EUROPEAN COMMISSION
DG Competition

Case M.8955 - TAKEDA / SHIRE

Only the English text is available and authentic.

REGULATION (EC) No 139/2004
MERGER PROCEDURE

Article 6(1)(b) in conjunction with Art 6(2)
Date: 20/11/2018

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EUROPEAN COMMISSION

Brussels, 20.11.2018
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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 Where possible the information omitted has been replaced by ranges of figures or a general description.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

Subject: **Case M.8955 – TAKEDA/SHIRE**
Commission decision pursuant to Article 6(1)(b) in conjunction with Article 6(2) of Council Regulation No 139/2004[1] and Article 57 of the Agreement on the European Economic Area[2]

Dear Sir or Madam,

(1) On 28 September 2018, the European Commission (the "Commission") received notification of a proposed concentration pursuant to Article 4 of the Merger Regulation by which Takeda Pharmaceutical Company Limited ("Takeda") acquires control of Shire plc ("Shire") by way of purchase of shares ("the Transaction").[3] Takeda and Shire are referred to hereinafter as the "Parties" and Takeda as the "Notifying Party".

1 OJ L 24, 29.1.2004, p. 1 (the 'Merger Regulation'). With effect from 1 December 2009, the Treaty on the Functioning of the European Union ('TFEU') has introduced certain changes, such as the replacement of 'Community' by 'Union' and 'common market' by 'internal market'. The terminology of the TFEU will be used throughout this decision.

2 OJ L 1, 3.1.1994, p. 3 (the 'EEA Agreement').

3 Publication in the Official Journal of the European Union No C355, 4.10.2018, p. 8.

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1. THE PARTIES AND THE OPERATION

(2) Takeda is a global pharmaceutical company, headquartered in Japan and traded on the Tokyo stock exchange. Its four main therapeutic areas are: oncology, gastroenterology, neuroscience and vaccines.

(3) Shire is a global biopharmaceutical company registered in Jersey. It is headquartered in Ireland and listed on the FTSE 100. It specialises in developing treatments for rare diseases across a range of therapeutic areas including immunology, haematology, neuroscience, gastroenterology, genetic diseases and ophthalmic. It recently sold its oncology business to Servier.

(4) The Transaction was announced on 8 May 2018 and will be implemented by way of a purchase of shares. Takeda will acquire the entire issued and to be issued ordinary share capital of Shire. The acquisition will be effected by means of a scheme of arrangement under Jersey Law, by which Takeda will acquire sole control of Shire. The Transaction therefore constitutes a concentration pursuant to Article 3(1)(b) of the Merger Regulation.

2. UNION DIMENSION

(5) The undertakings concerned have a combined aggregate world-wide turnover of more than EUR 5 000 million[4] (Takeda: EUR 14 151 million, Shire: EUR 13 354 million). Each of them has EU-wide turnover in excess of EUR 250 million (Takeda: EUR […] million, Shire: EUR […] million), but neither achieves more than two-thirds of its aggregate EU-wide turnover within one and the same Member State.

(6) The notified operation therefore has a Union dimension pursuant to Article 1(2) of the Merger Regulation.

3. THE PARTIES' ACTIVITIES

(7) Takeda and Shire are similar sized, major global pharmaceutical companies. Their portfolios are predominantly complementary, both from a product and a geographic perspective: Shire is particularly focused on rare genetic diseases and immunology whilst Takeda is a major player in vaccines, oncology and gastroenterology. Similarly, Shire has a strong presence in the US whilst Takeda achieves a significant proportion of its revenue in Japan and in emerging markets.

(8) The two main therapeutic areas where both companies are present are gastroenterology (GI) and neuroscience. Within GI, both Parties offer or are developing treatments for Crohn's disease (CD) and ulcerative colitis (UC) (collectively referred to as inflammatory bowel disease (IBD)), for chronic idiopathic constipation (CIC) and esophagitis. Affected markets arise within the first two of these areas: IBD and CIC.[5]

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4 Turnover calculated in accordance with Article 5 of the Merger Regulation and the Commission Consolidated Jurisdictional Notice (OJ C 95, 16.4.2008, p. 1).

5 Although Takeda offers a number of treatments for esophagitis, and Shire has a pipeline in this area, no affected market arises as the Parties' respective products are for different types of esophagitis and belong to

Within neuroscience, the Parties are neither currently offering nor developing treatments for the same disease areas.[6] The Parties' activities do not overlap in any other areas.[7]

4. COMPETITIVE ASSESSMENT

4.1. Product market definition

4.1.1. Treatments for inflammatory bowel disease (IBD)

(9) Takeda and Shire both offer treatments for inflammatory bowel disease (IBD). As explained below in more detail, the standard treatment approach for inflammatory bowel disease consists of three lines of treatment. Both Parties market *mesalazine*, a first line treatment indicated for use in mild to moderate ulcerative colitis ([…]*), under the respective brand names Asacol/Mesavancol (Takeda) and Mezavant (Shire). Takeda also offers a third line treatment, *vedolizumab*, under the brand name Entyvio, which is indicated for use in […]** ulcerative colitis (UC) and Crohn's disease (CD). Shire has a treatment currently under development (in Phase III clinical trials) for which it is targeting the same indication: use in […]** ulcerative colitis (UC) and Crohn's disease (CD).

(10) Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory diseases that affect the digestive system. They typically first occur in relatively young patients and are lifelong conditions, there being no treatment available which actually cures the disease. The cause of both diseases is unknown.

(11) The main difference between UC and CD is that CD can affect any part of the GI tract whereas UC is limited to the colon. Similarly, CD affects the full thickness of the intestinal wall whereas the inflammation caused by UC remains within the superficial lining of the intestine. Doctors emphasise, however, that both diseases can have similarly debilitating effects.

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different classes in the EphMRA classification, even at ATC3 level, the broadest plausible market normally considered by the Commission. Takeda's marketed products (which are all classified in ATC3 category A2B (anti-ulcerants)) are used predominantly for the treatment of erosive esophagitis and reflux disease. Shire's Phase III pipeline is likely to be indicated for use in eosinophilic esophagitis (EoE), and is expected to be approved under ATC class […].

6 Takeda is developing a new treatment for narcolepsy (TAK-925) based on an orexin 2 receptor agonist. This treatment, which is currently in Phase I trials, […]. There is technically a minor overlap in potential usage with a product based on methylphenidate that Shire currently markets under the brand name Equasym. Shire's drug is used to a limited extent off-label for narcolepsy in some EEA countries (its indication being for ADHD). The Commission's investigation confirmed that use of methylphenidate in treating narcolepsy is very limited and that where methylphenidate is prescribed, other brands are preferred over Equasym (see also Case M.6258 – Teva/Cephalon, Commission decision of 13 October 2011). Furthermore, methylphenidate belongs to ATC class N6B whilst Takeda's pipeline TAK-925 is expected to be approved under class […].

7 The Transaction creates a theoretical vertical link as Takeda produces and supplies a haemostatic patch and Shire offers CMO services related to such products to one third party. Shire is not, however, generally active as a CMO and […]. There is therefore no meaningful vertical relation between the Parties' activities.

* Should read “UC”.

** Should read “moderate to severe”.

(12) The European Crohn's and Colitis Organisation (ECCO) distinguish three levels of disease severity for each of UC and CD: mild, moderate and severe.

(13) Treatments for UC and CD are usually indicated as being for either mild-to-moderate levels of the disease or moderate-to-severe. The treatments for mild-to-moderate UC and CD (also termed conventional treatments) include amino salicylates (5-ASAs), corticosteroids, immunosuppressants and antibiotics. Once the disease has progressed to a moderate-to-severe stage, biologic drugs would then be prescribed with the aim of inducing remission.

(14) UC and CD are both characterised by phases of remission and relapse. Although three lines of treatment are generally identified (usually first line: 5-ASAs or corticosteroids, second line: corticosteroids or immunosuppressants, and third line: biologics) patients may also be switched back from biologics to immunosuppressants to maintain remission.

(15) Within biologic (third line treatment), patients are also often prescribed different biologics in succession (usually termed first line biologic, second line biologic etc.). This is most often either because the first line biologic loses efficacy after a certain time or for reasons related to safety and side effects.

(16) The general pattern of treatment for UC and CD is similar, but there are some differences, as some treatments are only indicated for one or the other disease. In particular, mesalazine (a type of 5-ASA) is the standard first-line treatment for UC but is not indicated for CD (although there is thought to be some off-label usage).

4.1.1.1. Separate markets for *mesalazine* and *biologics*

(17) In case M.7339 Abbvie/Shire,[8] the Commission concluded that *mesalazine* (a type of 5-ASA) and Humira (a biologic agent) belonged to separate markets, primarily because they form part of different lines of treatment and are not substitutable from either a demand or a supply perspective.

(18) The distinction between conventional treatments for mild-to-moderate UC and CD and biologic treatments for moderate-to-severe stages of the diseases appears to be well established in the literature, and features in particular in the treatment guidelines issued by the European Crohn's and Colitis Organisation (ECCO).

(19) In general terms, clinical guidelines recommend a phased treatment for UC and CD, consisting of at least three lines of treatment. The first-line treatment for UC involves a conventional therapy such as amino salicylates (which include *mesalazine*); this would then be followed in second line by a corticosteroid and then potentially an immunosuppressant; the third-line treatment, which is initiated when the disease symptoms progress due to a lack of response to conventional therapies, would involve a biologic drug, such as *vedolizumab*. The standard recommended treatment sequence for CD is slightly different as *mesalazine* is not indicated for this condition, meaning that corticosteroids may be prescribed in first line, followed by immunosuppressants in second line and biologics in third line.

8 Case M.7339 Abbvie/Shire, Commission decision of 16 October 2014.

(20) Clinical guidelines, in particular the ECCO guidelines mentioned above, recommend using *mesalazine* as a first-line treatment for ulcerative colitis (UC). Responses to the market investigation from key opinion leaders (KOLs)[9] confirmed that *mesalazine* is a standard first line treatment for mild-to-moderate UC, both as an induction therapy (i.e. for inducing remission in mild flare) and as a maintenance therapy.[10] One KOL explained, for example, that "a patient presenting a mild case of UC would almost always be prescribed mesalazine as a first line of treatment".[11]

(21) There is evidence to suggest that *mesalazine* may also be prescribed by some doctors as a first-line treatment for Crohn's disease (CD),[12] although it is not indicated for this condition and experts in the field generally consider it to be ineffective in treating CD.[13]

(22) The results of the market investigation clearly indicated that, in accordance with the ECCO treatment guidelines, biologics are used in moderate to severe stages of UC and CD, thus distinguishing them from *mesalazine*.[14]

(23) In addition, the respective modes of action of *mesalazine* and biologics are quite different. *Mesalazine* is a type of amino salicylate containing 5-aminosalicylic acid (5-ASA). It works by reducing inflammation on the wall of the intestine and as such has a predominantly topical action. *Mesalazine* is generally very well tolerated as it acts locally and has low toxicity. Different classes of biologic treatment have different modes of action but they have in common the fact that they target the cause of the inflammation, e.g. by suppressing the immune response directly or blocking the pathways that would usually lead to an immune response. Biologics therefore address the disease in a more fundamental way than *mesalazine*, which simply treats the symptoms topically.

(24) The mode of administration of *mesalazine* is also different from that of biologics. *Mesalazine* is administered either orally or rectally whereas biologics are available as either intravenous or subcutaneous formulations, and are therefore often administered in a hospital setting. The results of the market investigation confirmed that *mesalazine* is normally distributed through retail pharmacies for patients to take at home.[15] This means that the main purchasers of biologics are hospitals whereas *mesalazine* is predominantly purchased by retail pharmacies.

(25) In view of the above findings, the Commission concludes that *mesalazine* and biologics do not belong to the same product market, given the difference in their respective mode of action, their uses in different lines of treatment, and the difference in purchasing and prescribing settings. This is consistent with the Commission's conclusion in case

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9 The KOLs contacted during the Commission's market investigation are leading experts in the treatment of gastrointestinal diseases, and recognised figures in the European medical community.

10 Questionnaire 2 to physicians, Q3.1 and Q4.

11 Minutes of teleconference call with KOL in gastroenterology, 7 August 2018, 8.00.

12 Questionnaire 3 to pharmacies and hospitals, Q4.

13 Minutes of teleconference call with KOL in gastroenterology, 15 October 2018, 13.30. Minutes of teleconference call with KOL in gastroenterology, 9 August 2018, 12.00.

14 Questionnaire 2 to physicians, Q9.1. Minutes of teleconference call with KOL in gastroenterology, 7 August 2018, 8.00.

15 Questionnaire 3 to pharmacies and hospitals, Q3.1, Q17.

M.7339 Abbvie/Shire, in which *mesalazine* and biologics were considered to be in separate markets.

4.1.1.2. *Mesalazine*

(26) The Commission has not previously defined a specific market including *mesalazine*. As explained in Section 4.1.1.1, in case M.7339 Abbvie/Shire, the Commission concluded that *mesalazine* (a type of 5-ASA) and Humira (a biologic agent) belonged to separate markets, meaning that it would not be appropriate to define a market including *mesalazine* at the level of the ATC3 class (which in this case would be ATC A7E "IBD products").

(27) In line with the Commission's standard practice in cases involving pharmaceutical products, the market for *mesalazine*-based drugs could therefore either be defined at the molecule level, i.e. a market for *mesalazine* only, or at the level of the ATC4 class, which would be ATC A7E1 "intestinal amino salicylate products". This market would include, in addition to *mesalazine*, *sulfasalazine*, *balsalazide* and *olsalazine*.

(28) The Notifying Party submits that the appropriate market definition comprises all conventional treatments for mild to moderate UC and CD, including at least the other pharmaceuticals included in the ATC4 class A7E1 (*sulfasalazine*, *balsalazide* and *olsalazine*) and the ATC4 class A7E2 (corticosteroids).

(29) The market investigation confirmed that *mesalazine* is the standard first line treatment in UC. When asked to name alternatives to *mesalazine*, doctors tended to name those products currently used after *mesalazine* (i.e. second-line treatments) rather than other 5-ASAs.[16] The very fact that these treatments are currently recommended to be used in second line, rather than first line, in clinical guidelines, indicates that they are not direct substitutes for *mesalazine*. They have different modes of action and often a less good safety profile compared to *mesalazine*.

(30) For the purposes of this case, it is not necessary to determine the exact scope of the product market concerning *mesalazine*-based drugs as, in all plausible markets, including the narrowest plausible market, which would be the market restricted to the *mesalazine* molecule only, no competition concerns would arise.

4.1.1.3. Anti-integrins for use in treating UC and CD

(31) Apart from the decision in case M.7339 Abbvie/Shire, which did not deal specifically with *vedolizumab*, there are no other past Commission cases in which a market for biologics for use in CD and UC has been assessed.

(32) The Notifying Party submits that the correct market definition includes all biologics and small molecule agents for the treatment of UC and CD, as the same group of patients could be prescribed any of these treatments. Whilst acknowledging that the different biologic treatments have different modes of action, and that some are more commonly used as first line biologic and others as second or third line, the Notifying Party nonetheless claims that this choice is "fluid" and that it therefore would not be

16 Questionnaire 1 to physicians, Q7.

appropriate to define markets for the different lines of treatment or different classes of biologics.

(33) There are, however, in the Commission's view, a number of reasons for considering that it may be appropriate to define a narrower market for the group of biologics of the same type as *vedolizumab*, this being a market for anti-integrins.

(34) The biologic treatments currently available for UC and CD can be categorised into three main groups, on the basis of their mode of action. These are: (i) anti-TNFs: *adalimumab*, *infliximab* and *golimumab*; (ii) anti-integrins: *vedolizumab*[17]; and (iii) IL inhibitors (or anti-ILs): *ustekinumab* (an anti-IL23).

(35) Anti-TNFs target and suppress a protein called the tumour necrosis factor (TNF), which is part of the inflammatory response. The TNF-α cell signalling protein (cytokine) activates inflammatory transcription factors which regulate inflammatory response and, as a result, lead to chronic inflammation in IBD. The activation of these transcription factors stimulates the production of pro-inflammatory cytokines and the mobilisation of inflammatory cells. Anti-TNFs bind to TNF-α and, thereby, interrupt the inflammatory response.

(36) Anti-integrins reduce inflammatory activity by binding integrins (transmembrane receptors that facilitate cell-extracellular adhesion), and, thereby, blocking them from inflamed tissue. *Vedolizumab* in particular binds to the α4β7 integrin on white blood cells called lymphocytes. These cells are prevented from binding to a molecule found in the lining of the gut and thus reduce inflammation.

(37) IL inhibitors are immunosuppressive agents which inhibit the action of interleukins (signalling proteins that are synthesised by lymphocytes, monocytes, macrophages and certain other cells). Interleukins play a role in the regulation of the immune system. IL inhibitors work by preventing the sub-unit of the interleukin from binding to a receptor protein on the surface of the immune cells. They thus interrupt the signalling pathways that cause the immune reaction (and thus inflammation) in IBD.

(38) These three types of biologics, whilst all serving to reduce inflammation in IBD, therefore have clearly distinct modes of action. Moreover, there are a number of specific differences which set anti-integrins apart from both anti-TNFs and IL inhibitors, which have implications for prescribing practice and are therefore important to consider in the context of product market definition.

(39) First, anti-TNFs and IL inhibitors suppress the immune system generally, whilst anti-integrins act specifically on the gut wall as they prevent the trafficking of lymphocytes to this area. This means that anti-integrins reduce the inflammation in the gut, without causing a general immunosuppressant effect. Anti-TNFs and IL inhibitors, meanwhile, reduce the inflammation on the gut wall by suppressing the immune system. This has the side effect of increasing the risk that the patient contracts other, sometimes very serious, infections. As a result, anti-integrins have a much better safety profile than other biologics, as confirmed by the results of the market investigation.[18] A KOL explained,

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17 Marketed by Takeda under the brand name Entyvio.

18 Questionnaire 1 to physicians, Q27.1 and Q27.2. Questionnaire 2 to competitors, Q16.1 and Q16.2.

for example, that *"vedolizumab …. does not affect the immune cell trafficking elsewhere in the body, e.g. in the brain or lungs. As a result, there is no risk of patients developing pneumonia or other such conditions …. Entyvio has an advantage from a safety perspective, and equal efficacy."*[19]

(40) Furthermore, KOLs confirmed that the superior safety profile of Entyvio, as an anti-integrin, relative to other biologics has a strong influence on their prescribing choices. In particular, Entyvio can be used in various groups of patients for whom other biologics would not be suitable, including elderly people, very young patients, pregnant women, patients with previous or existing comorbidities (such as infections or cancer), and patients that have had problems with tolerance of other treatments in the past.[20]

(41) A leading physician in the filed explained that *"Entyvio is particularly suitable for use in older patients or those with comorbidities, where it is important not to suppress the immune system. When a patient has suffered with side effects from treatments given in the past or has had cancer, the treatment should be as gut-selective as possible, and Entyvio is therefore the ideal choice."*[21]

(42) The importance of the superior safety profile of anti-TNFs is also reflected in the fact that Entyvio is increasingly being used as a first-line biologic, not only in the specific groups of patients for which other biologics are not an alternative, but also more generally. Having been launched after anti-TNFs, Entyvio had traditionally been seen as an alternative biologic to be used when a patient loses response to anti-TNFs (which occurs very often). More recently, however, […][22] and doctors also confirmed that it is increasingly chosen as the first biologic to be prescribed, in particular in UC, as it offers equivalent efficacy to anti-TNFs combined with lower risks of infection and other side effects.[23]

(43) Responses to the market investigation indicated more generally that anti-integrins are used in different circumstances and are chosen for different reasons relative to other biologics, in particular anti-TNFs. Anti-TNFs have a quick onset of action and would therefore be preferred (other things being equal) when a severe form of the disease needs to be brought under control quickly. Similarly, if a patient is suffering from extra-intestinal symptoms, such as arthritis or skin conditions, then the more general immunosuppressant effect of anti-TNFs would be an advantage, as the same treatment would address the different symptoms.[24]

(44) Similarly, although IL inhibitors (specifically Stelara, the one IL inhibitor currently available, and which is only indicated for CD) are considered to have a slightly better safety profile than anti-TNFs, they nonetheless have a general immunosuppressant effect, and do not therefore offer the same advantages in terms of safety as anti-integrins. A leading expert in the field confirmed that, as a result, *ustekinumab* is more similar to

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19 Minutes of teleconference with KOL, specialist in gastroenterology, 9 August 2018 12.00.

20 Questionnaire 1 to physicians, Q24, Q25, Q27. Minutes of teleconference with KOL, specialist in gastroenterology, 7 August 2018 8.00.

21 Minutes of teleconference with KOL, specialist in gastroenterology, 15 October 2018 13.30.

22 [Information on Takeda's internal documents].

23 Questionnaire 1 to physicians, Q17.

24 Minutes of teleconference with KOL, specialist in gastroenterology, 15 October 2018 1:30pm.

anti-TNFs than to Entyvio, and is used in the same type of patients, for example those suffering psoriasis or arthritis in addition to IBD.[25]

(45) In addition to the three types of biologic treatments described above, a number of small molecules are also currently under development for the treatment of moderate to severe CD and UC. In particular, one small molecule developed by Pfizer (*tofacitinib*, a JAK inhibitor) is expected to soon become available for the treatment of UC. One of the differences between small molecules and biologic agents is the route of administration: while, as already explained, biologic agents are administrated either intravenously or in subcutaneous form, small molecules are taken orally. Although small molecule such as JAK inhibitors are not yet available on the market and thus their characteristics, including efficacy, cannot be fully assessed, doctors that responded to the market investigation indicated that these molecules are expected to have a poorer safety profile compared to gut-selective treatments such as anti-integrins.[26] As explained by the Notifying Party in the Form CO, […].[27]

(46) The specificity of anti-integrins (and, at present, Entyvio, as the only anti-integrin currently available on the market) is also confirmed by purchasing patterns. Information submitted by the Notifying Party […]. This is confirmed by the results of the market investigation,[28] which also indicated that anti-TNFs are frequently sourced through tender procedures.[29] The fact that Entyvio is not included in tenders alongside anti-TNFs is consistent with the finding that it is not substitutable in use, and that hospitals therefore require Entyvio to be purchased without reference to the price of anti-TNFs, as this class of biologics would often not constitute a suitable alternative for physicians.

(47) This is further confirmed by evidence suggesting that anti-TNFs exert little if any price pressure on Entyvio. The first *infliximab* biosimilars were introduced in the EEA after the reference medicine Remicade lost exclusivity in most EEA countries in 2015. There are now four such biosimilars approved in the EEA. The results of the market investigation indicated that, contrary to the Notifying Party's claims, the introduction of these biosimilars at a lower price compared to the anti-TNF originator Remicade, has had no or only very minimal effect on the price of Entyvio, whilst the price of Remicade itself has fallen considerably.[30] In particular, the majority of hospital purchasers confirmed that the price of Remicade had decreased since the introduction of biosimilars to infliximab, with a significant number observing dramatic drops. One hospital noted, for example, that "*the price of Remicade has been approximately divided by three during the last three years*".[31] Competitors expressed very similar views, with one stating, for example, that "*it decreased the overall value of the infliximab market by 60%*".[32] Only a much smaller proportion of competitors considered the introduction of infliximab biosimilars to have had an effect on the prices of other anti-TNFs, and this would appear

25 Minutes of teleconference with KOL, specialist in gastroenterology, 15 October 2018 1:30pm.
26 Minutes of teleconference with KOL, specialist in gastroenterology, 15 October 2018 1:30pm.
27 Form CO, paragraph 219.
28 Questionnaire 3 to hospitals and pharmacies, Q16.
29 Questionnaire 3 to hospitals and pharmacies, Q14.
30 Questionnaire 1 to physicians, Q36. Questionnaire 3 to pharmacies, Q24. Minutes of teleconference with KOL in gastroenterology, 9 August 2018 12.00.
31 Questionnaire 3 to hospitals and pharmacies, Q24.1.
32 Questionnaire 2 to competitors, Q21.1.

to depend very much on the specific tendering systems in different competitor. One competitor explained: "*In some countries, the entry of biosimilars has also led to decreases in the prices of other anti-TNFs, such as Humira and Simponi, however, the decrease in prices has been to a lesser extent than the decrease in the price of Remicade*."[33] The vast majority of both competitors and hospitals did not consider the introduction of infliximab biosimilars to have had any effect on the pricing of Entyvio.[34] This indicates that biosimilars to anti-TNFs exert competitive pressure on the originator, and potentially on other anti-TNFs, but do not appear to compete with Entyvio, suggesting again that they do not form part of the same product market.

(48) Lastly, [information related to Takeda's internal documents].[35]

(49) For the reasons presented above, the Commission concludes that there are strong indications that the appropriate market definition would be limited to anti-integrins for use in UC and CD. For the purposes of this Decision, it is not necessary to take a view as to whether a distinction should be made between anti-integrins for use in UC and anti-integrins for use in CD, since Takeda's marketed product is indicated, and Shire's pipeline is being developed, for both conditions. The Commission therefore concludes that, for the purpose of this Decision, the market for anti-integrins for use in UC and CD is the relevant market to be considered.

4.1.2. Treatments for chronic idiopathic constipation (CIC)

(50) CIC is a chronic motility disorder that typically affects women and older people. The main symptoms of the disease are infrequent stools, which are often difficult to pass, but the underlying cause is unknown.

(51) The standard treatment for CIC is over-the-counter (OTC) laxatives, followed by prescription laxatives if these are not effective. The effectiveness of these treatments is limited, and they are currently only indicated for use in women.

(52) The EphMRA classification groups all laxatives together at ATC3 level (under A6A "drugs for constipation"). Different types of laxative are then classified at ATC4 level, with A6A9 "other drugs for constipation" covering all products that do not fall into one of the other specific categories.

(53) In its most recent case involving treatments for constipation, M.7919 Sanofi/Boehringer Ingelheim Consumer Healthcare Business, the Commission concluded that the market should be assessed at the ATC3 level (i.e. all types of laxative) but left open whether a distinction should be made between OTC and prescription products. It should also be noted that no reference was made in that case to the class A6A9, the ATC4 class to which the products in question in this case belong. In another recent case, M.7379 Mylan/Abbott EPD-DM, the Commission did not exclude that the appropriate market may be defined at ATC4 level (in that case, A6A6 osmotic laxatives).

33 Questionnaire 2 to competitors, Q21.2.

34 Questionnaire 2 to competitors, Q21.3. Questionnaire 3 to hospitals and pharmacies, Q24.3.

35 [Information related to Takeda's internal documents].

(54) The Notifying Party submits that the appropriate market definition in this area would encompass all treatments for constipation, i.e. the entire ATC3 class A6A, on the basis of the argument that the different classes of laxative can be used as substitutes for one another.

(55) For the purposes of this case, the Commission can leave the exact product market definition open, as the Transaction is unlikely to create competition concerns in relation to treatments for CIC under any plausible product market definition.

4.2. Geographic market definition

(56) The Commission has consistently considered the markets for prescription pharmaceuticals to be national in scope.[36] For pipeline products, the Commission has considered the geographic scope of the market to be at least EEA-wide.[37] There would appear to be no reason to depart from this practice in the current case.

4.2.1. Treatments for inflammatory bowel disease (IBD)

4.2.1.1. Markets including *mesalazine*

(57) In accordance with the Commission's practice, as referred to above, the various plausible markets including *mesalazine* will be assessed at national level, as both Parties have marketed products of this type.

4.2.1.2. A market for anti-integrins for use in treating UC and CD

(58) In accordance with the Commission's practice, as referred to above, the market for anti-integrins will be assessed at EEA level, in view of the fact that the horizontal overlap involves a pipeline product.

4.2.1.3. Treatments for chronic idiopathic constipation (CIC)

(59) In accordance with the Commission's practice, as referred to above, the various plausible markets for treatments for CIC will be assessed at national level, as both Parties have marketed products of this type.

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[36] See, for example, M.8675 CVC/Teva's Women's Health Business, 20 December 2017, M.7559 Pfizer/Hospira, 4 August 2015.

[37] See, for example, M.8401 J&J/Actelion, 9 June 2017, M.7872 Novartis/GSK (Ofatumumab outoimmune indications), 18 December 2015.

4.3. Competitive analysis

4.3.1. Treatments for inflammatory bowel disease (IBD)

4.3.1.1. *Mesalazine*

(60) The only geographic market in which the Transaction would create an affected market for *mesalazine* (or any possible wider marketed including *mesalazine*) is the Netherlands. The table below shows the market shares on the narrowest possible basis, i.e. a market for *mesalazine*-based treatments.

Table 2: Market shares for *mesalazine* for use in UC and CD, 2015-2017[38]

	2015		2016		2017	
	Volume	**Value**	**Volume**	**Value**	**Volume**	**Value**
Takeda (Asacol)	[5-10]%	[5-10]%	[5-10]%	[5-10]%	[5-10]%	[5-10]%
Shire (Mezavant)	[10-20]%	[10-20]%	[10-20]%	[10-20]%	[10-20]%	[10-20]%
Combined	[20-30]%	[20-30]%	[20-30]%	[20-30]%	[20-30]%	[20-30]%
Ferring (Pentasa)	[40-50]%	[40-50]%	[40-50]%	[40-50]%	[40-50]%	[40-50]%
Dr Falk (Salofalk)	[30-40]%	[30-40]%	[30-40]%	[30-40]%	[30-40]%	[30-40]%

(61) As can be seen from the table above, the merged entity would be the third largest supplier of *mesalazine* in the Netherlands (as Shire is today), and would face competition from Ferring (the market leader with […] [40-50]% market share) and Dr Falk (with [30-40]% market share), in addition to at least four suppliers of generic *mesalazine* products that are not captured in the above market shares, but which also exert an effective competitive constraint on the Parties.[39] It is therefore most likely that the above figures overestimate the Parties' position on this market.

(62) The Notifying Party submits that Asacol is […]. Although these do not appear in the market shares (as explained above), the Notifying Party also points out that generic *mesalazine* products are available and exert considerable competitive pressure. Lastly, the Notifying Party submits that there is no particular closeness of competition between Takeda and Shire's products: Takeda's product (similarly to the Ferring and Dr Falk products) is taken three to four times a day whereas Shire's product has a delayed action mechanism and can be taken once a day only.

(63) The market investigation results confirmed that Ferring and Dr Falk, as suggested by the market shares, are generally considered to be the top suppliers of *mesalazine* in the Netherlands. Shire is generally named as a […] choice and only one competitor

38 Market shares were also provided for each of UC and CD separately. These are very similar to those for the two diseases together. The highest combined market share over a three year period is [20-30]% in CD, in value terms, in 2015.

39 The Notifying Party explained that there are no data available including all *mesalazine* products (i.e. both branded and generic) but restricted to sales for use in UC and CD. Data including generic products also includes sales for use in other diseases. Sales volumes suggest, however, that use in UC and CD accounts for a significant part of *mesalazine* use. Considering, for comparison purposes, all sales of *mesalazine* in the Netherlands – both branded and generic, for all diseases – the Parties' sales accounted for […] [10-20]% of the total in 2017.

mentioned Takeda amongst the top suppliers.[40] Although Shire and Takeda's products are similar to each other, in that they are both available as tablets whereas Ferring and Dr Falk's products are granules,[41] this does not appear to make them particularly close competitors, as it is not a decisive factor in doctors' choices. One physician explained, for example that "[t]*here is little clinically relevant difference between the mesalazine delivery systems*".[42] In general, both physicians and competitors generally considered there to be relatively little differentiation between the different brands of *mesalazine* available.[43] A competitor offering a generic *mesalazine* in the Netherlands explained, for example, that "[b]*ased on the scientific evidence available, there does not appear to be clinically relevant differences in efficacy or safety among the various mesalazine formulations and dosing regimens.*"[44] No market participants expressed concerns as to any potential consequences of the Transaction on a possible market for *mesalazine* in the Netherlands, or any wider market including *mesalazine*.

(64) Given the Parties' relatively modest combined market share (which never exceeds [20-30]%[45], but is most likely overestimated as does not take into account the generics competitors), and the presence of strong competitors whose products appear to be preferred to those of the Parties, the Commission concludes that the Transaction does not raise serious doubts as to its compatibility with the internal market on any plausible market including *mesalazine* in the Netherlands.

4.3.1.2. A market for anti-integrins for use in treating UC and CD

(65) Takeda's marketed product Entyvio would currently have 100% market share on any national market for anti-integrins in the EEA, it being the only biologic of this kind currently indicated for use in UC and CD in this region.

(66) Shire is developing one of two anti-integrins currently in clinical trials, the other being owned by Roche. Shire's pipeline product, like Roche's, is currently in Phase III clinical trials. The three products – Takeda's marketed product Entyvio and the two pipelines owned by Shire and Roche respectively – all belong to the class of anti-integrins, but are three different molecules: (i) Entyvio: *vedolizumab*; (ii) Shire's pipeline (SHP647): anti-MAdCAM-1; and (iii) Roche's pipeline: *etrolizumab*. The exact mode of action of the three molecules is slightly different but the overall effect in each case is to prevent the trafficking of lymphocytes to the intestinal wall.[46]

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40 Questionnaire 2 to competitors, Q5.

41 Questionnaire 2 to competitors, Q6 and Q7.

42 Questionnaire 1 to physicians, Q21.

43 Questionnaire 1 to physicians, Q21, Q22. Questionnaire 2 to competitors, Q7.

44 Questionnaire 2 to competitors, Q7.

45 Market shares were also provided for each of UC and CD separately. These are very similar to those for the two diseases together. The highest combined market share over a three year period is [20-30]% in CD, in value terms, in 2015.

46 The three molecules each block the binding of the integrin to its receptor in a slightly different way: *vedolizumab* targets the α4β7 integrin and prevents it from binding to its receptor, the MAdCAM molecule; *etrolizumab* targets both the β7 subunit of α4β7, and αEβ7; anti-MAdCAM-1 targets the MAdCAM antigen which in turn prevents the binding of MAdCAM to α4β7.

(67) The overriding similarity in the mode of action of these three molecules therefore sets them apart from all other biologic treatments, as they are all gut-specific and do not have the general immunosuppressant effect characteristic of other classes of biologics.

The Notifying Party's view

(68) The Notifying Party submits that the market-to-pipeline overlap between Takeda and Shire's products would not have any significant effect on this market due to the high general level of competition and […].

(69) In particular, the Notifying Party argues that […].

(70) In addition, the Notifying Party maintains that, even were Shire's SHP647 to be approved, it would be the third anti-integrin to reach the market after Roche's *etrolizumab*, and that the treatment landscape would be very competitive.

(71) In this regard, the Notifying Party also submits that a significant number of other pipelines may reach the market in the intervening period, with a range of modes of action. These include small molecule agents that have the added advantage of being administered orally. Similarly, the Notifying Party emphasises that an increasing number of existing treatments are losing exclusivity and that *adalimumab* biosimilars (the first of which is due to be launched later this year) […]. The Notifying Party maintains that both new originator products and biosimilars […].

(72) The Notifying Party therefore claims in the Form CO that […].

The Commission's assessment

(73) The Commission acknowledges that IBD, as claimed by the Parties, would appear to be a disease area where there is considerable R&D activity. There are a significant number of new treatments already in Phase III clinical trials (and an even greater number at earlier stages of development). Nonetheless, as mentioned above, there are only two anti-integrins at any stage of development (SHP647 and Roche's *etrolizumab*),[47] and their mode of action differentiates these compounds from other categories of treatment.

Closeness of competition

(74) In light of the market investigation results, the Commission considers that anti-integrins are likely to remain the closest competitors to one another, even if other biologic and small molecule treatments reach the market in the intervening period.

(75) As explained in more detail in the product market definition, anti-integrins have a better safety profile than other classes of biologics, due to their gut-specific mode of action,[48] and there are situations in which anti-integrins (and thus currently Entyvio) would be the only suitable treatment.[49]

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47 Another anti-integrin, natalizumab, is also available in the US, but is rarely used and was never launched in the EEA due to the high number of cases of progressive multifocal leukoencephalopathy (PML).

48 Questionnaire 1 to physicians, Q10, Q16.

49 Questionnaire 1 to physicians, Q30, Q31.

(76) A major competitor confirmed that the similarity in the mode of action of the two treatments is very likely to make them close competitors: "*Takeda's vedolizumab and Shire's SHP647 are both gut-homing T-cell blockers. While their mechanism of action is slightly different, they both aim to stop the trafficking of lymphocytes to the gut wall and thus have very similar effects. From a theoretical perspective, the products are very similar in their effects, speed of action and safety. Although Shire's SHP647 is not on the market yet and, thus, it cannot be assessed in practice, doctors are likely to consider this product and Takeda's vedolizumab as part of the same "class" of treatment.*"[50]

(77) Almost all competitors that expressed a view predicted that SHP647 would compete most closely with other anti-integrins, and thus Entyvio, due to the similarity in their mode of action.[51] One major competitor in the area of gastroenterology explained, for example, that *"it is likely that SHP647 would most closely compete with Entyvio, as they are both anti-integrins, with only subtle difference in the mode of action."*[52]

Insufficient competitive pressure from neighbouring markets

(78) Whilst concluding that the appropriate market is limited to anti-integrins, the Commission nonetheless recognises that competitive pressure could theoretically be exerted on Entyvio by products in neighbouring markets, i.e. other classes of biologics, these being anti-TNFs and IL-inhibitors, and potentially the new small molecule agents, the first of which (a JAK inhibitor) has been launched very recently.

(79) The results of the market investigation suggest, however, that competitive pressure from these neighbouring markets is limited. This is mainly because other types of biologic treatment 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, such as for patients with comorbidities.[53]

(80) A major competitor explained, for example, that *"[Entyvio's] advantage is in being a new targeted therapy which lacks systemic immunosuppression, with no cases of extra-pulmonary or systemic tuberculosis in contrast to anti-TNFs."*[54] Another competitor stated, similarly, that *"when compared to anti-TNFs, Entyvio has a new and more GI-specific MoA [mode of action] leading to a better safety profile (less risk of infection)."*[55]

(81) Some market participants also mentioned that Entyvio is particularly effective in maintaining remission in ulcerative colitis, whilst anti-TNFs in particular can lose effectiveness relatively quickly.[56]

(82) The lack of direct competitive pressure exerted by these other classes of biologics (and in future small molecule agents) is also demonstrated by the fact that Entyvio is purchased outside of tenders, whilst anti-TNFs in particular often compete against one another within the same tender procedures. Whilst purchasing patterns vary somewhat between

50 Minutes of teleconference with a competitor, 6 September 2018, 1:30pm.
51 Questionnaire 2 to competitors, Q34.
52 Questionnaire 2 to competitors, Q34.
53 See Section 4.1.1.3.
54 Questionnaire 1 to competitors, Q16.
55 Questionnaire 1 to competitors, Q16.
56 Questionnaire 1 to competitors, Q16.

countries, Entyvio is typically sourced by hospitals through bilateral negotiations,[57] whereas tenders for anti-TNFs create competition between (at least) the different biosimilars and originators of a specific molecule,[58] and, in some cases, the different anti-TNFs.[59]

(83) Similarly, as explained in Section 4.1.1.3, the introduction of biosimilars to Remicade (one of the two most often prescribed anti-TNFs) has had little if any effect on the pricing of Entyvio, whilst the price of Remicade itself has fallen considerably.[60] This shows that biosimilars to anti-TNFs exert competitive pressure on the originator, and potentially on other anti-TNFs, but do not appear to exert any significant price pressure on Entyvio.

(84) The Commission therefore notes that, while there may be some competitive pressure exerted on anti-integrins by other classes of biologics that are in neighbouring markets, this has not been sufficient in the past to affect pricing of Entyvio as the other classes of treatment often do not offer doctors a genuine alternative. As such, whilst there may be some competition between the different classes of biologics, for example in patients where a number of treatments would be possible, other types of biologics would not exert the same competitive pressure on Entyvio as would another anti-integrin.

Likely delay or discontinuation in the development of SHP647 post-Transaction

(85) The market investigation has revealed the concern of some respondents that Takeda would delay or discontinue the development of SHP647 due to the risk of cannibalising sales of Entyvio post-Transaction.

(86) KOLs are generally very positive about the prospects for SHP647 and emphasise the need for new treatment options, given in particular the tendency for specific drugs to lose effectiveness after a certain period of time and the lifelong nature of the diseases. Given in addition the importance of a good safety profile when choosing a biologic treatment, particularly for certain groups of patients, the addition of a further anti-integrin to the treatment landscape is seen by doctors as an important development.

(87) A KOL in the field explained that *"it would … be difficult for Takeda to differentiate Entyvio from the new anti-MAdCAM-1 if it held them both in the same portfolio. The arrival of another anti-integrin on the market could be expected to exert some price pressure on Entyvio."*[61]

(88) Both KOLs and competitors see Entyvio and SHP647 as close competitors and question whether Takeda would have the incentive to continue development, given the risk of cannibalising its own sales post-Transaction.

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57 Questionnaire 3 to hospitals and pharmacies, Q16.

58 To date, this has applied exclusively to *infliximab*, for which biosimilars have been available since 2015. Biosimilars to *adalimumab* have been approved more recently and could be expected to compete directly with the originator biologic (Humira) through similar tender procedures as of the end of 2018, by which time Humira will have lost exclusivity.

59 Questionnaire 3 to hospitals and pharmacies, Q15.

60 Questionnaire 1 to physicians, Q36. Questionnaire 3 to pharmacies, Q24. Minutes of teleconference with KOL in gastroenterology, 9 August 2018 12.00.

61 Minutes of teleconference with KOL, 7 August October 2018, 8.00.

(89) A KOL familiar with the Shire pipeline explained that *"[t]he main question that came to the minds of KOLs when hearing about the acquisition of Shire by Takeda was how it would affect the development of the anti-MAdCAM pipeline."*[62]

(90) Whilst the Notifying Party maintains that […]. A leading specialist explained that: *"If, for example, it emerges that the specific mechanism of action of the anti-MAdCAM has advantages, then even as the third in class, SHP647 could still win considerable market share. In any case, it would offer doctors a further option, which would be very welcome in a disease area where loss of responsiveness is a problem."*[63]

(91) A major competitor predicted that *"the two products would be likely to partially cannibalise each other on the market, rather than adding up to a higher overall market share"*.[64] This statement highlights exactly why the merged entity is unlikely to have the incentive that Shire would have had pre-merger to bring the pipeline SHP647 to market. As such, the Transaction creates a very real risk that the development of a promising new treatment will be delayed or abandoned.

(92) Internal documents also indicate that Takeda […].[65]

(93) In addition, whilst Entyvio would, in the normal course of events, lose patent protection in […]. Subject to the results of the clinical trials and the regulatory approvals, the new formulation is expected to be launched in the EU in […]. SHP647 would also be delivered as a subcutaneous treatment, thus further reducing any potential incentive to try to position the two treatments differently within the same portfolio.

(94) In view of the above, and taking into consideration that Entyvio and SHP647, if successfully developed, will compete closely with each other and will not face sufficient competitive constraints from other products, the Commission considers that Takeda will have the incentive to delay or discontinue the development of the SHP647 pipeline following the merger. The disappearance or delay of a promising new treatment 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.

(95) The Commission therefore concludes that the Transaction raises serious doubts as to its compatibility with the internal market in relation to the market for anti-integrins for use in the treatment of UC and CD.

4.3.2. Treatments for chronic idiopathic constipation (CIC)

(96) Were the market to be defined narrowly at ATC4 level (A6A9 "other drugs for constipation"), an affected market would arise in treatments for chronic idiopathic constipation in the UK, as both Parties currently market treatments for this condition.[66]

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62 Minutes of teleconference with KOL, 15 October 2018, 13.30.

63 Minutes of teleconference with KOL, 15 October 2018, 13.30.

64 Minutes of teleconference with a competitor, 6 September 2018, 13.30.

65 […].

66 Takeda markets Amitiza (lubiprostone), a chloride 2 activator, and Shire markets Resolor (prucalopride), a 5-HT4 receptor agonist, both of which belong to ATC4 class A6A9 "other drugs for constipation.

(97) The Transaction would not, however, lead to any merger-specific changes on this market as […]. […],[67] […].

(98) […].

(99) […].

(100) In view of the above, the Commission concludes that the Transaction would not create competition concerns on any plausible market for CIC in the UK, given that […].

5. COMMITMENTS

5.1. Framework for the assessment of the Commitments

(101) Where a concentration raises serious doubts as regards its compatibility with the internal market, the Parties may undertake to modify the concentration so as to remove the grounds for the serious doubts identified by the Commission. Pursuant to Article 6(2) of the Merger Regulation, where the Commission finds that, following modification by the undertakings concerned, a notified concentration no longer raises serious doubts, it shall declare the concentration compatible with the internal market pursuant to Article 6(1)(b) of the Merger Regulation.

(102) As set out in the Commission's Remedies Notice,[68] the commitments have to eliminate the competition concerns entirely, and have to be comprehensive and effective from all points of view.[69]

(103) In assessing whether commitments will maintain effective competition, the Commission considers all relevant factors, including the type, scale and scope of the proposed commitments, with reference to the structure and particular characteristics of the market in which the Transaction is likely to significantly impede effective competition, including the position of the Parties and other participants on the market.[70]

(104) In order for the commitments to comply with those principles, they must be capable of being implemented effectively within a short period of time. Concerning the form of acceptable commitments, the Merger Regulation gives discretion to the Commission as long as the commitments meet the requisite standard. Structural commitments will meet the conditions set out above only in so far as the Commission is able to conclude with the requisite degree of certainty, at the time of its Decision, that it will be possible to implement them and that it will be likely that the new commercial structures resulting from them will be sufficiently workable and lasting to ensure that effective competition will be maintained.[71] Divestiture commitments are normally the best way to eliminate competition concerns resulting from horizontal overlaps.

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67 […].

68 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. 1-27).

69 Remedies Notice, paragraphs 9 and 61.

70 Remedies Notice, paragraph 12.

71 Remedies Notice, paragraph 10.

5.2. Proposed Commitments

(105) In order to render the concentration compatible with the internal market, the Parties submitted a set of commitments under Article 6(2) of the Merger Regulation on 26 October 2018 (the "Initial Commitments"). The Commission market tested the Initial Commitments in order to assess whether they are sufficient and suitable to remedy the serious doubts identified in Section 4.3.1 of this Decision. Following the feedback received during the market test, the Initial Commitments were refined and improved, and amended commitments were submitted on 16 November 2018 (the "Final Commitments"). The Final Commitments are annexed to this Decision and form an integral part thereof.

5.2.1. Initial Commitments

(106) In order to dispel the serious doubts raised by the Commission, the Parties submitted commitments consisting of a full divestiture of the development, manufacturing and marketing rights related to Shire's SHP647 pipeline ("the Product"). The Product is under development by Shire following an out-licensing agreement with Pfizer whereby the latter granted […] rights to Shire. The Product is currently undergoing: (i) seven Phase III clinical trials for use in UC and CD; (ii) […]; and (iii) […]. Furthermore, in relation to the Product, Shire is developing […].

(107) The Divestment Business includes assets necessary to conduct and complete the Product's global clinical trials, obtain the required marketing authorisation from regulatory authorities (if the trials are successful) and bring the product to the EEA and (potentially) non-EEA markets. In particular, the Divestment Business includes the following main intangible and tangible assets: (i) rights to conduct the clinical trials, manufacture and market the Product globally; (ii) patents, copyrights, data and know-how related to the Product; (iii) trade names for the Product; (iv) licences, permits and authorisations issued by third parties in relation to the Product; (v) the relevant reports related to the clinical trials, regulatory files, books and records, and the documentation related to marketing and inventories for the Product; (vi) contracts with third parties, to the extent these are transferrable; and (vii) certain members of personnel working on the SHP647 programme.

(108) Furthermore, with the aim of ensuring a smooth transfer of the Divestment Business, the Parties committed to a number of transitional supply arrangements, including regarding: (i) the supply of services (e.g. technical assistance), for up to […]; (ii) the supply of the active ingredient for SHP 647, for up to […]; (iii) the continued sponsorship of the clinical trials, until […]; and (iv) the supply of products and services provided to Shire by third parties, through back-to-back arrangements, if the contracts in question cannot be transferred, for up to […].

(109) In addition to the standard Purchaser requirements, the Initial Commitments provided that the Purchaser must have: (i) established capabilities in the clinical development of biologic or biosimilar medicinal products for EEA approval; (ii) expertise and experience in interactions with EEA-wide and national bodies that decide on approval of biologic or biosimilar medicinal products and on pricing and reimbursement of biologic or biosimilar medicinal products; (iii) established capabilities or a track record in the distribution of biologic or biosimilar medicinal products in the EEA; and (iv) a complementary product portfolio in the clinical areas relevant to SHP647.

(110) In addition, the Commitments provide for the Parties to enter into related commitments, *inter alia* regarding the separation of the divested businesses from their retained businesses, the preservation of the viability, marketability and competitiveness of the divested businesses, including the appointment of a monitoring trustee and, if necessary, a divestiture trustee.

(111) Finally, the Initial Commitments provide for the rights to manufacture and market the Product outside the EEA to potentially be returned to the merged entity after the divestiture, on the basis of commercial arrangements to be agreed with the Purchaser.

(112) The Parties argued that the Commitments remedy the Commission's concerns since they remove the entire potential overlap with respect to the Parties' marketed and pipeline products used in the treatment of moderate-to-severe UC and CD. The Parties further argued that the assets to be transferred are sufficient for a Purchaser to continue the development and, depending on the outcome of the clinical trials, ultimately market the SHP647 compound, thus allowing the Purchaser to operate the Divestment Business as a viable and independent business in the EEA.[72] In addition, the Parties explained that Shire has already incurred […] part of the estimated development costs for the pipeline, which has already reached an advanced development stage (Phase III clinical trials), thereby making its divestment an attractive commercial opportunity for potential purchasers.[73]

5.2.2. Results of the market test

(113) The market test was launched on 29 October 2018 and sought to assess the scope and effectiveness of the Initial Commitments, their viability, the attractiveness of the Divestment Business, and the appropriateness of the Purchaser criteria.

(114) The majority of market participants that responded to the market test considered the Divestment Business to be an attractive asset likely to appeal to suitable purchasers.[74]

(115) In terms of its scope, market participants were of the opinion that the Divestment Business includes all the necessary assets for a purchaser to be able to continue the clinical trials and ultimately bring the product to the EEA market.[75] Some competitors indicated that specific additional documents related to pre-clinical studies may be required as part of the reporting and data that are transferred to the Purchaser.[76]

(116) As concerns the potential licence-back for the non-EEA rights, the respondents to the market test noted that it is very common for a particular biologic drug to be manufactured on two different sites.[77] Furthermore, all KOLs considered it customary for different companies to market the same drug in different geographic regions.[78] The majority of respondents were of the opinion that the potential split of the manufacturing and marketing rights for SHP647 (between the Purchaser in the EEA and potentially

72 Form RM, paragraph 19.
73 Form RM, paragraph 20.
74 Questionnaire R1 to competitors, Q12. Questionnaire R2 to KOLs, Q10.
75 Questionnaire R1 to competitors, Q3. Questionnaire R2 to KOLs, Q1.
76 Questionnaire R1 to competitors, Q3.
77 Questionnaire R1 to competitors, Q8 and Q11.
78 Questionnaire R2 to KOLs, Q9.

Takeda in non-EEA regions) would not affect the viability or competitiveness of the Divestment Business.[79] Similarly, the majority of competitors considered that there would not be any effect on the purchaser's incentive to continue development of the SHP647 and bring it to the market.[80]

(117) As regards potential implementation risks, while market participants acknowledged that the transfer of third party supply contracts is standard practice in pipeline divestments and does not generally entail particular hurdles, they explained that, if contracts with third parties are not transferred to the Purchaser (in particular as regards CRO services and cell line technology), this could cause delays in the pipeline development.[81]

(118) Overall, the vast majority of respondents confirmed that the Divestment Business has all the assets to be operated in a viable manner by a suitable purchaser,[82] and that the Key Personnel as identified in the Initial Commitments covered all the necessary roles.[83]

(119) As concerns the suitable purchaser, the results of the market test also indicated that the most suitable type of purchaser would be a large pharma company[84] with: (i) experience in developing biologics or biosimilars[85] and the capacity to market this type of treatment in the EEA,[86] (ii) experience in dealing with EEA authorities responsible for the approval of medicines,[87] and (iii) a complementary portfolio in GI and possibly even in the area of IBD.[88]

(120) Competitors were generally of the opinion that the transitional arrangements provided for in the Initial Commitments were sufficient to ensure a smooth transfer of the Divestment Business.[89] Respondents to the market test also indicated that a change in the contract research company (CRO) or in the cell line technology used in the development of SHP647 could lead to significant delays in its development and additional costs.[90]

5.2.3. Final Commitments

(121) In view of the results of the market test, the Parties amended the Initial Commitments and submitted the Final Commitments on 16 November 2018.

(122) In particular, the main changes aim to mitigate any risks of delays in product development during the transitional period and to ensure that the Purchaser has such capabilities as will further increase the chances of the product successfully reaching the market (and becoming available to patients in need of this treatment in the EEA), as was

79 Questionnaire R1 to competitors, Q9.
80 Questionnaire R1 to competitors, Q10.
81 Questionnaire R1 to competitors, Q19, Q20 and Q21. Questionnaire R2 to KOLs, Q17, 18 and 19.
82 Questionnaire R1 to competitors, Q5. Questionnaire R2 to KOLs, Q3.
83 Questionnaire R1 to competitors, Q6. Questionnaire R2 to KOLS, Q4.
84 Questionnaire R1 to competitors, Q14. Questionnaire R2 to KOLs, Q11.
85 Questionnaire R1 to competitors, Q16.1. Questionnaire R2 to KOLs, Q14.1.
86 Questionnaire R1 to competitors, Q16.3. Questionnaire R2 to KOLs, Q14.3.
87 Questionnaire R1 to competitors, Q16.2. Questionnaire R2 to KOLs, Q14.2.
88 Questionnaire R1 to competitors, Q16.4. Questionnaire R2 to KOLs, Q14.4.
89 Questionnaire R1 to competitors, Q17.
90 Questionnaire R1 to competitors, Q19, Q20 and Q21.

planned prior to the merger. Against this background, the Final Commitments submitted by the Parties specifically provide for the following improvements compared to the Initial Commitments:

(a) to ensure a smooth transfer of the Product without causing delays to its development, the Purchaser must have preliminarily concluded agreements with various third party providers (including the CRO and the provider of the cell line technology);

(b) the Purchaser must have a complementary product portfolio specifically in the area of GI and preferably IBD;

(c) Shire must, prior to the closing of the transaction between Takeda and Shire, take the necessary decisions to […] according to the planned schedule;

(d) Shire and subsequently Takeda (following closing of the transaction between Takeda and Shire) must continue to provide the CRO with all the input required to ensure that development of SHP647 continues uninterrupted during the transitional period; and

(e) the divestment business includes all the relevant documentation on the results of preclinical studies.

(123) The language of the Final Commitments has also been amended to clarify that any potential licence-back of the manufacturing and marketing rights outside of the EEA (paragraph (111)) will be at the option of the Purchaser.

5.2.4. Overall assessment of the Final Commitments

(124) The Final Commitments remove the entire overlap between the Parties' activities in relation to the market for which the Commission raised serious doubts following the results of the Phase I market investigation. In particular, the Final Commitments include the tangible and intangible assets necessary to conduct and complete the clinical trials at global level for the Product, and, if successful, obtain a marketing authorisation and bring the Product to the market.

(125) The Final Commitments also include transitional arrangements which are sufficient, both in scope and duration, to ensure a smooth transfer of the Divestment Business to the Purchaser. Furthermore, the Final Commitments include targeted purchaser criteria, such that the Divestment Business will be transferred to a suitable purchaser.

(126) The Final Commitments also address the shortcomings of the Initial Commitments, as identified by market participants in the market test.

(127) On this basis, and in view of the presence of a number of interested Purchasers, the Commission considers that the Divestment Business is attractive and likely to be acquired by a suitable Purchaser.

(128) For the reasons outlined above, the Commission concludes that the Final Commitments are sufficient in scope and suitable to eliminate the serious doubts as to the compatibility of the Transaction with the internal market given the purpose of Article 6(2) of the Merger Regulation.

5.3. Conditions and obligations

(129) Under the first sentence of the second subparagraph of Article 6(2) of the Merger Regulation, the Commission may attach to its decision conditions and obligations intended to ensure that the undertakings concerned comply with the commitments they have entered into *vis-à-vis* the Commission with a view to rendering a notified concentration compatible with the internal market.

(130) The achievement of the measure that gives rise to the structural change of the market is a condition, whereas the implementing steps which are necessary to achieve this result are generally obligations on the Parties. Where a condition is not fulfilled, the Commission's decision declaring the concentration compatible with the internal market no longer stands. Where the undertakings concerned commit a breach of an obligation, the Commission may revoke the clearance decision in accordance with Article 8(6) of the Merger Regulation. The undertakings concerned may also be subject to fines and periodic penalty payments under Articles 14(2) and 15(1) of the Merger Regulation.

(131) In accordance with the distinction described above, the Decision in this case is conditioned on the full compliance with the requirements set out in Section B of the Final Commitments (including the Schedule), which constitute conditions. The remaining requirements set out in the other Section of the Final Commitments constitute obligations on Takeda.

(132) The detailed text of the Final Commitments is annexed to this Decision. The full text of the final Commitments forms an integral part of this Decision.

6. CONCLUSION

(133) For the above reasons, the Commission has decided not to oppose the notified operation as modified by the commitments and to declare it compatible with the internal market and with the functioning of the EEA Agreement, subject to full compliance with the conditions in Section B of the Commitments annexed to the present decision and with the obligations contained in the other sections of the said Commitments. This Decision is adopted in application of Article 6(1)(b) in conjunction with Article 6(2) of the Merger Regulation and Article 57 of the EEA Agreement.

For the Commission

(Signed)
Margrethe VESTAGER
Member of the Commission

Dated 16 November 2018

Takeda Pharmaceutical Company Limited

Shire plc

Case No COMP/M.8955 –Takeda/Shire

Commitments to the European Commission

CASE NO. COMP/M.8955 – Takeda/Shire

Commitments to the European Commission

Pursuant to Article 6(2 of Council Regulation (EC) No. 139/2004 (the "**Merger Regulation**"), Takeda Pharmaceutical Company Limited ("**Takeda**") and Shire plc ("**Shire**") (the "**Parties**", each a "**Party**") hereby enter into the following Commitments (the "**Commitments**") vis-à-vis the European Commission (the "**Commission**") with a view to rendering the acquisition by Takeda of sole control over Shire (the "**Takeda/Shire Transaction**") compatible with the internal market and the functioning of the EEA Agreement.

This text shall be interpreted in light of the Commission's decision pursuant to Article 6(1)(b) of the Merger Regulation to declare the Takeda/Shire Transaction compatible with the internal market and the functioning of the EEA Agreement (the "**Decision**"), in the general framework of European Union law, in particular in light of the Merger Regulation, and by reference to the Commission Notice on remedies acceptable under Council Regulation (EC) No 139/2004 and under Commission Regulation (EC) No 802/2004 (the "**Remedies Notice**").

Section A. Definitions

1. For the purpose of the Commitments, the following terms shall have the following meaning:

Affiliated Undertakings: undertakings controlled by the Parties and/or by the ultimate parents of the Parties, whereby the notion of control shall be interpreted pursuant to Article 3 of the Merger Regulation and in light of the Commission Consolidated Jurisdictional Notice under Council Regulation (EC) No 139/2004 on the control of concentrations between undertakings (the "**Consolidated Jurisdictional Notice**").

Assets: the assets that contribute to the current operation or are necessary to ensure the viability and competitiveness of the Divestment Business as indicated in Section B, paragraph 5 (a), (b) and (c) and described more in detail in the Schedule.

Closing: the transfer of the legal title of the Divestment Business to the Purchaser.

Closing Period: the period of […] from the approval of the Purchaser and the terms of sale by the Commission.

Confidential Information: any business secrets, know-how, commercial information, or any other information of a proprietary nature that is not in the public domain.

Conflict of Interest: any conflict of interest that impairs the Trustee's objectivity and independence in discharging its duties under the Commitments.

Divestment Business: the business related to Shire's pipeline compound SHP 647 as defined in Section B and in the Schedule which Takeda commits to divest.

Divestiture Trustee: one or more natural or legal person(s) who is/are approved by the Commission and appointed by Takeda and who has/have received from Takeda the exclusive Trustee Mandate to sell the Divestment Business to a Purchaser at no minimum price.

Effective Date: the date of adoption of the Decision.

First Divestiture Period: the period of […].

Hold Separate Manager: the person appointed by the Parties, following approval by the European Commission, for the Divestment Business to manage the day-to-day business under the supervision of the Monitoring Trustee.

Key Personnel: all personnel necessary to maintain the viability and competitiveness of the Divestment Business, as listed in the Schedule, including the Hold Separate Manager.

Monitoring Trustee: one or more natural or legal person(s), who is/are approved by the Commission and appointed by Takeda, and who has/have the duty to monitor Takeda's compliance with the conditions and obligations attached to the Decision.

Personnel: all staff currently employed by the Divestment Business, including staff currently seconded to the Divestment Business and shared personnel.

Pfizer: Pfizer Limited, a company incorporated under the laws of England, with its registered office at Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom.

Pfizer Agreement: the License Agreement between Pfizer and Shire International GmbH, dated […], and modifications thereto, whereby Pfizer grants to Shire […].

Purchaser: […] or another third party entity, in each case approved by the Commission as acquirer of the Divestment Business in accordance with the criteria set out in Section D.

Purchaser Criteria: the criteria laid down in paragraph 17 of these Commitments that the Purchaser must fulfil in order to be approved by the Commission.

Schedule: the schedule to these Commitments describing more in detail the Divestment Business.

SHP 647: Shire's in-licensed pipeline biologic compound (derived from the monoclonal antibody to MAdCAM), for use in any indication, currently in Phase III clinical trials for the treatment of Ulcerative colitis ("**UC**") and Crohn's disease ("**CD**") and also expected to undergo […]. SHP 647 refers to the raw materials, work in progress, drug substance (including API) and drug product.

SHP 647 API: The active ingredient of SHP 647.

Shire: Shire plc, a company incorporated under the laws of Jersey, with its registered office at 22 Grenville Street, St Helier, JE4 8PX, Jersey.

Shire International GmbH: an Affiliated Undertaking of Shire incorporated under the laws of Switzerland, with its registered office at Zahlerweg 10, CH-6300, Zug, Switzerland.

Takeda: Takeda Pharmaceutical Company Limited, a company incorporated under the laws of Japan, with its registered office at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan.

Technical Expert: one or more natural or legal person(s), appointed by and reporting to the Monitoring Trustee, who has/have expertise relevant to the Divestment Business. If the Monitoring Trustee has the necessary technical expertise, the Monitoring Trustee and Technical Expert can be the same natural or legal person.

Trustee(s): the Monitoring Trustee and/or the Divestiture Trustee as the case may be.

Trustee Divestiture Period: the period of […] from the end of the First Divestiture Period.

Variation Agreement: […].

Section B. The commitment to divest and the Divestment Business

Commitment to divest

2. In order to maintain effective competition, Takeda commits to divest the Divestment Business by the end of the Trustee Divestiture Period as a going concern to a purchaser and on terms of sale approved by the Commission in accordance with the procedure described in paragraph 18 of these Commitments. To carry out the divestiture, the Parties commit to find a purchaser and to enter into a final binding sale and purchase agreement for the sale of the Divestment Business within the First Divestiture Period. If the Parties have not entered into such an agreement at the end of the First Divestiture Period, Takeda shall grant the Divestiture Trustee an exclusive mandate to sell the Divestment Business in accordance with the procedure described in paragraph 32 in the Trustee Divestiture Period. […].

3. Takeda shall be deemed to have complied with this commitment if:

(a) by the end of the Trustee Divestiture Period, Takeda, Shire, or the Divesture Trustee has entered into) a final binding sale and purchase agreement ([…]), and the Commission approves the proposed purchaser and the terms of transfer or sale, as the case may be, as being consistent with the Commitments in accordance with the procedure described in paragraph 18; and

(b) if the Closing of the sale of the Divestment Business to the Purchaser takes place within the Closing Period.

4. In order to maintain the structural effect of the Commitments, Takeda shall, for a period of 10 years after Closing, not acquire, whether directly or indirectly, the possibility of exercising influence (as defined in paragraph 43 of the Remedies Notice, footnote 3) over the whole or part of the Divestment Business, unless, following the submission of a reasoned request from Takeda showing good cause and accompanied by a report from the Monitoring Trustee (as provided in paragraph 45 of these Commitments), the Commission finds that the structure of the market has changed to such an extent that the absence of influence over the Divestment Business is no longer necessary to render the Takeda/Shire Transaction compatible with the internal market.

Structure and definition of the Divestment Business

5. The Divestment Business consists of all relevant rights, title and interests in SHP 647 worldwide including the assignment to the Purchaser of the Pfizer Agreement, as well as certain ancillary assets and the rights to or licence for certain technologies needed to successfully develop SHP 647. At the option of the Purchaser, the sale of the Divestment Business may include a licence-back to the Parties in respect of the right to manufacture and market SHP 647 in territories outside the EEA. The legal and functional structure of the Divestment Business as operated to date is described in the Schedule. The Divestment Business, described in more detail in the Schedule, includes all assets and staff that contribute to the current operation or are necessary to ensure the viability and competitiveness of the Divestment Business, in particular:

(a) all tangible and intangible assets (including intellectual property rights);

(b) all licences, permits and authorisations issued by any governmental organisation for the benefit of the Divestment Business;

(c) all contracts, leases and commitments of the Divestment Business; all credit and other records of the Divestment Business; and

(d) the Personnel.

6. For the sake of clarity, the Divestment Business shall not include any physical production assets or manufacturing units owned or operated by the Parties.

7. The Parties commit to provide the technical support necessary to ensure an effective transfer (i) of the Divestment Business's production process to a production location of the Purchaser's choice and (ii) of the clinical trials and, if need be, to enter into a supply agreement with the Purchaser for the supply of SHP 647 API for an appropriate period of time at cost. Furthermore, the Parties commit to continue to act as a sponsor for all clinical trials underway for a period until Closing. At the Purchaser's request, with respect to any clinical trial, this period can be extended for a mutually agreed period, subject to a service fee to be agreed with the Purchaser.

8. In addition, the Divestment Business includes the benefit, for a transitional period of up to […] after Closing and on terms and conditions equivalent to those at present afforded to the Divestment Business, of all current arrangements under which Shire or its Affiliated Undertakings supply services to the Divestment Business, as detailed in the Schedule, unless otherwise agreed with the Purchaser. Strict firewall procedures will be adopted so as to ensure that any competitively sensitive information related to, or arising from such supply arrangements (for example, product roadmaps) will not be shared with, or passed on to, anyone outside the Parties' entity(ies) providing such services.

Section C. Related Commitments

Preservation of viability, marketability and competitiveness

9. From the Effective Date until Closing, the Parties shall preserve the economic viability, marketability and competitiveness of the Divestment Business, in accordance with good business practice, and shall minimise as far as possible any risk of loss of competitive potential of the Divestment Business. In particular, the Parties undertake:

(a) not to carry out any action that might have a significant adverse impact on the value, management or competitiveness of the Divestment Business or that might alter the nature and scope of activity, or the industrial or commercial strategy or the investment policy of the Divestment Business;

(b) to make available, or procure to make available, sufficient resources for the development of the Divestment Business, on the basis and continuation of the existing business plans;

(c) to take all reasonable steps, or procure that all reasonable steps are being taken, including appropriate incentive schemes (based on industry practice), to encourage all Key Personnel to remain with the Divestment Business, and not to solicit or move any Personnel to the Parties' remaining businesses. Where, nevertheless, individual members of the Key Personnel exceptionally leave the Divestment Business, the Parties shall provide a reasoned proposal to replace the person or

persons concerned to the Commission and the Monitoring Trustee. The Parties must be able to demonstrate to the Commission that the replacement is well suited to carry out the functions exercised by those individual members of the Key Personnel. The replacement shall take place under the supervision of the Monitoring Trustee, who shall report to the Commission.

Hold-separate obligations

10. The Parties commit, from the Effective Date until Closing, to keep the Divestment Business separate from the business(es) they are retaining and to ensure that unless explicitly permitted under these Commitments:

(a) management and staff of the business(es) retained by the Parties have no involvement in the Divestment Business;

(b) the Key Personnel and Personnel of the Divestment Business have no involvement in any business retained by the Parties and do not report to any individual outside the Divestment Business.

11. The Parties shall assist the Monitoring Trustee in ensuring that the Divestment Business is managed as a distinct and saleable entity separate from the businesses which the Parties are retaining. Immediately after the adoption of the Decision, Shire shall propose a Hold Separate Manager to the European Commission for its approval and shall appoint said Hold Separate Manager once approval has been received. Should the first candidate proposed not be approved by the Commission, Shire shall propose further suitable candidates for the post of Hold Separate Manager. The Hold Separate Manager, who shall be part of the Key Personnel, shall manage the Divestment Business independently and in the best interest of the business with a view to ensuring its continued economic viability, marketability and competitiveness and its independence from the businesses retained by Takeda. The Hold Separate Manager shall closely cooperate with and report to the Monitoring Trustee, who may be assisted by the Technical Expert, and, if applicable, the Divestiture Trustee. Any replacement of the Hold Separate Manager shall be subject to the procedure laid down in paragraph 9(c) of these Commitments. The Commission may, after having heard the Parties, require the Parties to replace the Hold Separate Manager.

Ring-fencing

12. The Hold Separate Manager shall implement all necessary measures to ensure that Takeda does not obtain any Confidential Information relating to the Divestment Business and that any such Confidential Information obtained by Takeda before the Effective Date will be eliminated and not be used by Takeda. In particular, the participation of the Divestment Business in any central information technology network shall be severed to the extent possible, without compromising the viability of the Divestment Business. Takeda may obtain or keep information relating to the Divestment Business which is reasonably necessary for the divestiture of the Divestment Business or the disclosure of which to Takeda is required by law. In order to ensure that the measures are effective Takeda commits to create additional reasonable mechanisms with regard to the personnel involved in the provisions of such service to ensure that any Confidential Information is not shared with businesses that Takeda is retaining.

Non-solicitation clause

13. The Parties undertakes, subject to customary limitations, not to solicit, and to procure that Affiliated Undertakings do not solicit, the Key Personnel transferred with the Divestment Business for a period of […] after Closing.

Due diligence

14. In order to enable potential purchasers to carry out a reasonable due diligence of the Divestment Business, the Parties shall, subject to customary confidentiality assurances and dependent on the stage of the divestiture process:

(a) provide to potential purchasers sufficient information as regards the Divestment Business;

(b) provide to potential purchasers sufficient information relating to the Personnel and allow them reasonable access to the Personnel.

Reporting

15. The Parties shall submit written reports in English on potential purchasers of the Divestment Business and developments in the negotiations with such potential purchasers to the Commission and the Monitoring Trustee no later than 10 days after the end of every month following the Effective Date (or otherwise at the Commission's request). The Parties shall submit a list of all potential purchasers having expressed interest in acquiring the Divestment Business to the Commission at each and every stage of the divestiture process, as well as a copy of all the offers made by potential purchasers within five days of their receipt.

16. The Parties shall inform the Commission and the Monitoring Trustee on the preparation of the data room documentation and the due diligence procedure and shall submit a copy of any information memorandum to the Commission and the Monitoring Trustee before sending the memorandum out to potential purchasers.

Section D. The Purchaser

17. In order to be approved by the Commission, the Purchaser must fulfil the following criteria:

(a) The Purchaser shall be independent of and unconnected to Takeda and its Affiliated Undertakings (this being assessed having regard to the situation following the divestiture);

(b) The Purchaser shall have the financial resources, proven expertise and incentive to maintain and develop the Divestment Business as a viable and active competitive force in competition with the Parties and other competitors;

(c) The acquisition of the Divestment Business by the Purchaser must neither be likely to create, in light of the information available to the Commission, *prima facie* competition concerns nor give rise to a risk that the implementation of the Commitments will be delayed. In particular, the Purchaser must reasonably be expected to obtain all necessary approvals from the relevant regulatory authorities for the acquisition of the Divestment Business;

(d) The Purchaser shall have a binding agreement with […] in relation to the cell line technology necessary for the development of SHP 647;

(e) The Purchaser shall have a binding agreement with […] in relation to the production of the final drug product for SHP 647;

(f) The Purchaser shall have a binding agreement with […] for the CRO services provided in relation to SHP 647;

(g) The Purchaser shall have established capabilities in the clinical development of biologic or biosimilar medicinal products for EEA approval;

(h) The Purchaser shall have expertise and experience in having relevant interactions with relevant EEA-wide and national bodies that decide on approval of biologic or biosimilar medicinal products and on pricing and reimbursement of biologic or biosimilar medicinal products;

(i) The Purchaser shall have established capabilities or a track record in the commercialisation and distribution of biologic or biosimilar medicinal products in the EEA ; and

(j) The Purchaser shall have complementary product(s), either marketed or in development, in the clinical areas relevant to SHP 647, in particular in the area of gastrointestinal diseases (GI), preferably in the area of inflammatory bowel disease (IBD).

18. The final binding sale and purchase agreement (as well as ancillary agreements) relating to the divestment of the Divestment Business shall be conditional on the Commission's approval. The Parties shall ensure the sale and purchase agreement includes a provision specifying that:

(i) subject to (ii), the Purchaser shall not make any changes to the protocols previously agreed between Shire and […] such as that could lead to a delay in the progress of the clinical trials for SHP 647 (relative to the timing agreed between […] and Shire prior to the Effective Date); and

(ii) where changes to the protocol are deemed necessary or desirable (for example to comply with legal or safety requirements), the Purchaser shall notify the Commission and the Trustee, as applicable, and provide detailed explanation as to the background of these changes as well as their potential impact on the timing of the development of SHP 647.

When Takeda or Shire has reached an agreement with a purchaser, the Parties shall submit a fully documented and reasoned proposal, including a copy of the final agreement(s), within one week to the Commission and the Monitoring Trustee. The Parties must be able to demonstrate to the Commission that the purchaser fulfils the Purchaser Criteria and that the Divestment Business is being transferred, or, as the case may be, sold in a manner consistent with the Commission's Decision and the Commitments. For the approval, the Commission shall verify that the purchaser fulfils the Purchaser Criteria and that the Divestment Business is being transferred, or, as the case may be, sold in a manner consistent with the Commitments including their objective to bring about a lasting structural change in the market. The Commission may approve the transfer, or, as the case may be, sale of the Divestment Business without one or more Assets or parts of the Key Personnel, or by substituting one or more Assets or parts of the Key Personnel with one or

more different assets or different personnel, if this does not affect the viability and competitiveness of the Divestment Business after the sale, taking account of the proposed purchaser.

Section E. Trustee

I. Appointment procedure

19. Takeda shall appoint a Monitoring Trustee to carry out the functions specified in these Commitments for a Monitoring Trustee. Takeda commits not to close the Takeda/Shire Transaction before the appointment of a Monitoring Trustee.

20. Any Technical Expert shall be appointed by and report to the Monitoring Trustee. The Technical Expert will be independent of and will not have or be exposed to any conflict of interest in relation to the Parties. Takeda and the Purchaser shall have the right to be heard with any reasoned objections as to the suitability of any technical expert candidates, e.g., lack of competence or conflict of interest. In cases of controversy between Takeda and the Monitoring Trustee, and/or Purchaser and the Monitoring Trustee as to the suitability of the technical expert candidate, the Commission will decide on the matter.

21. If Takeda or Shire has not entered into a binding sale and purchase agreement or the Variation Agreement regarding the Divestment Business […] before the end of the First Divestiture Period or if the Commission has rejected a purchaser proposed by Takeda at that time or thereafter, Takeda shall appoint a Divestiture Trustee. The appointment of the Divestiture Trustee shall take effect upon the commencement of the Trustee Divestiture Period.

22. The Trustee shall:

(a) at the time of appointment, be independent of Takeda and its Affiliated Undertakings;

(b) possess the necessary qualifications to carry out its mandate, for example have sufficient relevant experience as an investment banker or consultant or auditor; and

(c) neither have nor become exposed to a Conflict of Interest.

23. The Trustee shall be remunerated by Takeda in a way that does not impede the independent and effective fulfilment of its mandate. In particular, where the remuneration package of a Divestiture Trustee includes a success premium linked to the final sale value of the Divestment Business, such success premium may only be earned if the divestiture takes place within the Trustee Divestiture Period.

Proposal by Takeda

24. No later than two weeks after the Effective Date, Takeda shall submit the name or names of at least two natural or legal persons whom Takeda proposes to appoint as the Monitoring Trustee to the Commission for approval. No later than one month before the end of the First Divestiture Period or on request by the Commission, Takeda shall submit a list of one or more persons whom Takeda proposes to appoint as Divestiture Trustee to the Commission for approval. The proposal shall contain sufficient information for the Commission to verify that the person or persons proposed as Trustee fulfil the requirements set out in paragraph 22 and shall include:

(a) the full terms of the proposed mandate, which shall include all provisions necessary to enable the Trustee to fulfil its duties under these Commitments;

(b) the outline of a work plan which describes how the Trustee intends to carry out its assigned tasks;

(c) an indication whether the proposed Trustee is to act as both Monitoring Trustee and Divestiture Trustee or whether different trustees are proposed for the two functions.

Approval or rejection by the Commission

25. The Commission shall have the discretion to approve or reject the proposed Trustee(s) and to approve the proposed mandate subject to any modifications it deems necessary for the Trustee to fulfil its obligations. If only one name is approved, Takeda shall appoint or cause to be appointed the person or persons concerned as Trustee, in accordance with the mandate approved by the Commission. If more than one name is approved, Takeda shall be free to choose the Trustee to be appointed from among the names approved. The Trustee shall be appointed within one week of the Commission's approval, in accordance with the mandate approved by the Commission.

New proposal by Takeda

26. If all the proposed Trustees are rejected, Takeda shall submit the names of at least two more natural or legal persons within one week of being informed of the rejection, in accordance with paragraphs 19 and 25 of these Commitments.

Trustee Nominated by the Commission

27. If further proposed Trustees are rejected by the Commission, the Commission shall nominate a Trustee, whom Takeda shall appoint, or cause to be appointed, in accordance with a trustee mandate approved by the Commission.

II. Functions of the Trustee

28. The Trustee shall assume its specified duties and obligations in order to ensure compliance with the Commitments. The Commission may, on its own initiative or at the request of the Trustee or Takeda, give any orders or instructions to the Trustee in order to ensure compliance with the conditions and obligations attached to the Decision.

Duties and obligations of the Monitoring Trustee

29. The Monitoring Trustee shall:

(i) propose in its first report to the Commission a detailed work plan describing how it intends to monitor compliance with the obligations and conditions attached to the Decision.

(ii) oversee, in close co-operation with the Technical Expert and the Hold Separate Manager, the on-going management of the Divestment Business with a view to ensuring its continued economic viability, marketability and competitiveness and monitor compliance by the Parties with the conditions and obligations attached to the Decision. To that end the Monitoring Trustee shall:

(a) monitor the preservation of the economic viability, marketability and competitiveness of the Divestment Business, and the keeping separate of the Divestment Business from the businesses retained by the Parties, in accordance with paragraphs 9 and 10 of these Commitments;

(b) supervise the management of the Divestment Business as a distinct and saleable entity, in accordance with paragraph 11 of these Commitments;

(c) with respect to Confidential Information:

– determine all necessary measures to ensure that Takeda does not after the Effective Date obtain any Confidential Information relating to the Divestment Business

– in particular strive for the severing of the Divestment Business' participation in a central information technology network to the extent possible, without compromising the viability of the Divestment Business,

– make sure that any Confidential Information relating to the Divestment Business obtained by Takeda before the Effective Date is eliminated and will not be used by Takeda; and

– decide whether such information may be disclosed to or kept by Takeda as the disclosure is reasonably necessary to allow Takeda to carry out the divestiture or as the disclosure is required by law;

(d) monitor the splitting of assets and the allocation of Personnel between the Divestment Business and the Parties or Affiliated Undertakings;

(iii) propose to the Parties such measures as the Monitoring Trustee considers necessary to ensure the Parties' compliance with the conditions and obligations attached to the Decision, in particular the maintenance of the full economic viability, marketability or competitiveness of the Divestment Business, the holding separate of the Divestment Business and the non-disclosure of competitively sensitive information;

(iv) review and assess potential purchasers as well as the progress of the divestiture process and verify that, dependent on the stage of the divestiture process:

(a) potential purchasers receive sufficient and correct information relating to the Divestment Business and the Personnel in particular by reviewing, if

available, the data room documentation, the information memorandum and the due diligence process, and

(b) potential purchasers are granted reasonable access to the Personnel;

(v) act as a contact point for any requests by third parties, in particular potential purchasers, in relation to the Commitments;

(vi) provide to the Commission, sending the Parties a non-confidential copy at the same time, a written report within 15 days after the end of every month that shall cover the operation and management of the Divestment Business as well as the splitting of assets and the allocation of Personnel so that the Commission can assess whether the business is held in a manner consistent with the Commitments and the progress of the divestiture process as well as potential purchasers;

(vii) promptly report in writing to the Commission, sending the Parties a non-confidential copy at the same time, if it concludes on reasonable grounds that the Parties are failing to comply with these Commitments;

(viii) within one week after receipt of the documented proposal referred to in paragraph 18 of these Commitments, submit to the Commission, sending the Parties a non-confidential copy at the same time, a reasoned opinion as to the suitability and independence of the proposed purchaser and the viability of the Divestment Business after the Sale and as to whether the Divestment Business is sold in a manner consistent with the conditions and obligations attached to the Decision, in particular, if relevant, whether the Sale of the Divestment Business without one or more Assets or not all of the Personnel affects the viability of the Divestment Business after the sale, taking account of the proposed purchaser; and

(ix) assume the other functions assigned to the Monitoring Trustee under the conditions and obligations attached to the Decision.

30. The Monitoring Trustee may, if this is deemed necessary by the Monitoring Trustee,[1] be assisted and advised by the Technical Expert with regard to all technical questions related to the Divestment Business. Any information provided to the Monitoring Trustee may also be exchanged with the Technical Expert.

31. If the Monitoring and Divestiture Trustee are not the same legal or natural persons, the Monitoring Trustee and the Divestiture Trustee shall cooperate closely with each other during and for the purpose of the preparation of the Trustee Divestiture Period in order to facilitate each other's tasks.

Duties and obligations of the Divestiture Trustee

32. Within the Trustee Divestiture Period, the Divestiture Trustee shall sell at no minimum price the Divestment Business to a purchaser, provided that the Commission has approved both the purchaser and the final binding sale and purchase agreement (and ancillary agreements) as in line with the Commission's Decision and the Commitments in accordance with paragraphs 17 and 18 of these Commitments. The Divestiture Trustee shall include in the sale and purchase agreement (as well as in any ancillary agreements) such terms and

[1] Subject to the Commission’s view and final decision on the necessity of involving the Technical Expert.

conditions as it considers appropriate for an expedient sale in the Trustee Divestiture Period. In particular, the Divestiture Trustee may include in the sale and purchase agreement such customary representations and warranties and indemnities as are reasonably required to effect the sale. The Divestiture Trustee shall protect the legitimate financial interests of the Parties, subject to Takeda's unconditional obligation to divest at no minimum price in the Trustee Divestiture Period.

33. In the Trustee Divestiture Period (or otherwise at the Commission's request), the Divestiture Trustee shall provide the Commission with a comprehensive monthly report written in English on the progress of the divestiture process. Such reports shall be submitted within 15 days after the end of every month with a simultaneous copy to the Monitoring Trustee and a non-confidential copy to the Parties.

III. Duties and obligations of the Parties

34. The Parties shall provide and shall cause their advisors to provide the Trustee and the Technical Expert with all such co-operation, assistance and information as the Trustee may reasonably require to perform its tasks. The Trustee and the Technical Expert shall have full and complete access to any of the Parties or the Divestment Business's books, records, documents, management or other personnel, facilities, sites and technical information necessary for fulfilling its duties under the Commitments and the Parties and the Divestment Business shall provide the Trustee and the Technical Expert upon request with copies of any document. Takeda and the Divestment Business shall make available to the Trustee and the Technical Expert one or more offices on their premises and shall be available for meetings in order to provide the Trustee and the Technical Expert with all information necessary for the performance of its tasks.

35. The Parties shall provide the Monitoring Trustee with all managerial and administrative support that it may reasonably request on behalf of the management of the Divestment Business. This shall include all administrative support functions relating to the Divestment Business which are currently carried out at headquarters level. The Parties shall provide and shall cause their advisors to provide the Monitoring Trustee, on request, with the information submitted to potential purchasers, in particular give the Monitoring Trustee access to the data room documentation and all other information granted to potential purchasers in the due diligence procedure. The Parties shall inform the Monitoring Trustee on possible purchasers, submit lists of potential purchasers at each stage of the selection process, including the offers made by potential purchasers at those stages, and keep the Monitoring Trustee informed of all developments in the divestiture process.

36. Takeda shall grant or procure Affiliated Undertakings to grant comprehensive powers of attorney, duly executed, to the Divestiture Trustee to effect the sale (including ancillary agreements), the Closing and all actions and declarations which the Divestiture Trustee considers necessary or appropriate to achieve the sale and the Closing, including the appointment of advisors to assist with the sale process. Upon request of the Divestiture Trustee, Takeda shall cause the documents required for effecting the sale and the Closing to be duly executed.

37. Takeda shall indemnify the Trustee and its employees and agents and the Technical Expert (each an "**Indemnified Party**") and hold each Indemnified Party harmless against, and hereby agrees that an Indemnified Party shall have no liability to Takeda for, any liabilities arising out of the performance of the Trustee's and the Technical Expert's duties under the Commitments, except to the extent that such liabilities result from the wilful default,

recklessness, gross negligence or bad faith of the Trustee, the Technical Expert, its employees, agents or advisors.

38. At the expense of Takeda, the Trustee may appoint advisors (in particular for corporate finance or legal advice), subject to Takeda's approval (this approval not to be unreasonably withheld or delayed) if the Trustee considers the appointment of such advisors necessary or appropriate for the performance of its duties and obligations under the Mandate, provided that any fees and other expenses incurred by the Trustee are reasonable. Should Takeda refuse to approve the advisors proposed by the Trustee the Commission may approve the appointment of such advisors instead, after having heard Takeda. Only the Trustee shall be entitled to issue instructions to the advisors. Paragraph 37 of these Commitments shall apply mutatis mutandis. In the Trustee Divestiture Period, the Divestiture Trustee may use advisors who served Takeda during the Divestiture Period if the Divestiture Trustee considers this in the best interest of an expedient sale.

39. The Parties agree that the Commission may share Confidential Information proprietary to the Parties with the Trustee. The Trustee shall not disclose such information and the principles contained in Article 17 (1) and (2) of the Merger Regulation apply mutatis mutandis.

40. The Parties agree that the contact details of the Monitoring Trustee are published on the website of the Commission's Directorate-General for Competition and they shall inform interested third parties, in particular any potential purchasers, of the identity and the tasks of the Monitoring Trustee.

41. For a period of 10 years from the Effective Date the Commission may request all information from the Parties that is reasonably necessary to monitor the effective implementation of these Commitments.

IV. Replacement, discharge and reappointment of the Trustee

42. If the Trustee ceases to perform its functions under the Commitments or for any other good cause, including the exposure of the Trustee to a Conflict of Interest:

(a) the Commission may, after hearing the Trustee and the Parties, require Takeda to replace the Trustee; or

(b) Takeda may, with the prior approval of the Commission, replace the Trustee.

43. If the Trustee is removed according to paragraph 40 of these Commitments, the Trustee may be required to continue in its function until a new Trustee is in place to whom the Trustee has effected a full hand over of all relevant information. The new Trustee shall be appointed in accordance with the procedure referred to in paragraphs 19-26 of these Commitments.

44. Unless removed according to paragraph 42 of these Commitments, the Trustee shall cease to act as Trustee only after the Commission has discharged it from its duties after all the Commitments with which the Trustee has been entrusted have been implemented. However, the Commission may at any time require the reappointment of the Monitoring Trustee if it subsequently appears that the relevant remedies might not have been fully and properly implemented.

Section H. The review clause

45. The Commission may extend the time periods foreseen in the Commitments in response to a request from the Parties or, in appropriate cases, on its own initiative. Where the Parties request an extension of a time period, they shall submit a reasoned request to the Commission no later than one month before the expiry of that period, showing good cause. This request shall be accompanied by a report from the Monitoring Trustee, who shall, at the same time send a non-confidential copy of the report to the Parties. Only in exceptional circumstances shall the Parties be entitled to request an extension within the last month of any period.

46. The Commission may further, 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. This request shall be accompanied by a report from the Monitoring Trustee, who shall, at the same time send a non-confidential copy of the report to the Parties. The request shall not have the effect of suspending the application of the undertaking and, in particular, of suspending the expiry of any time period in which the undertaking has to be complied with.

Section I. Entry into force

47. The Commitments shall take effect upon the date of adoption of the Decision.

duly authorised for and on behalf of **Takeda Pharmaceutical Company Limited**

Date: 16 November 2018

duly authorised for and on behalf of **Shire plc**

Date: 16 November 2018

Schedule

1. The Divestment Business as operated to date has the following legal and functional structure:

(a) The Divestment Business forms part of Shire's Internal Medicine business unit, which encompasses gastrointestinal disease products, internal medicine products and pipeline assets;

(b) SHP 647 is under development by Shire in accordance with […] rights granted to Shire by Pfizer under the Pfizer Agreement. SHP 647 is now undergoing seven Phase III clinical trials for UC and CD (the "**Clinical Trials**") – with a […][2] – and […]. […][3], **Annexes 1** and **2** to this Schedule provide a description of the Clinical Trials with an indicative study timeline;

(c) The manufacturing process of SHP 647 incorporates intellectual property rights […] and additional manufacturing and quality-control related know-how […];

(d) The manufacturing of the finished SHP 647 is […];[4]

(e) The Clinical Trials are conducted for Shire in external medical institutions on a global basis;

(f) Shire has […];

(g) The development of SHP 647 is supported within Shire's organisation by a number of Affiliated Undertakings. […].

2. In accordance with Section B, paragraph 5 of these Commitments and subject to the Purchaser's option to agree with the Parties on a licence back to the Parties in respect of the right to manufacture and market SHP 647 in territories outside the EEA, the Divestment Business includes but is not limited to:

(a) The following main tangible assets (together with the intangible assets listed below the "**Transferred Assets**"):

(i) All relevant reports, data and analysis for the Clinical Trials including those resulting from the preclinical studies, in particular but not limited to the preclinical toxicology package, and including all reports on studies undertaken in relation to the mechanism of action, all relevant study plans and results for […] and the Clinical Study, and all relevant study plans for […];

(ii) Inventories of SHP 647 for use in the ongoing Clinical Trials, including raw materials, work in progress, drug substance (including SHP 647 API) and drug product, owned by and in the possession or control of Shire or Affiliated Undertakings;

(iii) All relevant regulatory files, including but not limited to the following: the current investigator brochure, the investigational medicinal product dossier (**IMPD**) and the protocol for the Clinical Trials and the Clinical Study, […],

2 For development for use in the treatment of UC and CD, […].

3 […].

4 […].

the Statistical Analysis Plan (**SAP**); minutes and correspondence regarding interactions with the regulators regarding SHP 647, including the scientific advice from the regulators;

(iv) All relevant books and records relating exclusively or predominantly to SHP 647; the books and records relating to SHP 647 that also relate to other products developed or to be developed by Shire or its Affiliated Undertakings, shall only be transferred to the extent that they relate to SHP 647, it being understood that the other sections shall be redacted prior to the transfer to the Purchaser;

(v) All documents, including but not limited, to the marketing plans and forecasts which are specific for SHP 647; the marketing plans and forecasts that also relate to other products developed or to be developed by Shire or its Affiliated Undertakings, shall only be transferred to the extent that they relate to SHP 647, it being understood that the other sections shall be redacted prior to the transfer to the Purchaser;

(vi) Any other assets identified by the Purchaser and the Parties in the asset purchase agreement or in the Variation Agreement as overseen by the Monitoring Trustee.

(b) The following main intangible assets:

(i) Right to conduct the Clinical Trials, […] and the Clinical Study, […], and rights to develop SHP 647 globally;

(ii) Right to manufacture, have manufactured and market SHP 647 globally;

(iii) Sponsorship of any and all current Clinical Trials and Clinical Study authorisations or other regulatory filings for SHP 647, including in relation to […][5];

(iv) Patents and patent applications (as listed in **Annex 3**), copyrights, data and know-how (including but not limited to the manufacturing and quality-control related know-how developed for SHP 647) existing as of the Closing date and relating exclusively or predominantly to the clinical development, manufacture or sale of SHP 647 (the "**In-Scope IP**"), subject to a non-exclusive, perpetual, irrevocable, royalty-free license-back to the Parties of any such rights that are shared with any Shire retained business; patents and patent applications, copyrights, data and know-how existing as of the Closing date that are not predominantly relating to the clinical development, manufacture or sale of SHP 647, will be subject to a non-exclusive, perpetual, irrevocable, royalty-free licence.

(v) The proposed "Ontamalimab" International Nonproprietary Name ("**INN**"), the proposed trade name […], prospective design rights and trademarks for the SHP 647 compound and the domain names listed in **Annex 4**.

(vi) Subject to having obtained all required regulatory and data protection consents, the Clinical Trials databases, which will be transferred at a date

5 […].

to be mutually agreed by the Purchaser and the Parties, as overseen by the Monitoring Trustee.

(c) The following main licences, permits and authorisations:

(i) The assignment of Shire's rights under of the Pfizer Agreement and in accordance with its terms. […];

(ii) All licences, permits and authorisations issued by any governmental organisation for the benefit of the Divestment Business. Since SHP 647 is still in the clinical trial phase, no permits or authorisation have been granted yet in relation to SHP 647, other than the authorisations with respect to the Clinical Trials and the […]. Similarly, no permits or authorisations have been granted yet in relation to […].

(d) The following main contracts, agreements, leases, commitments and understandings:

(i) Contracts with third parties existing as of the Closing date to the extent relating exclusively or predominantly to the development, manufacture and marketing of SHP 647. A list of the key third party contracts is attached in **Annex 5**. The Parties undertake to use best efforts to obtain all necessary third party consents where applicable. To the extent any such third party consent could not be obtained, or any other contract could not be otherwise transferred, the Parties will, as appropriate, either work with the Purchaser and relevant third party to put in place arrangements to transfer any work product and work in process and support the Purchaser to put in place alternative arrangements, or seek to enter into, for a transitional period of up to […], back-to-back agreements with the Purchaser on the same terms and conditions of the contracts for which the third party consent could not be obtained, or of the contracts which could not be transferred. The […] period may be extended by the Monitoring Trustee for a further period of up to […] if the Purchaser demonstrates delays in securing regulatory approvals required to market SHP 647 in an EEA country.

(e) The following customer, credit and other records:

(i) Since SHP 647 is still in clinical trial phase, it is not yet being supplied for commercial use to customers;

(ii) The Parties will provide the full list of Key Opinion Leaders for SHP 647 on the date of Closing to the Purchaser.

(f) The Key Personnel listed in **Annex 6**.

(g) The Personnel listed in **Annex 7**. For a period of […] after Closing, the Purchaser shall have the opportunity to interview such employees and enter into employment contracts with employees (should the SHP 647 Purchaser wish to do so).

(h) The arrangements for the supply with the following products or services by the Parties:

(i) The arrangements for the provision of transitional services at cost, for a transitional period of up to […] after Closing, including technical assistance, that are currently supplied by Shire to the Divestment Business. At the

Purchaser's request, this period can be extended for a mutually agreed period as overseen by the Monitoring Trustee;

(ii) In addition to the SHP 647 API which is being transferred as part of the inventory, and at the option of the Purchaser, the Parties shall enter into a transitional supply agreement for the SHP 647 API for up to […]. Such transitional arrangement will be at cost and shall include appropriate provisions designed to ensure the continued supply by the Parties to the Purchaser;

(iii) At the option of the Purchaser, reasonable support to the Purchaser, or its designated third-party organisation, in qualifying and gaining regulatory approvals for the manufacturing of SHP 647;

(iv) The arrangements for the Parties to continue to act as a sponsor for all clinical trials underway for a period until Closing, it being understood that the Parties will continue all activities related to those clinical trials according to the plans existing at the Effective Date, in particular as set out in the schedule of milestones attached as **Annex 2**, as overseen by the Monitoring Trustee. At the Purchaser's request, with respect to any clinical trial, the above-mentioned period can be extended for a mutually agreed period, subject to a reasonable service fee to be agreed with the Purchaser, as overseen by the Monitoring Trustee;

(v) In addition, at the request of the Purchaser, the Parties, will undertake the transfer of SHP 647 manufacturing technology (i.e., the manufacturing and quality-control related know-how developed for SHP 647) to a facility of the Purchaser's choice in order to enable the Purchaser to manufacture SHP 647 or have it manufactured at launch of SHP 647 at the latest. At the request of the Purchaser, Shire will also assist the Purchaser in transferring technical information and know-how to the Purchaser itself or to a potential third party manufacturer; and

(vi) Until closing of the Takeda/Shire Transaction, Shire will continue in full all its interactions with […] in relation to SHP 647, and commits to support the ongoing work of […] in the way provided for in the contracts concluded between Shire and […] and in the spirit of this pre-existing commercial arrangement. In particular, and in accordance with the relevant contractual delegation of responsibilities, Shire will provide all information required by […], respond promptly to enquiries including those related to safety, pharmacovigilance and medical monitoring, review, contribute to and approve reports where appropriate, provide approvals where needed, take responsibility for decisions deferred to it, support Shire staff working with […], conduct oversight and monitoring activities, draft and submit, or cause to be submitted, submissions to health authorities as appropriate, manage matters related to site agreements, providing content for regulatory documentation, and carry out any other duties relating to its cooperation with […] in the way it would have done prior to any consideration of divesting the SHP647, in line with standard practice and as overseen by the Monitoring Trustee. Following closing of the Takeda/Shire Transaction, Takeda will fulfil all the duties as described in this paragraph, as overseen

by the Monitoring Trustee, until Closing or otherwise agreed in line with paragraph 2(h)(iv) of this Schedule to the extent applicable.

(vii) Prior to the closing of the Takeda/Shire Transaction, Shire commits to finalize […] in cooperation with […], in a manner that […] can continue […] during the transitional period as originally scheduled with Shire prior to the Effective Date. For the avoidance of doubt, the Purchaser shall be free to […].

3. In the event that materials to be transferred contain information that is confidential to the Parties' retained businesses and not relevant for the Divestment Business, the information shall be redacted as appropriate. The Divestment Business shall not include:

(a) any right, title or interest in or to any of the assets of Shire or Affiliated Undertakings other than those specified in paragraph 2 of this Schedule and, for the avoidance of doubt, will not include:

(i) the name "Shire", together with all variations thereof and all trademarks, service marks, domain names, trade names, trade dress, corporate names, logos and other identifiers of source containing, incorporating or associated with any of the foregoing, save as provided for in paragraph 2 of this Schedule;

(ii) any plant, tangible property or equipment of Shire or Affiliated Undertakings;

(iii) any right to manufacture, market or sell any product other that SHP 647 or any license to use any asset of Shire in connection with any product other than SHP 647;

(iv) any asset that is not a Transferred Asset and any asset that does not relate to the clinical development or sale of SHP 647; and

(v) accounts receivable, pre-paid expenses and any case or cash equivalents of Shire or Affiliated Undertakings.

(b) In the event that the Parties and the Purchaser agree on a licence back to the Parties in respect of the right to manufacture and market SHP 647 in territories outside the EEA, the relevant rights, title and interests in SHP 647s in territories outside the EEA, or ancillary assets and the rights to or license for certain technologies, needed to manufacture and market SHP 647 in territories outside the EEA. For the avoidance of doubt, the Purchaser shall remain free to manufacture or have manufactured SHP 647 (including its active ingredient) at one or more facilities, of its own or of a third party, of its choice.

4. The Parties commit that the assets to be transferred are sufficient for the Purchaser to continue the development and, depending on the outcome of the clinical trials, ultimately commercialise SHP 647, enabling the Purchaser to operate the Divestment Business as a viable and independent business in the EEA.

5. If there is any asset or personnel which is not be covered by paragraph 2 of this Schedule but which is both used (exclusively or not) in the Divestment Business and necessary for the continued viability and competitiveness of the Divestment Business, that asset or adequate substitute will be offered to potential purchasers, by transfer or license, as appropriate as overseen by the Monitoring Trustee.

Annex 1

Shire Sponsored Clinical Trials for SHP 647

NCT Number / Sponsor's Protocol Code Number / EudraCT Number	Description	Condition studied	Phase
NCT03283085 / SHP647-304 / 2017-000574-11	A Safety Extension Study of SHP647 in Subjects With Moderate to Severe Ulcerative Colitis or Crohn's Disease (AIDA)	CD UC	Phase III
NCT03627091 / SHP647-307	Efficacy and Safety of SHP647 as Maintenance Treatment in Participants With Moderate to Severe Crohn's Disease (CARMEN CD 307)	CD	Phase III
NCT03566823 / SHP647-306	Efficacy and Safety Study of SHP647 as Induction Therapy in Participants With Moderate to Severe Crohn's Disease (CARMEN CD 306)	CD	Phase III
NCT03559517 / SHP647-305	Efficacy and Safety Study of SHP647 as Induction Therapy in Participants With Moderate to Severe Crohn's Disease (CARMEN CD 305)	CD	Phase III
NCT03290781 / SHP647-303 / 2017-000573-37	Study of the Effect of SHP647 as Maintenance Treatment in Participants With Moderate to Severe Ulcerative Colitis Who Achieved Clinical Response in Induction Studies	UC	Phase III
NCT03259334 / SHP647-301 / 2017-000599-27	A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects With Moderate to Severe Ulcerative Colitis (FIGARO UC 301)	UC	Phase III
NCT03259308 / SHP647-302 / 2017-000572-28	A Phase 3 Randomized, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of SHP647 as Induction Therapy in Subjects With Moderate to Severe Ulcerative Colitis (FIGARO UC 302)	UC	Phase III

Annex 2

Indicative SHP 647 Study Timeline

[…]

Annex 3

SHP 647 Patents and patent applications*

[…]

* […]

Annex 4

Domain Names

[…]

Annex 5

List of key identified third party contracts

1. Unless otherwise specified in the table below, master agreements are […]. Many of Shire's Statement of Works ("**SOWs**") relating to the SHP647 program […]. Similarly, each SOW must have […].

2. Where contracts that cannot be assigned to the Purchaser pursuant to their terms or because the scope of the contract includes products or services not related to the Product, the Parties will use their best efforts to assist the Purchaser in putting in place appropriate alternative arrangements with the relevant third parties, for example:

    a. entering into back-to-back agreements; or

    b. as Shire has done previously, work with the relevant counterparty and the Purchaser to put in place a new master agreement, and then transfer ownership of any work product and work in process under a SOW to the Purchaser. The Parties would then support the Purchaser in putting in place alternative arrangements specific to the ongoing development of the Product, such as an equivalent SOW.[6]

3. Aside from master agreements and SOWs, there are various other ancillary agreements relating to the SPH647 program, such as Clinical Trial Agreements and patient Informed Consents[7]. […].

A. <u>Key supply contracts</u>

[…][8]

B. <u>List of active MAdCAM Clinical Trial Agreements</u>

[…]

6 For raw material contracts, the Parties would seek to transfer the relevant specification and approved vendor information to the Purchaser. As appropriate, the Parties will use best efforts to assist the Purchaser in putting in place appropriate agreements with the relevant third parties.

7 A list of active Clinical Trial Agreements is provided at "B" below.

8 […].

Annex 6

Key Personnel

Name	Role	Location	Allocation of time spent on SHP 647
[…]	Inflammatory Bowel Disease (“IBD”): Product Strategy Lead […][9]: New Products Lead	[…]	[…]
[…]	Global Development Lead	[…]	[…]
[…]	Global Clinical Development Lead - UC	[…]	[…]
[…]	Global Clinical Development Lead - CD	[…]	[…]
[…]	Biostatistics Project Lead	[…]	[…]
[…]	Global Program Manager	[…]	[…]
[…]	IBD: Global Regulatory Lead […]: Regulatory Affairs	[…]	[…]
[…]	Clinical Pharmacology Lead/Global Clinical Operations Lead	[…]	[…]
[…]	IBD: Chemistry Manufacturing &Control […]: Technical Operations	[…]	[…]

9 […].

Annex 7

List of Personnel for SHP647 program[10]

[…]

10 […].