EUROPEAN COMMISSION
DG Competition

Case M.8955 – TAKEDA / SHIRE

Only the English text is available and authentic.

REGULATION (EC) No 139/2004
MERGER PROCEDURE

Decision on the implementation of the commitments - Waiver of the Commitments
Date: 28.05.2020

EUROPEAN COMMISSION

Brussels, 28.05.2020
C(2020) 3597 final

PUBLIC VERSION

In the published version of this decision, some information has been omitted pursuant to Article 17(2) of Council Regulation (EC) No 139/2004 concerning non-disclosure of business secrets and other confidential information. The omissions are shown thus […]. Where possible the information omitted has been replaced by ranges of figures or a general description.

To the notifying party

Dear Sir or Madam,

Subject: Case M.8955 – Takeda/Shire
Commission decision on Takeda's request for a waiver of the commitments annexed to the Commission decision of 20 November 2018

1. INTRODUCTION

(1) By decision of 20 November 2018 (the "Clearance Decision") adopted in application of Article 6(1)(b) and Article 6(2) of Council Regulation No 139/2004 of 20 January 2004 on the control of concentrations between undertakings[1] (the "Merger Regulation"), the Commission declared the operation by which Takeda Pharmaceutical Company Limited ("Takeda" or the "Notifying Party") acquires sole control of Shire plc ("Shire") (the "Transaction") compatible with the internal market and with the EEA Agreement, subject to full compliance with the commitments submitted by the Notifying Party and annexed to the Clearance Decision (the "Commitments"). Takeda and Shire are hereinafter referred together as the "Parties".

(2) On 1st October 2019, Takeda requested to waive the Commitments in their entirety. In this decision, the Commission assesses Takeda's request.

[1] L 24, 29.1.2004, p. 1-22.

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2. BACKGROUND

2.1. The Clearance Decision and the Commitments

(3) The Commitments consist of the divestment of Shire's Phase III pipeline compound for the treatment of Ulcerative Colitis ("UC") and Crohn's disease ("CD"),[2] namely "SHP 647" or the "Divestment Business".

(4) The Commitments aimed at removing the serious doubts raised by the Transaction as a result of the combination of Takeda's blockbuster drug Entyvio (*vedolizumab*) and Shire's Phase III pipeline compound SHP 647. These two products are biologic pharmaceuticals intended to be used as third-line treatment for UC and CD, when the disease symptoms progress due to a lack of response to conventional therapies.[3]

(5) As explained in the Clearance Decision, biologic pharmaceuticals (used as third-line treatment for UC and CD) include drugs with different modes of action: (i) anti-Tumour Necrosis Factor ("anti-TNFs"), (ii) anti-integrins, and (iii) interleurkin ("IL")-inhibitors.[4] Both Takeda's Entyvio and Shire's Phase III pipeline compound SHP 647 are anti-integrins. Takeda's Entyvio is the only anti-integrin drug currently available on the market.

(6) During the investigation, the Commission found that drugs with different modes of action have distinct efficacy and safety profiles. In particular, the results of the market investigation revealed that, due to their gut specific mode of action, anti-integrins had a better safety profile than anti-TNFs and IL-12/23 inhibitors (which have a general immunosuppressant effect).[5] On this basis, the Commission concluded that anti-integrins constituted a distinct product market.[6]

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2 UC and CD, together referred as inflammatory bowel diseases ("IBD"), are chronic autoimmune diseases that cause inflammation and ulceration of the digestive system. The main differences between UC and CD are that (i) CD can affect any part of the gastrointestinal tract and causes inflammation of the full thickness of the intestinal wall whereas (ii) in UC, the inflammation is limited to the colon and remains within the superficial lining of the intestine. Both diseases can have similarly debilitating effects with comparable symptoms (*e.g.* abdominal pain, severe diarrhoea, fatigue, malnutrition and severe weight loss). IBD are lifelong conditions for which there is currently no cure.

3 The treatment for UC and CD follows sequences (or "algorithms"), meaning that the patient is initially treated with one type of drugs and moves on to another type if the initial drug does not work or stops working after a certain period of time. The algorithms for UC and CD are largely similar and consist of: (i) conventional treatments (used as first- and second-line treatments), including aminosalicylates, corticosteroids and immunosuppressants; and (ii) post-conventional treatments (prescribed after the failure of conventional therapies or in case of contraindication), including biologic drugs and innovative small molecules.

4 See recitals 35-37 of the Clearance Decision. Most recently, in case M.9461 – *AbbVie/Allergan*, the Commission found that, within IL-inhibitors, a distinction could be made between IL-12/23 inhibitors and novel IL-23 inhibitors, which are currently under development (see case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recitals 48 et seq).

5 See recitals 38 et seq. of the Clearance Decision. In *AbbVie/Allergan*, the market investigation highlighted the promising nature of IL-23 inhibitors, a new class of biologics for IBD, which are not marketed yet and are expected to have a better efficacy and safety profile than all other available post-conventional treatments, including anti-integrins (see case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recital 51).

6 See recital 49 of the Clearance Decision. In *AbbVie/Allergan*, the results of the market investigation revealed a certain degree of substitutability between post-conventional treatments for IBD. As a result, in that decision, the Commission left open the relevant product market definition and considered three

(7) On the market for anti-integrins for use in UC and CD, the Commission found that Takeda's marketed drug Entyvio and Shire's Phase III pipeline compound SHP 647 would face only one (future) competitor, *i.e.* Roche's *etrolizumab* (a Phase III pipeline drug for use in both UC and CD), with limited competitive pressure exerted by marketed and pipeline drugs in neighbouring markets.[7]

(8) The results of the market investigation confirmed that the overlap between Takeda's Entyvio and Shire's SHP 647 could lead to competition concerns, given the likelihood of Shire's pipeline compound being abandoned post-Transaction, Takeda having no incentives to continue its development.[8] More specifically, the market investigation revealed that Entyvio and SHP 647 would closely compete, due to their similar efficacy and safety profile, and that Key Opinion Leaders ("KOLs") were very positive about the prospects for SHP 647. Therefore, the Commission considered that, following completion of the acquisition of Shire, Takeda would likely discontinue the development of SHP 647 to avoid the risk of cannibalisation of Entyvio's sales. […]. Given the limited number of anti-integrin competing products, the disappearance of SHP 647 would represent a significant loss of innovation competition, leading to a loss of product variety and reduced intensity of future price competition in the product market, to the detriment of consumers. Thus, the Commission concluded that the Transaction raised serious doubts as to its compatibility with the internal market in relation to the market for anti-integrin drugs for use in UC and CD.[9]

(9) On 16 November 2018, the Parties submitted the Commitments to eliminate the Commission's serious doubts arising from the overlap between Takeda's Entyvio (*vedolizumab*) and Shire's pipeline compound SHP 647. The Commitments offered consisted in a full divesture of the development, manufacturing and marketing rights of Shire's pipeline compound SHP 647 to a suitable purchaser,[10] within a fixed time-limit after the Clearance Decision.

(10) The Commission concluded that the Commitments were sufficient to eliminate the serious doubts raised by the Transaction, as they removed the entire overlap between the Parties' activities in relation to anti-integrin drugs for use in UC and CD. In particular, the Commission noted that the Commitments included all tangible and intangible assets necessary to conduct and complete the development of SHP 647 and to bring it to the market. The market test also confirmed the viability and attractiveness of the Divestment Business, with several potential purchasers having expressed interest in the acquisition of the asset during the market test.[11]

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alternative market delineations namely: (i) the market for post-conventional treatments for IBD, including all biologics and innovative small molecules; (ii) the market for post-conventional treatments for IBD excluding anti-TNFs; and (iii) a segmentation of post-conventional treatments for IBD by mode of action (see case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recitals 36 et seq).

7 See recitals 73 et seq. of the Clearance Decision.

8 See recitals 85 et seq. of the Clearance Decision.

9 See recital 94 of the Clearance Decision.

10 See Purchaser Criteria set forth in paragraph 17 of the Commitments.

11 See recitals 113 et seq. of the Clearance Decision.

2.2. Chronology of the Divestiture process

(11) Under paragraph 2 of the Commitments, the Parties committed to divest or procure the divestiture of the business related to Shire's pipeline compound SHP 647, and to find a purchaser and enter into a final binding sale and purchase agreement for the Divestment Business within four months of the date of adoption of the Clearance Decision (the "First Divestiture Period"). The Parties also committed that, in the absence of such an agreement at the end of the First Divestiture Period, the Parties would grant an exclusive mandate to sell the Divestment Business to a divestiture trustee in accordance with the procedure described in paragraph 32 of the Commitments within three months from the end of the First Divestiture Period (the "Trustee Divestiture Period").

(12) By letter of 20 February 2019, Takeda requested an extension of the First Divestiture Period, which was to expire on 20 March 2019, by two months (the "First Extension Request"). Takeda explained that the divestiture process had not progressed as quickly as expected since various potential buyers, who had initially expressed interest in the Divestment Business, decided not to pursue the divestment process. On 21 February 2019, RSM Corporate Finance LLP (the "Monitoring Trustee") submitted a report endorsing Takeda's First Extension Request. By decision of 7 March 2019, the Commission extended the First Divestiture Period by two months, *i.e.* until 20 May 2019.

(13) On 19 April 2019, Takeda submitted a new request for an additional extension of the First Divestiture Period by one month. On 1 May 2019, Takeda submitted another request, superseding the one of 19 April 2019, for an extension of the First Divestiture Period by four months (the "Second Extension Request"). Takeda explained that the divestiture process had been further delayed due to the results of a reproductive toxicity study of SHP 647 conducted on non-human primates (the "Reproductive Toxicity Study") showing abnormal infant death rates, which created uncertainties about the Divestment Business and the need for further studies. On 13 May 2019, the Monitoring Trustee submitted a report on the Second Extension Request acknowledging the need for an additional extension of the First Divestiture Period but considering that a two-month extension would be more appropriate. By decision of 17 May 2019, the Commission extended the First Divestiture Period by two months, *i.e.* until 20 July 2019.

(14) On 21 July 2019, in the absence of a final binding sale and purchase agreement for the Divestment Business, the Trustee Divestiture Period started for a period of three months, ending on 20 October 2019.

(15) In August 2019, Greenhill & Co. International LLP (the "Divestiture Trustee") reached out to sixty potential purchasers to assess their interest in acquiring the Divestment Business. Fifteen of them signed non-disclosure agreements and received from the Divestiture Trustee a confidential teaser. In early September 2019, the Divestiture Trustee held management presentations with nine potential purchasers, which had expressed interests, and provided them with additional documentation, including a financial data pack.

(16) By letter of 20 September 2019, the Divestiture Trustee informed the Commission that an extension of the Trustee Divestiture Period would be necessary to finalise the divestiture process, as one of the few potential purchasers still involved in the divestiture process had requested four extra-weeks to conduct due diligence. The

Divestiture Trustee considered the above request to be reasonable given the amount and the complexity of information involved and indicated that it was in the interest of the divestiture process to preserve as many potential purchasers as possible. On the same day, the Monitoring Trustee submitted a report on the extension of the Trustee Divestiture Period, explaining that, given the status of the divestment process, it was highly unlikely that a binding sale and purchase agreement for the sale of the Divestment Business could be achieved by 20 October 2019. By decision of 4 October 2019, the Commission extended the Trustee Divestiture Period by 28 days, *i.e.* until 17 November 2019.

(17) On 1st October 2019, Takeda submitted a request to waive the Commitments in their entirety (the "Waiver Request"). As explained in Section 3 below, Takeda claims that the Commitments have become obsolete due to a combination of unforeseen adverse events, which took place after the adoption of the Clearance Decision and are outside of Takeda's control, namely the Divestment Business' difficulties to recruit patients for the clinical trials, the results of the Reproductive Toxicity Study and the absence of suitable purchasers. In order to assess the merits of the Waiver Request, and to enable the Divestiture Trustee to progress in parallel with its mandate, the Commission addressed several formal requests for information under Article 11(2) of the Merger Regulation to Takeda in relation to the implementation of the Commitments and the developments invoked in the Waiver Request. In response to such requests for information, Takeda produced a number of documents and presented substantive submissions on 4, 8, 9 and 11 November 2019.

(18) By letter of 13 November 2019, Takeda requested an additional extension of the Trustee Divestiture Period until 23 December 2019. In its letter, Takeda acknowledged that additional time was needed to review the elements provided in response to the above-mentioned requests for information, including notably a very large number of internal documents concerning the results of the Reproductive Toxicity Study. Takeda also explained that they were aware that discussions with potential bidders were still ongoing and that a final position was unlikely to be reached by 17 November 2019. On the same day, the Monitoring Trustee submitted a report in which it explained that a definitive agreement for the divestiture of SHP 647 could not be finalised by 17 November 2019 given the status of the divestiture process and the significant further work required in order to reach a final agreement. The Monitoring Trustee concluded that an extension of the Trustee Divestiture Period, possibly beyond 23 December 2019, was required. By decision of 15 November 2019, the Commission extended the Trustee Divestiture Period until 17 January 2020.

(19) As shown in the Table 1 below, during the Trustee Divestiture Period, the Divestiture Trustee received non-binding offers and/or binding offers from only three potential purchasers.[12] These offers all implied a highly negative sale price requiring very significant funding from Takeda (*i.e.* in the order of hundreds of millions of euros) to pursue the development of SHP 647.

12 Following the adoption of the Clearance Decision, the pharmaceutical sector experienced a wave of M&A activity in 2019. It follows that several companies who had expressed interest during the market test focused their efforts on other transactions and, thus, lost interest in the acquisition of SHP 647.

Table 1 – Offers received by the Divestiture Trustee

Bidder	Non-binding offer		Binding offer[13]	
	Original	Revised	Original	Revised
[…]	13 September 2019	23 October 2019	-	-
[…]	13 September 2019	-	17 October 2019	29 October 2019
[…]	27 October 2019	-	25 November 2019	17 January 2020

(20) By the end of the Trustee Divestiture Period on 17 January 2020, the Divestiture Trustee had not proposed any purchaser for the Commission's approval for the acquisition of the Divestment Business. In a detailed reasoned report on the divestiture process, the Divestiture Trustee concluded that the potential purchasers who submitted binding offers did not appear suitable, as they did not meet the Purchaser Criteria laid down in the Commitments.[14]

(21) On 27 January 2020, the Monitoring Trustee submitted a report assessing Takeda's request to waive the Commitments. This report was subsequently updated on 7 March 2020 (see Section 4 below).

3. WAIVER REQUEST

(22) On 1st October 2019, pursuant to paragraph 46 of the Commitments, Takeda formally requested the Commission to waive the Commitments entirely.[15] Takeda submits that the Commitments have become obsolete because of a set of three unrelated exceptional circumstances arising after the adoption of the Clearance Decision.

(23) *First,* Takeda argues that difficulties in recruiting patients in SHP 647's Phase III clinical trials have dramatically delayed its potential launch on the market (by respectively five and seven additional years for UC and CD) and, thus, substantially increased its development costs (by more than USD […]). These difficulties are notably explained by (i) the unexpected high proportion of patients failing the screening process and (ii) the increasing number of pipeline drugs competing for the limited pool of patients eligible in clinical trials for IBD treatments. It follows that, assuming the Phase III trials are successful, SHP 647 would only reach the market after the launch of Entyvio's biosimilars, thus substantially limiting its commercial prospects. In view of the above, Takeda considers that, absent the Transaction, it would have been irrational for Shire to pursue the development of the programme, which invalidates the Clearance Decision's key assumption that SHP 647 would have reached the market and constrained Entyvio.

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13 Whilst […] and […] characterised their submissions as binding offers, the Divestiture Trustee explained that none of the offers it received fully meet the requirements set out by the divestment process instructions.

14 Divestiture Trustee's Detailed Reasoned Report dated 24 January 2020 and subsequently updated on 26 February 2020, Section 4. The Commission considers that, irrespective of the suitability of the potential purchasers, the Commitments have become obsolete due to exceptional circumstances arising after the adoption of the Clearance Decision (see Section 5.2 below).

15 The Waiver Request was supplemented by additional submissions made on 7 November 2019, 28 January 2020, and 13 April 2020.

(24) Moreover, in an additional submission dated 13 April 2020, Takeda claims that the recent and rapid spread of the COVID-19 pandemic further affects the launch and development costs of SHP 647 as it impedes the ability of the Divestment Business to recruit new patients and compromises the data collected from already recruited patients.[16]

(25) *Second*, the results of the Reproductive Toxicity Study of SHP 647 in non-human primates, which came out in April 2019, show abnormal infant death rates. Takeda claims that these results will require new preclinical trials, with an uncertain outcome and additional development costs. Takeda argues that this adverse safety finding constitutes a negative differentiator compared to Entyvio, whose safety profile is steadily improving (with a growing body of clinical evidence and empirical data). According to the Notifying Party, the above invalidates another key assumption of the Clearance Decision that SHP 647 would ultimately emerge as a close substitute of Takeda's Entyvio and exert a strong competitive constraint on it.

(26) *Finally*, Takeda submits that no suitable purchaser meeting the Purchaser Criteria set out in the Commitments has emerged despite an extensive divestment process. Takeda considers that this outcome shows that SHP 647 is no longer perceived by the market as an attractive asset that would enable a potential suitable purchaser to compete with Takeda's Entyvio.

(27) In view of the above exceptional circumstances, Takeda considers that there is no prospect of SHP 647 being developed and commercialised as a viable, competitive or effective product in the foreseeable future. Consequently, the Waiver Request concludes that there is no longer any basis for maintaining the Commitments.

(28) In response to questions raised by the Commission,[17] Takeda indicated that, should the Commitments be waived, it would make all pre-clinical and clinical data in the possession of the Divestment Business available in the public domain. The data would be given to third party researchers by way of a sublicense to an independent third-party custodian (such as a university, public/private partnership or patient advocacy/research institution)[18] for research and publication purposes to the benefit of UC and CD patients and science more generally.[19]

(29) Takeda also indicated that, in case the Commitments were to be waived, all patients enroled in the clinical trials who are responding to the treatment would continue to receive the compound for medical ethical reasons (and despite the discontinuation of the development of SHP 647).[20] Takeda explained that, in order to be able to identify

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16 In order to be granted a marketing authorisation, data from clinical trials need to be collected at a specific point in time defined in the protocols agreed with regulators. Because of the COVID-19 pandemic, the Divestment Business will however not be able to collect this data at the required points in time since many patients are unable to attend the planned follow-up visits under the protocols and investigators are not able to perform the endoscopy procedures necessary to record data.

17 Takeda's response to the Commission's request for information n°3 on remedy implementation.

18 Takeda initiated discussions with the Crohn's & Colitis Foundation, which would be the custodian of the SHP 647 data. More information available at: https://www.crohnscolitisfoundation.org/.

19 Takeda explained that the data collected during the SHP 647's clinical trials are valuable for research purposes. They could notably enable the scientific community to better understand the pathogenesis of IBD and could help to improve the design of future clinical trials in IBD.

20 In order to be given access to SHP 647, these patients would have to enrol in a "post-trial access" study (to be designed in conjunction with the competent regulatory authorities). SHP 647 would be available

these patients and continue their medication, the Phase III studies will have to be "unblinded",[21] which would corrupt the data irrevocably[22] and prevent Takeda (or any third party) from using them with a view to seeking a regulatory approval for SHP 647 base on this data set in the future.

4. MONITORING TRUSTEE REPORT

(30) On 27 January 2020, the Monitoring Trustee submitted a report assessing the Waiver Request (the "Monitoring Trustee Report"). This report was subsequently updated on 7 March 2020.

(31) In this report, the Monitoring Trustee confirms that a number of factors have certainly "*adversely impacted*" the Divestment Business since the adoption of the Clearance Decision, including in particular (i) the fact that the recruitment rates for SHP 647's Phase III clinical trials have fallen significantly behind the forecast rates assumed at the time of the Clearance Decision and (ii) the abnormally high infant death rates recorded in the Reproductive Toxicity Study. The Monitoring Trustee stresses the fact that the above issues led the management of the Divestment Business (the "Management") to materially amend the initial business plan of SHP 647 (the "Revised Business Plan"), including revised forecasts, in June 2019. More specifically, the Monitoring Trustee notes the following.

(32) *First*, the Monitoring Trustee Report confirms that the very low recruitment rates experienced by the Divestment Business (and the consequent increase in the time required to meet the targeted number of patients for the clinical trials) led to significant delays for both UC and CD, as well as to a material increase in the forecasted development costs.

(33) In addition, the Monitoring Trustee notes that the difficulties in recruiting patients for the clinical trials have continued to date, the enrolment rate achieved during the second semester 2019 being even lower than those assumed in the Revised Business Plan. This led the Management to revise again its forecasts, anticipating additional material delays and increase in development costs (which are not reflected in the Waiver Request submitted on 1st October 2019). The Monitoring Trustee further notes that, according to the Management, the delay in launch dates could also adversely impact the pricing and revenues of SHP 647. Indeed, as a result of these delays, SHP 647 is now expected to be launched around the time of Takeda's Entyvio loss of exclusivity and, thus, to face competition from Entyvio biosimilars. Biosimilar competition would most likely lead to the decrease of the price of anti-integrin drugs and, therefore, negatively impact SHP 647's projected revenues.

(34) *Second*, the Monitoring Trustee reports that the Management, in consultation with internal safety experts, determined that the safety finding of the Reproductive

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to them until it is deemed that they are no longer receiving benefit. Regulatory authorities would need to approve (*i.e.* decide whether it is in the patients' interest to continue treatment with a compound that will ultimately not be commercialised) and oversee the "post-trial access" study.

21 Under the current protocols, it is not known which patients are administered SHP 647 and which are administered the placebo. This would be revealed by unblinding the clinical trial data.

22 The trial protocols agreed with regulatory authorities presuppose that data remain blinded during the trials.

Toxicity Study […]. Although the Monitoring Trustee submits that the future impact of the Reproductive Toxicity Study remains uncertain at this stage, it also notes that these results could potentially lead to label warnings or strict use-restrictions for women in childbearing age. The Monitoring Trustee states that, under some of the possible scenarios envisaged by the Divestment Business, the results of the Reproductive Toxicity Study would have a "*material adverse effect on the value of the Divestment Business due inter alia to the less favourable safety profile and potential impact on the addressable market and sales*". The Monitoring Trustee also acknowledges that additional pre-clinical studies may be required to assist the Divestment Business in understanding the risks but specifies that the decision as to whether these studies should be initiated has been put on hold.

(35) *Finally*, the Monitoring Trustee observes that an extensive divestment process has been undertaken to identify and reach an agreement with a suitable purchaser meeting the requirements of the Commitments. The Monitoring Trustee notes that, despite the large number of potential purchasers contacted during the divestiture process and the time given to them to assess SHP 647, the Divestiture Trustee received only two binding offers, which both implied a highly negative sale price requiring very significant funding from Takeda (*i.e.* in the order of hundreds of millions of euros) to pursue the development of the drug. Based on a preliminary analysis, the Monitoring Trustee considers, similarly to the Divestiture Trustee and Takeda, that the two purchasers who submitted binding offers for the Divestment Business are unlikely to fulfil all the Purchaser Criteria.

5. COMMISSION'S ASSESSMENT OF THE WAIVER REQUEST

5.1. Applicable legal framework

(36) Under Articles 6(2) and 8(2) of the Merger Regulation, the Commission may attach to its decision conditions and obligations (together generally referred to as commitments) to which its clearance is subject. The objective of such commitments is to render a transaction, that would otherwise be problematic from a competition point of view, compatible with internal market.

(37) In case *Lufthansa v Commission*, the General Court held that "*the purpose of* [such] *commitments is in fact to remedy the competition problems identified in the decision authorising the concentration; accordingly, the commitments might have to be amended, or the need for them might disappear, depending on how the market situation develops*".[23]

(38) As regards the conditions under which such a waiver may be granted, paragraph 46 of the Commitments attached to the Clearance Decision (the "Review Clause") provides that "*the Commission may* […] *in response to a reasoned request from the Parties showing good cause waive, modify or substitute, in exceptional circumstances, one or more of the undertakings in these Commitments*". Similarly, paragraph 73 of the Remedies Notice[24] states that: "*the Commission may grant*

[23] Case T-712/16, *Deutsche Lufthansa AG v Commission*, judgement of the General Court of 16 May 2018, para. 31.

[24] Commission notice on remedies acceptable under Council Regulation (EC) No 139/2004 and under Commission Regulation (EC) No 802/2004, OJ C 267, 22.10.2008, p. 1 (the "Remedies Notice").

waivers or accept modifications or substitutions of the commitments only in exceptional circumstances".

(39) It follows that, unlike extensions of divestment periods, which can be granted on the basis of "good cause" shown by the parties, a waiver of commitments under the Review Clause can only be granted in cases where the parties provide evidence of "exceptional circumstances".

(40) In this respect, the mere finding of a change in market conditions which is neither significant nor permanent does not suffice to conclude that exceptional circumstances have occurred within the meaning of the Review Clause. The assessment of the effects of a notified merger is carried out *ex ante* and the Commission must make a reasonable prediction of the developments on the basis of all information available at that time. But in order to qualify as exceptional circumstances for the purposes of the Review Clause, subsequent changes in market conditions must be significant, permanent and unforeseeable.[25]

(41) In addition, in order to constitute good cause for a waiver, modification or substitution request, the alleged changes in market circumstances must ensure that the objective of the commitments are effectively achieved on a lasting basis independently of the commitments (in case of a request for a complete waiver) or that the objective will be better achieved by the requested modification of the commitments.[26] In the context of a waiver request, such as the present one, the changes in question must therefore have as a consequence that the competition concerns laid out in the Clearance Decision no longer arise.

(42) Furthermore, the Review Clause puts the burden of proving that exceptional circumstances have occurred on the Parties.[27]

(43) In light of the above, to conclude that exceptional circumstances justify waiving the Commitments, it must be demonstrated that:

(a) the market conditions have changed significantly and permanently;

(b) the change(s) could not have been foreseen at the time of the adoption of the Clearance Decision; and

(c) the Commitments are no longer required for addressing the serious doubts raised in the Clearance Decision.

(44) The Commission will analyse the Waiver Request of Takeda against this framework in Section 5.2 below.

25 See Remedies Notice, paragraph 74.

26 See Remedies Notice, paragraphs 9 and 74.

27 See Remedies Notice, paragraph 74.

5.2. Application in the present case

5.2.1. The changes in market conditions are significant and permanent

(45) For the Commitments to be considered as no longer appropriate, market circumstances would need to have changed significantly and on a permanent basis. In the past, the Commission has granted waivers in cases where the market conditions or the regulatory framework had evolved to a significant extent, thereby eliminating the concerns identified in the conditional clearance decision, and where it did not appear proportionate to impose the commitment any longer,[28] or where the market had changed and the commitments had fulfilled their role and no longer responded to the market needs,[29] or where the initial concerns set out in the conditional clearance decision no longer arise, and will not arise again.

(46) In the present case, the investigation undertaken following the Waiver Request provides sufficient grounds demonstrating that a significant and permanent change took place following the Clearance Decision.

(47) As a preliminary remark, the Commission notes that the Commitments attached to the Clearance Decision concern the divestiture of a pipeline drug. Such projects present by their very nature a higher likelihood of being ultimately unsuccessful than established businesses which already generate a turnover on the market. It is indeed inherent to any drug development project that it may ultimately not reach the market since clinical trials are long and their outcome is by nature uncertain, including with respect to pipeline drugs that are at an advanced-stage of development such as SHP 647.[30]

(48) Since the adoption of the Clearance Decision, several developments took place: two events related to the development of SHP 647 significantly decreasing the likelihood that the drug would reach the market, *i.e.* the significant delays in the development of SHP 647 (**A**) and the negative results of the Reproductive Toxicity Study (**B**), but also the emergence of a novel and promising class of biologic drugs for the treatments of UC and CD, namely IL-23 inhibitors (**C**). As explained below, the evidence in the Commission's file supports Takeda's claims and allows the Commission to conclude that the above developments, affecting the market structure, are significant and permanent.

5.2.1.1. Significant delays in bringing the product to the market resulting from difficulties in recruiting new patients into the trials

(49) At the time of the Clearance Decision, SHP 647 was expected to be launched in 2023 for UC and 2024 for CD. However, during the divestiture process, the

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28 Cases M.2803 – *Telia/Sonera*, decision of 27.09.2006, and M.5549 – *EDF/Segebel*, decision of 13.12.2013.

29 Case IV/M.950 – *Hoffmann – La Roche/Boehringer Manheim*, decision of 03.05.2011.

30 The outcome of the clinical trials are always uncertain and only 50% of drugs in Phase III ultimately make it to the market. See cases M.9494 – *BMS/Celgene*, decision of 29.07.2019, footnote 27 and M.8401 - *J&J/Actelion*, decision of 9.06.2017, footnote 6.

Divestment Business has experienced difficulties in recruiting patients for its Phase III clinical trials, resulting in significant delays compared to the initial timeline.[31]

(50) These difficulties are mainly related to (i) the unexpected high proportion of patients failing the screening process[32] and (ii) the increasing number of pipeline drugs competing for the limited pool of patients eligible[33] and willing to participate in such trials. Albeit all companies conducting clinical trials in IBD are experiencing similar difficulties,[34] it appears that SHP 647 clinical trials are "*advancing at an even slower path than its competitors (including Roche's etrolizumab)*".[35] This is notably due to the fact that one country (*i.e.* Poland) outperformed other countries in terms of recruitment for the clinical trials of SHP 647 which forced the Management to cap the number of patients who could be enroled in this country in order to avoid a bias in the statistical analysis.[36] In addition, the Hold Separate Manager ("HSM") explained that, since "*SHP 647 is not* [currently] *supported by any pharmaceutical company,* […] *investigators may be giving priority to more established pharmaceutical companies for the recruitment of UC and CD patients, to the detriment of the Divestment Business*".[37]

(51) The recruitment rates for SHP 647 clinical trials – qualified has "*disappointing*" by a Key Personnel[38] – have fallen well behind the forecast rates expected by Shire and communicated to the Commission at the time of the Clearance Decision (the "Initial Forecasts"), especially with respect to CD. As detailed in Table 2 below, over the last year, the Divestment Business has experienced a continuous deterioration of its recruitment rates. The latest forecasts of the Management (from January 2020) (the "Latest Forecasts") anticipate recruitments rates in UC 73% below the Initial Forecasts.

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31 There are currently seven ongoing Phase III clinical trials assessing the SHP 647 compound including (i) three clinical trials in UC (*i.e* two induction studies (SHP 647-301 and SHP 647-302) and one maintenance study (SHP 647-303)), (ii) three clinical trials in CD (*i.e.* two induction studies (SHP 647-305 and SHP 647-306) and one maintenance study (SHP 647-307)), and (iii) one long-term safety study (SHP 647-304) for both UC and CD. These clinical trials are interlinked in the sense that patients enroled in one trial may roll-over into other trials (*e.g.* patients responding to the treatment during an induction study will move to the maintenance study).

32 For instance, in March 2020, the screening failure rates for SHP 647 induction studies were above 40% in UC and above 60% in CD (see 16th monthly report of the Monitoring Trustee, dated 15 March 2020, pp. 12 and seq).

33 There are strict regulatory requirements restricting the number of patients eligible for IBD clinical trials.

34 Non-confidential minutes of (i) a conference call with a competitor, dated 19 February 2020; (ii) a conference call with a KOL, dated 14 October 2019, (iii) a conference call with a competitor, dated 14 October 2019; and (iv) a conference call with a competitor, dated 11 February 2020.

35 Non-confidential minutes of a conference call with a competitor involved in the divestiture process, dated 14 October 2019. Similarly, other competitors, who had the opportunity to conduct due diligence on the Divestment Business, stressed that SHP 647 trials are progressing particularly slowly, which would lead to "*significant delays*" that are "*likely to worsen*" (see *e.g.* non-confidential minutes of a call with a competitor, dated 11 February 2020).

36 5th monthly report of the Monitoring Trustee, dated 15 April 2019.

37 Minutes of a meeting with the HSM of the Divestment Business, dated 14 February 2020.

38 Non-confidential minutes of a conference call with a Key Personnel of the Divestment Business, dated 26 March 2020.

Table 2 – Evolution of recruitment rates[39] for SHP 647 induction studies

Recruitment Rates	UC	CD
Initial Forecasts in November 2018	[…]	[…]
Achieved in June 2019 *(cumulative since study start)*	[…]	[…]
Achieved in December 2019 *(cumulative since study start)*	[…]	[…]
Latest Forecasts *(base scenario)*	[…]	[…]

Source: Monitoring Trustee Report

(52) As a result, the enrolment of patients in SHP 647 clinical trials, which started in October 2017 for UC and June 2018 for CD, is still far from being complete: only [0-10]% of the target number of CD patients and less than 50% of the target number of UC patients had been recruited at 6 March 2020 (see Table 3 below).[40]

Table 3 – Number of patients enroled in SHP 647 clinical trials (at 6 March 2020)

	Target patient enrolment	Patients enroled	% of target complete
UC clinical trials			
– *Induction*	1480	[…]	[40-50]%
– *Maintenance*	696	[…]	[40-50]%
CD clinical trials			
– *Induction*	2064	[…]	[0-10]%
– *Maintenance*	983	[…]	[0-10]%

Source: 16th monthly report of the Monitoring Trustee dated 15 March 2020

(53) The difficulties in recruiting patients experienced by the Divestment Business since the adoption of the Clearance Decision resulted in significant delays compared to the initial timeline. The Revised Business Plan prepared in June 2019 anticipated that the potential launch of SHP 647 would be delayed by seven years for CD (2031 *vs*. 2024 initially) and two years for UC (2025 *vs*. 2023 initially). This would not only delay the launch of the drug on the market but would also result in a significant increase in development costs (around USD […]).[41] Moreover, during the second half of 2019, the patient enrolment for SHP 647 clinical trials progressed at even slower pace than assumed in the Revised Business Plan, resulting in a further delay for the market launch in UC (and additional development costs of up to […] USD). According to the Latest Forecasts, the potential launch of SHP 647 in UC is not expected before 2027 (*i.e.* five years later than the Initial Forecasts) while the development costs hiked up at […] for UC only (*vs.* USD […] at the time of the Clearance Decision for both UC and CD).

39 Recruitment rates for clinical trials are calculated by multiplying the number of sites and randomized patients per site by the number of months of recruitment time.

40 At the time of the Clearance Decision, the induction studies for UC and CD were expected to conclude (*i.e.* last visit of the last patient) respectively in 2020 and 2021. See Schedule to the Commitments, Annex 2 (Indicative SHP 647 Study Timeline).

41 According to the Revised Business Plan (June 2019), the development costs for 2019-2032 are expected to reach USD […] (*vs.* USD […] at the time of the Clearance Decision) for both UC and CD. Based on the Latest Forecasts (January 2020), the development costs for the period 2019-2032 could be up to USD […] for UC only.

(54) Furthermore, a Key Personnel corroborated Takeda's submission that the COVID-19 pandemic is further "*significantly*" and "*negatively*" affects the development and launch of SHP 647 as it "*impedes (i) the ability of the Divestment Business to recruit new patients due to government restrictions to limit the number of non-critical patients in hospitals and (ii) compromise data from already recruited patients*".[42] In fact, the Management has temporarily suspended the enrolment of patients from the end of March until further notice.[43]

(55) The elements in the Commission's file suggest that the initial timeline cannot be restored as no measure appears able to remedy the above-mentioned delays. In fact, already in June 2019 (*i.e.* before the further deterioration of the recruitment rates in the second semester of 2019 and before the coronavirus crisis), the Management indicated that "*even including all imaginable mitigation efforts the launch in CD would still be delayed by several years*" and concluded that, with such a "*significant delay*", the CD programme was "*not considered viable*" from a commercial point of view.[44] The Commission also notes that the measures implemented pursuant to the Revised Business Plan to mitigate the delays in the UC trials[45] did not prevent a further degradation of the recruitment rates in the second half of 2019. In this respect, a competitor involved in the divestiture process indicated that "*while it may have been possible to implement measures to increase recruitment rates,* […] *these measures would likely <u>not have significantly improved recruitment to the levels needed</u>*".[46]

5.2.1.2. Abnormal infant death rate in the Reproductive Toxicity Study

(56) In September 2017, Shire initiated the Reproductive Toxicity Study in non-human primates to assess the effects SHP 647 may have on pregnancy. In particular, the Reproductive Toxicity Study investigated whether the administration of SHP 647 in pregnant primate subjects caused pre- or post-natal abnormalities, abortions or post-natal mortality. Reproductive toxicity studies are mandatory to support registration of biologic drugs.

(57) The Reproductive Toxicity Study was conducted by an independent contract research organisation company, namely […], in parallel with the Phase III clinical trials of SHP 647.

(58) On 23 April 2019, […] informed the Divestment Business that abnormal infant death rates had been recorded in the Reproductive Toxicity Study. More specifically, the

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42 In order to be granted a marketing authorisation, data from clinical trials need to be collected at a specific point in time defined in the protocols agreed with regulators. Because of the COVID-19 pandemic, the Divestment Business will however not be able to collect this data at the required points in time since many patients are unable to attend the planned follow-up visits under the protocols and investigators are not able to perform the endoscopy procedures necessary to record data. Non-confidential minutes of a conference call with a Key Personnel of the Divestment Business, dated 26 March 2020.

43 Email from the Monitoring Trustee to the Commission, dated 25 March 2020.

44 Annex 2 to the Waiver Request, […], slide 7.

45 These measures included […]. See Annex 2 to the Waiver Request, […], slides 19 and seq; and 7th monthly report of the Monitoring Trustee, dated 15 June 2019, p. 18.

46 Non-confidential minutes of a conference call with a competitor, dated 11 February 2020 (emphasis added).

results showed mortality rates in infant primates, born to mothers who were administered SHP 647 during pregnancy, substantially higher than the average.

(59) Based on the available data, the Divestment Business concluded that this […][47]. Thereafter, the Management (i) consulted internal and external experts to ensure that correct safety reporting actions were taken; (ii) notified the regulatory authorities where clinical trials are being undertaken; and (iii) updated site materials.

(60) While the impact of the Reproductive Toxicity Study remains uncertain at this stage, the Management indicated to the Commission that it constitutes "*a red flag, posing a significant risk to the success of the program*",[48] as it will likely be reflected in the label of SHP 647 and could potentially lead to use-restrictions for women in childbearing age. Table 4 below details the three potential scenarios envisaged by the Management regarding the implications of the Reproductive Toxicity Study on SHP 647.

Table 4 – Possible scenarios on the impact of the Reproductive Toxicity Study

	Worst case	**Base case**	**Optimal case**
Impact on use	Women in childbearing age effectively excluded	Risk management program with pregnancy prevention program	Label warning and pregnancy registry requirement
Likelihood	[10-20]%	[40-50]%	[40-50]%
Percentage of patients excluded	-[30-40]% [49]	-[10-20]%[50]	+/-0%

Source: the Divestment Business[51]

(61) It appears from the above Table that, in two of the three potential scenarios considered by the Management (*i.e.* the base and worst scenarios), which together have an estimated likelihood of [50-60]%, the results of the Reproductive Toxicity Study are expected to have a significant negative impact on SHP 647's sales (estimated around –[10-20]% and –[30-40]% depending on the scenario).[52] In this respect, a Key Personnel expressly confirmed that, if the worst-case scenario were to materialise, which is "*realistic*" and "*cannot be excluded*", it would have a "*significant negative impact on the commercialisation of SHP 647*".[53]

(62) This is also corroborated by market participants interviewed by the Commission during the investigation conducted in the context of the Waiver Request. For instance, one competitor expressly noted that "*the results of the reproductive toxicity study would most likely negatively impact the sales of SHP 647*".[54] Similarly, another competitor "*anticipate*[s] *that SHP 647's label will include (i) a warning that foetal harm had been observed in animal studies and (ii) a requirement for contraception*

47 Annex 3 to the Waiver Request, […].

48 Annex 2 to the Waiver Request, […].

49 -[30-40]% corresponds to an exclusion of almost all women in childbearing age.

50 Reflects the burden of the implementation of pregnancy prevention programs.

51 Annex 2 to the Waiver Request, […].

52 Minutes of a meeting with the HSM of the Divestment Business, dated 14 February 2020.

53 Non-confidential minutes of a conference call with a Key Personnel of the Divestment Business, dated 26 March 2020.

54 Non-confidential minutes of a conference call with a competitor, dated 11 February 2020.

to be used", which would have an "*important impact on the competitiveness of SHP 647*".[55]

(63) In order to mitigate the impact of the results of the Reproductive Toxicity Study on the Divestment Business, the Management assessed the merits of conducting additional pre-clinical studies and indicated that such a pre-clinical safety signal "*cannot be "easily" ruled out anymore*" as it "*creates suspicions and may only be ruled out by long-term clinical experience*".[56] This was confirmed by a competitor explaining that conducting additional studies to better understand the results of the reproductive toxicity study "*would prove to be very complex and expensive and would most likely not prevent the use of a restrictive label on SHP 647*".[57]

5.2.1.3. Emergence of a promising class of biologic treatments for UC and CD

(64) Since the adoption of the Clearance Decision, clinical trials of IL-23 inhibitors, a novel class of biologic drugs for the treatment of UC and CD, have emerged by showing promising results, both in terms of efficacy and safety.

(65) There are currently four IL-23 inhibitors in development, namely risankizumab developed by AbbVie and mirikizumab developed by Eli Lilly, which are currently in Phase III for both UC and CD, but also guselkumab developed by Johnson & Johnson, which is currently in Phase II for UC and Phase II/III for CD, and brazikumab initially developed by Allergan and divested to AstraZeneca in the context *AbbVie/Allergan*, which is currently in Phase II for UC and Phase II/III for CD.[58] These drugs are expected to be launched on the market before or at the same time as SHP 647 (based on the Latest Forecasts).

(66) At the time of the Clearance Decision, nothing in the Commission's file suggested that IL-23 inhibitors were a particularly promising class of biologics (neither the Parties, nor the KOLs and competitors specifically referred to it during the market investigation). On the contrary, the market investigation suggested that anti-integrins had the best safety profile. This can be explained by the fact that (i) IL-23 inhibitors were at an earlier stage of development, with more limited available clinical data, and that (ii) market participants assumed that the less favourable safety profile of the only IL-inhibitor available on the market at the time, *i.e.* Stelara (IL-12/23 inhibitor) would apply to all IL-inhibitors.[59]

(67) However, since then the clinical trials of IL-23 inhibitors have progressed and shown good results. Most recently, in case *AbbVie/Allergan*, the Commission found that, within IL-inhibitors, a distinction could be made between IL-12/23 inhibitors (Stelara) and IL-23 inhibitors. Indeed the market investigation in that case highlighted the promising nature of IL-23 inhibitors for the treatment of UC and CD. Whilst respondents to the market investigation in that case confirmed that "[a]*nti-*

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55 Non-confidential minutes of a conference call with a competitor, dated 14 October 2019.

56 Annex 2 to the Waiver Request, […], pp. 31-32 (emphasis added).

57 Non-confidential minutes of a conference call with a competitor, dated 14 October 2019 (emphasis added).

58 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recitals 56-60.

59 See recital 44 of the Clearance Decision: "*IL-inhibitors (specifically Stelara, the one IL-inhibitor currently available* […]*) have a general immunosuppressant effect, and do not therefore offer the same advantages in terms of safety as anti-integrins*" (emphasis added). See also recitals 34, 37 and 39.

integrins (Entyvio) are considered to be the safest drug currently available on the market (i.e. it leads to less adverse effects and a lower risk of infection), due to a more targeted (gut-specific) [mode of action]",[60] they also emphasised that IL-23 inhibitors are expected to have a better efficacy and safety profile than all other available post-conventional treatments, including anti-integrins.[61] Some customers and KOLs view IL-23 inhibitors as particularly "*promising*" or even as products that "*will change the market*" due to their expected better efficacy and safety profile.[62]

(68) The promising safety profile of IL-23 inhibitors was also stressed during the market investigation carried out by the Commission in the context of the Waiver Request. For instance, one KOL explained that "*based on the data currently available,* [the] *mode of action* [of IL-23 inhibitors] *is expected to be safer (particularly in terms of infections) than any other marketed and pipeline drugs currently being developed for the treatment of UC and CD*".[63]

(69) The emergence of IL-23 inhibitors as a promising class of drugs constitutes a significant and permanent change in market circumstances as it directly impacts the competitive landscape in UC and CD treatments and, thus, the competitive constraints exerted on the Parties' drugs.

5.2.2. The changes in market conditions were not foreseeable

(70) For the reasons explained below, the Commission considers that the changes in market conditions described in Section 5.2.1 were neither foreseen nor reasonably foreseeable at the time of the Clearance Decision.

(71) *First*, the low recruitment rates for the clinical trials of SHP 647 were reported to the Commission for the first time in January 2019 for CD[64] and June 2019 for UC[65] (*i.e.* several months after the adoption of the Clearance Decision). In fact, at the time of the Clearance Decision, nothing in the Commission's file suggested that Shire's forecasted enrolment rates could not be met. Moreover, the difficulties specifically faced by SHP 647 could not be foreseen. For instance, the fact that, in April 2019, the Management had to cap the number of patients enrolled in SHP 647's top recruiting country (*i.e.* Poland) to avoid a statistical bias,[66] could not be reasonably predicted in November 2018. In light of the above, the Commission considers that it could not be anticipated that the recruitment rates of the Divestment Business would be so "*disappointing*"[67] and fall so much behind the Initial Forecasts.

(72) *Second*, the Reproductive Toxicity Study, initiated in September 2017, yielded results that could not have been anticipated, on 23 April 2019 (*i.e.* five months after the adoption of the Clearance Decision).

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60 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recital 67.

61 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recital 51.

62 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recital 69.

63 Non-confidential minutes of a conference call with a KOL, dated 14 October 2019 (emphasis added).

64 2nd monthly report of the Monitoring Trustee, dated 15 January 2019, p. 16.

65 Annex 2 to the Waiver Request, […], slide 9; and 7th monthly report of the Monitoring Trustee, dated 15 June 2019, p. 12.

66 5th monthly report of the Monitoring Trustee, dated 15 April 2019, p. 16.

67 Non-confidential minutes of a conference call with a Key Personnel of the Divestment Business, dated 26 March 2020.

(73) *Third*, as explained above, at the time of the Clearance Decision, there was no indication in the Commission's file that IL-23 inhibitors were a particularly promising class of biologics. Neither the Parties, nor the KOLs and competitors who responded to the market investigation indicated that they expected IL-23 inhibitors to have a better efficacy and safety profile than anti-integrins. Since the adoption of the Clearance Decision, the clinical trials of the four IL-23 inhibitors have progressed and, based on the increasing available clinical data, leading experts in the treatment of gastrointestinal diseases are now confident that this specific class of IL-inhibitors may constitute a "*game-changer*" for the treatment of UC and CD.[68]

5.2.3. The exceptional circumstances remove the Clearance Decision's serious doubts

(74) As recalled in Section 2.1 above, the Commitments aimed at addressing the competition concerns arising from the Transaction on the market for anti-integrin drugs for use in UC and CD. More particularly, the Clearance Decision's conclusion that the discontinuation of SHP 647 would raise serious doubts is based on the following key findings:

- the elimination of SHP 647 would lead to the reduction in the number of players active on the anti-integrin market from three to two, the Parties facing only one (potential) competitor, *i.e.* Roche's *etrolizumab*;[69]

- Takeda's Entyvio and Shire's SHP 647 would closely compete, due to their similar and superior safety profile;[70] and

- other classes of biologics in neighbouring markets exert insufficient competitive pressure on anti-integrins due to their lower safety profile.[71]

(75) For the reasons explained below, the Commission considers that the above key findings have been undermined by the market developments that have occurred since the Clearance Decision (described in Section 5.2.1).

5.2.3.1. SHP 647 is no longer expected to reach the market before the entry of biosimilars to Takeda's Entyvio

(76) A key assumption of the Clearance Decision is that the Transaction would lead to the reduction in the number of players in the anti-integrin market from three to two, with Takeda's marketed drug (Entyvio) and Shire's pipeline drug (SHP 647) facing only one competitor, *i.e.* Roche's pipeline drug (*etrolizumab*).[72]

(77) As explained in Section 5.2.1.1 above, at the time of the Clearance Decision, SHP 647 was expected to be launched in 2023 for UC and 2024 for CD. However, the Divestment Business has experienced difficulties in recruiting patients for the clinical trials, leading to significant delays compared to the initial timelines. According to the Latest Forecasts, SHP 647 is not expected to be launched before at

68 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, footnote 48.
69 See recital 73 of the Clearance Decision.
70 See recitals 74-77 of the Clearance Decision.
71 See recitals 78-84 of the Clearance Decision.
72 See recitals 73 of the Clearance Decision.

least 2027 for UC (*i.e.* five years after the Initial Forecasts) and 2031 for CD (*i.e.* seven years after the Initial Forecasts).[73]

(78) It follows that SHP 647 is no longer anticipated to reach the market before Entyvio's loss of exclusivity. Indeed, Takeda's marketed drug is expected to lose its regulatory data protection in the EEA/UK in May 2024[74] (with a potential one-year extension). Consequently, the intravenous formulation of Entyvio currently marketed in the EEA/UK[75] could face biosimilar competition[76] as early as 2024 or 2025, *i.e.* several years before the potential launch of SHP 647 (in both UC and CD).

(79) In its Waiver Request, Takeda explains that it is aware of at least two companies, which already started the development of biosimilars to Entyvio, namely Bioceros and Dr Reddy. According to Takeda, "*Bioceros plans surfaced in 2017 and Dr Reddy has even initiated proceedings seeking the revocation of European Patent No. EP2704798 (which covers certain* [Takeda's Entyvio] *formulations) in European Patent Office opposition proceedings. Furthermore, numerous* [biosimilars] *manufacturers, such as Pfizer, Celltrion, and Samsung Bioepis are well placed to bring* [biosimilars to Takeda's Entyvio] *to market*".[77]

(80) Takeda's claim according to which biosimilars are expected to be available on the market by the time the Divestment Business is launched is supported by the Management. Indeed, the latter expressly acknowledged that SHP 647 is now expected to be launched around the time of Entyvio's loss of exclusivity and, thus, to face competition from Entyvio's biosimilars.[78] The Management also indicated to the Divestiture Trustee that "*there is a risk of biosimilars entering from 2024 to 2026. Vedolizumab biosimilars may be in advanced development* […]".[79] Similarly, several competitors indicated that they "*would expect Shire's SHP 647 to be launched on the market after the entry of Roche's etrolizumab, and possibly even after the entry of Entyvio's biosimilars*".[80]

(81) In addition to the above, the Commission notes that several elements suggest that biosimilar competition is likely to exert downward pressure on prices of the originator biologic drug (Entyvio) and other anti-integrin drugs.

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73 The Commission notes that the above revised potential launch dates are outdated since (i) the Latest Forecasts pre-date the suspension of the trials because of the coronavirus crisis and (ii) contrary to UC, the forecasts for CD have not been reassessed since June 2019 and, thus, do not take into consideration the deterioration of SHP 647's recruitment rates in the second half of 2019.

74 See Takeda's 2019 annual report, p. 38 (https://www.takeda.com/siteassets/system/investors/report/sec-filings/20-f_2019-06-28.pdf). In the US, Entyvio is expected to lose exclusivity in May 2026.

75 Takeda is currently developing a subcutaneous formulation of Entyvio, which has not reached the market yet and would benefit for a longer exclusivity (up to […]).

76 A biosimilar is a biologic drug which is highly similar to another already approved biologic drug (the reference or originator biologic drug) with the same therapeutic mechanism (See case M.7559 – *Pfizer/Hospira*, decision of 4 August 2015, recital 9).

77 Annex 23 to the Waiver Request.

78 Monitoring Trustee Report, pp. 9 and 25.

79 Divestiture Trustee report on the Divestiture Business Revenue Forecast, dated October 2019, p. 2.

80 Non-confidential minutes of a conference call with a competitor, dated 14 October 2019 (emphasis added). See also non-confidential minutes of a conference call with a competitor, dated 19 February 2020.

(82) *First*, the Management believes that competition from biosimilars to Entyvio will adversely impact SHP 647's pricing and revenues.[81] In fact, in its presentation of June 2019, the Management indicated that the timing of the launch of SHP 647 is "*critical*" due to the evolution of the "*competitive intensity in IBD*" and that, for CD, the "[revised] *launch timeline (post Entyvio LoE* [Loss of Exclusivity]*) is not considered a viable option*".[82]

(83) *Second*, in a recent report on "*Competition enforcement in the pharmaceutical sector (2009-2017)*", the Commission noted that "*effective competition from* […] *biosimilars typically represents a vital source of price competition on pharmaceutical markets and significantly drives down prices*".[83] In this report, the Commission acknowledged that "*competition from biosimilars can generate large savings in our healthcare systems, while enabling more patients to benefit from cheaper biological therapies*".[84]

(84) The above is notably illustrated by the fact that, since 2015, several anti-TNF biosimilars for use in UC and CD have been introduced in the EEA/UK. These biosimilars have been launched soon after the loss of exclusivity of their respective originator biologic drugs and "*exert competitive pressure on the originator, and potentially on other anti-TNFs*".[85] For instance:

- shortly after Johnson & Johnson's Remicade (*infliximab*) lost its exclusivity in most Member States (in February 2015), Hospira launched a biosimilar called Inflectra on 16 February 2015, followed by Celltrion (Remsima). In May 2016, Samsung also launched a biosimilar to Remicade (Flixabi). The Clearance Decision points out that, following the introduction of these biosimilars, the pricing of the originator drug (Remicade) has "*fallen considerably*", with a significant number of market participants observing "*dramatic drops*".[86] Similarly the Waiver Request notes that, IQVIA[87] recorded year-on-year growth of biosimilars to Remicade in several Member States, with significant price reductions for the originator drug (of up to 25% compared to the first year after its loss of exclusivity);[88]

- AbbVie's Humira (*adalimumab*) lost its exclusivity in Europe in October 2018. In the same month, two biosimilars were launched in the EEA/UK, namely Amgen's Amgevita, and Biogen's Imraldi. In the recent *AbbVie/Allergan*'s decision, the Commission found that "*Humira's market shares* [have generally declined following its loss of exclusivity and] *are expected to decrease further over the next few years, due to the health*

81 Monitoring Trustee Report, pp. 9 and 25.

82 Annex 2 to the Waiver Request, […], slides 4 and 7.

83 Report on "*Competition enforcement in the pharmaceutical sector (2009-2017)*", p. 1, available here: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/execsumm_en.pdf.

84 Report on "*Competition enforcement in the pharmaceutical sector (2009-2017)*", p. 37.

85 See recital 83 of the Clearance Decision.

86 See recitals 47 and 83 of the Clearance Decision.

87 IQVIA, formerly Quintiles and IMS Health, Inc. provides advanced analytics to the life sciences industry worldwide.

88 Takeda's response to the Commission's request for information n°2 on remedy implementation.

authorities' incentives to increase the use of biosimilars, priced lower than Humira".[89]

(85) In light of the above, it appears that, as a result of the significant delays experienced by the Divestment Business since the adoption of the Clearance Decision, biosimilars to Entyvio are expected to be introduced in the EEA/UK before the launch of SHP 647 and to exert a competitive pressure on Takeda's Entyvio (and other anti-integrins). In other words, SHP 647 would launch in a radically different and more competitive market environment compared to the one anticipated in the Clearance Decision and its discontinuation would thus likely no longer lead to the reduction in the number of competitors active on the anti-integrin market from three to two.

5.2.3.2. The Reproductive Toxicity Study affects the safety profile of SHP 647 and constitutes a negative differentiator compared to Takeda's Entyvio

(86) Another key finding of the Clearance Decision is the similarity in the safety profiles of Takeda's Entyvio and Shire's SHP 647. This assumption is a central feature of the competitive assessment in the Clearance Decision, which concludes that, due to their comparable and superior safety profiles, the Parties' drug would closely compete with each other (and with other anti-integrins).[90]

(87) However, since the adoption of the Clearance Decision, this assumption has been to a significant extent invalidated by the abnormal infant death rates observed in the Reproductive Toxicity Study on SHP 647. Indeed, as previously explained in Section 5.2.1.2, albeit the real impact of the Reproductive Toxicity Study will remain uncertain for some considerable time, the Divestment Business concluded that this […].[91] According to the Management, this safety finding would most likely be reflected in the label of SHP 647 and could potentially lead to use-restrictions for women in childbearing age (which would significantly affect the sales of the Divestment Business).

(88) Takeda submits that the above constitutes a significant negative differentiator for SHP 647 compared to Entyvio, whose safety profile is steadily improving. Indeed, Takeda stresses the fact that the safety record of Entyvio is robust and strengthened by a growing body of clinical evidence regarding its use in pregnant women. Available pharmacovigilance data, data from the ongoing pregnancy registry, as well as data from published case reports and cohort studies in pregnant women have not associated Takeda's Entyvio with a risk of birth defects, miscarriage or adverse maternal or foetal outcomes.[92] This is acknowledged in the Clearance Decision, which expressly states that, due to its superior safety profile, Takeda's Entyvio is particularly suitable for "*various groups of patients for whom other biologics would not be suitable*", including in particular "*pregnant women*".[93]

(89) The investigation conducted by the Commission in the context of the Waiver Request broadly confirmed Takeda's claim. Indeed, several KOLs and competitors

89 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recital 81.

90 See recitals 74-77 of the Clearance Decision.

91 Annex 3 to the Waiver Request, […].

92 Waiver Request, paragraph 142.

93 See recitals 40 and 41 of the Clearance Decision (emphasis added).

consider that the results of the Reproductive Toxicity Study could durably impair the safety profile of the Divestment Business (compared to other anti-integrins) and, thus, negatively impact the competitiveness of SHP 647 and its ability to exert a competitive constraint on Takeda's Entyvio. For instance:

- a KOL indicated that "*although the results of reproductive studies in non-human primates cannot automatically be transposed to humans, they constitute a helpful indicator on the safety of a drug on pregnant women. In the absence of human data, toxicity studies in pregnant animals are commonly used as guide, and drugs that showed teratogenicity even if used at much higher doses than in clinical practice are avoided in the clinical practice*";[94]

- a competitor stated that "*these results are likely to affect the safety profile of SHP 647 by restricting its use, which would constitute a negative differentiator compared to Takeda's Entyvio, which have good long-term clinical data. [..] it would be anticipated that SHP 647's label will include (i) a warning that foetal harm had been observed in animal studies and (ii) a requirement for contraception to be used. By contrast, the current label of Entyvio reports "no foetal harm was observed in animal reproduction studies"* […] *The restrictive label would have an important impact on the competitiveness of SHP 647 compared to competitors*";[95]

- another competitor noted that SHP 647 would "*likely be negatively differentiated compared to its main competitor, i.e. Takeda's Entyvio*" and that "*the results of the reproductive toxicity study would most likely negatively impact the sales of SHP 647*";[96] and

- a third competitor indicated that "*anti-integrin drugs are broadly differentiated from other drugs for UC and CD by the following characteristics: (i) they are safer* […]. *Thus, a novel anti-integrin that comes with black box warnings or label restrictions would have trouble gaining share unless it can demonstrate added benefit over Entyvio (e.g. higher efficacy or better convenience of use)*".[97]

(90) Similarly, a Key Personnel of the Divestment Business emphasised that the results of the reproductive toxicity study are *"concerning and can be detrimental to SHP 647 as they will negatively affect the safety profile of the drug* […]".[98]

(91) Therefore, although the exact impact of the Reproductive Toxicity Study remains unclear, it "*creates suspicions*" that "*may only be ruled out by long-term clinical experience*"[99] and , thus, gives rise to fundamental questions as to the safety profile

94 Non-confidential minutes of a conference call with a KOL, dated 14 October 2019 (emphasis added).

95 Non-confidential minutes of a conference call with a competitor, dated 14 October 2019 (emphasis added).

96 Non-confidential minutes of a conference call with a competitor, dated 11 February 2020 (emphasis added).

97 Non-confidential minutes of a conference call with a competitor, dated 19 February 2020 (emphasis added).

98 Non-confidential minutes of a conference call with a Key Personnel of the Divestment Business, dated 26 March 2020 (emphasis added).

99 Annex 2 to the Waiver Request, […], pp. 31-32 (emphasis added).

of SHP 647. The above differentiates the Divestment Business from Entyvio – negatively and durably – affecting its ability to compete effectively with Takeda's drug.

5.2.3.3. IL-23 inhibitors are likely to exert significant competitive pressure on anti-integrins

(92) Another central feature on the basis of which the Commission raised serious doubts in the Clearance Decision was the fact that drugs in neighbouring markets (*i.e.* other classes of biologics and potentially the new small molecule agents) exerted an insufficient competitive constraint on anti-integrins. This conclusion was based on the ground that "*other types of biologic treatment* [currently available on the market] *do not offer the same specific advantages as Entyvio, in particular with respect to safety, and do not therefore constitute suitable alternatives in many of the situations in which Entyvio would be prescribed*".[100]

(93) However, since the adoption of the Clearance Decision, IL-23 inhibitors have emerged as a promising class of biologics and several elements in the Commission's file suggest that they are likely to exert significant competitive pressure on anti-integrins.

(94) *First*, as explained as detailed in Section 5.2.1.3, the market investigation in *AbbVie/Allergan* revealed that IL-23 inhibitors are expected to have a better efficacy and safety profile than all other available post-conventional treatments, including anti-integrins. Should the results of the ongoing clinical trials confirm the efficacy and safety profile of IL- 23 inhibitors, the latter would likely constitute a suitable alternative to anti-integrins.

(95) *Second*, a clinical trial for brazikumab (Allergan's IL-23 inhibitor pipeline) compares the efficacy and safety of brazikumab against Takeda's Entyvio (rather than a placebo) in UC. This head-to-head trial aims at establishing the clinical superiority of Allergan's pipeline over Takeda's drug, which indicates that the two drugs can be used for the same group of patients. If successful, this head-to-head trial would likely give brazikumab a strong competitive advantage over Takeda's drug.[101]

(96) *Finally*, the market investigation recently carried out in *AbbVie/Allergan* revealed a certain degree of substitutability between post-conventional treatments for IBD. In particular, respondents to the market investigation indicated that they expect IL-23 inhibitors to compete with all other post-conventional treatments for UC and CD currently available on the market (including Entyvio).[102]

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100 See recitals 78-84 of the Clearance Decision (emphasis added).

101 See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recitals 70-72. For instance, one KOL noted that "*the head-to-head comparisons may be used as one of the strongest arguments (if not the strongest) for positioning of brazikumab*" and another one that "[i]*t is imperative to have head-to-head comparisons in order to identify the efficacy, safety, sustainability long-term of a new agent and position this new drug in the therapeutic algorithms of IBD*".

102 As a result, the Commission left open the relevant product market definition and considered the existence of a market encompassing all post-conventional treatments for IBD (including or excluding anti-TNFs). See case M.9461 – *AbbVie/Allergan*, decision of 10 January 2020, recitals 36 et seq.

(97) The above elements suggest that IL-23 inhibitors would likely exert a direct and significant competitive constraint on anti-integrins, including in particular Takeda's Entyvio, which undermine another key finding of the Clearance Decision.

5.2.4. Conclusion

(98) It appears from the above that SHP 647 is currently foreseen to launch in a radically different competitive environment compared to the one anticipated at the time of the Clearance Decision. Indeed, the Parties' drug are now expected to face competition from both anti-integrins (i.e. Entyvio's biosimilars) and a novel and promising class of biologic drugs (i.e. IL-23 inhibitors). This new competitive landscape and the existence of a safety finding for SHP 647 would significantly limit the competitiveness of the Divestment Business and its ability to exert a competitive constraint on Takeda's Entyvio.[103] In fact, the HSM of the Divestment Business indicated that, absent the Transaction and absent the Commitments, "*the management of the Divestment Business would have recommended the discontinuation of SHP 647 already in June 2019"*.[104]

(99) In view of the foregoing, the Commission considers that the combination of the above-described circumstances constitutes exceptional circumstances and concludes, on this basis, that the Commitments have become obsolete and are no longer required to address the competition concerns arising from the Transaction at the time of the Clearance Decision.

6. CONCLUSION

(100) The Commission has carefully assessed the arguments and the evidence submitted by Takeda, and concludes that the above-described market developments (i) are significant and permanent, (ii) could not have be foreseen at the time of the Clearance Decision; and (iii) imply that the serious doubts identified in the Clearance Decisions no longer arise, and will not arise again.

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103 This is notably illustrated by the fact that, according to the Latest Forecasts of the Management, the projected cumulative revenues have been divided by two compared to the Initial Forecasts (with a projected loss of cumulative revenues of at least USD […]).

104 Minutes of a meeting with the HSM of the Divestment Business, dated 14 February 2020. This finding invalidates the Clearance Decision's assumption that "*Takeda would delay or discontinue the development of SHP647 due to the risk of cannibalising sales of Entyvio post-Transaction*" since, absent the Transaction, SHP 647 would most likely have been discontinued in light of the adverse events that have impacted its development since the adoption of the Clearance Decision in November 2018.

(101) In view of the foregoing, the Commission concludes that Takeda has justified the existence of exceptional circumstances as required by paragraph 46 of the Commitments and, therefore accepts Takeda's request for a full waiver of the Commitments. This decision is adopted in application of Article 6(1)(b) in conjunction with Article 6(2) of the Merger Regulation as well as of paragraph 46 of the Commitments.

For the Commission

(Signed)
Margrethe VESTAGER
Executive Vice-President