CASE AUTH/3582/11/21

ABBVIE v GALAPAGOS

Jyseleca (filgotinib) promotional website

AbbVie Ltd complained about claims on the www.strengthofbalance.co.uk website produced by Galapagos Biotech Ltd relating to Jyseleca (filgotinib) in rheumatoid arthritis (RA).

AbbVie referred to particular claims presented on the Jyseleca www.strengthofbalance.co.uk website ('Safety' section UK-INF-2020-11-0063 and 'At a glance' section UK-INF-2020-11-0066). The website stated that it was intended for health professionals in the UK and Ireland and, in AbbVie's view, the claims at issue were not consistent with the requirements of the Code. AbbVie's concerns related to the robustness of the safety and sustained efficacy data supporting promotional claims.

AbbVie stated that it engaged in inter-company dialogue with Galapagos to resolve the issues, and had made progress, however, resolution had ultimately been unsuccessful. AbbVie stated that Galapagos had not adhered to the proposed timelines to update or withdraw materials as agreed with AbbVie.

1 'Safety' messaging

Strength of balance website (https://strengthofbalance.co.uk/safety) – Safety page (UK-INF-2020-11-0063, March 2021, last accessed 15 November 2021)

1.1 General concerns regarding the portrayal of safety data for Jyseleca on the safety page

AbbVie stated that the only adverse data that were shown on the 'Safety' tab of the website was what was deemed to be stated as Janus Kinase (JAK) inhibitor associated adverse events, with all other adverse event data, including the most frequently reported adverse events as listed in the Jyseleca SPC not shown at all. Despite the fact that there were RMM [Risk Minimisation Materials] associated with Jyseleca, there was no clear reference to the materials or the safety concerns and information highlighted in those materials which included serious infections, potential effects on male fertility, potential risks of major adverse cardiovascular events, and prescribing in the very elderly (75 years and above), on the safety page.

Other data such as common or serious adverse events were presented on the 'MOA [Mechanism of Action] & Dosing' page. However, as this information was in different places on the website, it was important to provide clear direction to health professionals where additional information could be found. AbbVie alleged that the way it was portrayed on the website did not satisfy the requirement that the prescriber should be able to form a reasonable impression of the medicine by reading the information.

The detailed response from Galapagos is given below.

The Panel noted that in its letter of 20 August 2021, Galapagos stated that the website would be undergoing an update following the transition of commercialisation responsibilities from Gilead to Galapagos and whilst there had been no intention to downplay any safety concerns, the safety data detailed on the site would be amalgamated in a single location accessed via the 'Safety' section. The Panel further noted that whilst Galapagos did not accept that the absence of a link from the 'Safety' page to the 'Resources' page constituted a breach of the Code, in the same letter of 20 August 2021 Galapagos agreed that providing a link from the 'Safety' section to the risk minimisation materials would increase their visibility and stated that as part of the website update, additional links to RMP materials would be added to the 'Safety' section. The Panel noted that Galapagos had committed to complete the changes in November 2021, as outlined in its letter to AbbVie dated 20 October 2021 and acknowledged by AbbVie in its email of 27 October 2021. The Panel therefore considered that at the time the complaint was submitted by AbbVie (15 November 2021), this matter had been settled during inter-company dialogue, and therefore it did not consider the allegations in relation to general concerns regarding the portrayal of safety data for Jyseleca on the safety page as set out in Point 1.1.

1.2 Claim 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2'3'].

AbbVie alleged that the claim was not supported by the references to the data in the table below the claim. 'Low' was related to adverse events with a frequency <1% and >0.1%. Not all the rates listed in the table fell within this categorization, which was inaccurate. At the foot of the table the explanation for the asterisk with further references was provided which made the interpretation of the table and its data misleading and ambiguous.

The detailed response from Galapagos is given below.

The Panel noted that the asterisk to the claim 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3'] took the reader to a very small footnote at the bottom of the webpage, beneath the highlighted box which housed the table and a separate footnote, which read 'Based on AE rates observed as "Uncommon" (<1% and >0.1%) or of lower frequency in the Jyseleca clinical trials'. The Panel noted that the claim at issue was referenced to the Genovese *et al* poster presented at the EULAR e-congress 2020 and Data on File, whilst the footnote was referenced to the Jyseleca SPC and Genovese *et al* poster presented at the EULAR e-congress 2020.

The Panel noted Galapagos' submission that even though the table included some information for adverse events with a higher rate, it did not mean that the information was misleading; the table contained data from individual studies that were included in the integrated safety analysis as stated in the text underneath the table. The Panel noted that beneath the table within the same highlighted box it stated '52-week exposure dataset: DARWIN 1 and 2 and FINCH 1-3 studies were integrated to represent the safety of JYSELECA 200mg in controlled clinical studies up to Week 52'. The Panel further noted Galapagos' submission that the inclusion of these data ensured that the information

presented was complete and would enable the recipients to develop their own informed opinion.

The Panel noted that the table would not be viewed in isolation but within the context of the page overall including, particularly, its subheading, 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3]' which introduced the table and was the claim at issue. The matter was further complicated by the footnote in small print at the bottom of the webpage. It was an established principle of the Code that claims could not be qualified by footnotes if such footnotes were necessary to ensure that a claim complied with the Code. In such circumstances, the footnote should be part of the claim at issue or within its immediate visual field. Whilst noting Galapagos' submission about the completeness of the data in the table, the Panel considered that some readers, on the balance of probabilities, might nonetheless assume, based on the subheading at issue including the unqualified phrase 'low rates', that the adverse events in the table immediately beneath were all of low incidence and that was not necessarily so. In the Panel's view, this was so, irrespective of the location of the footnote. The Panel considered that the claim in question within the context of the webpage, including the table, was misleading and ambiguous as alleged. A breach of the Code was ruled.

The Panel considered that the implication of the unqualified claim within the context of the webpage was incapable of substantiation and a breach of the Code was ruled.

1.3 Claim 'Similar observed rates of serious infections, herpes zoster and VTE [Venous thromboembolism] compared to adalimumab[2,3]'.

AbbVie alleged that with regard to herpes zoster rates compared to adalimumab, the references did not provide sufficient substantiation and might downplay the important safety considerations of herpes zoster rates for rheumatoid arthritis (RA) patients.

Based on the information made available to AbbVie, the company alleged that the claim could not be substantiated by the references provided.

AbbVie noted that the claim was also present on the 'At a Glance' page of the website and alleged that it was similarly in breach of the Code.

The detailed response from Galapagos is given below.

The Panel noted Galapagos' submission that the references accurately portrayed the results of clinical trials and that the publications had undergone peer review and had been subjected to the usual scientific scrutiny. The Panel noted Galapagos' submission that AbbVie accepted in its complaint letter that the confidence intervals in the stated studies overlapped and that the studies were not powered to compare adverse event differences.

The Panel further noted Galapagos' submission that the studies showed comparable absolute numbers. Galapagos agreed with AbbVie's conclusions in this respect and, therefore, in its view, the data from these studies substantiated its use of the term 'similar'.

The Panel noted that the claim at issue was referenced to Genovese MC, *et al.* Poster presented virtually at the European League Against Rheumatism (EULAR) 2020 E-Congress, June 3-6, 2020 and data on file. Figure 2 included herpes zoster: 1.4 for filgotinib 200mg and 0.9 for filgotinib 100mg vs adalimumab (0.7) at 52 weeks. The Panel noted that the discussion section stated 'With filgotinib, EAIR of serious infections and herpes zoster were generally similar to adalimumab and MTX'. No limitations of the study appeared to be included in the poster. The Panel noted that the Data on File included, *inter alia*, the herpes zoster data for filgotinib 100mg and 200mg QD with no reference to herpes zoster in relation to adalimumab.

The Panel noted Galapagos' submission that the statement could also be substantiated by more recent publications such as Winthrop and Alves. The Panel noted that it was possible to substantiate a claim by studies supplemental to those cited.

The Panel noted that in Winthrop which, according to the paper, appeared to be received for publication in May 2021 and accepted in September 2021, Exposure-adjusted incidence/event rates for herpes zoster were determined in patients receiving UPA [upadacitinib] (monotherapy or combination therapy) in six randomised phase III trials (data cut- off on 30 June 2020). Herpes Zoster incidence and event rates were also determined in patients receiving MTX monotherapy or adalimumab (ADA) + MTX. Multivariable Cox regression analysis was used to identify herpes zoster risk factors in UPA- treated patients. The Panel noted that filgotinib was not included within the study, upadacitinib was included and appeared to be an AbbVie medicine. The study authors stated that given the lack of direct comparison of head-to-head studies between JAK inhibitors, they were limited in drawing conclusions regarding the relative risk of herpes zoster with UPA as compared with other JAK inhibitors, including filgotinib.

The Panel noted that Alves, a systematic review and network meta-analysis, stated that, compared with filgotinib, adalimumab had an increased risk of herpes zoster infection (4.81; 95% CI, 1.39-16.66). It further stated, however, that although the initial results suggested that filgotinib could have a reduced risk of herpes zoster, the sensitivity analyses did not support those findings. Risk differences between the drugs became statistically non-significant when the sensitivity analysis was conducted.

Whilst the Panel had concerns about the page as a whole, it noted that the allegations appeared to be limited by AbbVie to substantiation of the claim in question by specific studies rather than the broader issues that potentially came within the clauses cited by AbbVie and the matter was considered on that basis.

The Panel considered that whilst neither the data on file the claim was referenced to, or Winthrop, substantiated the claim in question, Genovese *et al* 2020, the abstract the claim was referenced to and Alves could, on the balance of probabilities, substantiate the claim with regard to similar observed rates of herpes zoster compared to adalimumab. The Panel therefore, on this very narrow ground, ruled no breach of the Code in relation to the claim at issue and substantiation on the safety page and the 'at a glance' page. Noting it's no breach ruling in relation to substantiation, the Panel did not consider that the claim was misleading based on the very narrow allegation that it could not be substantiated, no breach of the Code was ruled.

1.4 Safety and high standards

AbbVie alleged that the issues in Points 1.1, 1.2 and 1.3 raised serious concerns about the balance of safety and efficacy information portrayed regarding Jyseleca in Galapagos' promotional materials.

AbbVie took patient safety extremely seriously and alleged that the portrayal of the safety profile of Jyseleca was insufficient to enable health professionals to appropriately evaluate the risk-benefit profile of prescribing Jyseleca. The information provided by Galapagos was misleading, incomplete and downplayed the safety concerns associated with the product. In addition to the above mentioned aspects, AbbVie alleged that high standards in preparing promotional materials had not been maintained.

The detailed response from Galapagos is given below.

The Panel noted that it had made no ruling about the matter raised at Point 1.1 above and which was therefore not relevant to the consideration of this point.

The Panel noted its comments and rulings above at Point 1.2, and its concerns regarding the safety page. It considered that, overall, high standards had not been maintained in this regard and a breach of the Code was ruled.

2 Sustained efficacy messaging

Strength of balance website (https://www.strengthofbalance.co.uk/summary) – At a Glance page (UK-INF-2020-11-0066, March 2021, last accessed 15 November 2021)

The 'At a glance' page was headed 'SUSTAINED EFFICACY' followed by 'In Phase 3 trials, Jyseleca demonstrated':

> **ACR20 response as early as Week 2 in 37% of patients (n=475) vs. 15% of patients in the MTX+ placebo group (n=475; p<0.001)[2].**
>
> **ACR70 response in 44% of patients by Week 52 (n=475)[2].**
>
> **DAS28-CRP <2.6 remission sustained up to Week 52 in 54% of patients (n=475)[3].**
>
> **Zero radiographic progression* at Week 52 in 88% of patients (n=475) vs. 82.4% for adalimumab patients (n=325)[4].**

AbbVie alleged that the information provided fell short of the relevant Code requirements for a number of reasons:

- **Firstly, there was a lack of explanation regarding the study description, primary endpoint, and it was not clearly stated that these data were for the filgotinib 200mg dose only.**
- **Secondly, it had not consistently been made clear what the comparator arm was (which was missing for the 2nd and 3rd bullet points).**
- **Thirdly, there were no statistical methods and p-values provided for the 2nd, 3rd or 4th bullet points.**

In this way, it was not possible 'At-a-glance' to determine if the percentages quoted were simply a statement of numerical value, or whether in fact, they had statistical significance and potential clinical benefit to the patient. Because there was a woeful lack of context to these claims, even allowing for the fact that they appeared on a 'summary' page, AbbVie believed this was a clear breach of the Code.

The detailed response from Galapagos is given below.

The Panel noted that the four bullet points on the 'At a glance' webpage were referenced to three separate data on file. The Panel noted that it did not have these data on file before it.

The Panel noted Galapagos' submission that the details of the study were provided in detail on the 'Efficacy' pages of the website. According to Galapagos, the bullet points beneath the headline claim were accompanied by a statement that clearly referred to the efficacy measures used, ie ACR20 and ACR70 and the 'Efficacy' page provided additional information, with tabs with clear graphs showing the evolution of response at various timepoints in FINCH 1, FINCH 2 and FINCH 3. Additional information about the studies was available via a box beneath the graphs entitled 'Study Details'. These 'Efficacy' pages also showed the timepoints at which the response was observed, ie Week 2, and over what period it was observed, ie 52 weeks. Radiographic progression was measured after a specified period, in the case of FINCH 3: 52 weeks, against a baseline examination. The Panel noted that it did not have access to the linked information via the 'Study Details' link.

Galapagos also stated that the claim was substantiated by the EPAR which stated that the absolute number of responders in the filgotinib 200mg-group increased from week 12 to week 24 and did not decrease from week 24 to week 52. Galapagos submitted that since the claim was not comparative, it was not necessary to state the comparator. The claims related to Jyseleca, not its relative performance. The Panel further noted Galapagos' submission that with respect to the lack of statistical method and p values, these were not a requirement of the Code. The statements were factually correct and were substantiated by the additional information on the linked pages. Therefore, the website did not mislead the reader.

The Panel noted Galapagos' reference to qualifying information elsewhere on the website and considered that each webpage should not be misleading if read in isolation. It was, of course, acceptable to have a page summarising data presented elsewhere but companies had to be particularly careful that such summary pages, nonetheless, complied with the Code and did not rely on data elsewhere to ensure Code compliance.

The Panel noted that whilst the first and last bullet points were comparative, the middle two were not and noted Galapagos' submission in that regard. Nonetheless, the Panel noted that given the first and fourth bullet points were comparative, some readers might consider the second and third bullet points in that light and assume that the data was favourable to Jyseleca and that was not necessarily so in relation to the 52 week data referred to. The Panel noted Galapagos' submission that specifying the dose was not required as 200mg was the licensed dose and the 100mg dose was only appropriate for specialist populations which was explained in detail on the 'Mechanism of Action & Dosing' page. In this regard, the Panel noted that within the website, the dose was not

stated at the top of pages which discussed clinical data and considered that it was relevant to the clinical outcomes and in this regard, considered that it would be helpful and relevant to state the dose in relation to the claims in question. The Panel noted that Jyseleca was indicated in combination and in monotherapy and in this regard, particularly given that the efficacy section discussed certain monotherapy data, considered that the claims in question, on a page that aimed to summarise the efficacy section, should be clear whether they related to combination or monotherapy treatment. In relation to the bullet point 'Zero radiographic progression* at Week 52 in 88% of patients (n=475) vs. 82.4% for adalimumab patients (n=325)', the relevant section within the efficacy page, Radiographic progression, stated as a footnote that 52 week data were not controlled for multiplicity, therefore treatment differences could represent chance findings. In the Panel's view, readers would assume that the bullet point on the page in question referred to statistically significant data at 52 weeks unless they were told clearly otherwise and that was not so. The Panel did not have a copy of the relevant studies but on the basis of the limited information on the website considered that the page in question on the 'At a glance webpage' was incomplete and misleading such that readers did not have sufficient information to form their own therapeutic value of the medicine and a breach of the Code was ruled. The Panel considered that high standards had not been maintained in this regard and a breach of the Code was ruled.

3 OVERALL CLAUSE 2

In summary, AbbVie alleged breaches of several clauses of the Code. Furthermore, due to the nature of the breaches, ie primarily focused around patient safety, combined with Galapagos not adhering to the agreements and spirit of the inter-company dialogue, AbbVie took the view that the PMCPA should also consider a breach of Clause 2.

The detailed response from Galapagos is given below.

The Panel noted the particular circumstances of this case and the evidence before it. The Panel did not consider that AbbVie had established, on balance of probabilities, that Galapagos did not adhere to the spirit of inter-company dialogue, as alleged.

The Panel further noted its comments and rulings above, including its rulings of a breach of the Code to reflect that high standards had not been maintained. The Panel noted that despite its concerns detailed at Point 1.2 above, it noted that the adverse event rates were given in the table in question at Point 1.2. The Panel considered that its ruling of a breach for failing to maintain high standards adequately covered its concerns on this point. On balance, the Panel did not consider that the complainant had established that patient safety had been prejudiced as referred to in the supplementary information to Clause 2 of the Code as alleged. In the particular circumstances of this case, the Panel therefore, and on balance, ruled no breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

AbbVie Ltd complained about claims on the www.strengthofbalance.co.uk website produced by Galapagos Biotech Ltd relating to Jyseleca (filgotinib) in rheumatoid arthritis (RA).

Jyseleca was indicated, *inter alia*, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who had responded inadequately to, or who were intolerant to, one or

more disease modifying anti-rheumatic drugs (DMARDs). It could be used as monotherapy or in combination with methotrexate (MTX).

AbbVie's product Humira (adalimumab) was indicated, *inter alia*, in combination with methotrexate for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs, including methotrexate, has been inadequate and the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

ABBVIE GENERAL COMMENTS ON INTER-COMPANY DIALOGUE AND BACKGROUND

AbbVie referred to particular claims presented on the Jyseleca www.strengthofbalance.co.uk website ('Safety' section UK-INF-2020-11-0063 and 'At a glance' section UK-INF-2020-11-0066). The website stated that it was intended for health professionals in the UK and Ireland and, in AbbVie's view, the claims at issue were not consistent with the requirements of the Code. AbbVie's concerns related to the robustness of the safety and sustained efficacy data supporting promotional claims.

AbbVie stated that it engaged in inter-company dialogue with Galapagos to resolve the issues, and had made progress, however, resolution had ultimately been unsuccessful. AbbVie stated that Galapagos had not adhered to the proposed timelines to update or withdraw materials as agreed with AbbVie at a face-to-face meeting (1 October 2021) and subsequently formalised in a letter to AbbVie (20 October 2021).

AbbVie provided a chronological order of events of the inter-company dialogue (ICD).

AbbVie noted that Galapagos was not a member of the Association of the British Pharmaceutical Industry (ABPI) and therefore was not under a clear obligation to abide by the ABPI Code. AbbVie noted that during the inter-company dialogue, Galapagos stated that it had agreed to comply with the Code and accept the jurisdiction of the Prescription Medicines Code of Practice Authority (PMCPA) and took the obligation to comply with the ABPI Code very seriously. Given the seriousness of the aspects raised to the PMCPA's attention by way of this complaint, in AbbVie's view, the PMCPA ought to ensure that Galapagos conducted its promotional activities in a responsible, ethical and professional manner, in line with the high standards applicable across the UK industry.

In conclusion, AbbVie stated that, as per the inter-company dialogue letter dated 20 October 2021, Galapagos had agreed to send a website update for review to AbbVie within 10 business days from the day of the meeting and would have the website fully agreed with AbbVie and updated by the end of October 2021 or otherwise take down the website until the necessary updates could have been implemented.

AbbVie stated that despite acknowledging the legitimacy of AbbVie's concerns, as of the date of the complaint (15 November 2021), Galapagos had still not adhered to the agreed timelines: no updated website information had been provided to AbbVie for review, as agreed during the inter-company dialogue, and the website itself had neither been updated, nor taken offline pending amendment.

AbbVie was very disappointed that Galapagos had chosen to ignore its written undertakings given to AbbVie as part of the inter-company dialogue. Additionally, given the significant period

of time (approximately five months) that had lapsed between the time when AbbVie first raised its concerns with Galapagos and the date of this complaint, it believed Galapagos was acting in clear violation of the spirit of inter-company dialogue, which was meant to enable companies to achieve a time-efficient and mutually acceptable resolution of their concerns, for the benefit of patients and the reputation of the industry as a whole, and without placing an undue burden on PMCPA resources.

GALAPAGOS' COMMENTS ON INTER-COMPANY DIALOGUE AND GENERAL COMMENTS

Galapagos was surprised and disappointed by AbbVie's escalation of the complaint to the PMCPA, in view of the progress made towards reaching an agreement during inter-company dialogue and in circumstances where the time agreed for implementation of changes had not expired.

Galapagos strongly disagreed with AbbVie's characterisation of Galapagos' approach to inter-company dialogue. Within the context of inter-company dialogue, at a face-to-face meeting on 1 October 2021, Galapagos agreed to make changes to the website. These were to be completed in November 2021, rather than by the end of October 2021 as incorrectly stated in the draft meeting notes of 6 October 2021 provided by AbbVie. This timeline commitment was reiterated by Galapagos in a letter dated 20 October 2021 and acknowledged by AbbVie on 27 October 2021.

Therefore, as a preliminary matter, AbbVie's assertion that Galapagos had failed to adhere to the agreement reached in relation to the website was misleading, and the complaint letter of 15 November, which claimed that Galapagos agreed to revise the website before the end of October 2021, overtly misrepresented Galapagos' letter of 20 October 2021 and the associated commitment.

Despite AbbVie's submission of a complaint to the PMCPA, Galapagos had continued to implement the changes agreed during inter-company dialogue and the updated version of the website went live on 30 November 2021. As AbbVie declined to wait until the website had been updated within the timelines agreed with Galapagos to assess whether such changes resolved the dispute between the companies, AbbVie's approach was inconsistent with a genuine commitment to inter-company dialogue and imposed unnecessary burden on the PMCPA.

Inter-company dialogue

Galapagos noted that although the full set of inter-company dialogue was listed by AbbVie, it did not appear to have been provided to the PMCPA and Galapagos therefore provided it. Galapagos submitted that from the correspondence, the issues raised by AbbVie had evolved and that not all points had been in discussion since June as AbbVie asserted.

Galapagos summarised the history of the inter-company dialogue.

In summary, Galapagos stated that the inter-company dialogue process to date had included two rounds of correspondence, prior to a face-to-face meeting on 1 October 2021 and a final round of written exchanges. Galapagos participated in this process in a professional manner, with a genuine wish to understand AbbVie's concerns and reach an acceptable resolution.

Following the initial correspondence, agreement was reached on the majority of issues.

The face-to-face discussions on 1 October 2021 were scheduled with a view to resolving the remaining issues between the companies. At that meeting, it was suggested that copies of the proposed website changes should be provided to AbbVie for its approval.

Galapagos subsequently determined that it would not be appropriate to submit its material to a competitor for 'approval'. This was communicated in Galapagos' letter of 20 October 2021. Galapagos did not believe this point to be inconsistent with the spirit of inter-company dialogue, in that inter-company dialogue did not require a respondent to obtain advance approval of its material by a competitor complainant. Galapagos communicated its considered position to AbbVie promptly and transparently. Contrary to AbbVie's assertions, Galapagos had not ignored its written commitment as set out in the letter dated 20 October 2021 but had complied with it in all respects.

Galapagos stated that it had engaged in inter-company dialogue in good faith throughout the process. As the initial wide-ranging concerns raised by AbbVie had narrowed, Galapagos believed this demonstrated there was clear progress in the inter-company dialogue.

Galapagos restated its commitment to the Code. Galapagos fully supported the principles of self-regulation and the associated requirement to benefit patients by operating in a professional, ethical and transparent manner to ensure the appropriate use of medicines and support the provision of high-quality healthcare.

Background to Janus Kinase (JAK) inhibitors

Galapagos submitted that RA was a complex, heterogenous and progressive systemic autoimmune disease that affected the joints as well as numerous other organs of the body. Treatments for RA targeted the dysregulation of the immune system, reducing inflammation and thereby restoring balance.

Galapagos submitted that there were several classes of medicinal products routinely used to treat RA, namely: conventional synthetic Disease Modifying Anti-Rheumatic Drugs (cDMARDs); and advanced therapies, which encompassed both biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) that had been available for some time, and newer targeted synthetic Disease Modifying Anti-Rheumatic Drugs (tsDMARDs) including JAK inhibitors (JAKi).

There were several medicines available within each of these categories, with differing mechanisms of action.

However, all DMARDs exerted their therapeutic effects by targeting aspects of the immune system and required routine monitoring. Therefore, DMARD therapy should be initiated by a physician experienced in the treatment of RA and patients should be managed in secondary care by multi-disciplinary health teams (MDTs).

Galapagos stated that bDMARDs included tumour necrosis factor inhibitors (TNFi), which were commonly used as first line advanced therapy after, or in addition to, cDMARD treatments. Rheumatologists were therefore experienced in use of TNFi treatments and more recently introduced advanced therapies were often compared to a TNFi, generally adalimumab, as the most widely used product, in head-to-head trials. Relative to TNFis, there was considerably less clinical experience with tsDMARDs, including the JAKi class of treatments of which four were

licensed to treat RA in the UK, therefore, clinicians were particularly interested in assessing the benefit: risk profile of newer classes of medicines in clinical practice.

'Strength of Balance' website structure

The website was directed towards UK health professionals (Galapagos referred to the 'Home' page.

Galapagos provided copies of the various pages on the website and stated that it was divided into sections: an 'At A Glance' summary page which was an overview of the main product benefits, and specific areas provided in depth Efficacy, Safety and Mechanism of Action (MOA) & Dosing information. A Resources page provided downloadable versions of the Jyseleca Prescribing Guide, and Patient Alert Card. The Prescribing Guide which, based on the summary of product characteristics (SPC) and risk minimisation materials (RMM), presented an overview to 'initiation, monitoring and risk management' for prescribers considering initiating patients on Jyseleca. The 'Safety', 'MOA & Dosing' and 'Resources' pages all provided safety information.

Galapagos submitted that a clear statement in the blue flash at the very top of every page directed health professionals to the prescribing information (PI) link in the footer, where links to the PI and SPC could both be found. The SPC link also provided access to the RMM.

The 'MOA & Dosing' page also linked directly to the Jyseleca Prescribing Guide.

1 'Safety' messaging

Strength of balance website (https://strengthofbalance.co.uk/safety) – Safety page (UK-INF-2020-11-0063, March 2021, last accessed 15 November 2021)

The first page of the safety section was headed 'Safety JYSELECA – A preferential JAK1 inhibitor for moderate to severe RA' which appeared on the background image of a lion walking through grass towards a red flower below which was an emblem with an image of a flower with the claim 'ACCEPTABLE TOLERABILITY'. The following section was titled 'In Phase 2 and 3 trials, JYSELECA demonstrated:' which was followed by two statements beside each of which it appeared an icon could be expanded for further information. The first statement read 'Low rates* of JAK inhibitor-associated adverse events†' The asterisk beside the phrase 'low rates' took the reader to a footnote in small font directly below the two statements which read 'Based on AE [adverse events] rates observed as 'Uncommon (<1% and >0.1%) or of lower frequency in the JYSELECA clinical trials' and the entire statement was linked to a second footnote which stated 'JAK inhibitor associated adverse events defined as VTEs [venous thromboembolisms], Herpes Zoster Reactivation and Serious Infections'. The second statement read 'Similar observed rates of serious infections, herpes zoster and VTE compared to adalimumab'.

This was followed by a bold heading 'Discover Strength of Balance' and a box which allowed the reader to select one of two tabs. The first tab stated 'JAK INHIBITOR-ASSOCIATED AEs' and included the claim 'Jyseleca JAK inhibitor-associated adverse events across phase 2 and phase 3 clinical trials' which was followed by the claim at issue in point 1.2 below 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3]'. The data in the table below compared the exposure adjusted incidence rates for Jyseleca at various doses (200mg plus MTX, 200mg and 100mg) with adalimumab plus MTX. The data with MTX were from Finch 1 and the data for Jyseleca at

200mg and 100mg were from Darwin 1 and 2 and Finch 1, 2 and 3. The explanation for the asterisk was the same as above and appeared again at the foot of the table in small font.

The second tab was titled 'AEs VS. ADALIMUMAB' followed by 'JAK inhibitor-associated adverse events vs. adalimumab FINCH 1 MTX-IR Similar observed rates of serious infections, herpes zoster and VTE compared to adalimumab[2,3]'. Below this was a box which was headed 'Throughout 1 year of treatment with JYSELECA' followed by three claims: 'Serious infections 3.0/100PY vs 3.4/100 PY adalimumab + MTX'; 'Herpes zoster 1.4/100PY vs. 0.7/100 PY adalimumab + MTX'; and 'VTE 0.2/100 PY vs. 0.3/100 PY ADALIMUMAB + MTX', below which it stated 'Exposure-adjusted incidence rates were calculated per 100 patient-years (PY) and Venous thromboembolism (VTE) included deep vein thrombosis and pulmonary embolism'. The 'vs. PY adalimumab + MTX' in each instance was in much smaller font below the data for Jyseleca.

1.1 General concerns regarding the portrayal of safety data for Jyseleca on the safety page

COMPLAINT

AbbVie stated that the only adverse data that were shown on the 'Safety' tab of the website was what was deemed to be stated as Janus Kinase (JAK) inhibitor associated adverse events, with all other adverse event data, including the most frequently reported adverse events as listed in the Jyseleca SPC (nausea (3.5%), upper respiratory tract infection (URTI, 3.3%), urinary tract infection (UTI, 1.7%) and dizziness (1.2%)) not shown at all. Despite the fact that there were RMM associated with Jyseleca, there was no clear reference to the materials or the safety concerns and information highlighted in those materials which included serious infections, potential effects on male fertility, potential risks of major adverse cardiovascular events, and prescribing in the very elderly (75 years and above), on the safety page.

Other data such as common or serious adverse events were presented on the 'MOA [Mechanism of Action] & Dosing' page. However, as this information was in different places on the website, it was important to provide clear direction to health professionals where additional information could be found. AbbVie alleged that the way it was portrayed on the website did not satisfy the requirement that the prescriber should be able to form a reasonable impression of the medicine by reading the information.

AbbVie quoted Clauses 6.1 and 14.4 and alleged that the safety page, as a whole, did not satisfy the requirements and was in breach of Clauses 6.1 and 14.4.

RESPONSE

Galapagos noted the allegation that:

- The website focussed on JAK inhibitor associated adverse events with other adverse events 'not shown at all'.
- There was no clear reference to the Jyseleca RMM.
- The safety data was insufficient for the prescriber to be able to form a reasonable impression of the medicine by reading the information.

Galapagos submitted that AbbVie's allegations were unfounded. As mentioned, the 'Safety', the 'MOA & Dosing' and 'Resources' pages all provided safety information. The 'MOA & Dosing' page included a table of common and serious adverse events under 'Considerations for initiation and monitoring of patients on Jyseleca', and all pages provided links to the SPC, including the 'Safety' page in question. The RMM were linked to from the 'Resources' page and the Prescribing Guide covered the same topics.

The 'At a Glance' page and the 'Safety' page presented information on how Jyseleca compared to other advanced therapies, ie bDMARDs and tsDMARDs, clearly labelled as follows:

- Low rates* of JAK inhibitor-associated adverse events.
- JAK-Inhibitor-associated adverse events.
- Adverse events versus adalimumab.

Galapagos noted that in its original letter dated 25 June 2021, AbbVie initially alleged that the safety profile was presented in a misleading and incomplete manner. AbbVie claimed that Galapagos was not providing full safety data, even though the website featured a table of common and serious adverse events as well information on JAKi class-related adverse events. In addition, the PI and the SPC were available from every page. If a clinician decided to prescribe Jyseleca, he/she could access Jyseleca specific information in the prescribing guide. Galapagos noted that AbbVie recognised the JAKi specific focus of the 'Safety' page in its formal complaint (Paragraph 1.1).

Subsequently, in its 2 August 2021 letter, AbbVie suggested that it would be helpful to provide a direct link from the 'Safety' page to the 'Resources' page:

> '*AbbVie understands that you have provided links to the necessary risk minimisation materials associated with Jyseleca® under the 'Resources' tab, however we believe that a link and/or a prompt to access the material should have been provided in the safety section of the website.'*

While Galapagos did not accept that the absence of a link from the 'Safety' page to the 'Resources' page constituted a breach of the Code, Galapagos agreed in its inter-company dialogue response on 20 August 2021 that additional links would be added during the next website update further to enhance the safety messaging:

> *'Galapagos notes that you have understood that the RMP materials are accessible through provided links. We agree that providing a link from the Safety section would increase their visibility*.
>
> *Proposed action: As part of the website update, additional links to RMP materials will be added to the Safety section.'*

Galapagos therefore understood that this matter had been addressed and resolved during inter-company dialogue. The face-to-face meeting on 1 October 2021 clarified the timelines and Galapagos' clear intention, as confirmed in its letter dated 20 October 2021, to complete the changes to the website during November 2021. Galapagos had met that commitment. This aspect of the complaint was therefore satisfactorily concluded during inter-company dialogue, and Galapagos believed there was no necessity for investigation by the PMCPA.

In summary, Galapagos was confident that the content of the website presented the safety profile of Jyseleca accurately and comprehensively. In addition, the provision of links to relevant reference material, including the PI, SPC and RMM, meant that users of the website were able to access sufficient information to form their own opinion of the therapeutic value of the product. Following inter-company dialogue, Galapagos had agreed to add links from the 'Safety' page to the RMM on the 'Resources' page, to further enhance the existing safety messaging on the website. Galapagos denied breaches of Clauses 6.1 and 14.1 of the 2021 Code.

PANEL RULING

The Panel noted AbbVie's allegation that the only adverse event data shown on the 'Safety tab' of the website were JAK inhibitor associated adverse events while the most frequently reported adverse events, as listed in the Jyseleca SPC (nausea (3.5%), upper respiratory tract infection (URTI, 3.3%), urinary tract infection (UTI, 1.7%) and dizziness (1.2%)), were not shown at all.

According to AbbVie, other data such as common or serious adverse events were presented on the 'MOA [Mechanism of Action] & Dosing' page. However, as this information was in different places on the website, it was important to provide clear direction to health professionals where additional information could be found. AbbVie alleged that the way it was portrayed on the website did not satisfy the requirement that the prescriber should be able to form a reasonable impression of the medicine by reading the information. The Panel further noted AbbVie's allegation that despite the fact that there were RMM associated with Jyseleca, there was no clear reference to the materials or the safety concerns and information highlighted in those materials which included serious infections, potential effects on male fertility, potential risks of major adverse cardiovascular events, and prescribing in the very elderly (75 years and above), on the safety page.

The Panel noted that in its letter of 20 August 2021, Galapagos stated that the website would be undergoing an update following the transition of commercialisation responsibilities from Gilead to Galapagos and whilst there had been no intention to downplay any safety concerns, the safety data detailed on the site would be amalgamated in a single location accessed via the 'Safety' section. The Panel further noted that whilst Galapagos did not accept that the absence of a link from the 'Safety' page to the 'Resources' page constituted a breach of the Code, in the same letter of 20 August 2021 Galapagos agreed that providing a link from the 'Safety' section to the risk minimisation materials would increase their visibility and stated that as part of the website update, additional links to RMP materials would be added to the 'Safety' section. The Panel noted that Galapagos had committed to complete the changes in November 2021, as outlined in its letter to AbbVie dated 20 October 2021 and acknowledged by AbbVie in its email of 27 October 2021. The Panel therefore considered that at the time the complaint was submitted by AbbVie (15 November 2021), this matter had been settled during inter-company dialogue, and therefore it did not consider the allegations in relation to general concerns regarding the portrayal of safety data for Jyseleca on the safety page as set out in Point 1.1.

1.2 Claim 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2'3'].

COMPLAINT

AbbVie alleged that the claim was not supported by the references to the data in the table below the claim. 'Low' was related to adverse events with a frequency <1% and >0.1%. Not all the

rates listed in the table fell within this categorization, which was inaccurate. At the foot of the table the explanation for the asterisk with further references was provided which made the interpretation of the table and its data misleading and ambiguous.

AbbVie noted that Clause 6.2 stated that any information, claim or comparison must be capable of substantiation and alleged that the claim was in breach of Clauses 6.1 and 6.2.

RESPONSE

Galapagos submitted that the statement: '*Treatment with Jyseleca® was associated with consistently low rates of JAK inhibitor-associated adverse events up to 52 weeks'* could be substantiated. The published data was referenced in the usual superscript format:

1 (Genovese MC, *et al.* Poster presented virtually at the European League Against Rheumatism (EULAR) 2020 E-Congress, June 3–6, 2020.

Galapagos noted AbbVie's allegation that Galapagos claimed 'low' rates (<1% and >0.1%) of adverse events even though the table included some information for adverse events with a higher rate. Galapagos submitted that this observation was correct but did not mean that the information was misleading. The table contained data from individual studies that were included in the integrated safety analysis, as stated in the text underneath the table. The inclusion of these data ensured that the information presented was complete and would enable the recipients to develop their own informed opinion.

For the above reasons, Galapagos did not believe the complaint by AbbVie had any merit. Accordingly, Galapagos denied breaches of Clauses 6.1 and 6.2.

PANEL RULING

The Panel noted the parties' submissions about inter-company dialogue. Whilst it appeared that a conditional agreement had been reached at the face-to-face meeting in October 2021, it appeared that neither party considered that a final agreement had been reached on this point. It was not included in Galapagos' list of matters upon which definite agreement had been reached in its letter dated 20 October 2021, subsequent to the face-to-face meeting and in its letter dated 2 November 2021, AbbVie did not appear to consider matters concluded within the required initial deadline. In any event the matter had been referred to the Panel for consideration.

The Panel noted AbbVie's allegation that the claim 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3]' was not supported by the references to the data in the accompanying table below the claim. 'Low' was related to adverse events with a frequency <1% and >0.1% and not all the rates listed in the table fell within this categorization, which was inaccurate. At the foot of the table the explanation for the asterisk with further references provided made the interpretation of the table and its data misleading and ambiguous.

The Panel noted that the asterisk to the claim 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3]' took the reader to a very small footnote at the bottom of the webpage, beneath the highlighted box which housed the table and a separate footnote, which read 'Based on AE rates observed as "Uncommon" (<1% and >0.1%) or of lower frequency in the Jyseleca clinical trials'. The Panel

noted that the claim at issue was referenced to the Genovese *et al* poster presented at the EULAR e-congress 2020 and Data on File, whilst the footnote was referenced to the Jyseleca SPC and Genovese *et al* poster presented at the EULAR e-congress 2020.

The Panel noted Galapagos' submission that even though the table included some information for adverse events with a higher rate, it did not mean that the information was misleading; the table contained data from individual studies that were included in the integrated safety analysis as stated in the text underneath the table. The Panel noted that beneath the table within the same highlighted box it stated '52-week exposure dataset: DARWIN 1 and 2 and FINCH 1-3 studies were integrated to represent the safety of JYSELECA 200mg in controlled clinical studies up to Week 52'. The Panel further noted Galapagos' submission that the inclusion of these data ensured that the information presented was complete and would enable the recipients to develop their own informed opinion.

The Panel noted that the table would not be viewed in isolation but within the context of the page overall including, particularly, its subheading, 'Treatment with JYSELECA was associated with consistently low rates* of JAK inhibitor-associated adverse events up to 52 weeks[2,3]' which introduced the table and was the claim at issue. The matter was further complicated by the footnote in small print at the bottom of the webpage. It was an established principle of the Code that claims could not be qualified by footnotes if such footnotes were necessary to ensure that a claim complied with the Code. In such circumstances, the footnote should be part of the claim at issue or within its immediate visual field. Whilst noting Galapagos' submission about the completeness of the data in the table, the Panel considered that some readers, on the balance of probabilities, might nonetheless assume, based on the subheading at issue including the unqualified phrase 'low rates', that the adverse events in the table immediately beneath were all of low incidence and that was not necessarily so. In the Panel's view, this was so, irrespective of the location of the footnote. The Panel considered that the claim in question within the context of the webpage, including the table, was misleading and ambiguous as alleged. A breach of Clause 6.1 was ruled.

The Panel considered that the implication of the unqualified claim within the context of the webpage was incapable of substantiation and a breach of Clause 6.2 was ruled.

1.3 Claim 'Similar observed rates of serious infections, herpes zoster and VTE [Venous thromboembolism] compared to adalimumab[2,3]'.

COMPLAINT

AbbVie alleged that with regard to herpes zoster rates compared to adalimumab, the references did not provide sufficient substantiation and might downplay the important safety considerations of herpes zoster rates for rheumatoid arthritis (RA) patients, for the following reasons:

- The data presented from the FINCH 1 study in the table on the safety page showed that herpes zoster (HZ) was 2-fold higher for filgotinib 200mg + MTX (1.4 patient years of exposure (PYE), 6 patients) versus adalimumab + MTX (0.7 PYE, 2 patients, which was not similar.
- The abstract 'Genovese MC *et al* 2020' provided further evidence the claim was inaccurate since it showed the 'Exposure Adjusted Incidence Rate' (EAIR) for Filgotinib (FIL) 200mg: 1.7 (1.3, 2.3), FIL 100mg: 1.1 (0.7, 1.8) and ADA: 0.7 (0.2, 2.8), which was a 2.4 fold increase of filgotinib 200mg versus adalimumab. The abstract also stated

'EAIR for HZ were low overall, but numerically slightly higher for FIL relative to PBO [placebo], ADA [adalimumab], and similar to MTX'.

- The confidence intervals in Genovese *et al* overlapped, however, the limitations sections of the FINCH 1 (Combe B *et al* 2021) and FINCH 2 (Genovese MC *et al* 2019) studies clearly mentioned these studies were not powered to compare adverse events between arms, so no definitive conclusions about safety could be reached.
- AbbVie had not seen the data on file referred to as reference 3.

Based on the information made available to AbbVie, the company alleged that the claim could not be substantiated by the references provided and was therefore in breach of Clauses 6.1, 6.2 and 6.4.

AbbVie noted that the claim was also present on the 'At a Glance' page of the website and alleged that it was similarly in breach of Clauses 6.1, 6.2 and 6.4.

RESPONSE

Galapagos submitted that the references accurately portrayed the results of clinical trials. The publications had undergone peer review and had been subjected to the usual scientific scrutiny.

Galapagos noted that AbbVie accepted in its complaint letter that the confidence intervals in the stated studies overlapped and that the studies were not powered to compare adverse event differences. The studies also showed comparable absolute numbers. Galapagos agreed with AbbVie's conclusions in this respect and, therefore, the data from these studies substantiated its use of the term 'similar'.

Galapagos submitted that these statements could also be substantiated by more recent publications such as Winthrop and Alves (2021) which had been included for completeness.

Galapagos noted that concerns related to herpes zoster were not mentioned in AbbVie's inter-company dialogue letters of 2 and 20 August 2021. Galapagos therefore understood that inter-company dialogue had successfully concluded on this point. The issue was, however, reintroduced by AbbVie at the face-to-face meeting on 1 October 2021 and Galapagos provided a substantive answer in its letter of 20 October 2021. AbbVie had not officially stated that it did not accept the position Galapagos put forward on this in that letter. Accordingly, Galapagos asked the PMCPA to disregard this aspect of the complaint. If AbbVie had further concerns in relation to this issue they should be pursued through inter-company dialogue.

Galapagos noted that the complaint by AbbVie related to accurate representation of data and Galapagos, as explained above, disagreed with its interpretation and therefore, it denied breaches of Clauses 6.1, 6.2 and 6.4.

PANEL RULING

The Panel noted Galapagos' submission that the references accurately portrayed the results of clinical trials and that the publications had undergone peer review and had been subjected to the usual scientific scrutiny. The Panel noted Galapagos' submission that AbbVie accepted in its complaint letter that the confidence intervals in the stated studies overlapped and that the studies were not powered to compare adverse event differences. In this regard, the Panel noted that Combe *et al*, which appeared to detail FINCH-1 whilst noting that the frequency of herpes zoster

was low and similar across all groups through to week 24, stated within the limitations of the study that it was not powered to compare AEs between arms, so no definitive conclusions about safety could be reached. Additional safety data would come from the integrated safety analysis across all phase II and III filgotinib trials, long-term extension study (ClinicalTrials.gov NCT03025308) and future registries.

The Panel further noted Galapagos' submission that the studies showed comparable absolute numbers. Galapagos agreed with AbbVie's conclusions in this respect and, therefore, in its view, the data from these studies substantiated its use of the term 'similar'.

The Panel noted that the claim at issue was referenced to Genovese MC, *et al.* Poster presented virtually at the European League Against Rheumatism (EULAR) 2020 E-Congress, June 3-6, 2020 and data on file. The Panel noted that Genovese *et al* 2020, an abstract, stated that it assessed the long-term safety of filgotinib using integrated data from three phase 3 (FINCH 1-3), two phase 2 (DARWIN 1, 2), and two long-term extension (LTE) (FINCH 4, DARWIN 3) trials in patients with early to biologic-refractory RA. Exposure adjusted incidence rates (EAIRs) per 100 patient-years (PY) and 95% confidence intervals were estimated for AEs of interest using a Poisson regression model including study and treatment with an offset of natural log of exposure time. Patient Years exposure was calculated as the total exposure time in years. Figure 2 included herpes zoster: 1.4 for filgotinib 200mg and 0.9 for filgotinib 100mg vs adalimumab (0.7) at 52 weeks. The Panel noted that the discussion section stated 'With filgotinib, EAIR of serious infections and herpes zoster were generally similar to adalimumab and MTX'. No limitations of the study appeared to be included in the poster. The Panel noted that the Data on File included, *inter alia*, the herpes zoster data for filgotinib 100mg and 200mg QD with no reference to herpes zoster in relation to adalimumab.

The Panel noted Galapagos' submission that these statements could also be substantiated by more recent publications such as Winthrop and Alves. The Panel noted that it was possible to substantiate a claim by studies supplemental to those cited.

The Panel noted that in Winthrop which, according to the paper, appeared to be received for publication in May 2021 and accepted in September 2021, Exposure-adjusted incidence/event rates for herpes zoster were determined in patients receiving UPA (upadacitinib) (monotherapy or combination therapy) in six randomised phase III trials (data cut- off on 30 June 2020). Herpes Zoster incidence and event rates were also determined in patients receiving MTX monotherapy or adalimumab (ADA) + MTX. Multivariable Cox regression analysis was used to identify herpes zoster risk factors in UPA- treated patients. The Panel noted that filgotinib was not included within the study, upadacitinib was included and appeared to be an AbbVie medicine. The study authors stated that given the lack of direct comparison of head-to-head studies between JAK inhibitors, they were limited in drawing conclusions regarding the relative risk of herpes zoster with UPA as compared with other JAK inhibitors, including filgotinib.

The Panel noted that Alves, a systematic review and network meta-analysis, stated that, compared with filgotinib, adalimumab had an increased risk of herpes zoster infection (4.81; 95% CI, 1.39-16.66). It further stated, however, that although the initial results suggested that filgotinib could have a reduced risk of herpes zoster, the sensitivity analyses did not support those findings. Risk differences between the drugs became statistically non-significant when the sensitivity analysis was conducted.

Whilst the Panel had concerns about the page as a whole, it noted that the allegations appeared to be limited by AbbVie to substantiation of the claim in question by specific studies rather than the broader issues that potentially came within Clauses 6.2 and 6.4 and the matter was considered on that basis.

The Panel noted that AbbVie referred to data beneath the claim in question showing that herpes zoster was 2 fold higher for filgotinib 200mg and MTX which AbbVie stated was from Finch-1, as an example that the claim at issue could not be substantiated. The Panel noted its comments above about Finch-1 as described in Combe *et al:* it was not powered to compare adverse events between the study arms so no definitive conclusions about safety could be made. The Panel noted that the data beneath the claim at issue was derived from Genovese *et al*, 2020, an abstract rather than Finch-1 as stated by AbbVie. The Panel had concerns about the layout of the page but did not consider that this was relevant to the issue of substantiation which was the subject of the complaint.

The Panel considered that whilst neither the data on file the claim was referenced to, or Winthrop, substantiated the claim in question, Genovese *et al* 2020, the abstract the claim was referenced to and Alves could, on the balance of probabilities, substantiate the claim with regard to similar observed rates of herpes zoster compared to adalimumab. The Panel therefore, on this very narrow ground, ruled no breach of Clauses 6.2 and 6.4 in relation to the claim at issue and substantiation on the safety page and the 'at a glance' page. Noting it's no breach ruling in relation to substantiation, the Panel did not consider that the claim was misleading based on the very narrow allegation that it could not be substantiated, no breach of Clause 6.1 was ruled.

1.4 Safety and high standards

COMPLAINT

AbbVie alleged that the issues in Points 1.1, 1.2 and 1.3 raised serious concerns about the balance of safety and efficacy information portrayed regarding Jyseleca in Galapagos' promotional materials.

AbbVie took patient safety extremely seriously and alleged that the portrayal of the safety profile of Jyseleca was insufficient to enable health professionals to appropriately evaluate the risk-benefit profile of prescribing Jyseleca. The information provided by Galapagos was misleading, incomplete and downplayed the safety concerns associated with the product. In addition to the above mentioned aspects, AbbVie alleged that high standards in preparing promotional materials had not been maintained in breach of Clause 5.1.

RESPONSE

Notwithstanding Galapagos' arguments regarding the ongoing nature of inter-company dialogue, it had set out above why it believed the safety data for Jyseleca was presented in a responsible and appropriate manner.

Contrary to AbbVie's position, Galapagos submitted that it had demonstrated that the information on the website was sufficient to allow health professionals to properly evaluate the safety profile of the product and that it did not downplay the safety concerns.

Galapagos submitted that AbbVie had not presented any evidence that Galapagos had failed to maintain high standards in preparing its materials and it denied this additional allegation of a breach of Clause 5.1.

PANEL RULING

The Panel noted that it had made no ruling about the matter raised at Point 1.1 above and which was therefore not relevant to the consideration of this point.

The Panel noted its comments and rulings above at Point 1.2, and its concerns regarding the safety page. It considered that, overall, high standards had not been maintained in this regard and a breach of Clause 5.1 was ruled.

2 Sustained efficacy messaging

Strength of balance website (https://www.strengthofbalance.co.uk/summary) – At a Glance page (UK-INF-2020-11-0066, March 2021, last accessed 15 November 2021)

COMPLAINT

The 'At a glance' page was headed 'SUSTAINED EFFICACY' followed by 'In Phase 3 trials, Jyseleca demonstrated':

> ACR20 response as early as **Week 2** in **37%** of patients (n=475) vs. 15% of patients in the MTX+ placebo group (n=475; p<0.001)[2].
>
> ACR70 response in **44%** of patients by **Week 52** (n=475)[2].
>
> DAS28-CRP <2.6 remission sustained up to **Week 52** in 54**%** of patients (n=475)[3].
>
> Zero radiographic progression* at **Week 52** in **88%** of patients (n=475) vs. 82.4% for adalimumab patients (n=325)[4].

AbbVie alleged that the information provided fell short of the relevant Code requirements for a number of reasons:

- Firstly, there was a lack of explanation regarding the study description, primary endpoint, and it was not clearly stated that these data were for the filgotinib 200mg dose only.
- Secondly, it had not consistently been made clear what the comparator arm was (which was missing for the 2nd and 3rd bullet points).
- Thirdly, there were no statistical methods and p-values provided for the 2nd, 3rd or 4th bullet points.

In this way, it was not possible 'At-a-glance' to determine if the percentages quoted were simply a statement of numerical value, or whether in fact, they had statistical significance and potential clinical benefit to the patient. Because there was a woeful lack of context to these claims, even allowing for the fact that they appeared on a 'summary' page, AbbVie believed this was a clear breach of Clauses 6.1 and 5.1.

RESPONSE

Galapagos noted that the first element of the complaint was an allegation that the study description, primary endpoint and dose were not detailed. However, the details of the study were provided in detail on the 'Efficacy' pages of the website and specifying the dose was not required as 200mg was the recommended dose for Jyseleca and the 100mg dose was only appropriate for specialist populations. This was explained in detail on the 'MOA & Dosing' page.

The bullet points beneath the headline claim were accompanied by a statement that clearly referred to the efficacy measures used, ie ACR20 and ACR70.

The 'Efficacy' page provided additional information, with tabs with clear graphs showing the evolution of response at various timepoints in FINCH 1, FINCH 2 and FINCH 3.

Additional information about the studies was available via a box beneath the graphs entitled 'Study Details'.

These 'Efficacy' pages also showed the timepoints at which the response was observed, ie Week 2, and over what period it was observed, ie 52 weeks. Radiographic progression was measured after a specified period, in the case of FINCH 3: 52 weeks, against a baseline examination.

The claim was substantiated by the European Public Assessment Report (EPAR) which stated that the absolute number of responders in the filgotinib 200mg-group increased from week 12 to week 24 and did not decrease from week 24 to week 52.

Therefore, Galapagos maintained that the claim for sustained efficacy was adequately explained and that health professionals had been provided with sufficient information to form an opinion of the therapeutic value of Jyseleca.

AbbVie also alleged that the comparator was not clearly stated in bullets two and three on the original efficacy page. Since the claim was not comparative, it was not necessary to state the comparator. The claims related to Jyseleca, not its relative performance.

Galapagos submitted that with respect to the lack of statistical method and p values, these were not a requirement of the Code. The statements were factually correct and were substantiated by the additional information on the linked pages. Therefore, the website did not mislead the reader.

Galapagos did not consider that AbbVie had presented any evidence that Galapagos had failed to maintain high standards in preparing these materials.

Accordingly, Galapagos denied breaches of Clauses 6.1 and 5.1.

PANEL RULING

The Panel noted that the four bullet points on the 'At a glance' webpage were referenced to three separate data on file. The Panel noted that it did not have these data on file before it.

The Panel noted Galapagos' submission that the details of the study were provided in detail on the 'Efficacy' pages of the website. According to Galapagos, the bullet points beneath the headline claim were accompanied by a statement that clearly referred to the efficacy measures used, ie ACR20 and ACR70 and the 'Efficacy' page provided additional information, with tabs

with clear graphs showing the evolution of response at various timepoints in FINCH 1, FINCH 2 and FINCH 3. Additional information about the studies was available via a box beneath the graphs entitled 'Study Details'. These 'Efficacy' pages also showed the timepoints at which the response was observed, ie Week 2, and over what period it was observed, ie 52 weeks. Radiographic progression was measured after a specified period, in the case of FINCH 3: 52 weeks, against a baseline examination. The Panel noted that it did not have access to the linked information via the 'Study Details' link.

Galapagos also stated that the claim was substantiated by the EPAR which stated that the absolute number of responders in the filgotinib 200mg-group increased from week 12 to week 24 and did not decrease from week 24 to week 52. Galapagos submitted that since the claim was not comparative, it was not necessary to state the comparator. The claims related to Jyseleca, not its relative performance. The Panel further noted Galapagos' submission that with respect to the lack of statistical method and p values, these were not a requirement of the Code. The statements were factually correct and were substantiated by the additional information on the linked pages. Therefore, the website did not mislead the reader.

The Panel noted Galapagos' reference to qualifying information elsewhere on the website and considered that each webpage should not be misleading if read in isolation. It was, of course, acceptable to have a page summarising data presented elsewhere but companies had to be particularly careful that such summary pages, nonetheless, complied with the Code and did not rely on data elsewhere to ensure Code compliance.

The Panel noted that whilst the first and last bullet points were comparative, the middle two were not and noted Galapagos' submission in that regard. Nonetheless, the Panel noted that given the first and fourth bullet points were comparative, some readers might consider the second and third bullet points in that light and assume that the data was favourable to Jyseleca and that was not necessarily so in relation to the 52 week data referred to. The Panel noted Galapagos' submission that specifying the dose was not required as 200mg was the licensed dose and the 100mg dose was only appropriate for specialist populations which was explained in detail on the 'Mechanism of Action & Dosing' page. In this regard, the Panel noted that within the website, the dose was not stated at the top of pages which discussed clinical data and considered that it was relevant to the clinical outcomes and in this regard, considered that it would be helpful and relevant to state the dose in relation to the claims in question. The Panel noted that Jyseleca was indicated in combination and in monotherapy and in this regard, particularly given that the efficacy section discussed certain monotherapy data, considered that the claims in question, on a page that aimed to summarise the efficacy section, should be clear whether they related to combination or monotherapy treatment. In relation to the bullet point 'Zero radiographic progression* at Week 52 in 88% of patients (n=475) vs. 82.4% for adalimumab patients (n=325)', the relevant section within the efficacy page, Radiographic progression, stated as a footnote that 52 week data were not controlled for multiplicity, therefore treatment differences could represent chance findings. In the Panel's view, readers would assume that the bullet point on the page in question referred to statistically significant data at 52 weeks unless they were told clearly otherwise and that was not so. The Panel did not have a copy of the relevant studies but on the basis of the limited information on the website considered that the page in question on the 'At a glance webpage' was incomplete and misleading such that readers did not have sufficient information to form their own therapeutic value of the medicine and a breach of Clause 6.1 was ruled. The Panel considered that high standards had not been maintained in this regard and a breach of Clause 5.1 was ruled.

3 OVERALL CLAUSE 2

COMPLAINT

In summary, AbbVie alleged breaches of Clauses 5.1, 6.1, 6.2, 6.4 and 14.4 of the Code. Furthermore, due to the nature of the breaches, ie primarily focused around patient safety, combined with Galapagos not adhering to the agreements and spirit of the inter-company dialogue, AbbVie took the view that the PMCPA should also consider a breach of Clause 2.

RESPONSE

Galapagos stated that it presented the rationale for its rejection of the individual allegations regarding specific claims above.

Galapagos did not believe that the nature of the allegations in any way constituted a breach of Clause 2. Galapagos had presented appropriate product data accurately and clearly, such that a health professional could make an informed decision about the therapeutic value of Jyseleca.

PANEL RULING

The Panel noted the particular circumstances of this case and the evidence before it. The Panel did not consider that AbbVie had established, on balance of probabilities, that Galapagos did not adhere to the spirit of inter-company dialogue, as alleged.

The Panel further noted its comments and rulings above, including its rulings of a breach of Clause 5.1 to reflect that high standards had not been maintained. The Panel noted that despite its concerns detailed at Point 1.2 above, it noted that the adverse event rates were given in the table in question at Point 1.2. The Panel considered that its ruling of a breach of Clause 5.1 adequately covered its concerns on this point. On balance, the Panel did not consider that the complainant had established that patient safety had been prejudiced as referred to in the supplementary information to Clause 2 of the Code as alleged. In the particular circumstances of this case, the Panel therefore, and on balance, ruled no breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **15 November 2021**

Case completed **9 January 2023**