CASE AUTH/3011/1/18

GLAXOSMITHKLINE v ASTRAZENECA

Press release issued by AstraZeneca

GlaxoSmithKline complained about an AstraZeneca PLC press release dated 10 November 2017. The press release was entitled 'Benralizumab receives positive EU CHMP [Committee for Medicinal Products for Human Use] opinion for severe, uncontrolled eosinophilic asthma'. The press release referred to the European Medicines Agency (EMA) positive opinion which recommended the marketing authorization of benralizumab as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled, despite high dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA). The press release was issued by AstraZeneca PLC, an ABPI member, on the www.astrazeneca.com website which clearly stated that 'This website was operated by AstraZeneca UK Limited'.

GlaxoSmithKline alleged that the data on the clinical endpoints presented in the press release (including annual asthma exacerbations rate [AAER], lung function [LF] and median reduction in daily oral corticosteroids [OCS] use and adverse events [AE]) based on clinical trials SIROCCO, CALIMA and ZONDA were unbalanced and misleading due to the omission of the full available evidence.

GlaxoSmithKline alleged that the statement 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo' did not give a balanced picture of benralizumab efficacy. It was data from only one of the two regulatory studies with the more favourable efficacy result. In the other regulatory study, there was a 28% reduction vs placebo.

GlaxoSmithKline alleged that the statement 'Rapid improvement in lung function (290mL increase in forced expiratory volume in one second (FEV1) from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness' did not give a balanced picture of the onset of benralizumab efficacy in a placebo-controlled trial and was misleading as it was not corrected for the placebo response. An improvement in the placebo arm was relevant to this claim. Also, secondary endpoints in CALIMA and in SIROCCO showed respectively a 116ml and 159ml improvement vs placebo in FEV1 at the end of the studies. 'Rapid improvement' was alleged to be an all-encompassing claim without the context of whether this was sustained or how efficacy in this case related to effectiveness. GlaxoSmithKline alleged, therefore, this was exaggerated, misleading and unbalanced.

GlaxoSmithKline alleged that the statement '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients' was unbalanced and misleading for a number of reasons firstly the exacerbation reduction was presented as 'versus placebo' while FEV1 improvement and OCS reduction data were presented as 'from baseline'. The placebo arm had a 25% reduction, to give a true representation of OCS reduction, efficacy vs placebo data should be presented as a 'median reduction in daily OCS use of 50% versus placebo'.

GlaxoSmithKline was also concerned that the statement 'An overall adverse event profile similar to placebo' was misleading with respect to patient safety. Without any context of the adverse event profile, and any differences with placebo, it was inappropriate to present the safety profile of a new, black triangle medicine in this way. It raised false hopes and could result in inappropriate prescribing and mislead with respect to the safety of the product.

GlaxoSmithKline stated that indeed, any medicine related adverse events in CALIMA were 8% for placebo vs 13% in the benralizumab arm, 10 benralizumab patients (2%) and 4 (<1%) who received placebo discontinued treatment because of adverse events and 2 patients had an adverse event leading to death vs none in the placebo arm. A comparable trend could be observed in SIROCCO: 18 benralizumab patients (2%) and three (1%) who received placebo discontinued treatment because of adverse events. Although these might be low numbers it was not only a factually incorrect statement but also not acceptable to state they were similar to placebo without any detail or context.

GlaxoSmithKline stated that if key clinical data had not been omitted and the vs placebo data had been included, the conclusion on clinical efficacy and safety would have been different.

In addition, GlaxoSmithKline alleged that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' was inappropriate as in particular 'speed of onset', 'convenience' and would 'make a real difference' were promotional and could not be substantiated by clinical trial data. GlaxoSmithKline stated that this also set unfounded hopes and misled the media into believing that all patients would have a response with no context of the response rate nor any clinical context regarding the speed of onset. In addition, GlaxoSmithKline alleged that to claim that benralizumab was convenient when it was administered by subcutaneous injection, every 4 weeks for 3 doses and then every 8 weeks, compared with inhalers or oral medication, was misleading.

In summary, GlaxoSmithKline alleged breaches of the Code as well as of the MHRA Blue Guide Section 6.6. To present clinical trial data in a misleading way and to issue a promotional press release did not maintain the high standards expected from a pharmaceutical company. In addition, the intent to promote in a misleading manner and the incorrect and misleading presentation of safety data had a potential impact on patient safety, and the failure to address GlaxoSmithKline's concerns, brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2.

The detailed response from AstraZeneca appears below.

The Panel noted that its role was to consider matters in relation to the Code and not the MHRA Blue Guide.

The Panel considered that the press release was subject to the Code. It then went on to consider the allegations made by GlaxoSmithKline.
The Panel noted that the summary of product characteristics (SPC) stated that Fasenra (benralizumab) was first authorised on 8 January 2018. The recommended dose of benralizumab was 30mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Fasenra was intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. The SPC stated, under special warnings and precautions for use, that abrupt discontinuation of corticosteroids after initiation of Fasenra therapy was not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

The Panel noted that the press release stated that patients in SIROCCO and CALIMA received standard of care medicine (including high dose inhaled corticosteroids and long acting beta 2 agonists) and were randomized to receive benralizumab 30mg every 4 weeks, 30mg every 4 weeks for the first 3 doses followed by 30mg every 8 weeks or placebo via a subcutaneous injection.

With regard to the claim 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo', the Panel noted this was from SIROCCO. CALIMA stated that annual exacerbation rates were approximately 28% lower than with placebo. The Panel considered that the use of the phrase 'up to 51%' was misleading as it did not reflect the range and information made available to the public had not been presented in a balanced way. Breaches of the Code were ruled.

With regard to the claim 'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness', the Panel noted that SIROCCO concluded that both benralizumab dosing regimens significantly improved pre-bronchodilator FEV1 in patients at week 48 compared with placebo. The difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl was 159ml (p = 0.0006). The Panel noted AstraZeneca's submission that the 290ml increase in FEV1 from baseline at week 4 data as stated in the press release came from SIROCCO. Data on file had been created which stated that at week 4 there was a 290ml increase in FEV1 for benralizumab and a 209ml increase for placebo (p=0.039) versus baseline. The estimated difference between benralizumab and placebo was 81ml.

CALIMA concluded that benralizumab significantly improved pre-bronchodilator FEV1. Improvements in pre-bronchodilator FEV1 were present within 4 weeks of treatment start and were maintained through the treatment period. At week 56 the difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl) was 116ml (p = 0.0102). The Panel noted that CALIMA stated that annual exacerbation rates, pre-bronchodilator FEV1 and total asthma scores were not affected by benralizumab for the subset of patients receiving medium-dosage inhaled corticosteroids plus LABA with blood eosinophils ≥ 300 cells per mcl at baseline.

The data on file for CALIMA at week 4 showed there was a 280ml increase in FEV1 for benralizumab 30mg every 8 weeks and 152ml for placebo (p=0.002) versus baseline. The estimated difference between benralizumab and placebo was 127ml.

The SIROCCO and CALIMA data on file stated that the analysis of these endpoints were not multiplicity protected and therefore p values were reported as nominal. Results were descriptive only.

The Panel noted that the ZONDA study (Nair *et al* (2017)) assessed the effects of benralizumab versus placebo on the reduction in oral glucocorticoid dose whilst maintaining asthma control in adults with severe asthma. ZONDA concluded that benralizumab showed significant clinically relevant benefits compared with placebo on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on FEV1.

The Panel noted that the claim in the press release referred to a rapid improvement in lung function. It appeared to the Panel that if the improvements in FEV1 at 4 weeks in SIROCCO and CALIMA were seen as rapid improvement in lung function then there was evidence to support the change in both the treated and placebo groups. The Panel considered that it was misleading and exaggerated not to include the placebo data in the press release to ensure that the improvements from baseline were not confused with improvements compared with placebo. Information to the public had not been presented in a balanced way and breaches of the Code were ruled. The data was capable of substantiation so no breach was ruled in that regard.

With regard to the claim '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients', the Panel considered that

it was not clear that the reduction in daily OCS use difference was compared to baseline. The SPC gave the placebo reduction as 25%. The Panel considered that the data in the press release was not placed in context; the press release was misleading in this regard and information to the public had not been presented in a balanced way. Breaches of the Code were ruled.

With regard to the claim 'an overall adverse event profile similar to placebo', the Panel noted that the medicine was new and at the time of the press release it was not licensed in the UK. The intended audience would not necessarily be familiar with the incidence of adverse events with placebo. The claim referred to the addition of benralizumab rather than the overall incidence of adverse events when the medicine was used in addition to high-dose inhaled corticosteroids plus long acting beta agonists. The SPC stated that the most common adverse reactions during treatment were headache (8%) and pharyngitis (3%). Injection site reactions (eg pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the recommended benralizumab dose compared with 1.9% in patients treated with placebo.

The Panel was concerned about the lack of context for the claim in the press release to an audience that were, in effect, members of the public. There was no further data in the press release about adverse events. The press release was misleading in this regard; it was not balanced. The Panel considered that the claim exaggerated the properties of the product and information to the public about the adverse event profile had not been presented in a balanced way. Breaches of the Code were ruled.

The Panel considered that as the press release was not specifically intended for patients taking the medicine, there was no need to include an inverted black equilateral triangle together with a statement about additional monitoring and reporting of side-effects. No breach was ruled.

With regard to GlaxoSmithKline's general allegation that the omission of both key clinical data and the placebo data meant that the conclusion on efficacy and safety would be different, the Panel considered that this allegation had been addressed by its rulings of breaches of the Code above. It would be relevant in considering the allegations of breaches below. It therefore ruled no breach in relation to the broad allegation.

With regard to the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' the Panel considered that this was a broad, strong claim for the medicine. It was a quotation from the AstraZeneca executive vice president, global medicines development and chief medical officer. The Panel considered that readers of the press release would be clear that the benralizumab was to be dosed every eight weeks. However, it was not clear that the first 3 doses were to be given every 4 weeks. The Panel did not accept AstraZeneca's submission that the use of the word 'potential' meant that readers would be aware that any clinical benefits observed in studies to date were not applicable to all patients.

Patients using Fasenra would need to continue with other asthma medication as stated in the package information leaflet (high doses of corticosteroids). Use of Fasenra might allow patients to reduce or stop daily OCS. This would be done gradually under supervision of a doctor.

On balance, the Panel did not consider that the claim in the press release was an advertisement for Fasenra, a prescription only medicine, to the public. The medicine was unlicensed at the time of the press release and thus not classified as a prescription only medicine and ruled no breach. It considered that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' might raise unfounded hopes of successful treatment, particularly given the lack of information about the need to be monitored before changing the doses of a patient's current medication.

The Panel noted the allegations about the speed of onset and the data for FEV1, and the changes at 4 weeks for patients with baseline eosinophils ≥ 300 cells per mcl. The Panel queried whether adding in an additional therapy was convenient for patients. It was not clear until page two of the press release that benralizumab was a subcutaneous injection. The Panel noted that there were other medicines available, one of which was GlaxoSmithKline medicine, mepolizumab (Nucala), which was to be given every 4 weeks. The basis of the claim for convenience in the press release was not clear to the Panel. AstraZeneca submitted that it related to the 8 week maintenance dosing schedule which the Panel noted was longer than for GlaxoSmithKline's medicine. The Panel considered that, given AstraZeneca's product had 3 doses at 4 week intervals, it was possible that maintenance treatment at 8 weeks would not be seen as convenient compared to treatment at 4 weeks. The Panel considered that, overall, the claim could be read as a comparison with inhalers and/or oral medication and compared to inhalers or oral medication, benralizumab was not convenient. Overall, it considered that the claim for convenience was misleading and that information to the public had not been presented in a balanced way. Breaches of the Code were ruled.

The Panel did not consider that GlaxoSmithKline had provided evidence that when a health professional asked for substantiation this was not provided and ruled no breach.

Noting all its rulings above, the Panel ruled a breach as high standards had not been maintained.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Panel noted that one of the reasons for GlaxoSmithKline to support a breach of Clause

2 was AstraZeneca's alleged failure to address GlaxoSmithKline's concerns. The Panel did not consider that this was relevant to its consideration regarding Clause 2. The Panel noted its rulings of breaches of the Code. It considered that it was extremely important that press releases were accurate, balanced and not misleading. On balance, the Panel considered that the circumstances did not warrant a ruling of a breach of Clause 2 and ruled accordingly.

GlaxoSmithKline complained about an AstraZeneca PLC press release dated 10 November 2017. The press release was entitled 'Benralizumab receives positive EU CHMP [Committee for Medicinal Products for Human Use] opinion for severe, uncontrolled eosinophilic asthma'. The press release referred to the European Medicines Agency (EMA) positive opinion which recommended the marketing authorization of benralizumab as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled, despite high dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA).

COMPLAINT

GlaxoSmithKline alleged that the press release was in breach of Clauses 2, 7.2, 7.3, 7.4, 7.9, 7.10, 9.1, 26.1, 26.2 and 26.3 of the Code due to a number of misleading and/or unsubstantiated statements.

Inter-company dialogue

GlaxoSmithKline stated that in line with PMCPA guidance on inter-company dialogue it contacted AstraZeneca's UK medical director to outline the basis of GlaxoSmithKline's complaint on 6 December 2017. This was followed by a letter on 7 December 2017 to raise its detailed concerns. AstraZeneca's UK medical director subsequently informed GlaxoSmithKline that AstraZeneca UK would not be responding but AstraZeneca's global functions would which it did on 20 December. GlaxoSmithKline noted that AstraZeneca's response did not originate from the UK affiliate, nor from a person responsible for certifying material, activity, etc under the Code as recommended in the guidance on inter-company dialogue.

GlaxoSmithKline stated that AstraZeneca failed to address any of its detailed concerns and stated that, 'The Release was factual and balanced and met the standards required by applicable law and regulation' although which standards were considered was not stated. GlaxoSmithKline considered this response to be wholly unsatisfactory and not in keeping with the guidance on inter-company dialogue that the (initial) response should address all of the points raised and include any proposed amendments or actions and timelines.

GlaxoSmithKline wrote again to AstraZeneca on 4 January 2018 offering AstraZeneca another opportunity and respectfully requesting a detailed response to the concerns raised. The subsequent response of 11 January again made no attempt to address the detailed concerns now raised twice by GlaxoSmithKline and again questioned the applicability of the Code in this matter and referred to Case AUTH/2046/9/07, Takeda v GlaxoSmithKline.

During a conference call on 12 January AstraZeneca was not willing to discuss the specific details of the points raised in GlaxoSmithKline's letter of 7 December 2017 and again underlined AstraZeneca's position that the press release did not fall under the Code and therefore the jurisdiction of the PMCPA. Both companies had failed to reach an agreement on this fundamental point, which was key to the complaint. AstraZeneca offered to meet and discuss further but requested that the meeting be in conjunction with discussing global press releases in a broader context including a consideration of their overall governance. In GlaxoSmithKline's view, in order to have meaningful inter-company dialogue about the press release, the matter should be discussed separately. GlaxoSmithKline was disappointed and surprised that AstraZeneca had refused to respond to any of the specific issues outlined, given that in response to a complaint about an almost-identical press release to AstraZeneca's German affiliate, AstraZeneca had provided undertakings which addressed many of GlaxoSmithKline's concerns.

Since no agreement had been reached on whether the press release fell under the remit of the PMCPA, and AstraZeneca had failed to address the substantive concerns, despite two formal letters and a teleconference at a senior level, GlaxoSmithKline had no alternative but to bring the matter to the PMCPA.

Jurisdiction of the PMCPA

GlaxoSmithKline noted that, AstraZeneca, in its first response, drew attention to the fact that the press release was issued by AstraZeneca PLC, the global holding company of the AstraZeneca Group. It went on to state that this was done to meet its disclosure obligations under the UK Listing Rules and indeed GlaxoSmithKline recognised that this was a global press release which principally affected European markets as a similar press release relating to the FDA approval of benralizumab for the USA market was issued a few days later on 14 November 2017.

However, the press was released on the legal domain of www.astrazeneca.com (www.astrazeneca.com/Legal-notice) which clearly stated that 'This website was operated by AstraZeneca UK Limited'. As such, this was a web page hosted by the UK affiliate of a multinational company which was obliged to abide by the Code as well as the Medicines and Healthcare products Regulatory Agency (MHRA) Blue Guide for the Advertising and Promotion of Medicines. Moreover, AstraZeneca PLC was a member of the ABPI and had therefore committed to adhere to the Code as was clear from the ABPI website full membership list where Astra Zeneca was listed with a link to the global website.

GlaxoSmithKline stated that in Case AUTH/2046/9/07 the Panel ruled that the disputed press release did not fall within the Code, since it was not issued in the

UK and it did not specifically refer to the availability or the use of a medicine within the UK. Hence it did not meet the requirement of what was now Clause 28.2 of the Code. GlaxoSmithKline believed that Case AUTH/2046/9/07 was not applicable as it related to a US corporate press release covering FDA regulatory activity for a US and financial audience. The AstraZeneca press release in this case concerned a CHMP opinion which related directly to the availability and use of benralizumab in the UK and was without question published in the UK. However, in Case AUTH/2046/9/07 GlaxoSmithKline responded to the concerns about the press release being factual, balanced and non-promotional, whilst AstraZeneca had never offered any explanation as to why it believed the press release similarly complied with the Code.

In the letter of 11 January, AstraZeneca stated that its UK affiliate separately issued a UK-specific press release about the positive CHMP opinion, which was sent to UK pharmaceutical trade and medical media outlets. GlaxoSmithKline stated, however, that when trying to access a UK press release on the EU CHMP opinion for benralizumab through AstraZeneca's UK website (www.astrazeneca.co.uk/media-press-releases.html), the link led back to the global press release website, with a link to the global press release only, for a UK audience.

Finally, the supplementary information to Clause 14.3 stated that 'material issued by companies which relates to medicines but which is not intended as promotional material for those medicines *per se*, ..., press releases, ..., financial information to inform shareholders, the Stock Exchange and the like, ..., should be examined to ensure that it does not contravene the Code or the relevant statutory requirements'.

GlaxoSmithKline therefore believed that the publication of the press release was a matter regulated by the Code and any question of its compliance with requirements of the Code was subject to the jurisdiction of the PMCPA.

Complaint

GlaxoSmithKline stated that in line with the Code, press releases should be non-promotional and the information provided in them should also be non-promotional. They must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Any data should be presented in a balanced and appropriate way to avoid the audience reaching any misleading conclusions due to omission of evidence. In particular, the supplementary information to Clause 26.2 made it clear that information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc must be factual and presented in a balanced way.

GlaxoSmithKline alleged that the data on the clinical endpoints presented in the press release (including annual asthma exacerbations rate [AAER], lung function [LF] and median reduction in daily oral corticosteroids [OCS] use and adverse events [AE]) based on clinical trials SIROCCO, CALIMA and ZONDA were unbalanced and misleading due to the omission of the full available evidence.

GlaxoSmithKline alleged that the statement 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo' did not give a balanced picture of benralizumab efficacy. It was data from only one of the two regulatory studies (SIROCCO) with the more favourable efficacy result. In CALIMA, the other regulatory study, there was a 28% reduction vs placebo. Both regulatory studies were considered by the EMA for marketing authorisation. GlaxoSmithKline alleged that to only present the endpoint from the study which showed a greater reduction was misleading, unbalanced and did not reflect the entirety of the data in breach of Clause 7.2 and 26.2.

GlaxoSmithKline alleged that the statement 'Rapid improvement in lung function (290mL increase in forced expiratory volume in one second (FEV1) from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness' did not give a balanced picture of the onset of benralizumab efficacy in a placebo-controlled trial and was misleading as it was not corrected for the placebo response. An improvement in the placebo arm was relevant to this claim. Also, secondary endpoints in CALIMA and in SIROCCO showed respectively a 116ml and 159ml improvement vs placebo in FEV1 at the end of the studies. 'Rapid improvement' was alleged to be an all-encompassing claim without the context of whether this was sustained or how efficacy in this case related to effectiveness. GlaxoSmithKline alleged therefore, this was an exaggerated and misleading claim, in breach of Clauses 7.2, 7.4 and 7.10 as well as an unbalanced statement of the findings of these studies in breach of Clause 26.2.

GlaxoSmithKline alleged that the statement '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients' was unbalanced and misleading for a number of reasons firstly the exacerbation reduction was presented as 'versus placebo' while FEV1 improvement and OCS reduction data were presented as 'from baseline'. Furthermore, in the '75% median reduction in daily OCS use' statement it was not explicit as to how the data had been presented as 'from baseline' had been omitted. The placebo arm had a 25% reduction, to give a true representation of OCS reduction, efficacy vs placebo data should be presented as a 'median reduction in daily OCS use of 50% versus placebo'. GlaxoSmithKline alleged that this unbalanced and misleading representation of data was in breach of Clauses 7.2 and 26.2.

GlaxoSmithKline was also concerned that the statement 'An overall adverse event profile similar to placebo' was misleading with respect to patient safety. Without any context of the adverse event profile, and any differences with placebo, it was inappropriate to present the safety profile of a new, black triangle medicine in this way. It raised

false hopes and could result in inappropriate prescribing and have an impact on patient safety. GlaxoSmithKline alleged a breach of Clauses 7.9, 7.10, 26.2 and 26.3 and of the MHRA Blue Guide Section 6.6 which stated 'Advertising which states or implies that a product is "safe" is unacceptable. All medicines have the potential for side-effects and no medicine is completely risk free as individual patients respond differently to treatment. For example, the term "placebo-like" in relation to safety or side-effects in general is considered to be misleading as it implies that there are no drug associated side-effects'.

GlaxoSmithKline stated that indeed, any medicine related adverse events in CALIMA were 8% for placebo vs 13% in the benralizumab arm, 10 benralizumab patients (2%) and 4 (<1%) who received placebo discontinued treatment because of adverse events and 2 patients had an adverse event leading to death vs none in the placebo arm. A comparable trend could be observed in SIROCCO: 18 benralizumab patients (2%) and 3 (1%) who received placebo discontinued treatment because of adverse events. Although these might be low numbers it was not only a factually incorrect statement but also not acceptable to state they were similar to placebo without any detail or context.

GlaxoSmithKline stated that if key clinical data had not been omitted and the vs placebo data had been included, the conclusion on clinical efficacy and safety would have been different. This was not acceptable in any press release, albeit to the financial or medical media. GlaxoSmithKline alleged that the press release raised unfounded hopes of successful treatment and misled with respect to the safety of the product in breach of Clause 26.2.

In addition, GlaxoSmithKline alleged that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' was inappropriate as in particular 'speed of onset', 'convenience' and would 'make a real difference' were promotional and could not be substantiated by clinical trial data. GlaxoSmithKline alleged a breach of Clauses 26.1 and 26.2. The press release must be capable of being substantiated and based on actual data and therefore a breach of Clause 7.5 was also alleged. GlaxoSmithKline stated that this also set unfounded hopes and misled the media into believing that all patients would have a response with no context of the response rate nor any clinical context regarding the speed of onset. In addition, GlaxoSmithKline alleged that to claim that benralizumab was convenient when it was administered by subcutaneous injection, every 4 weeks for 3 doses and then every 8 weeks, compared with inhalers or oral medication, was misleading in breach of Clause 7.3.

In summary, GlaxoSmithKline alleged breaches of Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 26.1, 26.2 and 26.3 of the Code as well as of the MHRA Blue Guide Section 6.6. To present clinical trial data in a misleading way and to issue a promotional press release did not maintain the high standards expected from a pharmaceutical company in breach of Clause 9.1. In addition, to the intent to promote in a misleading manner and the incorrect and misleading presentation of safety data had a potential impact on patient safety, and the failure to address GlaxoSmithKline's concerns, brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2.

RESPONSE

As the press release was issued by AstraZeneca's global organisation, that organization responded rather than the UK marketing organisation. Whilst AstraZeneca was headquartered in the UK, its global and corporate teams were located around the world, in the US and Sweden as well as the UK. AstraZeneca had taken the same approach throughout its correspondence with GlaxoSmithKline as it was most appropriate for the organisation which was responsible for the press release to respond directly.

AstraZeneca disagreed with GlaxoSmithKline's implication that this conflicted with the guidance on inter-company dialogue and submitted this was a deliberately narrow interpretation of the guidance which provided that communication 'should be between appropriate levels of relevant departments of the companies concerned. This will vary given the size and resources available within each company, but ideally those responsible for certifying the material, activity etc under the Code should be involved in the initial contact'.

AstraZeneca did not understand why a response from its global organisation had been characterized as inappropriate given that GlaxoSmithKline acknowledged that the material at issue was a global press release.

AstraZeneca stated that it took very seriously its compliance with all applicable laws and regulations, including pharmaceutical industry codes. AstraZeneca submitted that it had always addressed this matter in accordance with the high standards expected of a pharmaceutical company.

In summary AstraZeneca stated that:

- the press release was a non-promotional mandatory announcement issued pursuant to AstraZeneca PLC's obligations under the UK Listing Rules to disclose potentially share price sensitive information to investors and potential investors.

- the press release fell outside the scope of the ABPI Code because it was issued by AstraZeneca's headquarters and did not specifically refer to the availability of benralizumab in the UK. The treatment of financial information under the Code was different compared with other information made available to the public.

- even if the Code applied, the press release complied with the relevant provisions – and

specifically that neither the press release nor AstraZeneca's actions breached the Code or the MHRA Blue Guide.

- it was concerned at a number of inaccuracies in GlaxoSmithKline's descriptions of AstraZeneca's statements, actions and its websites, which it addressed in detail below.

- it was disappointed to have received a complaint from GlaxoSmithKline alleging multiple breaches of the Code in a case with numerous similarities to Case AUTH/2046/9/07 (Takeda v GlaxoSmithKline) and where GlaxoSmithKline sought to take an opposite position to that taken in that case. AstraZeneca questioned GlaxoSmithKline's motivation for making such an extensive complaint.

- GlaxoSmithKline had not engaged in inter-company dialogue as envisaged by the procedure and guidance on inter-company dialogue. The complaint had been made prematurely. The company regretted that it did not have the opportunity to complete inter-company dialogue and attempt to resolve these issues with GlaxoSmithKline.

Background on the release and information requested by the PMCPA

AstraZeneca PLC issued the press release on 10 November 2017; it was a mandatory announcement issued pursuant to AstraZeneca PLC's obligations under the UK Listing Rules to disclose potentially share price sensitive information to investors and potential investors. It was issued through the Regulatory News Service and to AstraZeneca's media distribution list for corporate business releases (aimed at financial and business media covering the pharmaceutical industry and AstraZeneca PLC).

The press release, which gave notice of the positive EU CHMP opinion for benralizumab for severe uncontrolled eosinophilic asthma, did not specifically refer to the availability or use of benralizumab in the UK and was available on the global website (astrazeneca.com) which was clearly labelled as intended for people seeking information on AstraZeneca's global business. Country-specific information, including for the UK, was available via country-specific websites. Further information on the website location of the release was set out in the section below (Jurisdiction of the Code). AstraZeneca separately issued a UK-specific press release in respect of the positive CHMP opinion to UK pharmaceutical trade and medical media outlets which was not available on any of AstraZeneca's websites.

AstraZeneca submitted that the press release was not promotional in nature. The information and data included in the press release was intended to inform investors, not patients or health professionals.

When the press release was issued, benralizumab was not approved in the UK or elsewhere in Europe. It was approved by the European Commission on 10 January 2018 (brand name Fasenra) as an add-on maintenance treatment in adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists.

AstraZeneca stated that the release did not fall within the materials for which certification was required by Clause 14 of the Code and therefore no certificate was produced and Clause 14.3 was not breached. Details of the process by which the release was examined were provided. A copy of the benralizumab summary of product characteristics (SPC) was provided. It was not available when the press release was issued as benralizumab was not approved until 10 January 2018.

Jurisdiction of the Code

AstraZeneca submitted that the press release fell outside the scope of the Code because it did not specifically refer to the availability of benralizumab in the UK (as per Clause 28 and Case AUTH/2046/9/07 as analysed below). In addition, the Code treated financial information differently compared with other information made available to the public (Clause 26 and its supplementary information).

AstraZeneca believed that this was in line with the overarching purpose of the Code as set out in Clause 1 and its supplementary information. Those provisions made it clear that the Code captured product promotion and product information when directed at, or otherwise influenced, an audience that played any part in the decision-making unit about the promotion of medicines, including the public as consumers and patients.

Information on the Internet

GlaxoSmithKline's complaint was based on the location of the press release on the Internet, with GlaxoSmithKline suggesting that the operation or hosting of the relevant website by a UK based company determined the jurisdiction of the Code. As such, Clause 28 (The Internet) was the relevant part of the Code. AstraZeneca, however, found GlaxoSmithKline's reasoning on this subject confused, as it had not explained how Clause 28 operated to bring the press release in scope. This was one of the topics on which clarification was sought during the truncated inter-company dialogue. In this regard, AstraZeneca stated that:

- GlaxoSmithKline's first letter (7 December 2017) stated that the press release was subject to the Code because it was released on 'a web page hosted by the UK affiliate of a multinational company which was obliged to abide by the Code and the MHRA Blue Guide.

- GlaxoSmithKline's second letter (5 January 2018) stated that the press release was clearly an activity regulated by the Code and suggested that the release was in fact a UK-specific release because it was possible to navigate to its location on AstraZeneca's global website from AstraZeneca's UK-specific website (astrazeneca.co.uk).

- GlaxoSmithKline's complaint to the PMCPA (15 January 2018) repeated the above statements and then included an additional line of reasoning (which did not appear in the letters of 7 December or 5 January) that the Code applied because AstraZeneca PLC was a member of the ABPI.

AstraZeneca did not dispute the location of the release on the Internet. The release was made available on AstraZeneca's global website which clearly stated that 'This website is intended for people seeking information on AstraZeneca's worldwide business. Our country sites can be located in the AZ Network'. When the press release was issued the Legal Notice and Terms of Use link incorrectly stated that the website was 'operated by AstraZeneca UK Limited'; that had since been corrected to refer to AstraZeneca PLC.

AstraZeneca submitted that the following was the correct interpretation of the Code in assessing whether the release was caught by Clause 28:

- promotional materials directed to a UK audience were within the scope of the Code (Clause 28.1).

- information or promotional materials placed on the Internet outside the UK were within the Code if they were placed on the Internet by an ABPI member or an affiliate and made specific reference to the availability or use of the medicine in the UK (Clause 28.2).

- AstraZeneca noted that the Code did not expressly deal with the situation under discussion where information (as distinct from promotional material) was placed on the Internet within the UK by an ABPI member or an affiliate, for global circulation, and which did not refer specifically to the availability or use of the medicine in the UK. AstraZeneca suggested that the correct interpretation of the Code, its intent and previous rulings (including Case AUTH/2046/9/07) was that the same principles should apply whether the relevant information was placed on the Internet within or outside the UK – ie that the Code only applied if it contained specific reference to the availability or use of the medicine in the UK.

In support of this interpretation, AstraZeneca referred to the facts and the decision in Case AUTH/2046/9/07 where information was placed on the GlaxoSmithKline corporate website which was UK based. In that case, the Panel found that a global press release was not subject to the Code because it did not make specific reference to the availability or use of the medicine in the UK. It was noted that the relevant medicine was actually available in the UK at the time. AstraZeneca noted GlaxoSmithKline's attempts to distinguish this case because the relevant press release was placed on the GlaxoSmithKline corporate website by GlaxoSmithKline's US affiliate and that the subject of that release was a meeting of the FDA Advisory Committee rather than a European event. AstraZeneca did not consider these to be distinguishing features in the current matter:

- a positive CHMP opinion was not a specific reference to a medicine being available in the UK. There was no reference to benralizumab being available in the UK as it was not approved when the press release was issued. It was therefore incorrect to suggest that a positive CHMP opinion was somehow a proxy for specific reference to a medicine being available in the UK. The release was for global consumption and was not specific to any particular market as the positive CHMP opinion was relevant for the investment community.

- the legal entity responsible for GlaxoSmithKline's press release should be irrelevant. Clause 28 applied to ABPI members and their affiliates, so whether it was one of GlaxoSmithKline's UK entities or its US affiliates was irrelevant. In addition, GlaxoSmithKline argued in Case AUTH/2046/9/07 that the press release was a corporate release relevant to its investors and it was issued on its global corporate website – as was the release for AstraZeneca.

AstraZeneca noted that GlaxoSmithKline, in concluding its arguments on jurisdiction, had referred to Clause 14.3 (supplementary information) and suggested that because of that provision the release was regulated by the Code. This reference was not made expressly in either of GlaxoSmithKline's letters to AstraZeneca. In addition, it contradicted GlaxoSmithKline's allegation that the release was promotional. Whilst AstraZeneca agreed the release was not promotional, it did not agree that, as a result, Clause 14 applied automatically. AstraZeneca submitted this interpretation was inconsistent with the meaning and effect of Clause 28 and the outcome of Case AUTH/2046/9/07. Clause 14 could not be the determining factor in the jurisdiction of the Code and should only apply if the information in question otherwise fell within the Code (eg pursuant to Clause 28).

Accessibility of the press release

With regard to GlaxoSmithKline's suggestion that the release was in fact a UK-specific release because it was possible to navigate to its location on AstraZeneca's global website from AstraZeneca's UK-specific website (astrazeneca.co.uk), whilst that potential navigation route was factually correct, GlaxoSmithKline had mischaracterised how that would happen. AstraZeneca alleged that GlaxoSmithKline was wrong to state 'However, when trying to access a UK press release on the EU CHMP opinion for benralizumab through AstraZeneca's UK website … the link leads back to the global press release website, with a link to the global press release only, for a UK audience'. AstraZeneca noted:

- there was no reference to the positive CHMP opinion for benralizumab on the AstraZeneca UK-specific website.

- if someone looked for any AstraZeneca news on the UK-specific website, he/she was directed to contact various AstraZeneca media teams. The

same page also provided a link to the global website homepage, beneath the statement 'For media information about our Global operation please visit our global website'. This link went through to the global website www.astrazeneca.com. It did not, as GlaxoSmithKline suggested, link directly to the global press release website – or even UK-focused information.

- the global website was clearly labelled with the following disclaimer on the bottom of each webpage, 'This website is intended for people seeking information on AstraZeneca's worldwide business. Our country sites can be located in the AZ Network'.

- on the global website homepage, news releases were found either via (i) Investor Relations/ Stock Exchange Announcements or (ii) Media/ Media Centre. As such, a visitor who looked for an AstraZeneca global release and who arrived at that site from the UK-specific website, would have to navigate several pages and make at least two clicks before reaching a global release. In addition, the two most recent corporate news releases were also featured at the bottom of the global website homepage. The press release was featured in this location from 10 to 15 November 2017 (labelled as a corporate press release).

GlaxoSmithKline provided exactly this path in its complaint and AstraZeneca was unclear why GlaxoSmithKline mischaracterised these matters.

Treatment of financial information under the Code

AstraZeneca stated that even if GlaxoSmithKline was correct in its assertion that the press release was within the scope of the Code, it did not believe that it would be appropriate to assess the release with reference to the provisions of Clause 7 (Information, Claims and Comparisons). In those circumstances the release would fall within the classification of financial information (as referred to in the supplementary information to Clause 26.2), which was treated differently to other information made available to the public. Clause 26.2 covered information made available to the public. The supplementary information to Clause 26.2, Information to the Public, specifically applied the provisions of Clause 7 to such information and press releases. However, supplementary information for Clause 26.2 (Financial Information) provided only that the relevant information must be factual and presented in a balanced way. There was no reference to Clause 7 and therefore Clause 7 did not apply to financial information.
GlaxoSmithKline made a similar submission in Case AUTH/2046/9/07; the case report recorded that 'GlaxoSmithKline submitted that a press release clearly intended for business and financial media was not promotional and as such was not subject to the promotional aspects of the Code'. AstraZeneca was surprised that GlaxoSmithKline's complaint conflicted with submissions that it had made to the PMCPA in respect of its own conduct.

AstraZeneca submitted that its position was consistent with the MHRA Blue Guide (section 7.7) and the EFPIA code (page 6 and also section 2, content of websites page 21) in that financial press releases were treated differently from advertisements to persons qualified to prescribe or supply medicines.

Content of the press release

AstraZeneca submitted that the press release was not within the scope of the Code. In the event that the Panel disagreed, AstraZeneca asserted that the press release complied with the Code, and that neither the press release nor AstraZeneca's actions breached the Code (Clause 7) or the MHRA Blue Guide (Section 6.6).

The press release was a non-promotional communication, aimed at a worldwide audience and sent to business and financial media. The information provided in the release was factual, presented in a balanced way, of clear commercial importance and was sufficient to inform the investment decisions of the financial and investment audience to which it was directed. In addition, for completeness, transparency and to ensure that readers who wished to see further detail, active hyperlinks within the press release directed readers to the study publications for each of the relevant clinical trials (CALIMA, SIROCCO, and ZONDA) (both ahead of the high level bulleted attributes and again in the section 'About the WINDWARD Programme).

AstraZeneca responded to each of GlaxoSmithKline's concerns about statements in the press release:

1 **'Up to 51% reduction in the annual exacerbations rate (AERR) versus placebo'**

AstraZeneca stated that the reduction in AERR vs placebo in the two registrational studies, SIROCCO and CALIMA, were 51% and 28% respectively. The inclusion of 'up to' ensured that the claim was factually correct and not misleading: 51% was the maximum response observed across both studies. The claim was therefore accurate, balanced and provided in a succinct and easily comprehensible manner for the intended audience to inform investment decisions.

2 **'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness'.**

AstraZeneca disagreed that the claim was unbalanced or misleading for the intended audience. It was acceptable to provide the improvement in FEV1 at the 4 week time point as it was relevant to the reader's understanding of the medicine's profile.

AstraZeneca disagreed that the phrase 'Rapid improvement' was an all-encompassing claim because it was not a claim but a factual statement in non-promotional material. It was also not all-encompassing as it did not cover all endpoints, but referred specifically to lung function using FEV1 as a surrogate. The context was very clear.

The statement specifically described the benralizumab mechanism of action with respect to the timing of effect on lung physiology, as indicative of a rapid FEV1 response. The statement was that this was 'providing an early indication of effectiveness' not all-encompassing effectiveness. GlaxoSmithKline queried how 'efficacy relates to effectiveness'. AstraZeneca submitted that it was appropriate to use the word 'effectiveness' given the intended financial audience. The statement did not represent an all-encompassing claim of clinical efficacy.

AstraZeneca submitted that the statement was accurate, balanced and presented in succinct manner which was easily comprehensible for the intended audience.

3 **'75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients'**

AstraZeneca strongly disagreed that this claim was misleading or unbalanced. It was factually correct and appropriate given the audience. Additional context was provided in the press release in the section titled 'About the WINDWARD Programme'. There was also no reason why the data relating to reduction in daily OCS use must be presented in exactly the same way as the exacerbation reduction data.

4 **'An overall adverse event profile similar to placebo'**

AstraZeneca was committed to patient safety and took any communications relating to all its medicines (both marketed and in development) very seriously, especially when safety profiles were discussed. AstraZeneca strongly refuted the allegations that the above claim was misleading or that it raised false hopes and could lead to inappropriate prescribing. Indeed, the intended financial and investment nature of the audience precluded this.

AstraZeneca submitted that the claim was factually correct and in line with relevant study reports. In the press release, the term 'overall' adverse events referred to the 'any' adverse event analysis for the studies. During the treatment period in the SIROCCO study, adverse events were reported by similar percentages of patients who received benralizumab Q8W (71%) or placebo (76%). The ZONDA study reported that 'Frequencies of adverse events were similar between each Benralizumab group and placebo group'. In CALIMA, the percentage of any reported adverse events for patients who received placebo was 78% and 75% for benralizumab (Q8W).

It was generally well accepted that adverse events were observed in the placebo arms of studies, and so it was reasonable to present an overall comparison of the adverse events observed in the placebo and active comparator arms of the study in a succinct and easily comprehensible manner that was tailored to the audience and would be appropriately understood. In addition, the press release did not state or imply that benralizumab was 'safe' or that there was an observed lack of side-effects and did not, therefore, breach Clause 7 of the Code or Section 6.6 of the MHRA Blue Guide. As stated above, links to the full study publications for the data presented were included in the press release.

5 **'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use'**

This claim was used with the knowledge that in the registration trials benralizumab had demonstrated efficacy, the ability to reduce oral corticosteroids usage and speed of onset in relation to both reduction of FEV1 and eosinophil depletion beginning after the first dose.

AstraZeneca believed that the word 'potential' ensured that the audience knew that any clinical benefits observed in studies to date were not applicable to all patients.

The suggestion by GlaxoSmithKline that the word 'convenience' was intended as a comparison of benralizumab with oral medications and inhalers was incorrect, and not an obvious conclusion to draw about the phrasing of that sentence. The use of the 'convenience' referred to the every 8-week maintenance dosing schedule and this was acknowledged in GlaxoSmithKline's letter of 7 December 2017. Every 8-week dosing was currently the longest dosing interval for a marketed asthma biologic.

Inter-company dialogue

AstraZeneca did not believe that GlaxoSmithKline had engaged in inter-company dialogue as envisaged by the PMCPA guidance. AstraZeneca therefore believed that the complaint was submitted prematurely.

GlaxoSmithKline had never suggested an in-person conversation regarding the issues raised and it had ignored or declined AstraZeneca's repeated offers of conversations and requests for specific clarification of issues, as explained below:

- GlaxoSmithKline's first letter (7 December 2017) did not include an offer of inter-company dialogue. Instead, it referred to inter-company dialogue but demanded that AstraZeneca agree to specified steps (providing information on distribution and examination of the release; giving an undertaking; and, issuing a corrective statement).

- AstraZeneca's response (20 December 2017) concluded with a statement that if GlaxoSmithKline had any further concerns, AstraZeneca would be happy to discuss them. AstraZeneca acknowledged that it did not deal with the detailed complaints raised by GlaxoSmithKline but instead focused on the detailed background of the release which it hoped

would help clarify that the release was global in nature and intended for a financial and business audience.

- GlaxoSmithKline's letter of 5 January 2018 (emailed on 4 January) demonstrated that it continued to have further concerns but it did not take up AstraZeneca's offer of a conversation. This second letter reiterated GlaxoSmithKline's demand that AstraZeneca agreed to the specified steps, again without any suggestion of a conversation.

- AstraZeneca's response (11 January) explicitly stated that it needed further information to respond to GlaxoSmithKline's concerns. Specific reference was made to dates and attendees for that meeting which demonstrated AstraZeneca's continued commitment to have a genuine dialogue.

- GlaxoSmithKline and AstraZeneca spoke by telephone on 12 January. AstraZeneca stated that GlaxoSmithKline's account above did not accurately represent that telephone conversation.

    - AstraZeneca requested that call to amplify the request for a meeting made in its 11 January letter and to emphasise that the complexities around global financial releases meant that appropriate attendees included corporate personnel as well as medical. It was not to rehearse the dialogue intended for the proposed meeting, nor were all of the relevant AstraZeneca personnel on that conference call to enable that dialogue to occur.

    - The relevant AstraZeneca personnel were not all on the call. Whilst it was correct that AstraZeneca was 'not willing to discuss the specific detail of the points raised in the GlaxoSmithKline letter' on the call, it was misleading to imply that such unwillingness displayed an overall refusal to engage in a dialogue. AstraZeneca had expressly requested a separate meeting to do so and to obtain the requested clarification. AstraZeneca gave assurances that each point of the complaint would be addressed at such a meeting, with the relevant personnel present.

    - It was not correct that AstraZeneca had 'underlined its position that the press release did not fall under the ABPI Code'. No such statement was made.

    - AstraZeneca had suggested that the proposed face-to-face meeting also covered the broader question of global press releases but did not believe that that suggestion automatically rendered the proposed meeting redundant. If GlaxoSmithKline was interested in pursuing an inter-company dialogue but had issues with that topic, it could have proposed excluding that topic from the meeting; instead, it rejected the meeting in its entirety.

- Following the 12 January telephone conversation, GlaxoSmithKline and AstraZeneca corresponded by email. AstraZeneca believed that such correspondence was relevant background and it noted that GlaxoSmithKline had not provided that correspondence with its complaint. The email exchange was provided.

    - GlaxoSmithKline's email on 12 January declined AstraZeneca's proposed meeting on the grounds that 'GlaxoSmithKline and AstraZeneca fundamentally have a different view on this matter and that our concerns raised will not be adequately resolved through further intercompany dialogue'. AstraZeneca stated that it did not discuss its view of the specific detail of GlaxoSmithKline's complaints on the 12 January telephone call. It was therefore difficult to see how GlaxoSmithKline could have concluded that the positions were irreconcilable and pre-empt the outcome of such a meeting by concluding that GlaxoSmithKline and AstraZeneca would not be able to agree.

    - AstraZeneca's response to that email (15 January 2018) restated its request for clarification of GlaxoSmithKline's position on several matters in order to respond to GlaxoSmithKline's issues. It also reaffirmed AstraZeneca's commitment to a genuine dialogue and AstraZeneca's continued availability for a face-to-face meeting.

Further details

AstraZeneca explained that the press release was prepared in line with its procedures for the generation of a Regulatory News Service disclosure.

In anticipation of the positive CHMP opinion, drafting of the press release began in early November 2017. The press release was developed and approved by the global team responsible for benralizumab. Details of the roles involved in this process were provided.

The press release was issued through the Regulatory News Service. It was also distributed electronically to AstraZeneca's media distribution list for corporate business releases (aimed at financial and business media covering the pharmaceutical industry and AstraZeneca PLC). The media distribution list was provided.

In response to a request for further information AstraZeneca confirmed that the 290ml increase in FEV1 from baseline at week 4 seen in the benralizumab 30mg every eight weeks arm was taken from the SIROCCO study. The data on file created was provided. The pooled post-hoc analysis (for SIROCCO and CALIMA studies) mentioned in the press release FitzGerald, *et al* 2018, was provided. This was published in September 2017 (ahead of print).

AstraZeneca stated that the study explored the relationship between benralizumab efficacy and baseline patient characteristics including blood eosinophil counts, historical exacerbations, OCS use and the history of nasal polyps, among other baseline factors.

PANEL RULING

The Panel noted that its role was to consider matters in relation to the Code and not the MHRA Blue Guide; GlaxoSmithKline's allegations regarding the Blue Guide were thus not considered.

The Panel noted the comments from both parties about the inter-company dialogue and that there were clearly some differences of opinion. GlaxoSmithKline contacted AstraZeneca on 7 December 2017, 5 January 2018 and 12 January. It appeared that AstraZeneca had not responded to the detailed points raised. In an email dated 15 January, AstraZeneca requested further clarification of GlaxoSmithKline's position and interpretation to be able to respond in more detail and offered to address each matter at a proposed meeting. GlaxoSmithKline had not agreed to the meeting and had submitted a complaint to the PMCPA approximately a month (allowing for the Christmas break) after first raising detailed points when it had not received a response. The matter had been referred to the Panel by the case preparation manager who by accepting the complaint was satisfied that the requirements for inter-company dialogue had been met.

This had not changed following receipt of further details from AstraZeneca.

The Panel noted the requirements of Clause 1.11. The supplementary information to Clause 1.11, Applicability of Codes, stated that pharmaceutical companies must ensure that they complied with all applicable codes, laws and regulations to which they were subject. This was particularly relevant when activities/materials involved more than one country or when a pharmaceutical company based in one country was involved in activities in another country.

Activities carried out and materials used by a pharmaceutical company located in a European country must comply with the national code of that European country as well as the national code of the country in which the activities took place or the materials were used. In the event of a conflict of requirements the more restrictive requirements would apply. The only exemption for companies based in the UK not to follow the UK Code was with regard to the limits on subsistence set in European countries.

Clause 1.11 and its supplementary information were based on requirements in the EFPIA Health Professional Code. The Panel considered that, as a minimum, companies located in the UK were clearly required to comply with the UK Code and this would apply to AstraZeneca global. There might be occasions when it could be clearly demonstrated that the ABPI Code did not apply. In the Panel's view the press release at issue came within the scope of the ABPI Code; it had been produced by a company located in the UK (AstraZeneca global) and placed on a UK website described at the time as operated by AstraZeneca UK Limited. This had since been changed to AstraZeneca PLC. The Panel considered that the fact there was a UK specific press release did not mean that the press release in question was not covered by the ABPI Code.

The Panel did not accept AstraZeneca's submission that the Code did not expressly deal with the current situation where information was placed on the Internet within the UK for global circulation. In the Panel's view, for the reasons outlined above, the UK Code applied.

The Panel considered the points made by both GlaxoSmithKline and AstraZeneca about the relevance of Case AUTH/2046/9/07 when GlaxoSmithKline US had placed a press release on the GlaxoSmithKline corporate website. That press release referred to use of the product in the US and a meeting of the FDA Advisory Committee. The Panel at the time had decided that Clause 21.2 applied (now Clause 28.2) as the press release was placed on the Internet by a company outside the UK but as it did not meet the second requirement, ie specifically refer to its availability or use in the UK, then there was no breach of that clause of the Code and the press release was not within the scope of the Code. The Panel now noted, however, that in considering Case AUTH/2046/9/07, no reference was made to what was then Clause 1.7 but now Clause 1.11 ie that activities carried out and materials used in a European country by a pharmaceutical company located in a country other than a European country must comply with the EFPIA Code as well as the national code of the country in which the activities are carried out and materials are used. It appeared that no account had been taken of the fact that GlaxoSmithKline Global was based in the UK. The Panel's rulings of no breach of the Code were not appealed.

The Panel noted that Clause 28.2 of the Code stated that information or promotional material about medicines covered by Clause 28.1 which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK. The Panel, however, did not consider that Clause 28.2 was relevant in the case now before it as the AstraZeneca press release was not placed on the Internet outside the UK. In any event, the press release at issue referred to a product with a positive EU opinion recommending a marketing authorization which would be valid in the UK.

The Panel noted AstraZeneca's submission regarding the EFPIA Guidelines for Internet Websites Available to Healthcare Professionals, Patient and the Public in Europe. The Guidelines stated that member associations might find it necessary to adapt these guidelines to meet their particular requirements or needs and were encouraged to adopt additional

measures which extended further than the EFPIA Guidelines. The EFPIA Guidelines stated that general information on the company was not regulated by the EFPIA Guidelines or provisions of medicines advertising law.

The Panel noted that unlike the EFPIA codes the ABPI Code had detailed requirements for relations with the public and the media (Clause 26). The Panel considered if general information on the company promoted a prescription only medicine then such information was likely to be covered by medicines regulation which prohibited the advertising of prescription only medicines to the public.
The Panel noted the supplementary information to Clause 26.2 that information made available in order to inform stakeholders, the Stock Exchange and the like by way of annual reports and announcements etc might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. Business press releases should identify the business importance of the information.

The Panel noted that the press release referred to the positive CHMP opinion. It referred to features of benralizumab and its potential to make 'a real difference to patients with its combination of efficacy, speed of onset, convenience and ability to reduce oral steroid use'. The results of studies were described and a quotation from a UK investigator included the use of benralizumab to 'help transform severe asthma care'.

The press release ended with notes to editors which covered severe asthma, benralizumab, the Windward Programme in asthma which consisted of Six Phase III trials, AstraZeneca in respiratory diseases, Medimmune (part of AstraZeneca), AstraZeneca and referred to the AstraZeneca.com website. After the list of contacts for media relations and investor relations it was stated that the announcement contained inside information. The Panel noted that the press release did not identify the business importance of the information at the start. The Panel did not consider, given its clinical content, that the press release was clearly a business press release.

The Panel noted the distribution of the press release which included business reporters/editors, markets reporters and a small number of health reporters/ editors. The circulation was not limited to financial journalists.

The Panel agreed with AstraZeneca that press releases were treated differently from advertisements to health professionals. This distinction was clear in the Code in that information to the public about prescription only medicines was covered by Clause 26 of the Code which referred to relations with the public and media. Clause 26.2 covered information made available to the public either directly or indirectly. The supplementary information to Clause 26.2, Information to the Public, was clear that Clauses 7.2, 7.4, 7.5, 7.8, 7.9, 7.10 and 7.11, which set out the information quality standards in the Code, also applied and thus whether the material was an advertisement to a health professional or information to the public, similar standards applied. That the specific supplementary information relating to financial information did not refer to the information quality standards did not mean that these standards did not apply to such material, the supplementary information added clarity that there was often a need for Stock Exchange announcements to refer to medicines not yet authorized. It also referred to the need to identify the business importance of the information and that the information must be factual and presented in a balanced way.

Taking all the circumstances into account as set out above, the Panel considered that the press release was subject to the Code. It then went on to consider the allegations made by GlaxoSmithKline.

The Panel noted that the SPC available on the electronic medicines compendium (eMC) stated that Fasenra (benralizumab) was first authorised on 8 January 2018. The recommended dose of benralizumab was 30mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. Fasenra was intended for long-term treatment. A decision to continue the therapy should be made at least annually based on disease severity, level of exacerbation control and blood eosinophil counts. The SPC stated, under special warnings and precautions for use, that abrupt discontinuation of corticosteroids after initiation of Fasenra therapy was not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

The Panel noted that the press release stated that patients in SIROCCO and CALIMA received standard of care medicine (including high dose inhaled corticosteroids and long acting beta 2 agonists) and were randomized to receive benralizumab 30mg every 4 weeks, 30mg every 4 weeks for the first 3 doses followed by 30mg every 8 weeks or placebo via a subcutaneous injection.

With regard to the claim 'Up to 51% reduction in the annual asthma exacerbations rate (AERR) versus placebo', the Panel noted this was from the SIROCCO trial (Bleecker *et al* 2016). The CALIMA trial (FitzGerald *et al* 2016) stated that annual exacerbation rates were approximately 28% lower than with placebo. The Panel considered that the use of the phrase 'up to 51%' was misleading as it did not reflect the range. The balance of the data had not been reflected and a breach of Clause 7.2 was ruled.

The Panel considered that the information made available to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled accordingly.

With regard to the claim 'Rapid improvement in lung function (290mL increase in forced expiratory volume in FEV1 from baseline at 4 weeks) after the first dose, providing an early indication of effectiveness', the Panel noted that SIROCCO concluded that both benralizumab dosing regimens significantly improved pre-bronchodilator FEV1 in patients at week 48 compared with placebo. The

difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl was 159ml (p = 0.0006). The Panel noted AstraZeneca's submission that the 290ml increase in FEV1 from baseline at week 4 data as stated in the press release came from SIROCCO. Data on file had been created which stated that at week 4 there was a 290ml increase in FEV1 for benralizumab and a 209ml increase for placebo (p=0.039) versus baseline. The estimated difference between benralizumab and placebo was 81ml.
CALIMA concluded that benralizumab significantly improved pre-bronchodilator FEV1. Improvements in pre-bronchodilator FEV1 were present within 4 weeks of treatment start and were maintained through the treatment period. At week 56 the difference between benralizumab 30mg every 8 weeks and placebo (in patients with baseline eosinophils ≥ 300 cells per mcl) was 116ml (p = 0.0102). The Panel noted that CALIMA stated that annual exacerbation rates, pre-bronchodilator FEV1 and total asthma scores were not affected by benralizumab for the subset of patients receiving medium-dosage inhaled corticosteroids plus LABA with blood eosinophils ≥ 300 cells per mcl at baseline.

The data on file for CALIMA at week 4 showed there was a 280ml increase in FEV1 for benralizumab 30mg every 8 weeks and 152ml for placebo (p=0.002) versus baseline. The estimated difference between benralizumab and placebo was 127ml.

The SIROCCO and CALIMA data on file stated that the analysis of these endpoints were not multiplicity protected and therefore p values were reported as nominal. Results were descriptive only.

The Panel noted that the ZONDA study (Nair *et al* (2017)) assessed the effects of benralizumab versus placebo on the reduction in oral glucocorticoid dose whilst maintaining asthma control in adults with severe asthma. ZONDA concluded that benralizumab showed significant clinically relevant benefits compared with placebo on oral glucocorticoid use and exacerbation rates. These effects occurred without a sustained effect on FEV1.

The Panel noted that the claim in the press release referred to a rapid improvement in lung function. It appeared to the Panel that if the improvements in FEV1 at 4 weeks in SIROCCO and CALIMA were seen as rapid improvement in lung function then there was evidence to support the change in both the treated and placebo groups. The Panel considered that it was misleading and exaggerated not to include the placebo data in the press release to ensure that the improvements from baseline were not confused with improvements compared with placebo. The Panel therefore ruled a breach of Clauses 7.2 and 7.10 of the Code. The data was capable of substantiation so no breach of Clause 7.4 was ruled.

The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the claim '75% median reduction in daily OCS use and discontinuation of OCS use in 52% of eligible patients', the Panel considered that it was not clear that the reduction in daily OCS use difference was compared to baseline. It noted that the placebo data also showed a decrease in daily OCS use. The SPC published on the eMC gave the placebo reduction as 25%. The Panel considered that the data in the press release was not placed in context; the press release was misleading in this regard and the Panel therefore ruled a breach of Clause 7.2.
The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the claim 'an overall adverse event profile similar to placebo', the Panel noted that the medicine was new and at the time of the press release it was not licensed in the UK. The intended audience would not necessarily be familiar with the incidence of adverse events with placebo. The claim referred to the addition of benralizumab rather than the overall incidence of adverse events when the medicine was used in addition to high-dose inhaled corticosteroids plus long acting beta agonists. The SPC published on the eMC stated that the most common adverse reactions during treatment were headache (8%) and pharyngitis (3%). Injection site reactions (eg pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with the recommended benralizumab dose compared with 1.9% in patients treated with placebo.

The Panel was concerned about the lack of context for the claim in the press release to an audience that were, in effect, members of the public. There was no further data in the press release about adverse events. The press release was misleading in this regard; it was not balanced and a breach of Clause 7.9 was ruled. The Panel considered that the claim exaggerated the properties of the product and thus it ruled a breach of Clause 7.10.

The Panel considered that information to the public about the adverse event profile had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

The Panel noted that Clause 26.3 covered material which related to a medicine and which was intended for patients taking that medicine and required, *inter alia*, that when the material related to a medicine which was subject to additional monitoring, an inverted black equilateral triangle must be included on it together with a statement about additional monitoring and reporting of side-effects. The Panel considered that as the press release was not specifically intended for patients taking the medicine Clause 26.3 did not apply and the Panel ruled no breach of that clause.

With regard to GlaxoSmithKline's general allegation that the omission of both key clinical data and the placebo data meant that the conclusion on efficacy and safety would be different, the Panel noted that it had ruled various statements and claims in breach of Clause 26.2. It considered that this allegation had

been addressed by its rulings of breaches of the Code above. It would be relevant in considering the allegations of breaches of Clause 9.1 and 2 below. It therefore ruled no breach of Clause 26.2 in relation to the broad allegation.

With regard to the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' the Panel considered that this was a broad, strong claim for the medicine. It was a quotation from the AstraZeneca executive vice president, global medicines development and chief medical officer. The Panel considered that readers of the press release would be clear that the benralizumab was to be dosed every eight weeks. However, it was not clear that the first 3 doses were to be given every 4 weeks. The Panel did not accept AstraZeneca's submission that the use of the word 'potential' meant that readers would be aware that any clinical benefits observed in studies to date were not applicable to all patients.

Patients using Fasenra would need to continue with other asthma medication as stated in the package information leaflet (high doses of corticosteroids). Use of Fasenra might allow patients to reduce or stop daily OCS. This would be done gradually under supervision of a doctor.

On balance, the Panel did not consider that the claim in the press release was an advertisement for Fasenra, a prescription only medicine, to the public. The medicine was unlicensed at the time of the press release and thus not classified as a prescription only medicine. The Panel ruled no breach of Clause 26.1. It considered that the claim 'Benralizumab has the potential to make a real difference to patients with its combination of efficacy, speed of onset, convenience and the ability to reduce oral steroid use' might raise unfounded hopes of successful treatment, particularly given the lack of information about the need to be monitored before changing the doses of a patient's current medication.

The Panel noted the allegations about the speed of onset and the data for FEV1, and the changes at 4 weeks for patients with baseline eosinophils ≥ 300 cells per mcl. The Panel queried whether adding in an additional therapy was convenient for patients. It was not clear until page two of the press release that benralizumab was a subcutaneous injection. The Panel noted that there were other medicines available, one of which was GlaxoSmithKline medicine, mepolizumab (Nucala), which was to be given every 4 weeks. The basis of the claim for convenience in the press release was not clear to the Panel. AstraZeneca submitted that it related to the 8 week maintenance dosing schedule which the Panel noted was longer than for GlaxoSmithKline's medicine. The Panel considered that, given AstraZeneca's product had 3 doses at 4 week intervals, it was possible that maintenance treatment at 8 weeks would not be seen as convenient compared to treatment at 4 weeks. The Panel considered that, overall, the claim could be read as a comparison with inhalers and/or oral medication and compared to inhalers or oral medication, benralizumab was not convenient. Overall, it considered that the claim for convenience was misleading and therefore ruled a breach of Clause 7.3.

The Panel considered that information to the public had not been presented in a balanced way and a breach of Clause 26.2 was ruled.

With regard to the alleged breach of Clause 7.5, the Panel noted that this required that substantiation be provided as soon as possible and within 10 working days following a request from a health professional. GlaxoSmithKline had provided no information in this regard. The Panel noted that GlaxoSmithKline was dissatisfied with AstraZeneca's response to the intercompany dialogue. The Panel did not consider that GlaxoSmithKline had provided evidence that when a health professional asked for substantiation this was not provided. The Panel ruled no breach of Clause 7.5.

Noting all its rulings above, the Panel did not consider that high standards had been maintained and therefore ruled a breach of Clause 9.1.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Panel noted that one of the reasons for GlaxoSmithKline to support a breach of Clause 2 was AstraZeneca's alleged failure to address GlaxoSmithKline's concerns. The Panel did not consider that this was relevant to its consideration regarding Clause 2. The Panel noted its rulings of breaches of the Code. It considered that it was extremely important that press releases were accurate, balanced and not misleading. On balance, the Panel considered that the circumstances did not warrant a ruling of a breach of Clause 2 and ruled accordingly.

Complaint received **17 January 2018**

Case completed **4 May 2018**