate drug is not "similar" to one that already has an orphan designation or, if it is "similar", that it is "clinically superior" to the latter, according to the provisions of Article 8(1) and (3) of Regulation (EC) No 141/2000 (see paragraph 41 above).

430. The aforementioned set of regulations represents a significant barrier to enter the market for potential competitors of Leadiant. In fact, proving the "significant beneficial effects" and/or "clinical superiority" in this case is tricky, given the presence on the market of the orphan drug owned by Leadiant, which contains an active substance currently considered as the "first line treatment" for CTX. In other words, the scientific, and therefore economic, effort required from any future competing undertaking due to the applicable regulations is much greater than that faced by Leadiant. While, on the one hand, Leadiant was in fact able to enter the market despite the fact that *Kolbam*® was already present, on the other hand, however, its comparative

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[495] See doc. 22.7.17 (*"I don't see any new drug arising in the treatment of CTX and I think that it will be very difficult to see somebody investing resources in this sector in the coming years……it's a too small pathology… it's an orphan who nobody wants to adopt!"*).

[496] On this point, the information set out previously under in paragraphs 383-387 above in relation to the clinical support necessary to provide such evidence applies.

research aiming to demonstrate the existence of a significant beneficial effect of CDCA compared to cholic acid in order to maintain the orphan designation, took place with respect to an active substance that in clinical practice had *already* long been considered inferior to CDCA. In other words, the demonstration of a significant benefit of a medicinal product compared to existing therapies is certainly easier when, as in this case, their therapeutic inferiority is already known in the medical/scientific community, who has already proven the superiority of the candidate orphan drug through its own established prescription choices. Quite to the contrary, it is much more difficult to demonstrate the therapeutic superiority of an orphan drug compared to what the scientific field considers the standard therapy for the disease at a given time.

431. Moreover, it should be noted that the investigation analysis carried out clearly shows that at present there are no other therapies, even in the experimental phase, for the treatment of the rare disease in question and that the only lines of research currently in existence are at an embryonic stage, with the goal of developing a gene therapy in the future. This piece of evidence therefore allows us to state with reasonable certainty that there are no other therapies for CTX that can be approved by the regulatory authorities in the near future (see paragraph 71 above).

432. Based on the foregoing, it follows that the regulatory context that characterises this case makes it highly unlikely that other companies would obtain an orphan designation and MA for a drug with the same therapeutic indication for which *CDCA Leadiant*® is registered and effectively enter the market within a reasonable time frame, or in any case before the expiration of the exclusivity right that the dominant company enjoys.

V.3.4 Conclusions on Leadiant's dominant position in Italy

433. Given the above, it is believed that, from 2016, Leadiant unquestionably holds a dominant position on the national market for CDCA-based drugs used for the treatment of CTX.

V.4 Leadiant's comprehensive strategy in preparation for abusive conduct

434. The investigation has shown that Leadiant relied on a carefully structured and pre-ordained strategy over time that subsequently allowed it to

engage in the abusive behaviour ascertained by this decision.

435. In this regard, the dominant company believes, first and foremost, that the documents related to this complex strategy cannot be used as evidence, since they pre-date the conduct. In support of this argument, it cites a ruling of the Lazio Regional Administrative Court from 2021, in which the administrative judges found that the documents on file could not be used as evidence, as they dated to a moment "*beyond the time frame of the alleged [anti-competitive] practice*", i.e. "*referring to facts having occurred prior to the term of the alleged agreement*"[497].

436. The ruling cited by the Party, however, is irrelevant to the case at hand, since the documents deemed to be illegitimately used as evidence in the cited case constituted the proof of the existence of the disputed conduct, and specifically of the starting of it, and not, as in the present case, elements that paved the way for and enabled the disputed conduct, the consideration of which is necessary to understand how the dominant company was then able to carry it out.

437. These elements consist of *i)* the increase in the price of *Xenbilox*® even before obtaining the MA for *CDCA Leadiant*®, as a tool to prepare the market for the future price of the orphan drug; and *ii)* the artificial differentiation between *Xenbilox*® and *CDCA Leadiant*® obtained through the withdrawal of the former from the market at the time of the introduction of the latter drug, as well as the assignment of the ownership of the orphan drug to a company other than the one that owned the off-label drug.

V.4.1 The increase in the price of Xenbilox® *in preparation for the price of the orphan drug*

438. The investigation indicates that the objective pursued by the company since 2007 through the project of registration of the orphan drug in Europe was to introduce it to the market at a particularly high price with the aim of increasing its profits.

439. This aim was pursued through a strategy of gradual price increase ("*step price increase*"[498]) of the only CDCA-based drug that remained on the

[497] See Regional Administrative Court of Lazio, judgment no. 8239 / 2021

[498] See docs. 96.213, 22.7.3 Annex "*121 06 Report Draft 250307*" ("[…] *step price increase should be possible; step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current pack (to evaluate best option requires further analysis); precedent in Germany for novelty being recognised of old product in new indication; Clear rationale and KOL support will be needed to facilitate reimbursement of CDC after a step price increase*"), 22.7.3 Annex "*006060_2 Report*", 96.75, 96.99 and 96.165.

market and was administered off label for the treatment of CTX, of which the company had become the owner in 2008, and which in the future would be replaced by the on-label orphan drug at an even higher price.

440. In particular, the long-term price objective for the orphan drug was achieved through the pursuit of medium-term objectives consisting of two distinct increases in the price of the off-label drug. An initial increase in the price of *Chenofalk*®, then renamed *Xenbilox*® as of December 2009, took place in February 2010 when the company set the ex-factory price for the sale of the medicine on the German market at €660 per pack of 100 capsules of 250 mg, whereas the same pack of *Chenofalk*® had previously been sold on that market at the ex-factory price of €37.75 (see paragraph 97 above).

441. Subsequently, in early 2014, when the CDCA Project was about to start, it returned to the idea of a progressive increase in the price of the off-label drug. Thus, after various scenarios, the company finally decided to set the ex-factory price for the sale of *Xenbilox*® in Germany to €2,900 per pack, starting from 1 July 2014 (see paragraphs 120-123).

442. The application of a "*premium price"* for the off-label drug, with such price strategy having been designed some time before and justified on the basis of the rare therapeutic indication[499], thus prepared the market – including the domestic market, from 2016 when *Xenbilox*® entered the Italian market – for the future price at which Sigma Tau wanted to launch the on-label orphan drug in Europe[500].

443. The evidence acquired on this point (see paragraphs 92, 98, 99 and 122) shows that the Party's assertions about the correlation between the increase in the price of *Xenbilox*® and the drastic reduction in demand are groundless. This is primarily because the demand for CDCA had been drastically falling for quite some time, well before the price increases of 2014 and 2009; in particular, the scientific literature shows that the prevalence of the rare therapeutic indication of CDCA dates back at least 20/25 years earlier, because CDCA had not been used for the treatment of gallstones at least since the beginning of the 1990s (see paragraph 61 above). The considerable time gap, in particular, between the price increase of 2014 and the commercial reason that Leadiant would like to attribute to it today, can also be seen in the

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[499] See doc. 96.213 ("[...] *step price increase should be possible, based on rationale of: − Ultra orphan status*").

[500] See doc. 96.213 and 22.7.3 Annex "121 06 Report Draft 250307" (*[...] "Price should ideally be at desired level post-approval. Desired step price increase can happen pre-or post CTX MA approval"*).

same defence statements from the Party[501], which indicate that the demand for CDCA had already decreased significantly in 2006 due to the exclusive use of the ingredient for the treatment of CTX.

444. However, the Party's arguments are mainly refuted by the numerous pieces of evidence that demonstrate the company's true intent, namely that the increase in the ex-factory price of *Xenbilox*® to €2,900 per pack in 2014 had no connection to the reduction in demand for CDCA and was, conversely, connected with the CDCA Project that Sigma Tau had decided to relaunch at exactly that time. The fact that the company implemented a new increase in the *ex-factory* price of *Xenbilox*® right before requesting orphan designation for CDCA, i.e., just before the achievement of another medium-/long-term goal important for the fulfilment of its project ("*1/ short term goal: price increase (in 2 steps) [...] 2/ medium/long term goal: registration process Goal: to get the ODD in the wider indication as possible*")[502], and that it has itself linked the said price increase to the development of the orphan indication for the drug ("*In order to be able to maintain and further develop CDCA for this rare disease indication, Sigma Tau has to revise the price in accordance with an orphan indication (CTX)")*[503], constitutes a clear indication of the connection between the new price increase and the fulfilment of the regulatory activities included in the CDCA Project that would have allowed the launch of the orphan drug. With the concrete start of the second phase of the project for the introduction of the orphan drug to the market, the objective to "prepare" the market for the future price became relevant once again and required that the new price increase of the off-label drug, envisaged some time before, be implemented.

445. Furthermore, the price evaluations found in the investigation documents cannot be considered as mere market access evaluations, as claimed by the Party, since the preparatory value of the price increase of *Xenbilox*® in 2014 is clearly evident from the documents already mentioned, in which the company expressly links the price increases to the price of the future orphan drug (" *[…] Impact of current price on future potential price*

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[501] See paragraph 282 on page 74, which states: "*At this stage, the revenues from Chenofalk were essentially exclusively attributable to sales made by Dr. Falk to German wholesalers, which in turn sold Chenofalk to pharmacies that imported CDCA-based products in order to treat patients with CTX"*. The wording "*at this stage*" must mean the period prior to the purchase of Chenofalk by Sigma Tau, as can be deduced from the context in which the aforementioned period falls and from the title of the section in which it is contained: "*The market context in 2006*".

[502] See doc. 96.228.

[503] See docs. 96.43 and 96.217.

[…] - step price increase should be possible - step price increase could be achieved by 'withdrawal and reintroduction' or simple price increase on current pack"[504]).

446. Finally, the existence of a functional relationship between the 2014 price increase and the future price of the orphan drug cannot be called into question simply because, as the company claims, sales made outside the German market were managed by Juers Pharma in total autonomy and independence (see paragraph 108 above). In fact, the acquired evidence clearly shows that the involvement of the German wholesaler in the *Xenbilox*® distribution chain was purposely planned by the company, so that in markets other than Germany the price increase decided by Sigma Tau was formally attributable to a third party. The sole purpose of the interposition of this operator in the distribution chain was to save the pharmaceutical company having to justify and/or negotiate the new price increase with patients and the hospitals treating them. This distribution strategy not only allowed the company to overcome the profit constraint set by German regulation (where the reimbursement price was set at €660 per pack and therefore the difference with respect to the new ex-factory price of *Xenbilox*®, set at €2,900 per pack, had to be paid to the health insurance companies) by increasing the price to the desired level in the EU national markets (where it was not subject to regulation), which at the time imported *Xenbilox*® from Germany[505], but it also allowed it to prepare these markets for the price that would be applied in the future.

447. Lastly, the link between the price increase implemented by Leadiant in 2014 and the pricing policy that the company intended to apply for the orphan drug can be clearly seen in a document dated December 2014, which contains ex-post comments on what had already been done in the past by the company and could be repeated in the future ("*Sigma Tau wants to increase the monthly treatment cost of Xenbilox® and has already introduced some*

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[504] See doc. 22.7.3, Annex "121 06 *Report draft 250307 (PA again again*)".

[505] See doc. 96.141 ("[…] *we have developed an idea how we can keep the price in Germany but increase it for foreign markets (by rationing German wholesalers and have Juers as our wholesaler and point of sale for Xenbilox – who would sell the product to (foreign) customers at a higher price*. […] *we can increase our profit without being stuck by the price moratorium*. […] *increase the price to 860 Euros per unit to ALL customers (incl. German market). Everything that ends up in Germany will be reimbursed with 660 Euros and we have to refund the German sick funds with the price difference of 200 Euros.*
All units that are being sold to foreign markets will not have to be refunded -> 2,511 packs x 200 Euro = ca. 500,000 Euro increase in sales (+ ca. 300 units x 200 Euros = 60,000 Euros) -> all additional sales are profit.
We will only supply the German wholesalers. All other customers will be referred to JUERS who manage he distributors for us").

price increases")[506].

V.4.2 The artificial differentiation of the orphan drug from Xenbilox®

448. The investigation also indicates that Sigma Tau pursued its objective by implementing a strategy of artificial differentiation of *CDCA Leadiant*® from the off-label drug ("*brand differentiation*"[507]), the foundation of which was initially laid in Germany between 2014 and 2017 and whose effects then reverberated in other European countries, including Italy. This strategy, which included the withdrawal of *Xenbilox*® from the market and the attribution of ownership of *CDCA Leadiant*® to a company other than the MA holder for the off-label drug, was aimed at avoiding the difficulties that would inevitably arise where the regulatory authorities asked, as was subsequently the case, for justification of the high price that Sigma Tau intended to apply to the orphan drug. in view of the fact that the project carried out by the dominant company consisted in the reuse of an old drug, *Xenbilox*®, for a new therapeutic indication ("repurposing") that was already being treated with the old off-label drug[508].

449. The fact that this strategy primarily concerned Germany does not make it irrelevant to the purpose of this decision, as the Party claims when it classifies these events as relating to a different geographic market and indicative of the alleged violation of national law other than Italian law, in relation to which the Italian Competition Authority would have no jurisdiction. Indeed, the inspection documents thoroughly disprove these arguments, insofar as it clearly demonstrates that the success of the designed commercial strategy in Germany would also have had a positive impact on the prices of the other Member States ("*getting an increase in the German price is necessary (or removing this product as a price benchmark) if a higher level of price is the ambition for Chenorm across Europe [...]"*)[509]. In other words, the investigation showed that it was particularly important for Sigma Tau to obtain a high price in Germany, the national market of choice from which the dominant company operated throughout Europe, since this would also represent a point of reference for price negotiations in other Member States, including Italy.

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[506] See doc. 78.71.
[507] See doc. 78.57.
[508] See doc. 78.225 ("*Stakeholder perception of transition from Xenbilox to CDCA Leadiant. […] Payers might take CDCA Leadiant as an example of repurposing not being acceptable, even under ODD*").
[509] See doc. 22.7.3, Annex "006060_2 Report".

450. Leadiant's arguments, specifically as regards the economic rationale for the withdrawal of *Xenbilox*®, in response to commercial considerations on the cost of keeping a drug on the market whose therapeutic indication had become obsolete, appear to be completely contradicted by the acquired evidence.

451. Sigma Tau itself included *Xenbilox*® (see paragraph 123 above) among the risk factors of a competitive nature that could have hindered the pricing policy that it decided to apply for the orphan drug.

452. *Xenbilox*® represented a threat primarily in Germany, since the drug price moratorium set by German regulation until 2022 for products marketed from 2010, which also applied to the orphan drug, as it contains an active substance already marketed in Germany, would have triggered an automatic binding discount equal to the difference between the price of *CDCA Leadiant*® and the reimbursement price of *Xenbilox*® to be paid to German health insurance providers (see paragraph 159 above). This would have hindered the planned pricing policy devised for the launch of the orphan drug.

453. In order to overcome the regulatory obstacle blocking Sigma Tau's price targets, it was necessary for *CDCA Leadiant*® to be perceived as a new and different product compared to *Xenbilox*®. This objective was first pursued and achieved with the withdrawal of *Xenbilox*®, which began in October 2016 (with the formal cessation of sales by Sigma Tau and the continuation of sales until stocks were exhausted by Juers Pharma) and concluded between April and May 2017. Once the procedure for withdrawing the off-label drug from the German market was completed, in May 2017 Sigma Tau requested the removal of the *Xenbilox*® from the official list at exactly the same time as the request for registration of *CDCA Leadiant*® on the same list. This meant that the two products were never on the market at the same time (*"Xenbilox and the new CDCA Leadiant will not co-exist in the market"*[510]) (see paragraphs 166 and 168 above).

454. The evidence of the link between the withdrawal of *Xenbilox*® from the market and Leadiant's profit objective can be seen in one document in particular (which has repeatedly been referred to) dating from September 2014, where the company itself identifies the withdrawal of *Xenbilox*® from the market as a necessary instrument for increasing the price of the CTX

[510] See docs. 78.262 and 78.249.

drug[511].

455. The other element upon which Sigma Tau based its differentiation between *Xenbilox*® and *CDCA Leadiant*® consisted of the establishment of a new company under German law that is the MA holder for the orphan drug. This was because Sigma Tau realised that, although necessary, the withdrawal of *Xenbilox*® from the market would not have been sufficient to exclude the anchoring of the orphan drug's reimbursement price to the off-label drug's reimbursement price because under German law, *CDCA Leadiant*®, despite having a new therapeutic indication, contains a compound that already existed on the market, regardless of whether it was still being marketed or not (see paragraph 164 above). It therefore set up a company under German law that was formally different from the company that previously owned *Xenbilox*®, to which it assigned the ownership of the orphan drug.

456. The Party's arguments that such a decision would not in any way have prevented the German insurance companies from referring to the reimbursement price of *Xenbilox*® in the negotiation of the reimbursement price of the orphan drug, but at most would have prevented them from obtaining the binding automatic discount equal to the difference between the price of *CDCA Leadiant*® and the reimbursement price of *Xenbilox*®, do not hold water.

457. In fact, aside from the fact that, in material terms, the two effects of the establishment of the new company under German law to which Leadiant refers are identical (taking the price of *Xenbilox*® as a reference in the negotiation of the reimbursement price of *CDCA Leadiant*® specifically served the purpose of obtaining the discount to which the Party refers), it should be noted in any case that these statements are contradicted by the words of the same dominant company contained in the inspection documents, which accurately accounts for the fact that the project to establish the new company holding the MA for the orphan drug, Leadiant GmbH, was outlined at the beginning of 2016 and carried out until the launch of the orphan drug with the primary and exclusive purpose of not allowing German health insurance companies to refer to the price of *Xenbilox*® when setting the reimbursement price of the orphan drug ("*[…] we will need a newco in Germany because*

[511] See doc. 22.7.17 ("*[...] In some countries a further price increase may only be possible with combination of current license withdrawal, approval in CTX and rebranding"*). Since the ex-factory price increase of *Xenbilox*® to €2,900 per pack had already taken place, the "*further price increase*" planned by the company must refer to the price at which the orphan drug would have been launched on the market, after the registration of the new therapeutic indication.

neither ST GmbH nor STRDL can be MA holders and/or distributors of the new CDCA without an immediate reference to the old Xenbilox price. A name change is not enough. This must be a new pharmaceutical entrepreneur (new numbers, register, etc.)[512]") and to obtain the desired price for the future orphan drug (see paragraph 171-174 above).

458. The establishment of the new German company was also part of a broader strategy implemented at the European level aimed at excluding the possibility, from a corporate standpoint, of establishing links between the ownership of *Xenbilox*® and *CDCA Leadiant*® so that they would appear as two completely separate assets[513]. As early as mid-2015, ownership of *Xenbilox*® was formally entrusted to the group's British subsidiary, while ownership of the orphan drug under preparation was formally held by the German subsidiary. The sole purpose of the establishment of a new German subsidiary with a new trade name different from that of the previous *Xenbilox*® distributor on the German market and from the owner of the mentioned off-label drug was therefore to further separate the two businesses from a formal standpoint.

459. This strategy enabled the dominant company to claim before the competent authorities that Leadiant GmbH had no connections with Sigma Tau Arzneimittel GmbH and that the orphan drug was not linked in any way with *Xenbilox*® (see paragraph 176 above).

460. All of this completed the work of differentiation of the two products and allowed the dominant company to present to the German market a drug that, at least formally, was dissimilar from what had been present until then on the market, and to definitively overcome the constraint placed by the price moratorium on the profit objectives pursued by the dominant company.

461. In other words, through this composite strategy, Leadiant created a formal distinction between *Xenbilox*® and *CDCA Leadiant*®, which was deliberately established to artificially differentiate between the two products

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[512] See doc. 96.79.

[513] The numerous transfers of ownership of the administrative rights to *Xenbilox*® and the orphan drug that have occurred over time between group companies are telling in this regard. Since October 2008, Sigma Tau Arzneimittel GmbH has been the marketing authorisation holder for *Xenbilox*® in Germany (see paragraph 97 above). In August 2015, this administrative title was transferred from Sigma Tau Arzneimittel GmbH to Sigma Tau Rare Disease Ltd., which then became Leadiant Biosciences Ltd. in December 2016 (see paragraph 141 above). The request for the preliminary orphan designation of CDCA was submitted by Sigma Tau Rare Disease Ltd. on 28 August 2014 and obtained by the same company on 16 December 2014. This administrative title was transferred on 7 May 2015 to Sigma Tau Arzneimittel GmbH (see paragraphs 117-118). The MA application for the orphan drug was submitted by Sigma Tau Arzneimittel GmbH on 29 October 2015 and obtained on 10 April 2017. Ownership was then transferred to Leadiant GmbH on 31 May 2017 (see paragraphs 141 and 156 above).

from a substantial point of view.

462. Several pieces of evidence indicate that this differentiation has led to the desired effects: the German health insurance association's arguments regarding the identities of the two compounds were, in fact, contested by Leadiant successfully. Consequently, the association could not refer to the reimbursement price of *Xenbilox*® to obtain the binding automatic discount on the price of *CDCA Leadiant*® (see paragraph 177 above).

463. This strategy, which started in Germany, was then extended to the other Member States interested in purchasing the orphan drug, including Italy. More specifically, the formal and substantial discrepancy between *Xenbilox*® and *CDCA Leadiant*® was again proposed to AIFA when the Agency asked for explanations about the price difference between the orphan drug and *Xenbilox*®, in order to obtain the high price that the dominant company had set itself (see section V.5.1.iii below).

V.5 Leadiant's abusive behaviour

V.5.1 Negotiating levers adopted during the CDCA Leadiant® reimbursement price determination procedure

464. The acquired evidence indicates that, during the negotiation procedure of the reimbursement price of the orphan drug, Leadiant intentionally maintained a dilatory and obstructive attitude towards AIFA. Indeed, for a year and a half, despite repeated requests from the Agency, the dominant company did not provide any information or documents on investments in research and development that could adequately support its initial and/or subsequent price proposals, and thus justify the price difference between *CDCA Leadiant*® and *Xenbilox*®, and strategically extended the time of the negotiation procedure with the late submission of economic offers rectifying the initial one.

i) The delay in provision of the data on costs

465. In relation to the cost data incurred for the execution of the project of registration of the orphan drug, it should be noted that, from the beginning of the negotiations for the price of the orphan drug, and in particular as a result of the CPR session dated 19 March 2018, AIFA formally requested that the dominant company justify its initial request of €15,506.93 per pack by

providing appropriately detailed information on the costs incurred for the registration project of the orphan drug, with particular regard to investments in research and development (see paragraph 194 above). This request was repeated a second time at the meeting in July 2019 and a third time, again in writing, in September 2019 (see paragraphs 207-208 above). It originated from the finding that this price was too high and unjustified compared to the presumed financial effort incurred and the activities carried out for the introduction of the drug to the market, given that, for the Agency, "*the authorisation procedure was based exclusively on retrospective studies and literature data*"[514].

466. This information was only sent, however, in aggregate form and without specific supporting documents, with a major delay, on 26 November 2019 (see paragraphs 208-209 above), i.e., more than a year and a half after the first formal request submitted by the Agency, thus hindering the AIFA assessment.

467. The arguments of the Party, who objects in many respects to this reconstruction since it argues that AIFA was not entitled by CIPE Resolution no. 3/2001 to ask the dominant company for information about the investments made for the development of the orphan drug but merely had to consider the therapeutic value of the drug on the basis of the cost-effectiveness criterion, appear, however, to be based on a partial and reductive reading of the applicable regulation. First of all, it should be noted that CIPE Resolution no. 3/2001 assumes cost-effectiveness as the main criterion in Article 3.1[515] but does not rule out the possibility that the Agency might ask the applicant company for information on the investments made for the development of a given drug. On the contrary, Article 6 establishes that the parties (and therefore also the dominant company), "*for the purpose of defining the price*, [must] *support their proposals with adequate economic assessments of the product and the industrial (with reference to investments in production, research, development and exports), market and competitive context in which such product is located*". Furthermore, Article 3.3.5 of CIPE Resolution no. 3/2001

[514] See docs. 78.77 and 78.79, Annex

[515] See Article 3.1 of CIPE Resolution no. 3/2001 which states: "*3. Criteria for the negotiation request. The Company must support its price request with documentation showing:*

3.1. A favourable cost–effectiveness relationship in one of the following situations:

3.1.1 the new medicinal product is useful for the prevention or treatment of relevant diseases or symptoms for which there is no effective treatment;

3.1.2 the new medicinal product has proven useful for the prevention or treatment of relevant diseases or symptoms for which the medicinal products already available provide an inadequate response;

3.1.3 the new medicinal product has a more favourable risk/benefit relationship compared to medicinal products already available in the National Pharmaceutical Handbook for the same indication".

clearly states that "*In any case, other elements relating [...] to any other information that may be useful to the parties must be provided"*. This final clause, clarifying that "*other elements that may be useful*" must be provided "*in any case*", gives AIFA the power to always ask the applicant company for any information it deems useful for its assessment.

468. Moreover, with regard to the usefulness to AIFA of the information relating to investments in research and development made for the development of the orphan drug, it should be noted that these were of particular importance in the case in question. In fact, it should be noted that in relation to *CDCA Leadiant*®, it was impossible to apply the cost-effectiveness criterion according to the terms required by Article 48 of Legislative Decree no. 326/2003, i.e., "*assuming as terms of comparison the reference price for the relevant homogeneous therapeutic category and the comparative daily cost in the context of drugs with the same therapeutic indications"*, because, as AIFA observed during the investigation, this comparator – an on-label drug with the same therapeutic indication - did not exist. Hence the importance of having a reference point for negotiation, which, in this case, could only be provided by the level of investment in research and development incurred by the dominant company for the registration of the orphan therapeutic indication, and which explains why the Agency has asked for this pivotal element three times.

469. In this regard, the delay in the transmission of information relating to the cost of production of *CDCA Leadiant*® has therefore undoubtedly had a negative impact on the Agency's ability to adequately assess the value of the drug and on the activity carried out by the dominant company for the purposes of registration. Therefore, it cannot be claimed, as Leadiant does, that it promptly provided information on the total costs incurred in Italy over the last three years and then that it has worked to quantify the data expressly requested by AIFA by contacting a consulting company, whose calculations took some time. These statements are, in fact, contradicted by the evidence, which clearly demonstrates that the dominant company was aware of the difference between the data provided and the data requested by the Agency and that, a full year before the request it had internally quantified the costs specifically incurred for the development of the orphan drug until that time (where, instead, the quantification requested from the *Copenhagen Economics* consultants was subsequently commissioned in the context of the investigation of the Dutch ACM).

470. As early as March 2017, in fact, the dominant company knew that the costs related to the CDCA Project that could be qualified as research and

development in Italy amounted to *[€100,000-€200,000]* (excluding the cost of the retrospective study commissioned from the University of Siena of *[€100,000-€200,000]*) (see paragraph 186 above). As early as May 2017, the dominant company was also aware of the amount of all costs incurred until then (2007-2017) for the project to register the orphan drug globally, equal to approximately *[€10-€20]* million (see paragraph 188 above). Leadiant also had a detailed account of the composition of these costs, their nature and the weight that each of them possessed in the overall investment made[516].

471. Despite having them available, the dominant company did not provide these data in March 2018 either, when AIFA formally requested for the first time a cost-based justification of the price proposal, or subsequently. Nor can Leadiant's mere illustration of the cost items that made up the financial investment incurred to keep the orphan drug on the market, which took place in June 2018 during a meeting with AIFA, be invoked as an element that demonstrates that the dominant company had at that time responded to the requests of the Agency, since, as pointed out by AIFA itself, Leadiant did not present any evidence to support this (see paragraph 202 above).

472. The reasons for this reluctance lie in the previously illustrated evidence, which indicates that the costs associated with the drug registration project hitherto incurred, especially those that could be considered investments in research and development (equal to more than *[€200,000-€300,000]*) within the total investments made in Italy in the three-year period 2014-2016 (*[€2-€3]* million) (see paragraphs 186-187 above), were, in fact, small and could never have justified the price request made to AIFA.

473. Even the level of investment of approximately *[€10-€20]* million that emerged as a result of the quantification of all costs incurred until that time for the project to register the orphan drug globally – carried out precisely because of the awareness that it would be difficult for Leadiant to justify the price that it intended to ask for the orphan drug[517] – was evidently not considered by the dominant company to be sufficient to justify the price request. This can be seen in the evidence, which shows very clearly how in July 2018, four months after the first AIFA request, after having ascertained the amount of the costs requested, Leadiant decided that it was better not to continue the internal investigations that it had carried out the previous year on

[516] See in particular doc. 22.7.5.
[517] See doc. 78.438.

the costs for the orphan drug registration project[518].

474. After the third request by the AIFA's CPR during the July 2019 meeting, Leadiant finally decided to communicate the data requested by AIFA in November 2019, after the data on the total costs incurred globally was updated by the *Copenhagen Economics* consultants to *[€100-€200]* million over the 2014-2023 period (see paragraph 209 above).

475. However, not even on this occasion did the dominant undertaking provide "*detailed*" or adequately "*documented*" information as requested by AIFA; instead, it merely submitted aggregated data, without supporting evidence, which thus proved of little use to the Agency (see paragraph 212 above). Leadiant therefore complied on a solely formal basis with AIFA's request but in essence it did not allow the Agency to concretely assess the information provided.

476. Moreover, over the following months the dominant undertaking did not bother to provide the Agency with the updated value of the total costs incurred globally, which was much lower than that reported: *[€70-€80]* million instead of the initial *[€100-€200]* million (see paragraph 210 above).

477. Based on this, it follows that the Party has intentionally exploited an obvious information asymmetry and behaved in a way that is anything but cooperative and inspired by good faith.

ii) The lengthening of the negotiation procedure time frame

478. The evidence indicates that Leadiant further exploited AIFA's weak bargaining position – which was already weakened by the fact that the negotiation concerned the price of a life-saving orphan drug – by letting time pass without the negotiations making any progress.

479. On this point, the Party's arguments that are based on a comparison between the duration of the *CDCA Leadiant*® price negotiation (18 months) and the average time that a drug takes to obtain reimbursement by AIFA from the time it is approved by the EMA (24 months) are not compelling. To this end, it should first be noted that neither the drug type nor the scientific and market context that characterised these negotiations is known, nor is their possible similarity to this case. The fact that they were of longer or shorter duration than the price negotiation procedure in question does not, therefore, enable the drawing of any significant conclusions on the matter. Secondly,

[518] See doc. 78.150 ("*Pierre in fact pulled the number together for me a while ago and after seeing it I thought it best not to take it any further"*).

what matters is not only the duration of the negotiation procedure, but rather the manner in which it was conducted by the parties and, in particular, in the present context, by the dominant company.

480. In this regard, the evidence acquired during the investigation shows that the parties met three times, in June 2018, July 2019 and December 2019, and that between March 2018 and November 2019 they had a substantial exchange of correspondence regarding several economic proposals and counter-proposals (see paragraphs 194-209 above).

481. What is immediately apparent is the significant time gap – a full thirteen months – between the first and the second meeting between the parties. During the first meeting, after the CPR repeated that it was dissatisfied with the first two price-volume agreement proposals presented by Leadiant (which modified the initial price proposal) and the procedure was consequently suspended, the dominant company resolved to submit a third modified offer only in March 2019 (detailed only in April 2019), meaning seven months late (almost eight when considering when the detailed proposal arrived) compared to the 15-day deadline established by AIFA to send the mentioned offer, and after two reminders from the Agency (in November 2018 and February 2019) (see paragraphs 201-207 above). This is the first element that makes it possible to state that the negotiation procedure for the orphan drug was extended as a result of the attitude adopted by Leadiant.

482. As proof, one needs merely consider the fact that no fewer than five months passed after the second meeting between the parties (July 2019) before Leadiant, after a further reminder in September 2019, decided to submit a fifth modified proposal to AIFA, which then led to the agreement of December 2019 (see paragraphs 207-208 above).

483. As for the Party's argument that the length of the negotiation procedure in question was instead caused by the particular complexity of the reference context due to the uncertainties about the actual number of patients affected by CTX, it should be noted that the acquired evidence shows that the dispute between the parties in relation to this element occurred only on the occasion of the first meeting, in March 2018. As of April 2018, the issue of the number of patients, which was also defined more closely to the company's initial estimates in the December 2019 agreement (see paragraph 213 above), was no longer the subject of discussion and the negotiation was largely redirected to another level, i.e., the economic impact that any price lower than what was initially requested would have on the Italian National Health Service budget and, therefore, on the turnover objectives of the dominant company

("*We should set the turnover that we want to secure and move from there*"[519]). Subsequent proposals were submitted to AIFA purely for this purpose and not, as the Party claims, based on epidemiological data[520], on the peculiarity of the drug and on its effectiveness in treating the disease.

484. In summary, therefore, taking into account *i)* the long time frames according to which Leadiant submitted its economic offers; *ii)* the lack of care shown towards the deadlines for response established by the Agency; and, finally, *iii)* the fact that the Agency has sent three reminders over a period of almost one year to obtain these offers (November 2018–September 2019), it seems reasonable to affirm that the dominant company caused the extension of the time frame for the price negotiation procedure for the orphan drug with the sole purpose of maximising its profit.

485. This was not a problem for Leadiant, since it was already present in the market with its own product, a factor that contributed to make the demand captive, and since it enjoyed the extremely favourable commercial conditions granted by the Cnn class regulation. Conversely, owing to these delays, the Agency feared that the negotiations would end with a lack of agreement and with the definitive inclusion of *CDCA Leadiant*® in class C (see paragraph 216 above). AIFA viewed this outcome as extremely negative, given that a drug for which there are no therapeutic alternatives, making it therefore essential, as in this case, should not be included in this class.

486. In fact, AIFA stated during the investigation that it considered it appropriate to avoid the scenario of including *CDCA Leadiant*® in class C, by agreeing to waive the 80% discount on the price initially requested and accepting a much higher price (see paragraphs 215-216 above). This negotiation outcome appears very far from the maximum deviation that AIFA, considering the added value of *CDCA Leadiant*® compared to *Xenbilox*®, and without the aforementioned unfavourable contextual elements characterising the negotiation, would have accepted with respect to its starting bargaining position. According to AIFA, in fact, this maximum deviation would have led

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[519] See doc. 78.113.

[520] A series of documents on file indicates that the company itself had uncertainties regarding the actual spread of the disease in Italy, even though it was aware of the fact that Italy was one of the countries with the greatest prevalence. This was perceived as a concern over the need to justify the request for a high price for the orphan drug, which was more justifiable in other countries that have a lesser spread of the disease (see docs. 78.113, 78.170 and 78.441 (*[…] Given that in some countries we have a very large number of pts and a negligible OEPX it seems that we must do this on a EU basis with an ability to then drill down to a country specific level if needed. By example – in the UK and Germany we could quite easily justify a high price based on pts numbers, OPEX requirement and subsequent product profit contribution, in Italy, Spain, Netherlands however we will have to adopt a different approach given pts numbers are so high and OPEX requirement is so low [...]*).

at most to accepting a price 10% higher than that at which *Xenbilox*® had been marketed on the Italian market between 2016 and mid-2017 (see paragraph 217 above).

487. As for the Party's claims that the negotiation of the price of *CDCA Leadiant*® was concluded with a more favourable outcome for AIFA than for the company, it should be noted that the December 2019 agreement was reached after the initiation of the investigation proceedings by the Italian Competition Authority in October 2019. This allows to reasonably assume that, if the investigation proceedings had not been launched, due to the aforementioned unfavourable bargaining conditions, AIFA would have been unable to obtain even the current ex-factory price of *[€5,000-€7,000]* per pack and would probably have had to accept an even higher price. This conclusion is not, as the Party claims, a mere unfounded assumption, but is based on precise documents on file that indicate that Leadiant, in June 2018, a few days before the meeting with AIFA, planned to obtain a compromise price which, in the worst-case scenario (that it had expressly decided to reserve for subsequent negotiation rounds) was equal to about €9,000 (see paragraph 200 above).

488. For the same reasons, the Party's assertion that the fact that AIFA expressed satisfaction with the conclusion of the *CDCA Leadiant*® price negotiation procedure demonstrates the correctness of its conduct in negotiations, as well as the legitimacy of the negotiated price, is not acceptable. On this point, it should be noted that the Agency's statement that the price agreement was "*sufficiently satisfactory*" in view of the starting bargaining positions and the difficult context described above only confirms that, in more favourable circumstances, the negotiation outcome would certainly have been different. The economic and commercial terms of the price agreement reached represent, in other words, the best of the sub-optimal results that could be achieved under the described conditions.

489. In conclusion, therefore, Leadiant relied on a negotiation context that was already unfavourable to AIFA, exacerbating it through a delaying strategy that prevented the Agency from negotiating the price of the orphan drug fairly and on the basis of objective assessment elements.

iii) The impact of the artificial differentiation between Xenbilox® *and* CDCA Leadiant® *on negotiation with AIFA*

490. A third factor that negatively influenced the *CDCA Leadiant*® price

negotiation procedure lies in the series of initiatives and precautions taken by the dominant company to exclude any type of link between *Xenbilox*® and the orphan drug, and thus avoid having to justify the difference between the price of the latter and the price required for the former, despite the fact that they are identical from a chemical and pharmacological point of view and both used for the same therapeutic indication.

491. These are the lenses with which the evidence acquired during the investigation should be read, showing that, close to the start of the orphan drug price negotiation procedure with AIFA, the dominant company made sure that hospitals did not request early access for *Xenbilox*® pursuant to Law no. 648/1996 or access to the AIFA 5% National Fund. This was done with the purpose of diverting the access request towards the new orphan drug that would soon be placed on the market and thus preventing AIFA from then associating the two products in the negotiation (see paragraph 185 above).

492. To the same end, at the request of the dominant company, the dossier to be submitted to AIFA in order to apply for reimbursement of the *CDCA Leadiant*®, was drafted with the indication that the drug was not based on a known active substance with a new therapeutic indication, but a completely new drug for the Italian market that had nothing to do with *Xenbilox*® or with the magistral preparations produced by the Pharmacy of the University Hospital of Siena[521] (see paragraph 184 above).

493. Subsequently, during the *CDCA Leadiant*® price negotiation procedure, after AIFA's communications in March and June 2018 attempting to highlight the disproportion of the price requested for *CDCA Leadiant*® compared to the price with which *Xenbilox*® had been marketed in Italy until then (see paragraphs 194, 201 and 202 above), the dominant company decided to act by avoiding as much as possible any discussion on the merits of *Xenbilox*® ("[...] *I want to avoid a discussion and price comparison with* Xenbilox" [522]) (see paragraph 199 *above*).

494. In fact, at the meeting in June 2018 in which the CPR requested information on *Xenbilox*® for the third time, in particular on its unavailability

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[521] See docs. 78.172 and 78.291 ("*[…] new indication of a known compound. OK? No, not ok. I understand your comment about this being strange, but in fact this is a 1st registration of a new pharmaceutical product in Italy. Let us keep it like that, because this is something we can argue from a Legal standpoint. We should state it as is and not mention the compounding if we do not have to*").

[522] See doc. 78.116. See also doc. 22.7.143 ("*I would prefer avoid discussing direct relations with Xenbilox. Especially because Leadiant Biosciences or the ST companies never sold Xenbilox in Italy, the commercialization of Xenbilox in Italy was always done by a 3rd party and hence outside our control*") and doc. 78.141 ("*[…]7. XENBILOX discussion is a lost one. Will not enter lost d[i]scussions*") and docs. 78.118 and 78.119.

on the market, Leadiant avoided providing the required information on the off-label drug using legal/formal arguments that relied on the non-authorisation of *Xenbilox*® in Italy and its different therapeutic indication, thus making it a distinct product, or on the existence of market exclusivity for Leadiant linked to the orphan designation (see paragraph 203 above).

495. In this regard, the Party's objections concerning the illegality of the reference to *Xenbilox*® by AIFA during the negotiation procedure do not appear appropriate. Apart from the fact that the information about the unavailability of *Xenbilox*® on the Italian market and the relationship between the off-label drug and the orphan drug, from both a therapeutic and commercial point of view, are also among the "*other elements that may be useful"* that must be provided "*in any case*" and that therefore AIFA, pursuant to CIPE Resolution no. 3/2001, is entitled to request, it should be noted, however, that the Agency has not viewed *Xenbilox*® as a formal comparator for price setting purposes. In contrast, given that the compound in *CDCA Leadiant*® is identical to the compound in *Xenbilox*®, which until then had been used off label for the treatment of the rare disease, and given that there was evidence that the dominant company had based the registration of the new therapeutic indication of the compound on retrospective studies and on the literature review, AIFA asked Leadiant to justify its price request for the orphan drug, the level of which was far removed from *Xenbilox*®'s price in economic terms. In other words, since the CDCA Project consists of the transition from an off-label drug to an on-label drug, the Agency requested the quantification of the economic effort required for the completion of the Project to understand whether this justified the price requested.

496. The fact that Leadiant never raised the illegitimacy of AIFA's references to *Xenbilox*® during the negotiation procedure seems particularly indicative of the misleading nature of the Party's argument. Moreover, the aforementioned documents on file (see paragraph 493 above), along with numerous other documents where the dominant company itself often identifies the orphan drug with the name of the off-label drug ("*Xenbilox/CDCA"*; "Xenbilox *in CTX – EMA*; Xenbilox *[...] Filing for CTX indication in EU in 2015 (approval 2016)*"; "Xenbilox *2014 very important project*" [523]), highlights Leadiant's full awareness of the fact that *Xenbilox*® was inevitably part of the *CDCA Leadiant*® "history".

497. What is more, the investigation documents also highlight the attempt

[523] See docs. 95.4, 95.5, 95.6 and 96.228.

of the dominant company to prevent the part of the *CDCA Leadiant*® development project linked to *Xenbilox*® from playing a role in the negotiations. It is not otherwise explained why Leadiant sought to "*carefully avoid creating [...] connections with the name Sigma-Tau*"[524], i.e. with *Xenbilox*®, during the negotiation with AIFA. All of this is clearly reflected in AIFA's statements, which argued that the choice to launch the orphan drug when *Xenbilox*® was no longer available in Italy and to assign ownership of the new orphan drug to another company had the main purpose of depriving the Agency of opportunities to verify the reasons for the huge price difference between the orphan drug and *Xenbilox*® (see paragraph 197 above).

498. In conclusion, the initiatives taken by the dominant company to ensure that AIFA did not have adequate information, despite being explicitly and repeatedly requested, concerning the therapeutic and market context relating to CTX prior to the introduction of the orphan drug, demonstrate the existence of a strongly obstructive behaviour implemented during the negotiation procedure and certainly not adherent, as Leadiant claims, to good faith.

V.5.2 The imposition of unjustifiably excessive prices for the sale of the orphan drug in Italy by Leadiant

i) The case-law principles to be applied to the case in question

499. Article 102 (a) of the TFEU prohibits a company in a dominant position from directly or indirectly imposing purchase or sales prices or other unfair commercial conditions, and, in particular, it prohibits the application of excessive prices that are not justified by any legitimate reason.

500. The Court of Justice of the European Union ruled in the *United Brands* judgment that a price is unlawful under this provision when a company obtains commercial advantages through its dominant position that it would not have had if there had been normal and sufficiently effective competition in the relevant market[525]. For this reason, the price charged does not appear to have a reasonable relationship to the economic value of the service provided[526].

501. It is known that there is no single method prescribed by the law or resulting from the case law of the Court of Justice to assess the mentioned

[524] See doc. 78.95.

[525] See EU Court of Justice, 14 February 1978, Case *27/76 United Brands Company and United Brands Continentaal BV v Commission of the European Communities. Chiquita bananas*, paragraph 249.

[526] See EU Court of Justice, *United Brands*, paragraph 250.

relationship between the economic value of a product or service and its price. On the contrary, the Court itself pointed out that different methods may be used to determine whether a price charged by a dominant company is excessive and unfair and, therefore, abusive[527].

502. One of these methods is based on the "*comparison between the sale price of the product in question and its cost of production [...], which would give the size of the profit margin*"[528]. This price–cost comparison analysis, according to the methodology indicated by the European judges, is performed over two phases: the first is aimed at verifying "*whether there is an excessive disproportion between the effectively incurred cost and the effectively requested price*" and the second is intended to ascertain whether the excessive price compared to costs is also "*unfair, in absolute terms or compared to competing products*"[529]. It should be noted that the analysis aimed at identifying possible justifications for the discrepancy between price and cost must be particularly stringent when it concerns goods on which consumers are completely dependent[530], as in the case in question.

503. The two criteria for measuring the unfairness of an excessive price are alternatives. Therefore, in order to establish that a price is unlawful within the meaning of Article 102(a) of the TFEU, it is enough that even only one of the two alternatives provided for in the second stage of the test is satisfied[531].

504. Given the above, the application of these principles to this case shows that Leadiant, by exploiting its dominant position, charged excessive prices that had no reasonable relationship to the economic value of the service provided for the sole purpose of gaining an economic advantage. In other words, the prices charged by the dominant company for the sale of the orphan drug in Italy are excessive and unfair and therefore violate Article 102(a) of the TFEU.

ii) The excessiveness of the prices charged by Leadiant for the sale of the

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[527] See EU Court of Justice, *United Brands*, paragraph 253.
[528] See EU Court of Justice, *United Brands*, paragraph 251.
[529] See EU Court of Justice, *United Brands*, paragraph 252. See also EU Court of Justice, *OSA*, C-351/12, paragraph 88; C-52/07, *Kanal 5 and TV 4*; C-226/84, *British Leyland v. Commission*; C-26/75, *General Motors v Commission*; C-30/87, *Corinne Bodson v. SA Pompes funèbres des régions libérées*; C-323/93, *Crespelle*; European Commission, COMP/C-1/36.915 - *Deutsche Post AG - Cross-border mail interception*; European Commission, COMP/A.36.568/D3, *Scandlines Sverige AB v. Port of Helsinborg*.
[530] See the opinion of Advocate General Jacobs of 26 May 1989 in Case C-395/87 *Ministère public v Jean-Louis Tournier*, paragraphs 43, 65 and 66.
[531] See also EU Court of Justice, order of 25 March 2009, in Case C-159/08 P, *Isabella Scippacercola and Ioannis Terezakis v Commission*, paragraph 47

orphan drug in Italy

505. With regard to determining the economic value of the service provided, which is necessary for the first part of the *United Brands* test, on the basis of the aforementioned established practice and jurisprudence[532], it should be considered that this value must at least reflect a measure of the costs incurred by the dominant company to create the good or service.

506. On a preliminary basis, it should be noted that numerous pieces of evidence clearly show that, from the initial phases of the project, the dominant company has never set the price level of *CDCA Leadiant*® on the basis of the costs incurred. The different price assumptions formulated by Leadiant (see sect. III.5.4 above) instead refer to its expectations regarding the maximum price that the demand was willing to pay for the drug in question, also considering the inelasticity of the demand to the price of a good such as a drug for the treatment of an ultra-rare disease, regardless of any measurement of the costs incurred.

507. In particular, the quantification of the overall costs incurred for the registration of the *CDCA Leadiant*®, which the dominant company carried out internally to support the requested price, indeed show a level of costs that in no way is appropriate to justify such a high price (see paragraph 188 above); furthermore, such data was not presented during the negotiations with the Italian Medicine Agency. A different and broader cost reconstruction was only created *ex post* in a study commissioned from the consultancy firm *Copenhagen Economics*, as part of the antitrust proceedings initiated by the Dutch Competition Authority pursuant to Article 102(a) of the TFEU. The costs declared by the Party during the present investigation constitute an updated version of this study.

508. That said, and also taking into account the costs declared by the Party based on this *ex-post* reconstruction, the investigation showed a very high disproportion between the prices applied in Italy for the sale of *CDCA Leadiant*® to the Italian National Health Service and the value of this drug, which should reflect the costs for its production, marketing and maintenance on the Italian market.

509. Although not necessarily required by the case law of the European

[532] See EU Court of Justice, *United Brands*, paragraph 251.

Court of Justice[533], two different methods were used to assess the excessiveness: one of a financial nature and the other of an accounting nature, which allows to confirm the strength of the analysis carried out, thus in keeping with that part of legal and economic doctrine that encourages the parallel application of several methods[534].

a. Financial methodology

510. The first methodology applied took account of the internal rate of return (IRR) of the CDCA Project, which began in 2014 with the increase in the price of *Xenbilox*® and the request for orphan designation for CDCA with the new therapeutic indication; it will end in 2027 when the market exclusivity for *CDCA Leadiant*® expires (section III.6.2.ii).

511. The IRR of the project was calculated on the basis of the cash flows deriving from the project in question, taking into account the ex-factory price applied by Leadiant to sales of *Xenbilox*® in Italy for the period January 2016-May 2017 (€2,900 euro), as well as the ex-factory price of *CDCA Leadiant*® in the years 2017-2019, when the medicine was included in the Cnn class (€15,506.93), and from 2020, following the agreement with AIFA (*[€5,000-€7,000]*).

512. The IRR was calculated by taking into account both all the cash flows deriving from the revenues made, less the costs incurred for the project in question, and only the incremental flows compared to those that would otherwise have been achieved with the continuation of off-label sales of *Xenbilox*®. The value of the IRR is, in the two cases, equal to *[50-60%]* and *[40-50%]*, respectively.

513. In order to assess the profitability of the project, the two IRR values were compared with the value of the cost of capital of the project in question (WACC), as quantified by Leadiant in the project start-up phases: 12% in the

[533]As already stated, the Court of Justice of the European Union pointed out that different methods may be used to determine whether a price charged by a dominant company is excessive and unfair and, therefore, abusive. See *United Brands*, paragraph 253. The Court also recognised that it is for the competition authority to select the appropriate method and "define its framework" in a specific case. In particular, "it should be borne in mind that '*[...] an authority has some room to manoeuvre and that there is no single appropriate method*'. As to the chosen method, what matters is for the method to be "considered valid". See EU Court of Justice, 14 September 2017, in Case C-177/16 *Autortiesību un komunicēšanās konsultāciju aņentūra v Latvijas Autoru apvienība c. Konkurences padome*, paragraphs 38 and 49.

[534] To this end, see M. Motta and A. de Steel (2017), *Excessive Pricing in Competition Law; Never say Never?*. In addition, see the Opinion of Advocate General Nils Wahl delivered on 6 April 2017, Case C-177/16 *Biedrība 'Autortiesību un komunicēšanās konsultāciju aņentūra – Latvijas Autoru apvienība' c. Konkurences padome*; reference for a preliminary ruling from the Augstākā tiesa (Supreme Court, Latvia).

base case and 15% in the best case, with the latter identified as riskier[535]. The comparison between the project IRR and the WACC led to the conclusion that not only is the project profitable for the dominant company, but also that the first value is significantly higher than the second.

514. Based on the analysis, in fact, the IRR equals at least to the *[250-350%]* of the cost of capital. This means that, even considering all the assumptions favourable to the Party, the sales of *CDCA Leadiant*® generated extremely high, and therefore excessive, returns for the dominant company.

515. In relation to the Party's arguments, which criticise this conclusion as based on an allegedly underestimated WACC, the following can be noted. The value of the cost of capital reflects a premium for the specific riskiness of the project, as estimated by the same dominant company in the initial phase of the project. In fact, in 2014 Leadiant had identified a WACC of more than 15% as an adequate cost of capital to account for all the risk factors that the dominant company mentioned in its arguments aimed at justifying the prices charged for *CDCA Leadiant*® in Italy.

516. In this regard, the Party's defensive arguments, which aim to diminish the value of the company's internal document containing the aforementioned value of the WACC, do not make sense; moreover, according to Leadiant, such WACC relates to the entire company and not to the specific project. In fact, the document in question was prepared internally by Leadiant's management when deciding whether to undertake the project to assess its profitability and constitutes the most reliable information on the company's *ex-ante* expectations about the risks, costs and expected revenues of the CDCA Project. The fact that the WACC identified therein is different for the two project scenarios (base case and best case) totally refutes the Party's argument that such value refers to the cost of the company's capital and not to that of the specific project.

517. Moreover, it should be noted that using the cost of capital identified by the dominant company for the riskiest scenario constitutes an extremely favourable choice, in light of various elements that characterise the case at hand.

518. In this regard, it should firstly be noted that the turnover achieved between 2014 and 2016, thanks to the increase in the ex-factory price of *Xenbilox*® to €2,900 per pack, largely contributed to financing the cost of the regulatory activities undertaken by the dominant company to obtain the orphan

[535] See doc. 95.6.

designation and the marketing authorisation of the orphan drug (see paragraphs 113-114 above). Therefore, Sigma Tau did not run the risk of suffering irreparable economic damage in the event of the project's failure.

519. In addition, during the course of the project, Sigma Tau anticipated that if the said project were unsuccessful, in the worst-case scenario it would have continued its business with the sale of *Xenbilox*® as an off-label drug for the treatment of CTX ("*With no ODD, request for approval withdrawn; - Xenbilox sold off-label; - No price increase vs current; - No volume increase*"[536]). This means that despite the failure of the CDCA Project, Sigma Tau could still have remained on the market and achieved turnover targets that were already benefiting significantly from the increase in the price of *Xenbilox*® in mid-2014. The fact that in just two years, from 2013 to 2015, turnover of *Xenbilox*® had increased from €2 to €7 million (see paragraph 114 above) is remarkable in this regard[537]. It should also be noted that Leadiant, having maintained the authorisation for *Xenbilox*® in Germany without requesting its revocation until June 2019, for a long time reserved the possibility of resuming the marketing of the off-label drug even after its withdrawal from the market. This also protected it from the risks linked to the maintenance of the authorisation of the *CDCA Leadiant*® (see paragraph 169 above), which the company today fears.

520. With regard to the Party's criticism of the valuation model used, which does not take due account of the project's risk, and the need to carry out this assessment on the basis of a different model (risk-adjusted NPV) from the perspective of an *ex-ante* investor, the following should be noted. First, Leadiant itself carried out its own profitability assessment of the CDCA Project in 2014, i.e., when deciding whether to *[omitted]* and to invest in the project in question to market the product, based on the real expectations of risks, revenues and costs available at that time, using the methodology that it considered most appropriate (see section III.6.2.i above). This assessment, as already highlighted above, took due account of the risk through the project-specific WACC. The Party's expectation for an evaluation, today, of the profitability of the project from the perspective of an *ex-ante* investor, but using probabilities of success and discount rates set retrospectively according

[536] See doc. 22.7.129.

[537] It should be noted that in October 2016, the dominant company limited itself to withdrawing the off-label drug from the German market, without, however, immediately requesting the revocation of the relevant authorisation. In this way, it was able to benefit from the period of time (three years) provided for by the sunset clause, which would have allowed it to 'reactivate' its MA at any time simply by resuming sales of *Xenbilox*® before the expiry of the aforementioned term.

to the literature or a survey of experts in the sector, is a fruitless and unreliable exercise, since a more realistic *ex-ante* evaluation was actually carried out in 2014 by the dominant company itself. In other words, when Leadiant analysed the profitability of the project in 2014, it was exactly in the position of the *ex-ante* investor that the Party is attempting to reconstruct *ex-post* today.

521. Moreover, the project profitability assessment carried out by the Party in its own defence arguments shows significant inconsistencies. On the one hand, the estimate of the risk and sales volumes was prepared on the basis of what the Party considers to be the expectations of an *ex-ante* investor (probability of being able to bring *CDCA Leadiant*® to the market estimated at only *[30-40%]* and expected volumes lower than both those expected by Leadiant in its *ex-ante* evaluation and those actually realised). On the other hand, for the estimation of the expected costs, the Party used the costs it had allocated *ex-post* to *CDCA Leadiant*® for the 2014-2020 period and those expected in 2020 for the 2021-2027 period (over €100 million). As already noted several times, these costs appear to overestimate the project costs predicted by a hypothetical investor in 2014. Suffice it to say that these expected costs also include the high legal expenses (*[€5-€10]* million) incurred by Leadiant due to the antitrust proceedings opened by various Competition Authorities in Europe (see paragraphs 239-240 above). In this regard, it should be noted that in its 2014 assessment, Leadiant had estimated the total expected costs of the project at approximately €5 million[538].

522. Furthermore, on the basis of the assumptions described above the analysis conducted by the Party to estimate the Minimum Viable Price of *CDCA Leadiant*® (with which the negotiated price under assessment is being compared) is undermined by a further erroneous hypothesis. In fact, in identifying this Minimum Viable Price, the Party assumes that this price applies to all sales of *CDCA Leadiant*®, ignoring the fact that, from June 2017 until the entry into force of the agreement with AIFA (March 2020), the orphan drug was purchased by the ASLs at a price much higher than the agreement price, and that the payback mechanism from 2020 and 2021 only partially compensated for this difference if the time value of money is considered. In other words, the Party's analysis does not take into account the actual timing of cash flows, which is essential in a financial analysis. This leads to a significant underestimation of the Minimum Viable Price.

523. The Party's two additional criticisms of the excessiveness analysis

[538] See doc. 95.6, p. 19.

resulting from the IRR methodology, are not convincing, either. As regards the price level of *Xenbilox*®, which in Leadiant's opinion would have increased even without the CDCA Project, thus reducing the rate of return attributable to the project, it should be noted that, in an analysis of the incremental cash flows, the "inertial" scenario (i.e., the "if there were no project" scenario against which the cash flows deriving from the project under evaluation should be assessed) is the scenario that existed when the investment decision was made. Several pieces of evidence referred to on several occasions attest that the increase in the price of *Xenbilox*® implemented on the 1st July 2014 was introduced to finance the costs of obtaining orphan status and to prepare the market for a much higher price once registration was obtained (see paragraph 113 above). In other words, this increase is part of the CDCA Project and would not have occurred without it, contrary to the Party's claims. This is supported by an internal Leadiant document in which, were there no project, the forecasted revenues generated by the sale of *Xenbilox*® for the 2015-2019 period were constant and estimated at €2 million, in line with those achieved in the previous years when *Xenbilox*® was sold at a price of €660 per package[539]. Therefore, in its internal documents Leadiant qualifies as incremental revenues attributable to the CDCA Project all those deriving from the increase in the price of the *Xenbilox*® compared to the price charged until June 2014.

524. Regarding the negotiated price of *CDCA Leadiant*®, which according to the Party could be reduced even before the end of the exclusivity period due to periodic renegotiations with AIFA, it should be noted that there is no document on file that provides proof of this. On the contrary, in its investment evaluation model created in 2014, the dominant company planned for a constant price for the entire period. Leadiant confirmed the validity of this assumption in its financial report: "*once a repayment price agreement is in force, a hypothetical investor in 2014 would have expected that such an agreement would continue under the same conditions with a 100% probability*"[540]. The literature cited by Leadiant on the alleged price reductions during the period of legal exclusivity refers, indeed, to the generality of the drugs covered by a patent; the situation of *CDCA Leadiant*® is quite different, since the renegotiation levers of the regulatory authorities are substantially zero, with there being no therapeutic alternatives for patients suffering from the rare disease.

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[539] See doc. 95.4, p. 41.
[540] See doc. 186.

525. In conclusion, contrary to the claims of the Party, the analysis carried out with the IRR methodology made it possible to correctly ascertain the existence of the excessive disproportion between the price charged in Italy by the dominant company for *CDCA Leadiant*® and the costs it incurred.

b. Accounting methodology

526. The second method used in the excessive pricing analysis is based on a comparison between the sales revenues made in Italy by applying the price whose excessive level is being assessed (in this case the negotiated price of *[€5,000-€7,000]* euro) and the cost plus, which corresponds to the direct and indirect costs incurred by the dominant company for Italy for *CDCA Leadiant*®, including a reasonable profit margin. In this specific case, this profitability measure was quantified at a rate of return on sales of 21%. The excess percentage of sales revenues on *CDCA Leadiant*® at the price of *[€5,000-€7,000]* compared to the cost plus was equal to *[60-70%]* for the period from the start of the marketing of *CDCA Leadiant*® in Italy until the end of 2020, and *[90-100%]* considering the expiry of the market exclusivity, set for April 2027 (see section III.6.3 above).

527. With regard to the criticisms made by the Party to the cost-plus methodology and its method of application, it should first be noted that this valuation criterion is of an accounting/income type and therefore, by its very nature, is a static model that does not take into account the time value of money, unlike the valuation criteria for investments of a financial nature, such as the IRR. Precisely for this reason, in the analysis of the disproportion between price and cost the cost-plus methodology was accompanied by a financial methodology, which the Party considers more appropriate for evaluating this type of project, in order to corroborate the results and ensure a more robust evaluation. Moreover, the fact that the cost-plus methodology does not consider the time value of money is not in itself unfavourable to the Party. Because of this very specific feature, in fact, in the assessment of the cost plus it was assumed – to the benefit of the Party – that the negotiated price had been applied from the beginning, since the first sales of *CDCA Leadiant*® in Italy in 2017, whereas we know that this price only came into effect in March 2020 and was then applied retroactively to previous sales (see paragraph 265 above). This considerably reduced the Party's revenues for the sales of *CDCA Leadiant*® in the years 2017-2020 and, consequently, their level of excess over the cost plus, which nevertheless remains extremely high.

528. Regarding Leadiant's criticism of the year from which the cost plus was applied (2017), it should be noted that the average profitability of a product can only be measured from when it is marketed, i.e., in this case from June 2017. It should also be noted that the expenses incurred in the years prior to the marketing of the orphan drug have been adequately considered in the IRR methodology, which seeks, by its very nature, to determine the profitability of the project throughout its life cycle.

529. Finally, the use of the average ROS for the sector, which in the opinion of the Party does not constitute an adequate benchmark to reflect the specific risks of the CDCA Project, appears, on the other hand, to be extremely favourable to the Party, given that the project in question consists of the repurposing of a product already present in the portfolio of the dominant company, an activity with risk and investment characteristics well below those of the development of an entirely new pharmaceutical product. The measure of the reasonable rate of profit adopted in the analysis in question is, moreover, much higher than the measure used in previous cases of excessive pricing in the pharmaceutical sector[541].

530. Both methodologies applied, therefore, reach the same conclusion about the existence of a major disproportion between the prices applied by the dominant company and the costs it incurred. This excess is well above the levels of disproportion that were found to be abusive in the main decisions finding infringement of Article 102(a) of the TFEU[542].

531. It is appropriate to reiterate that the above-mentioned analyses were carried out using a series of extremely prudent assumptions in favour of the Party, in the absence of which the excessive prices charged by Leadiant would have been much greater. They can be summarised as follows:

- the costs provided by the Party with regard to both *Xenbilox*® and[543] *CDCA Leadiant*® were used. For the latter product, the Party allocated the shared costs incurred on the basis of its own estimate, also carried out *ex post*, of the time worked by employees on *CDCA Leadiant*® compared to all other products in its portfolio. This criterion leads to allocating to *CDCA Leadiant*®

[541] See *A480 – Price Increase of Aspen's Drugs*, paragraphs 174, 182, 319, in which a ROS of 13% was used.
[542] See European Commission decision of 25 July 2001, COMP/C-1/36.915 - *Deutsche Post AG - Cross-border mail interception*, paragraphs 156, 162, 166 and 167; UK Competition Appeal Tribunal, judgment of 7 November 2008, *Albion Water Ltd, Albion Water Group Limited v Water Services Regulatory Authority and Dwr Cymru Cyfyngedig, United Utilities Water PLC intervening*, Case Number 1046/2/4/04 [2008] CAT 31, paragraph 265.
[543] The only cost item provided by the Party and not considered in the analysis concerns the intercompany royalties paid by the British company to the group's US company for the license to market *Xenbilox*® in Europe (see paragraph 238 above and the related footnote).

[30-40%] of all the shared costs incurred by the dominant company for the entire 2014-2027 period and more than 60% for the 2016-2020 period, i.e. the period that also includes the complex strategy described above, implemented by Leadiant to obtain extremely high prices for the orphan drug. In other words, the shared costs were attributed to *CDCA Leadiant*® based on the time the dominant company's employees spent carrying out numerous and complex regulatory and market access activities (such as the planning of the withdrawal of the *Xenbilox*® or the establishment of a new company that owned the orphan drug) which, as the investigation highlighted, were not (only) necessary to launch *CDCA Leadiant*® on the market, but also to obtain a particularly high price. The criterion used by the Party appears, therefore, to overestimate the shared costs attributable to the product and to be impaired by circularity, since it seeks to justify the level of prices charged on the basis of costs deriving from activities that constitute the instrument of the abuse. Finally, it should be noted that the shared costs that the Party allocated to *CDCA Leadiant*® in the manner mentioned above constitute a considerable share, to say the least, of the total costs of the product (over 50%). In conclusion, the fact that the cost data provided by the Party in the analyses in question were still used is particularly concessive (see paragraph 241 above);

- among the direct costs provided, the Party also reported the significant legal costs it incurred and plans to incur in the coming years as part of the various proceedings in which it was involved with the national competition authorities pursuant to Article 102 of the TFEU, precisely because of the allegedly excessive and unfair prices of *CDCA Leadiant*®. These costs, directly attributable to the conduct in question, should not be taken into account in the excessiveness analysis. Nevertheless, the analysis was carried out considering all the costs declared by the Party and therefore also these (see paragraph 240 above);
- the data relating to the incremental costs of *CDCA Leadiant*® was not considered usable in identifying the incremental cash flows useful to calculate the IRR. In the absence of such information, the data relating to the total costs of the orphan drug, which by definition are higher than the incremental costs (as they also include the non-incremental costs), have been used, very favourably for the Party (see paragraph 257 above);
- the application of the negotiated price of *CDCA Leadiant*® to all sales made in Italy in 2020 (despite the agreement entering into force in March) and

the reimbursement of almost the entire amount of the payback[544] in the same year (*[6-7]* of *[€6-€7]* million euro) was assumed. This assumption anticipates the negative cash flows borne by the Party as a result of the payback, reducing the value of the most recent cash flows and, therefore, the overall IRR of the project. In the absence of such an assumption, the IRR of the project would therefore have been even higher (see paragraph 236 above);

- the highest cost of capital value (WACC) (which was, therefore, associated with the greatest risk) used by the dominant company in its internal calculations to evaluate the project in question, equal to 15%, was the WACC used for comparison with the IRR. This is an extremely concessive hypothesis, considering that the average WACC for the pharmaceutical sector in Europe in the project start-up year (2014) was significantly lower and equal to 10%, due to the specific risk of the project (see paragraph 247 above);
- the average tax rate borne by Leadiant in the 2014-2019 period (21%) was used, which is higher – and therefore more favourable to the Party – than both the average rate in Europe for the pharmaceutical sector over the same period and the rate used by the Party in its *ex-ante* analysis (see paragraph 244 above);
- finally, as mentioned above, in the cost-plus analysis an extremely concessive profitability benchmark was used, considering the type of project in question, characterised by lower levels of risk and investment than the average project in the pharmaceutical sector, and the previous cases of excessive prices in the sector in question (see paragraph 267 above).

532. In conclusion, for the reasons set out above, it is considered that the arguments put forward by the Party are not capable of calling into question the conclusions reached regarding the existence of a high disproportion between the prices applied and the costs incurred by the dominant company for *CDCA Leadiant*®, and that these prices should therefore be considered excessive.

iii) The unfairness of the prices charged by Leadiant for the sale of the orphan drug in Italy

533. This section is dedicated to verifying the existence of non-cost-related factors that may justify such disproportion. Where these elements are not considered to exist, the prices charged by Leadiant would be "*without any reasonable relationship*" to the economic value of the service rendered and

[544] Meaning the refund, provided for in the December 2019 agreement, of the difference between the price paid by the ASLs before the *CDCA Leadiant* agreement and the negotiated price.

would, therefore, be unfair.

534. Firstly, it should be pointed out that the unfairness test suggested by the Party, who considers that in the case at hand it is necessary to look both at price unfairness in the absolute sense, determined according to the economic value of the drug and the benefits for patients and society, and in comparison with the price of the same drug in other European countries or comparable pharmaceutical products, is not supported by the case law of the Court of Justice of the European Union, which did not follow the indications of Advocate General Wahl in his opinion on the *AKKA/LAA* case, cited by Leadiant. As already mentioned, the case law states rather that the national competition authorities enjoy a margin of discretion both in the choice of the test for determining the legitimacy of the commercial policy of a dominant company within the meaning of Article 102(a) of the TFEU and in the choice between the two criteria identified for the purposes of the unfairness analysis (see paragraphs 501 and 503 above) under the *United Brands* test.

535. The Party's statement regarding the possibility of applying the criterion of unfairness in the absolute sense, without a comparative analysis, solely for cases in which consumers do not receive any product in exchange for the price paid, is equally unsupported by the rulings of the Court of Justice. It is well known, in fact, that the Court did not follow the approach taken by Advocate General Wahl in his opinion on the *AKKA/LAA* case, also in relation to this interpretation of the *United Brands* test[545]. Likewise, this interpretation is not even supported by the decisional practice of the Italian Competition Authority, which applied the criterion of unfairness in itself to cases that fail to meet the requirements of those identified by Leadiant[546], receiving recent approval from the administrative judges[547].

536. In light of the foregoing, for the reasons set out below, in this case it is considered more appropriate to opt for an assessment of the unfairness in itself of the pricing policy applied by Leadiant, and not for an assessment based on comparative criteria.

a. The inapplicability of comparative criteria for the unfairness test in

[545]Indeed, it cannot be sustained that the Court upheld Advocate General Wahl's opinion solely on the grounds that, in the case in question, it considered the method based on a comparison between the prices charged in the Member State concerned and those charged in other Member States to be applicable (see paragraph 38 of the decision). This method was chosen instead of the *United Brands* test, which was thus replaced in its entirety, because it was considered inappropriate in the case of intangible assets whose cost cannot be easily determined.

[546] See Measure 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*, paragraphs 329-351.

[547] See Council of State, 13 March 2020, judgment no. 1832/2020, paragraphs 12.116 and 12.7.

the case in question

537. The second option that the Court of Justice of the European Union provides to competition authorities for the purposes of assessing the unfairness of the price charged by a dominant company refers to the comparison of that price with those of "*competing products*". In the previous *Port of Helsinborg* case, the European Commission considered, in abstract terms, that it was possible to apply the wording adopted by the Court through a comparison to the price of the same product produced by the same company on other markets or to the price of "similar products" sold on other markets, as two second best options in the event that "competing products", or those belonging to the same relevant market in which the product under examination is located, cannot be identified[548].

538. Given that, for the reasons set out under section V.2.iii above, in this case there are no "competing products" to *CDCA Leadiant*® to be considered within a potential price comparison of *CDCA Leadiant*® to other drugs, and with the aim of applying the decisional practice of the European Commission and the case law of the Court of Justice, by considering the price of orphan drugs indicated as comparable to *CDCA Leadiant*® by the Party, the following should be noted.

a.1 Comparison with similar products

539. Primarily, it must be borne in mind that, precisely in order to avoid inappropriate comparisons, both the European Commission and the Court of Justice have stated that comparison between similar products must take place under uniform conditions. In other words, the products considered similar should indeed be actually comparable for the comparison to be valid and for the results of the comparison to be meaningful. For this reason, the conditions underpinning the comparison are of fundamental importance[549].

540. The comparison proposed by the Party does not pass this screening, since it is methodologically incorrect in many respects.

541. First of all, it should be noted that Leadiant assumes as the point of comparison the average price of an unidentified group of 75 orphan drugs marketed in Italy and the average price of a group of 14 orphan drugs that are

[548] See European Commission, COMP/A.36568/D3, *Port of Helsingborg*, paragraphs 170-171.

[549] See European Commission, COMP/A.36568/D3, *Port of Helsingborg*, paragraph 169 and EU Court of Justice, 14 September 2017, Case C- 177/16, *AKKA/LAA*, paragraphs 38 and 44; see also Council of State, judgment no. 1823 of 13 March 2020, paragraph 12.8.

similarly unidentified, instead being indicated as belonging to similar therapeutic areas.

542. Given that the Party does not provide information in this regard, it seems reasonable first of all to assume that, given the size of the sample, the 75 orphan medicinal products included in the first group have completely different therapeutic indications. In itself, this already makes them unsuited for comparison from a product point of view, and therefore not 'similar' to *CDCA Leadiant®*, with which their sole point in common is the fact that they are orphan drugs. In addition, the Party makes its comparison on the basis of an average price, which in itself does not say anything about the comparability of the price of the orphan drug owned by Leadiant to the prices of the 75 orphan drugs considered.

543. As regards the 14 drugs included in the second group, similar considerations apply to those already expressed above. These are medicinal products belonging to the following therapeutic classes of ATC classification: A16AA, which includes medicinal products used for the treatment of various metabolic deficits; A16AB, which includes medicinal products containing enzymes used to treat metabolic disorders; A16AX, which includes products used to treat the metabolism and digestive tract; and N07XX, which includes medicinal products used to treat diseases affecting the nervous system. However, these therapeutic indications do not, in themselves, make these drugs comparable, and therefore similar, to *CDCA Leadiant®*. In fact, it is not enough that two or more drugs treat any metabolic deficit or any disease of the nervous system for them to be considered therapeutically similar to *CDCA Leadiant®*, for the sole reason that CTX consists of a metabolic dysfunction that causes, *inter alia*, disorders of the nervous system.

544. It should also be considered that, by clarification of the Party itself, the comparative analyses do not take into account the number of patients taking the drugs included in the two groups considered. In other words, the prices of these products are determined by unknown epidemiological data that are assumed to be distinct. Yet, it is known that the determination of the price level of a specific drug is necessarily influenced by the size of the demand, since volumes, together with price, determine the overall impact on the budget of the National Health Service, as also demonstrated by the facts that characterised the price negotiations for *CDCA Leadiant®*. This means that, in the absence of information demonstrating that the prices of the drugs included in the two groups considered by the Party refer to drugs that treat diseases with epidemiological characteristics similar to those of the orphan drug in question,

even in this regard it does not appear correct to make any significant comparison between them and *CDCA Leadiant*®.

545. Finally, the comparison proposed by the Party does not take due account of the innovative character of some orphan drugs included in the larger sample. The distinction between medicinal products that, like the orphan drug in question, are repurposed and medicinal products based on active substances that are not known and have been developed from scratch should not be ignored. Indeed, the two categories of drugs are distinguished by the amount of resources invested in their development. As acknowledged by the European Commission, in fact, the investments in research and development made for repurposed orphan drugs are much lower than those made for completely new orphan drugs[550]. This explains why they are (or at least should be) marketed at lower prices on average. This can also be observed from the data that Leadiant itself has produced in its defences[551]. The failure to consider separately the category of innovative and non-innovative drugs (which is what the Party did) thus leads to the use of an overestimated term of comparison, inappropriate for assessing the unfairness of the price of *CDCA Leadiant*®.

546. Lastly, it should be considered that the unsuitability of the comparative analysis proposed by the Party for the purposes of assessing the unfairness of Leadiant's price policy, emerges also from several pieces of evidence. For example, research commissioned by the dominant company in October 2015 showed that the stakeholders interviewed (health economists, doctors and pharmacists/consultants for national regulatory authorities) were extremely reluctant, if not "offended", by the attempt of Sigma Tau's consultants to

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[550] See Technopolis, Ecorys, *Study to support the evaluation of the EU Orphan Regulation*, July 2019, study carried out for the European Commission as part of the review of the Orphan Regulation, which states: "[…] *the costs a sponsor has had to make to repurpose or reposition a product may be substantially smaller than in cases where a sponsor has developed a wholly new medicinal product through all phases of the R&D pipeline, including the conduct of clinical trials*" (p. 232); "*in case of an "average" orphan medicine there is a risk over overcompensation if turnover levels are high (in our analysis 14% of orphan medicines showed an annual turnover of €100m or more). […] In case of repurposed products (including well-established use products and known active substances), overcompensation may occur because the R&D costs may be "below average"* " (p. 271); "*Price increases such as these appear to be unrelated to actual costs of R&D as the development had already been completed many years before and the products were previously sold at a much lower price. Here, it is likely that the market exclusivity that the marketing authorisation holders gained from the orphan designation was the main factor that enabled them to engage in monopolistic price setting*" (p. 260-261). Note that this final stage of the study refers to some specific cases of repurposed drug price increases, which explicitly include *CDCA Leadiant*®. See also European Commission, *Commission Staff Working Document Evaluation*, SWD(2020) 163 final, of 11 November 2020, pp. 60 and 103-104.

[551] See Figure 13 on page 98 of the Economic Report (doc. 186). It should also be noted that the same Figure also indicates that drugs consisting of synthetic compounds, such as *CDCA Leadiant*®, have lower average prices than the price of the orphan drug in question.

persuade them to compare the price of the future orphan drug with the medicines registered for other ultra-rare diseases ("*None of the respondents wanted to use benchmark or analogue products produced for the pricing exercise. […] In some cases respondents were slightly affronted that and attempt was being made to make pricing decisions by this approach*"[552]). It should also be noted that *Orphacol* (see paragraph 123 above and the following section below) was among the drugs proposed as a comparator and rejected by the stakeholders.

a.2 Comparison to Orphacol

547. In relation to the comparison proposed by the Party between the drug last mentioned and the *CDCA Leadiant®,* it should be noted first of all that this does not represent a correct application of the judgment of the Court of Justice of the EU, *Bodson v Pompes Funèbres,* cited by the same Leadiant. In that judgment, in fact, the Court considered in abstract terms the possibility of comparing two identical services provided in two different markets, where the difference lied on the fact that one was subject to a concession while the other was rendered in competition. Therefore, the Court assumed that it was possible to assess the unfairness of the price at which the service under concession was rendered through comparison to a competitive benchmark. In this case, however, the Party suggests drawing a comparison between products that both have an exclusivity right (the market exclusivity connected to the orphan designation), which by definition allows them to benefit from a significant mark up. In other words, *Orphacol* cannot be considered a competitive benchmark able to provide adequate indications about the unfairness of *CDCA Leadiant®*'s price.

548. Aside from this, albeit decisive, finding, it should be noted in any case that the Party came to the conclusion that *Orphacol* is more expensive than *CDCA Leadiant®* by *[50-60%]* on the basis of incorrect or unverified assumptions. The conclusion about the comparability between the two drugs, in fact, starts from the assumption that, since *Orphacol* is a repurposed drug, the registration costs are similar, if not even lower, since its registration procedure was based on the *well-established use,* i.e., mainly based on the scientific literature. However, this remains an unproven assumption that was not substantiated by Leadiant in any way. Any conclusion about the similarity

[552] See doc. 78.80.

between the two drugs on the basis of this criterion would therefore entail the risk of being a 'false positive'.

549. Secondly, it is based on the consideration of incorrect epidemiological data. The Party, in fact, states that *Orphacol* is aimed at a patient population in Europe of about 2,300 individuals, while there are around 250 patients with CTX, calling them "comparable". Beside the fact that these data can certainly not be defined as "comparable", with one equal to ten times the other, anyhow the comparison made by Leadiant suffers from some important errors.

550. Firstly, it is incorrect to assess the price level of two products at the national level by taking European epidemiological data as a reference. Indeed, it is appropriate to point out that, in the current structure of the Treaty, the competence to set prices (even if only reimbursement) of drugs remains the exclusive responsibility of the governments of the Member States[553], which for this purpose consider the number of patients who take it, exclusively at national level. Likewise, even in healthcare systems where drug prices are not statutory, instead being based on mechanisms that exploit the forces of the free market or replicate its dynamics (to this end, see paragraph 554 below), price discrimination strategies implemented by companies are based, *inter alia*, on the size of each national market, as also shown by the assessments of the dominant company itself.

551. Secondly, while the number of patients with CTX in Europe consists of real data based on diagnoses, the data concerning the two congenital defects treated with *Orphacol*, in addition to being obsolete[554], are statistical and based on the theoretical prevalence of the disease[555]. In addition, careful analysis of public sources should have led the Party to notice that the figure of 2,300 patients refers to *all the congenital errors in the synthesis of primary bile acids*[556], of which the two congenital defects treated with *Orphacol* represent only a small part. The specific prevalence of the two congenital defects that *Orphacol* intends to treat is, in fact, 3-5 patients out of 10 million (or 0.003-0.005 patients out of 10,000) for one defect, and 0.3-0.5 patients out of 10 million (or 0.0003-0.0005 patients out of 10,000) for the other[557]. Applying the prevalence rate of the rare disease to the Italian population, there

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[553] See Article 167 TFEU.

[554] The data is, in fact, taken from https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302127 and dates back to 2002.

[555] The data concerning the prevalence of this type of disease is much higher than the data concerning the patients diagnosed with them, due to significant underdiagnosis.

[556] See *https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302127*.

[557] See *https://www.ema.europa.eu/en/documents/product-information/orphacol-epar-product-information_en.pdf*.

would be 12-20 patients on the domestic market with the two congenital defects mentioned above, while, according to the Leadiant itself, there are *[40-50]* patients with CTX, i.e., a number that is more than double, if not triple. This easily explains the price differential of about *[50-60%]* between the two drugs.

a.3 Comparison to the price of CDCA Leadiant® *in other Member States*

552. It is also not appropriate to assess the unfairness of the price of *CDCA Leadiant*® in Italy through a comparison to the prices charged for the same drug in the other European countries identified by the Party (United Kingdom, France and Germany). In fact, the investigation clearly indicates that Sigma Tau/Leadiant had implemented a pan-European commercial strategy that is subject to the antitrust scrutiny by several national competition authorities. The foreign prices of *CDCA Leadiant*® could therefore be the result of the strategy put in place by the dominant company, just as much as the price charged in Italy could be[558]. In this regard, the acquired evidence clearly shows how averse the demand in other Member States was towards the sale prices at which the orphan drug was launched in those countries (see section III.5.8 above).

553. However, cross-border comparisons in the pharmaceutical market more generally risk not respecting the criterion of homogeneity required by EU jurisprudence, because they take place in a context of strong economic, institutional and epidemiological discrepancies that still characterises the national pharmaceutical markets of the European Union. Indeed, the European pharmaceutical market is characterised by the persistence of price differentials from one Member State to another, linked not only to the price differentiation strategies implemented by pharmaceutical companies, which should reflect the price elasticity (based on the willingness to pay and the size of the market), but also, and above all, to the institutional and economic differences that inform the different national pharmaceutical policies[559]. In this context, it is

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[558] See on this point AGCM Measure no. 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*, paragraph 330.

[559] See on this point AGCM Measure no. 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*, paragraph 330. These differences have also been recognised by Council of State, no. 1823 of 13 March 2020, paragraph 12.8. In the literature, see WHO, *Medicines Reimbursement Policies in Europe*, 2018; C. JOMMI, *Pharmaceutical regulation in 15 European countries review*, in *Health Systems In Transition - European Observatory on Health Systems and Policies*, 2016, vol. 18, no. 5, pp.1-122; C. JOMMI, *Innovation and drugs price and reimbursement: a comparison between Italy and the other major EU countries*, in *Grhta*,

clear that the comparison between prices of the same product in the various EU Member States does not provide any significant result or indication of the fairness or unfairness of the price of this product in a given Member State.

554. The three Member States taken as reference by the Party for the *CDCA Leadiant*® price comparison, namely Germany, France and the United Kingdom, have pricing and reimbursement systems very different from Italy's. Unlike Italy, Germany and the United Kingdom allow free prices at launch, something not permitted by domestic law[560]. The two countries are in turn different from one another because in Germany the reimbursement price is negotiated in the form of a discount on the retail price originally set by the dominant company and paid by the health insurance funds[561]; on the other hand, in the United Kingdom there is no direct regulation of prices, which are indirectly governed through a profit cap established by the PPRS (*Pharmaceutical Price Regulation Scheme*), which determines a continuous modulation of product pricing[562]. In France, where the launch price is regulated as in Italy, the technical assessment of a drug and the negotiation of the price are carried out by two different authorities, competences that in the domestic legal system both belong to AIFA[563]. Finally, the evaluation procedure established in France and Germany to define reimbursement prices gives rise to a sort of participation of the private demand in pharmaceutical spending, which goes hand in hand with the financing provided by public

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2015, vol.2, no. 3, pp.117-162; Hai Europe, *Variations in Prices and Reimbursement of medicines in the European Union*, 2014; M. Grau, J. Fernandez, *Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries*, in *OHE Briefing*, no. 52, October 2009; OECD, *Pharmaceutical Pricing Policies in a Global Market*, 2008; E. MOSSIALOS, M. MRAZEK, T. WALLEY, *Regulating Pharmaceuticals in Europe: Striving for efficiency, equity and quality*, Oxford University Press, 2004; P. KANAVOS, *Pharmaceutical regulation in Europe*, in *Institute for Research on Public Policy Conference – Toward a National Strategy on Drug Insurance: Challenges and Priorities*, 2002.

560 See C. JOMMI, *Innovation and drugs price and reimbursement*; pp. 119-121.

561 See footnote 290 above.

562 Pursuant to section 261 of the NHS Act, the NHS *Pharmaceutical Price Regulation Scheme* (PPRS), renegotiated every five years between the *Department of Health* (DH) and the *Association of the British Pharmaceutical Industry* (ABPI), regulates the profits that manufacturers can make from their sales to the Italian National Health Service of (patented and unpatented) branded drugs. Pharmaceutical companies can set the price of new drugs freely, but any future increase must be offset by reductions in the price of other drugs so that the total overall expenditure for the Italian National Health Service respects the profit cap established by the PPRS.

563 In France, the price of drugs is first negotiated by the *Comité économique des produits de santé* (CEPS), generally on the basis of their therapeutic usefulness, but also in relation to other factors, such as the price of the medicine in other countries. Subsequently, the *Commission de la transparence* of the *Haute Autorité de Santé* assesses *i)* the therapeutic value (*soin médical rendu* or SMR) to verify whether the drug is sufficiently effective from a therapeutic point of view to merit partial or full payment by the social security system, and *ii)* the added therapeutic value (*amélioration du soin médical rendu* or ASMR) to verify whether the drug can be considered an improvement over other available drugs, to thus set the amount to be reimbursed by the social security system. See also C. Jommi, *Innovation and drugs price and reimbursement*; p. 119-121.

demand, in no way comparable to the soft forms of cost-sharing established by the different Italian regions (in the form of co-payments)[564]. All of this in itself makes the four price and refund systems incomparable and any comparison between the prices charged in these markets potentially inappropriate, even if they relate to the same product.

555. This is also reflected in the price of *CDCA Leadiant*®, for which there emerged, as early as 2014 (from the same market research commissioned by Sigma Tau), a structural price difference that would have been applicable in the various Member States (in France, €25-€35,000 per year, in Italy around €15-€20,000 per year, in Spain around €20-€30,000 per year, while in the United Kingdom about £50,000 per year) (see paragraph 121 above). These structural differences, which also relate to the number of patients, can be seen in the same assessments of the dominant company[565] and can also be observed in relation to the prices currently applied for the orphan drug, for the reasons set out below.

556. For example, the price of *CDCA Leadiant*® in the UK was negotiated by Leadiant with the NHS for approximately 24 CTX patients, i.e. almost half of Italian patients. This, together with a very different willingness to pay from the British NHS, explains why the price of *CDCA Leadiant*® in the UK is almost double the price in Italy (*[£10,000-£20,000]* per pack of 100 capsules of 250 mg).

557. In France, *CDCA Leadiant*® is sold at a negotiated price of *[€10,000-€20,000]* per pack of 100 capsules of 250 mg[566], which is reimbursed at 30%[567]. Therefore, the price negotiated in France for *CDCA Leadiant*® cannot really represent a good point of comparison because it was set using institutional mechanisms completely different from those provided for in our legal system, and also enjoys a substantial financial participation of the private

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[564] Co-payment in fixed form (such as the "ticket" in Italy) is very different from co-payment in percentage form, especially when this percentage is significant in terms of the incentive to choose more expensive or cheaper therapies.

[565] See doc. 78.441 (*[…] Given that in some countries we have a very large number of pts and a negligible OEPX it seems that we must do this on a EU basis with an ability to then drill down to a country specific level if needed. By example – in the UK and Germany we could quite easily justify a high price based on pts numbers, OPEX requirement and subsequent product profit contribution, in Italy, Spain, Netherlands however we will have to adopt a different approach given pts numbers are so high and OPEX requirement is so low [...]*).

[566] See *https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000041497659*.

[567] *https://www.has-sante.fr/upload/docs/application/pdf/2019-03/chenodeoxycholic_acid_leadiant_11072018_ct16384_transcription.pdf*; *https://www.has-sante.fr/jcms/c_2865403/fr/chenodeoxycholic-acid-leadiant-acide-chenodesoxycholique-medicament-a-base-d-acides-biliaires*; *http://www.codage.ext.cnamts.fr/codif/bdm_it/fiche/index_fic_ucd.php?p_code_cip=9426887&p_site=AMELI.*

demand which, on the other hand, is not provided for by in Italy.

558. In light of these considerations, in the case at hand the homogeneity required by the decisional practice of the European Commission and by the case law of the Court of Justice of the European Union to carry out a comparative assessment of the unfairness of the price charged by Leadiant for the orphan drug, does not exist.

b. The unfairness in itself of the price of CDCA Leadiant®

559. Given the above, many documents on file allow to affirm that the prices charged by the dominant company for *CDCA Leadiant*® in Italy are unfair in themselves. These include qualitative factors related to the nature of the product, the investments in research and development carried out by the Party, the added therapeutic value of the orphan drug compared to pre-existing therapies – which cannot be measured through the consumer's willingness to pay, given that the willingness to pay for life-saving drugs without a therapeutic alternative tends to be limitless, making any price level plausible[568] – and the effects of the conduct on the Italian National Health Service.

b.1 Nature of the product

560. First, as *CDCA Leadiant*® is a repurposed drug, i.e., a drug whose compound was already on the market with a given therapeutic indication and then remarketed with a new therapeutic indication, cannot be considered a newly introduced medicinal product. This is not intended to characterise repurposed drugs in a negative light, but merely to note that, although *CDCA Leadiant*® is a drug that, compared to previous therapeutic alternatives, has a specific registration for the treatment of CTX and an orphan designation, it cannot be considered a completely new medicine.

561. This applies first of all at a chemical/pharmaceutical level. Although the improvement of the drug production method resulting from the implementation of a new purity test (see paragraph 127 above) enabled a reduction in the level of impurities, it did not alter the essential characteristics

[568] To this end, see AGCM Measure no. 26185 of 29 September 2016, *A480 – Price Increase of Aspen's Drugs*, paragraphs 137 and 346; and indirectly Council of State, 13 March 2020, judgment no. 1832/2020, paragraph 12.6(d) and (e), where reference is made to the fact that the elasticity of the demand for life-saving drugs is substantially zero.

of the active substance.

562. In this regard, it should be noted that even after these changes to the production process, *CDCA Leadiant*® remains equivalent to *Xenbilox*®, and even to the magistral preparations of the Pharmacy of the University Hospital of Siena, from a chemical and pharmaceutical point of view: in fact, the three drugs have the same active substance, the same dosage, are produced using the same raw material produced by the same chemical company, and are bioequivalent.

563. This can be seen in the acquired evidence, which indicates that although there are some differences in the excipients between the capsules produced by the Pharmacy and *Xenbilox*®, the two drugs are essentially similar, as recognised by the EMA[569] on the basis of the comparability studies carried out by the same dominant company (see paragraph 144 above). In addition, other documents collected during the investigation indicate that there is a relationship of chemical-pharmaceutical equivalence, or even sameness, between *Xenbilox*® and *CDCA Leadiant*®[570], as demonstrated by *i)* the statements contained in the documents submitted to the EMA by the dominant company ("*[...] the reference and proposed product are the same"*[571]; *ii)* the fact that for the purposes of the MA request for the orphan drug, the company did not need to carry out bioequivalence studies; and *iii)* the fact that the orphan drug MA was requested using the abbreviated hybrid procedure (see paragraphs 141 and 143 above), made possible precisely because of the fact that *CDCA Leadiant*®, despite having a distinct therapeutic indication, is equivalent to *Xenbilox*® from a pharmaceutical perspective. It was therefore enough for the dominant company to refer to the relevant part of the *Xenbilox*® dossier, which served to prove its pharmaceutical equivalence.

b.2 Lack of investment in research and development

564. The evidence acquired during the investigation also clearly shows that, as part of the CDCA Project, the Party did not incur significant research and development costs that could justify the price initially requested from AIFA

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[569] With regard to CDCA-based galenic products in particular, the EMA *Assessment Report* of September 2016 states: "*Results of studies of dissolution comparing the two products demonstrated that, despite minor differences in excipients contained in the compounded and reference formulations, both products can be considered similar*".

[570] See EMA, *Assessment Report*, p. 8: "*The application for Chenodeoxycholic acid sigma tau only referred in certain areas to Xenbilox and in all these areas there was no need for bioequivalence or comparable bioavailability studies to the reference medicinal product*".

[571] See doc. 78.30, Annex "Annex 1 – Overview of product development", p. 33.

or the price subsequently negotiated with the Agency.

565. In fact, although the two retrospective studies commissioned by the University Hospital of Siena and the Casinius Wilhelmina Hospital in Nijmegen are still very important for the knowledge of the rare disease in medical and clinical terms, especially given their (hitherto unsurpassed) breadth and duration, it should be noted that this activity was carried out by public structures that have developed and consolidated extensive clinical experience in the administration of CDCA to patients with CTX over a period of more than forty years (see paragraphs 147, 149 and 150 above) and that the financial effort undertaken by Leadiant to remunerate this activity and this experience was decidedly negligible, since these figures amounted to *[€300,000-€400,000]* and, at most, *[€500,000-€600,000]* (see paragraph 151 above) in the future.

566. Even the aforementioned activities carried out by PCA on behalf of Sigma Tau to implement the purity test developed by the dominant company for the improvement of CDCA production required a minimum disbursement. According to the statements of the dominant company itself, it in fact paid PCA an amount of *[€300,000-€400,000]* (see paragraph 127 above). These are, therefore, also extremely limited investments, which, although able to provide a benefit to patients, do not represent a "significant innovation", given that, as PCA itself states, even with the new purity test the production process of CDCA as a pharmaceutical-grade active substance remains rather simple (see paragraph 50 above). Therefore, they certainly cannot contribute to the justification of the price requested from AIFA for the purchase of the orphan drug.

567. Beyond these specific expenditures, several pieces of evidence also prove the extreme limitation of the investments in research and development that Leadiant generally planned over the course of the CDCA Project. The planned investments were always very limited, not only if considered in terms of their absolute value, but also in comparison to the majority of the investments made in the other drugs of the dominant company's portfolio and the total of the investments made in research and development that it expected to support (see paragraph 188 above). Additionally, the economic study carried out by *Copenhagen Economics* reveals a similar result: the costs it classified as research and development incurred by the dominant company as part of the CDCA Project appear to be less than 1% of the total cost incurred (see paragraph 239 above).

568. In relation to the Party's argument that Leadiant would still have made

substantial and major investments, although not strictly classifiable as research and development, such as the drafting of an *ad hoc* DMF for the orphan drug and the often mentioned improvement of the drug's production method, and would have had to incur others associated with regulatory obligations in terms of pharmacovigilance and scientific information and maintenance of the MA that are broader and stricter than those to which it previously incurred with *Xenbilox*®, the following should be observed.

569. As is clear from the investigation, most of the activities mentioned by Leadiant had a marginal impact on the costs that the dominant company stated that it incurred and would have to incur. The direct costs relating to the production of the orphan drug are, in fact, minor (*[10-20%]* of the total), despite the increase in remuneration owed to PCA for the purchase of the raw material, compared to the previous supply agreement (see paragraphs 137 and 239 above). Furthermore, the costs of providing scientific information are almost irrelevant[572]. Pharmacovigilance activities for the orphan drug, which, it should also be mentioned, were also required for *Xenbilox*®, are not considered particularly expensive as they were related to a function that the dominant company already performed for the other products in its portfolio.

570. As regards, on the other hand, the direct costs related to regulatory activities (market access, marketing and legal fees), which account for *[30-40%]* of the total costs, it should be noted that, as clearly shown in section V.4.1 above, these are derived from activities that made up the majority of the strategy put in place by Leadiant to pursue its price policy and/or are specifically linked to the legal expenses incurred in the context of the various antitrust proceedings concerning this commercial policy. This means that a large part of the costs based on which the dominant company believes it can justify the prices charged in Italy for the orphan drug are related to activities that represent Leadiant's instruments for the abuse currently under dispute. Lastly, indirect costs accounting for more than 50% of the total cost (see paragraph 239 above) (administrative costs, overhead, personnel costs), represent burdens that, at least in part, the dominant company would have incurred in any case.

571. Lastly, the costs and the risk that Leadiant claims to have faced in the context of the CDCA Project are not thought to have been considered by the EMA for assigning the orphan designation. This is because the dominant company submitted its application on the basis of the prevalence (and

[572] See doc. 110.3.

significant beneficial effects) criterion, and not on the basis of the return on investment criterion (see paragraph 38 above), also because, as already stated, the measurement of the investments incurred was carried out *ex post* by the dominant company in the context of the ACM antitrust proceedings (see paragraph 209 above). There is, therefore, no document on file that would make it possible to claim that the prices requested by the dominant company are necessary to compensate for the investments made and for the risk faced, and that lower prices would decrease the incentive to innovation and the value of the orphan designation conferred by the EMA.

572. On the contrary, the acquired evidence shows that in the same analysis carried out by Leadiant in 2014, the incentive to undertake the investment was very significant, even with a price lower than what was actually applied. In the aforementioned analysis, in fact, Leadiant estimated a particularly high NPV, even with a price of €5,000 per pack. This means that Leadiant would have had the incentive to undertake the project even at a much lower price, which would in any case have made it possible to compensate for the costs and ensure the dominant company a profit margin, and to compensate for the risk incurred. In other words, Leadiant's excessive pricing cannot be justified by the need to encourage incentive to undertake the registration project by compensating for the risk associated with the said project, since, as Leadiant itself estimated, even at a price of €5,000 euro, the project was already extremely profitable, meaning that with such price, the risk was already largely compensated for.

b.3 Added therapeutic value of the orphan drug

573. These investments, however, did not lead to an added value from a therapeutic point of view compared to the existing therapies on the Italian market (*Xenbilox*® and the magistral preparations produced by the Pharmacy of the University Hospital of Siena). This is clearly shown by several elements found in the acquired evidence.

574. Among the three drugs mentioned, there is, in fact, a relationship of identity from a therapeutic point of view. Firstly, this was strongly confirmed by the specialist during the hearing, who stated that, in his clinical experience, which is based on the administration over the last forty years of the magistral preparation produced by the Pharmacy of the University Hospital of Siena, then of *Xenbilox*®, and finally of *CDCA Leadiant*®, there is no therapeutic difference between them (see paragraph 81 above).

575. Some documents on file prove, moreover, that the dominant company was aware of the fact that the orphan drug did not have an added therapeutic value over *Xenbilox*®; in fact, Sigma Tau did not want to subject the orphan drug to the added therapeutic value assessment process carried out by the competent German authorities for the newly introduced drugs on the market. Furthermore, when the dominant company explored the possibility of requesting the assessment, it was not advised to do so; according to the consultants, the outcome of the process for assessing the added therapeutic value was uncertain, specifically because of the absence of supporting clinical studies. Particularly suggestive in this context is the fact that the consultants recommended that the dominant company request the assessment only if it were actually convinced that it could demonstrate a significant added therapeutic value justifying the anticipated price increase that the company intended to apply for the orphan drug (see paragraphs 161-162 above).

576. In essence, therefore, the only difference between the orphan drug and the existing therapies is that the former is formally registered for the treatment of CTX. The added value of Leadiant's activities therefore consists of having formalised the therapeutic indication with which the drug had already been administered for decades to patients with CTX. In other words, such activities allowed the transition from off-label to on-label treatment.

577. In relation to the Party's argument that it is necessary to give adequate recognition to the value that the CDCA Project has given to patients and the Italian National Health Service specifically because of the registration of the rare therapeutic indication, the following is observed.

578. According to AIFA, the registration of the orphan drug achieved through the CDCA Project was in itself socially useful, but it is not sufficient, either in terms of the resources used or of the actual result achieved, to justify the prices requested by the dominant company for the sale of the orphan drug in Italy (see paragraph 198 above), since the registration of the orphan drug was based "*exclusively on retrospective studies and literature data*"[573].

579. In addition to the fact that the activity carried out by Leadiant was based mostly on activities other than innovation, it should also be stressed that the registration of the therapeutic indication, while entailing undoubted benefits for patients, cannot in any case lead to the assertion, as made by the Party, that Leadiant was the first to formally demonstrate the efficacy and safety of the drug and its risk/benefit profile. On the contrary, since it did not

[573] See docs. 78.77 and 78.79, Annex

carry out prospective placebo-controlled studies (albeit for understandable reasons), the efficacy and safety and risk/benefit of CDCA in the treatment of CTX is still not fully known scientifically. Moreover, this was also stated by the expert consulted by the dominant company, who noted: "*In fact, comprehensive evidence [...] was not even established at the time the MA was granted*"[574]. On the other hand, it would not otherwise explain why the European Commission granted the marketing authorisation of the orphan drug "in exceptional circumstances" (see paragraph 155 above), whereas most orphan drugs are authorised with a "full" authorisation [575]. In fact, the conditional release of the administrative title is aimed precisely at monitoring the efficacy and safety of the drug over time, since this had not been demonstrated at the time the MA was issued.

580. This opinion is supported by the statements of the Dutch Ministry of Health, which considered that the annual price of €160,000-€220,000, equal to €14,000-€20,000 per pack, proposed by Leadiant to health insurance providers in 2017 for the purchase of the orphan drug was disproportionate to the actual investment in innovation made in the specific case. The activities carried out by the dominant undertaking for the registration of the orphan drug were considered useful but not "revolutionary" at the therapeutic level (see paragraph 183 above).

581. This fact was expressed even more clearly by the *Commission de la transparence* of the *Haute Autorité de Santé*, which, for the purposes of identifying the therapeutic added value of *CDCA Leadiant®,* found that the data on efficacy presented by the dominant company were very limited and not particularly robust, as they were based on the retrospective analysis of the medical records of groups of patients treated with CDCA-based drugs, which indicated conflicting results on the clinical criteria concerning symptoms. The *Commission* also found that both the data on the criteria of clinical morbidity and mortality and the comparative data were missing[576]. Indeed, as already explained, the *Commission* established that the orphan drug has a low therapeutic added value and has not made any improvement or made a non-significant improvement from a therapeutic standpoint compared with the past, deserving of a reimbursement price equal to 30% of the negotiated price,

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[574] See doc. 138.4.13.
[575] See doc. 138.4.13.
[576] See *https://*www*.has-sante.fr/jcms/c_2865403/*fr*/chenodeoxycholic-acid-leadiant-acide-chenodesoxycholique-medicament-a-base-d-acides-biliaires.*

or *[€4,000-€5,000]* per package[577].

582. It should be noted that the reimbursement price established by the French authorities has an order of magnitude similar to what AIFA stated can be granted to the dominant company for the sale of *CDCA Leadiant*® on the Italian market during the investigation (i.e., higher than the price of €3,400/€3,600 per pack paid by the ASLs for the import of *Xenbilox*® between 2016 and 2017, by 10% at most) (see paragraphs 116 and 217 above).

583. It should also be noted that the price levels identified by the two national regulators are also higher than those identified by assessing demand in 2008 and in 2014 to discern the suitable price to be attributed to the orphan drug. Market research conducted in 2008 indicated, in fact, that the price of the orphan drug considered "*reasonable*" was €1,327 per pack (see paragraph 102 above). Even the market research commissioned by Leadiant in 2014 indicated, in fact, that in Italy the medical community and demand supported that the "*reasonable*" price for a CDCA-based drug registered for the treatment of CTX could be around €1,300-€1,800 per pack, in line with the price previously identified in 2008. Both the introductory price of *CDCA Leadiant*® for the Italian market and the price subsequently negotiated with AIFA are therefore far from the price levels indicated in the assessment done by demand for the drug.

584. Moreover, Leadiant was aware that the price requested went well beyond what could be considered an adequate economic compensation for its activities ("*Sigma Tau wants to increase the monthly treatment cost of Xenbilox® and has already introduced some price increases but there are some concerns regarding a potential back-lash from treating clinicians*"[578]), and its fears were fully realised when the drug was introduced on the domestic market at the ex-factory price of €15,506.93 per pack. Doctors, in fact, reacted extremely negatively, since the price of *Xenbilox*® was already considered inappropriate[579]. Indeed, they defined the price as "*extremely burdensome*"

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[577] See https://www.has-sante.fr/upload/docs/application/pdf/2019-03/chenodeoxycholic_acid_leadiant_11072018_ct16384_transcription.pdf; https://www.has-sante.fr/jcms/c_2865403/fr/chenodeoxycholic-acid-leadiant-acide-chenodesoxycholique-medicament-a-base-d-acides-biliaires;
http://www.codage.ext.cnamts.fr/codif/bdm_it/fiche/index_fic_ucd.php?p_*code_cip=9426887&p_site=AMELI*.

[578] See doc. 78.71.

[579] See doc. 78.124 ("*Given that all companies need t/o make money (no doubt on that), the x 1k increment is not perceived as "fair" toward the investments (retrospective study in Siena and production upgrade, that he wasn't even aware of) - A second increment with change to Leadiant will sound even more inappropriate*").

and "*inadmissible*"[580] (see paragraph 139 above).

iv) The characterisation of Leadiant's behaviour as abuse of a dominant position

585. In light of the foregoing, it is believed that, by exploiting its dominant position in the domestic market for the production and sale of CDCA medicines for the treatment of CTX, Leadiant violated Article 102(a) of the TFEU by imposing unfair prices for the sale of the orphan drug called *CDCA Leadiant*® on the Italian National Health Service.

586. This unlawful conduct was carried out through a complex and elaborate strategy of a commercial and regulatory nature, which also includes dilatory and obstructive behaviour towards AIFA when negotiating the price of the orphan drug.

587. This abuse has caused direct economic damage to the Italian National Health Service, generated by the purchase of a drug at an unjustifiably excessive price. Leadiant defended itself on this point by stating that the drug's budget was absolutely negligible and that, during the negotiation procedure, it committed to AIFA and the ASLs to return any difference between the price charged pending an agreement and the price that would subsequently be negotiated with the Agency. However, in this regard it should be noted that this commitment is standard in negotiations between pharmaceutical companies and AIFA and holds no meaning as to the unwillingness of Leadiant not to cause damage to the Italian National Health Service, since the amount of the price differential to be returned would depend on the level of the negotiated price.

588. On the contrary, it should be noted that the high excess obtained by Leadiant over the economic value of the orphan drug, regardless of its limited budget, has had a direct effect on the limited resources of the Italian National Health Service allocated to pharmaceutical spending.

v) Attribution of the conduct to the companies of the Leadiant group

589. The acquired evidence shows the existence of a complex strategy that has seen the involvement of the companies belonging to the Leadiant group throughout its various phases and components: Leadiant Biosciences Ltd.,

[580] See docs. 22.7.68, 22.7.69, 28.2.121, 28.2.136, 28.2.140, 28.2.141, 28.2.189, 28.2.191, 78.89, 78.98, 78.122, 78.158, 78.213, 78.286, 78.347, 78.350, 78.367.

Leadiant GmbH, Sigma tau Arzneimittel GmbH, in liquidation, Leadiant Biosciences S.p.A., and the current parent company Essetifin S.p.A., which enabled the abusive conduct under examination to be carried out. For the purposes of assessing the subjective aspect of the offence, it is necessary to verify whether it can be attributed to the aforementioned companies.

590. Firstly, it emerges that Leadiant Biosciences Ltd. implemented the abusive conduct consisting of imposing unjustifiably excessive prices for the sale of *CDCA Leadiant*® to the Italian National Health Service as part of the negotiations of price of this drug with AIFA.

591. The abusive conduct also appears to be attributable to the parent company Essetifin S.p.A., by virtue of the fact that it fully controls Leadiant Biosciences Ltd. As stated in now established case law, it is believed that "*the conduct of a subsidiary can be attributed to the parent company if, despite having a distinct legal personality, such subsidiary does not independently determine its course of conduct on the market, but essentially follows the instructions given to it by the parent company, taking into account, in particular, the economic, organisational and legal constraints that exist between the two legal entities*"[581]. On this point, the case law has also stated that "*the parent company and its subsidiary are part of the same economic unit and constitute a single company, and therefore fines may well be imposed on the parent company even without the need to demonstrate the personal involvement of the latter in the infringement*"[582].

592. More specifically, "*in the particular case in which a parent company holds all or almost all of the share capital of a subsidiary that has committed an infringement of EU competition rules, there is a rebuttable presumption that the parent company actually exercises a decisive influence over its subsidiary. [...] Unless rebutted, such a presumption implies that the actual exercise of decisive influence by the parent company over its subsidiary is considered established and gives grounds for the Commission to hold the former company responsible for the conduct of the latter, without having to*

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[581] See EU Court of Justice, 14 July 1972, Case 48/69, *Imperial Chemical Industries v Commission*; 16 November 2000, Case C-294/98 P, *Metsä-Serla and Others v Commission*; 29 March 2011, Cases C-201/09 P and C-216/09 P, *ArcelorMittal Luxembourg v Commission and Commission v ArcelorMittal Luxembourg and Others*; 26 November 2013, Case C-50/12 P, *Kendrion v Commission*; 10 April 2014, in Joined Cases C-231/11P to C-233/11P, *Commission et al. v Siemens Österreich et al.*; 8 May 2014, Case C-414/12 P, *Bolloré v Commission*; 24 June 2015, Cases C-293/13 P and C-294/13 P, *Fresh Del Monte Produce Inc. v Commission*; 27 April 2017, Case C-516/15 P, *Akzo Nobel NV, Akzo Nobel Chemicals GmbH, Akzo Nobel Chemicals BV v Commission.*

[582] See Regional Administrative Court of Lazio, 10 March 2016, judgment no. 3077, case *I759 - Trenitalia Supplies (Firema Trasporti SpA).*

produce any further evidence"[583].

593. Ultimately, in accordance with the principles mentioned above regarding the liability for anticompetitive conduct – with particular reference to the rebuttable presumption of the effective exercise of a decisive influence of the parent company over its subsidiary, deriving from the ownership of all share capital – as well as in light of the factual evidence referred to above, it is believed that the conduct described above must be attributed to Leadiant Biosciences Ltd. and the parent company Essetifin S.p.A..

VI. EFFECT ON INTRA-EU TRADE

594. The disputed conduct falls within the scope of application of EU competition law and, in particular, within the scope of Article 102 of the TFEU, concerning the prohibition of abuse of a dominant position potentially capable of affecting intra-EU trade. According to the *Commission Notice — Guidelines on the effect on trade concept contained in Articles 81 and 82 of the Treaty*[584], the concept of effect on trade between Member States must be interpreted taking into account the influence, whether direct or indirect, actual or potential, on trade flows between Member States.

595. Given the above, the abuse in question concerns drugs distributed throughout the territory of the Italian Republic, therefore, corresponding to a significant part of the European market. Leadiant's abuse is therefore, by its very nature, a potential obstacle to the economic integration pursued by European Union legislation.

596. Therefore, on the basis of the foregoing, it is believed that such abuse is likely to affect trade between Member States and that the conduct attributable to the Party is relevant within the meaning of Article 102 of the TFEU.

VII. SERIOUSNESS AND DURATION OF INFRINGEMENT

597. Article 15(1) of Law No 287/90 states that, in the event of serious infringements, taking into account their seriousness and duration, the Italian Competition Authority shall provide for the application of an administrative

[583] In particular, see EU Court of Justice, *Akzo Nobel*.
[584] Published in OJEU C 101, 27.4.2004, p. 81–96.

fine of up to ten per cent of the turnover of the dominant company responsible for the infringement in the last financial year, taking into account the seriousness and duration of the infringement.

598. According to established European and national case law[585], when assessing the gravity of an infringement, account must be taken of a number of factors, the nature and importance of which vary according to the type of infringement and the particular circumstances thereof. Some of the most important factors include the nature of the disputed conduct, as well as the context in which the infringements were committed.

599. As regards the nature of the conduct in question, it should be noted that Leadiant has committed an abuse of exploiting the limited resources of the Italian National Health Service, consisting of imposing unjustifiably excessive prices for the sale of *CDCA Leadiant*® to the NHS.

600. In relation to the context, it should be noted that the imposition of an excessive price was achieved through a consciously planned and persistently pursued complex strategy over the course of time, which Leadiant used in negotiations to weaken AIFA, thus managing to obtain an extremely high and disproportionate reimbursement price compared to the costs incurred.

601. Leadiant Biosciences Ltd. is, moreover, an operator with the legal and economic knowledge necessary to grasp the illegitimate nature of its conduct and the relative consequences in terms of competition. It must be considered that, as per the established case law, for a conduct to be considered intentional, it is not necessary for the company in question to have been aware of breaking these rules, but merely that it could not have been unaware of the purpose of its conduct[586].

602. In this case, not only could Leadiant Biosciences Ltd. not ignore the illegitimate nature of its conduct and the consequences thereof, but the investigation has shown that it intentionally committed these acts.

603. In this case, it is also significant that the imposition of unjustifiably excessive prices concerned a drug without therapeutic alternatives intended for the treatment of an ultra-rare disease that leads to death.

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[585] See, *ex multis*, Council of State, judgments nos. 896 of 9 February 2011 and 5171 and 5172 of 16 September 2011, in relation to Case I694 - *Listino prezzi della pasta* (pasta price list); Court of Justice, judgment of 15 July 1970, C-45/69, *Boehringer Mannheim GmbH v Commission* [1970] p. 769, paragraph 53. The latter judgment was referred to and clarified by the Court of Justice in its judgment of 7 June 1983, Joined Cases C-100-103/80, *Musique Diffusion Française*, ECR 1983, p. 1825, and in its judgment of 9 November 1983, C-322/81, *Michelin*, ECR 1983, p. 3461.

[586] See EU Court of Justice, 8 November 1983, IAZ, paragraph 35; EC Court of First Instance, 6 April 1995, Case T-141/89, Trefileurope, paragraph 176 and 14 May 1998, Case T-310/94 Gruber Weber, paragraph 259; 12 July 2001, British Sugar, paragraph 127.

604. The objective pursued by the dominant company was, moreover, fully achieved, given that following negotiations with AIFA, Leadiant Biosciences Ltd. obtained and effectively applied a price that the analyses carried out proved to be unjustifiably excessive. The conduct has, therefore, produced concrete effects.

605. In view of the above circumstances, Leadiant Biosciences Ltd.'s abuse of a dominant position must be considered very serious and the arguments put forward by the Party to demonstrate the non-seriousness of the conduct, which reiterate the defence arguments put forward to advocate the fairness of the price of *CDCA Leadiant®*, are not likely to call these conclusions into question.

606. With regard to the duration of the disputed conduct – and in particular, when it began – it can be traced back to 15 June 2017, i.e., when, with the submission to AIFA of the request for reimbursement and classification of *CDCA Leadiant®* at the ex-factory price of €15,506.93 per pack, Leadiant was able to negotiate and apply an unjustifiably excessive price through a preparatory strategy of the abuse devised long before and intentionally pursued.

607. The infringement is still ongoing. In fact, the ex-factory price negotiated with AIFA in December 2019, applied retroactively from 15 June 2017 to date, for the reimbursement of *CDCA Leadiant®* by the Italian National Health Service at *[€5,000-€7,000]* per pack, is unjustifiably excessive on the basis of the investigation carried out.

VIII. QUANTIFICATION OF THE FINE

608. Having ascertained the seriousness and duration of the infringements committed by Leadiant Biosciences Ltd., for the purposes of identifying the quantification criteria, it is necessary to bear in mind the provisions of Article 11 of Law no. 689/1981, as referred to in Article 31 of Law no. 287/90, as well as the interpretative criteria set out in the "*Guidelines on the method of application of the criteria for quantifying administrative fines imposed by the Authority pursuant to Article 15(1) of Law no. 287/90*" (hereinafter referred to as "Guidelines"), approved by the Italian Competition Authority on 22 October 2014.

609. As regards the turnover relevant for the purposes of the fine, the Authority's Guidelines on fines state that fines "*should be calculated based on the value of the sales of goods or services that are directly or indirectly*

related to the infringement committed by the company on the relevant market(s) in the last full financial year of its participation in the infringement (hereinafter, value of sales)" (points 8 and 9). In this case, the said value consists of the value of sales generated by Leadiant in Italy for the drug *CDCA Leadiant*® in 2021, equal to *[€2-€3 million]*.

610. For the purpose of determining the base amount of the fine, a percentage determined on the basis of the seriousness of the infringement is applied to the value of the sales as determined above. For full details, see section VII. According to the Guidelines, in particular, this percentage must be set at a level that can reach 30% of the value of sales, "*according to the degree of seriousness of the violation*" (point 11).

611. Pursuant to point 14 of the Guidelines and the criteria provided for therein, and based on the provisions of paragraphs 599-605 above regarding the seriousness of the case, the percentage of the base fine amount must be set as *[20-25%]* of the value of the sales made by Leadiant in Italy for the drug *CDCA Leadiant*® in the year 2021. The result is an amount of *[€500,000-€600,000]*.

612. The amount thus obtained must be multiplied by the duration of the infringement. In this case, on the basis of paragraphs 606-607 above, this is equal to 4 years, 11 months and 2 days. Therefore, the base amount was calculated using 4.922222 as the multiplier of the amount referred to in paragraph 611 above, and thus an amount of *[€2-€3 million]* was obtained.

613. In order to ensure that the Italian Competition Authority's power to impose fines has the necessarily deterrent effect, with specific reference to the most serious restrictions on competition, regardless of their duration and actual implementation, pursuant to point 17 of the Guidelines, the Authority may consider it appropriate to include in the base amount an additional amount of between *[20-25%]* of the value of the sales of the goods or services subject to the infringement (the entry fee), i.e., *[€600,000-€700,000]* euro. Specifically, it is considered that this additional amount is justified precisely in view of the particular gravity of the infringement committed by Leadiant, given the confirmed premeditation of the conduct (see section V.4 and V.5.1. above) and the life-saving nature of the drug (see paragraph 478 above).

614. In this case, the amount of the fine, as determined so far, should be increased in accordance with point 25 of the Guidelines, in view of the fact that during the last financial year ending before the communication of the notice, the company responsible for the infringement generated a total worldwide turnover that was especially high compared to the sales of the

goods or services subject to the infringement.

615. However, in view of the fact that the actual specific deterrence is, in this case, also guaranteed by the procedural steps taken by the other national competition authorities pursuant to Article 102(a) of the TFEU against Leadiant (see paragraph 14 above), and of the opportunity of a coordination between the relevant authorities in relation to the application of the sanction, in order to ensure that all fines imposed are proportional to the seriousness of the infringements committed, the above-mentioned increase in the fine is considered inapplicable, even if the case is one that deserves such an increase.

616. In the light of the foregoing, the final amount of the fine is set to €3,501,020, which, so determined, does not exceed the maximum amount set out under Article 15(1) of Law no. 287/1990.

617. Finally, it is considered that, pursuant to point 32 of the Guidelines, which states that "*in the event that more than one company belonging to the same group has participated in the infringement, the Authority may impose the fine jointly and severally on the said companies*", and given that the infringement can be attributed to Leadiant Biosciences Ltd. as well as to Essetifin S.p.A. by virtue of the described controlling relationship between them, these companies are jointly and severally liable for the payment of the fine as calculated above.

In consideration of the above, the Authority hereby

RESOLVES

a) that the companies Leadiant Biosciences Ltd. and Essetifin S.p.A. imposed unjustifiably excessive prices on the sale to the Italian National Health Service of *Leadiant® Chenodeoxycholic Acid*, used to treat the rare disease called cerebrotendinous xanthomatosis, in breach of Article 102 of the Treaty on the Functioning of the European Union;

b) that the companies Leadiant Biosciences Ltd. and Essetifin S.p.A. shall satisfy all obligations aimed at defining prices that are not unjustifiably high for *Chenodeoxycholic Acid Leadiant®* and shall refrain, in the future, from engaging in behaviours similar to those subject to the infringement established in point a);

c) that within sixty days from notification of this decision, the companies Leadiant Biosciences Ltd. and Essetifin S.p.A. shall notify the Italian Competition Authority of the initiatives taken to comply with the requirements of letter b) above, sending a specific written report;

d) to jointly and severally impose on the companies Leadiant Biosciences Ltd. and Essetifin S.p.A. a total administrative fine of €3,501,020.13 (three million five hundred one thousand twenty/13).
For undertakings with registered offices in Italy, the administrative fine imposed must be paid within ninety days from the notification of this decision using the tax codes indicated in annexed form F24 with identification elements, as per Legislative Decree no. 241/1997. Payment must be made through electronic debit from their bank or postal current account through the home-banking or CBI services made available by the banks or Poste Italiane S.p.A., or using the electronic services of the Italian Revenue Agency, available on the website www.agenziaentrate.gov.it.
Pursuant to Article 37(49) of Decree-Law no. 223/2006, parties with a VAT number are obliged to submit the F24 form electronically.
For undertakings with registered offices in a foreign country, the administrative fine must be paid within ninety days by bank transfer (in euros) to the Italian Treasury, using IBAN code IT04A0100003245348018359214 (BIC code: BITAITRRENT), corresponding to the three-digit accounting code 18/3592/14.

Upon expiration of this term, for a period of delay of less than six months, default interest must be paid at the legal rate from the day following the expiry of the payment deadline and up to the date of payment. In case of further delay, pursuant to Article 27(6) of Law no. 689/81, the sum due for the fine imposed is increased by one tenth every six months starting from the day following the expiry of the payment deadline and until the day the case is transmitted to the concessionaire for collection; in this case the increase absorbs the default interest accrued over the same period.
The Italian Competition Authority must be immediately notified of the payments by sending a copy of the form certifying that the payment has been made.
Under Article 26 of the same law, companies in economically-disadvantaged conditions may ask to pay the fine in instalments.

This decision will be notified to the Parties concerned, and it will be published

in the Bulletin of the Italian Competition Authority.

An appeal may be filed against this decision with the Lazio Regional Administrative Court, pursuant to Article 135(1), letter b), of the Code of Administrative Procedure (Legislative Decree no. 104 of 2 July 2010), within sixty days from the date of notification of the decision, without prejudice to the longer terms set forth by Article 41(5), of the Code of Administrative Procedure. Moreover, an extraordinary appeal may be made to the President of the Republic, pursuant to Article 8 of Italian Presidential Decree no. 1199 of 24 November 1971, within one hundred twenty days from the date of notification of the decision.

THE SECRETARY GENERAL
Guido Stazi

THE PRESIDENT (acting)
Michele Ainis