CASE AUTH/2800/10/15

SANOFI v AMGEN

Promotion of Repatha

Sanofi complained about a Repatha (evolocumab) leavepiece distributed by Amgen at the European Society of Cardiology (ESC) Congress, London, 29 August – 2 September 2015. Repatha was a lipid lowering medicine for, *inter alia*, adults with primary hypercholesterolaemia or mixed dyslipidaemia.

Sanofi alleged that the claim '75% additional LDL-C reduction vs placebo', which appeared on the front cover of the leavepiece, was misleading and had been 'cherry-picked' from the supporting reference (Robinson *et al* 2014). Robinson *et al* made it clear that the 75% efficacy claim vs double-placebo was not a primary endpoint nor was it likely to be a secondary endpoint. The primary endpoint was stated to be percentage change from baseline in LDL-C level; secondary endpoints included change from baseline in LDL-C level, percent change from baseline in additional lipid parameters and the proportion of patients achieving LDL-C levels < 70mg/dL. The leavepiece should, at the very least, state the results of the primary endpoint in addition to the 75% claim. A breach of the Code was alleged.

Sanofi noted the complex study design; the 75% efficacy claim was derived from only one of the 24 treatment groups so that although 1,896 patients were involved in the study as a whole, the claim was derived from a group of only 109; this was not stated. The only place any patient number was stated was in a footer which mentioned that 1,896 patients were involved in the entire study. Sanofi alleged that readers would think that the 75% efficacy claim was derived from the entire study rather than just 109 patients; they would give the efficacy claim less credibility if they realised that it was based on fewer patients than the 1,896 cited.

Sanofi stated that the group from which the 75% claim was derived was one of two in the 'high-intensity statin' category; the corresponding result for the other group in this category was 66% vs double-placebo (59% vs baseline). Sanofi submitted that in order not to mislead Amgen should have given a range of results, ie 66%-75% under the 'high-intensity statin' category. By not doing so Amgen had 'cherry-picked' the results thus misleading readers into thinking that Repatha had a higher efficacy figure than the range demonstrated in the study. As such, prescribers would be misled into prescribing Repatha for a wider group of patients than would be done otherwise. Sanofi alleged breaches of the Code.

Sanofi stated that when using the 75% efficacy claim, Amgen should also have added that the double-placebo arm (who were not on any form of lipid-lowering therapy) had an increase of LDL-C of 13%. Hence, the actual efficacy result vs baseline was much lower at 62%. Readers should be told about the 13% increase so that an informed assessment could be made about the true efficacy of Repatha from baseline. Sanofi noted that Robinson *et al* stated that the primary endpoint was percentage change from baseline in LDL-C. Therefore, headlining a result of Repatha plus a high intensity statin vs double-placebo implied a larger efficacy effect and was clinically misleading. Sanofi alleged breaches of the Code.

Sanofi further stated that positioning the 75% efficacy claim above an outline of Repatha's indications implied that the claim applied to all adult patient types with primary hypercholesterolaemia and mixed dyslipidaemia, which was not so. Sanofi alleged that such positioning the 75% efficacy claim was misleading and inconsistent with the Repatha summary of product characteristics (SPC), in breach of the Code.

Sanofi noted that the 75% efficacy claim was made at one of the world's largest cardiology scientific congresses with about 30,000 delegates in attendance. In that regard Sanofi alleged that Amgen had not upheld high standards by misleading so many health professionals and scientists.

The detailed response from Amgen is given below.

The Panel noted that Robinson *et al* was a randomized, double-blind, placebo- and ezetimibe-controlled trial to evaluate the efficacy of evolocumab (dosed once every two weeks or once a month) in patients with hypercholesterolaemia on background statin therapy. In that regard Sanofi was incorrect to state that patients in the double-placebo arm were not on any form of lipid-lowering therapy; they were on background statin therapy. The study consisted of 24 different treatment arms and so although 1,896 patients received at least one dose of the study medicines, the number of patients in each treatment arm ranged from 55 to 115. The co-primary endpoints were the percentage change from *baseline* in LDL-C level at the mean of weeks 10 and 12 and at week 12. The Panel noted that although a footnote on the front page of the leavepiece gave a brief description of the study at issue, it stated that 1,896 patients were involved without explaining that the numbers of patients in the treatment groups were considerably fewer.

The results section of Robinson *et al* stated that at the mean of weeks 10 and 12, percent reduction from baseline in LDL-C (one of the co-primary endpoints) was 59-66% with every two week dosing of evolocumab and 62-65% with monthly dosing. It was stated that these reductions corresponded to changes vs *placebo* of 66-75% and 63-75% respectively; it was from these higher figures that the claim in question was derived. The

study result highlighted in the leavepiece ('75% additional LDL-C reduction vs placebo') was that obtained from patients on atorvastatin 80mg plus evolocumab given every two weeks (n=109) vs patients on atorvastatin 80mg and double-placebo. In that regard the Panel noted Amgen's submission that the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice. For patients on other background statins the treatment differences vs placebo for evolocumab dosed every two weeks ranged from 66% to 70%. In that regard the Panel noted that 75% applied only to patients on atorvastatin 80mg and the treatment differences were otherwise no more than 70%. The Panel noted that although a footnote gave brief details of the design and outcome of Robinson *et al* (including the range (66-75%) of additional LDL-cholesterol lowering vs placebo), it was an established principle under the Code that footnotes should not be used to qualify otherwise misleading headlines. The Panel further noted that the discussion section of Robinson *et al* it stated that the limitations of the study included, *inter alia*, the small sample sizes in some of the groups. In conclusion the authors stated that further studies were needed to evaluate the longer-term clinical outcomes of adding evolocumab to background statin therapy.

The Panel noted that the claim '75% additional LDL-C reduction vs placebo' appeared prominently on the front cover of the leavepiece. The claim was qualified below, in smaller print, with 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg, Repatha 140mg [every two weeks] delivered an additional 75% LDL-C reduction vs placebo'. The Panel noted, however, that the headline claim was that Repatha delivered consistent LDL-C reductions and in that regard it noted its comments above about the range of percentage reductions vs placebo. The Panel further noted that the 75% additional reductions in LDL-C levels were vs placebo. Although this figure was *based* on the co-primary endpoint it was not the co-primary endpoint *per se* which, according to the study, was vs baseline and which was a lower percentage.

The Panel further noted that detailed below the claim in question were the therapeutic indications for Repatha. In that regard the Panel considered that some readers might assume that the clinical results referred to ('75% additional LDL-C reduction vs placebo') could be achieved in all patients eligible for therapy. This was not so; that result was achieved only in a very specific treatment group. However, the Panel did not consider that the relative position of the claim to the therapeutic indications meant that the claim was inconsistent with the particulars listed in the Repatha SPC. No breach of the Code was ruled.

The Panel did not consider that the claim at issue, by emphasising the results from just one study arm, represented the balance of the evidence from Robinson *et al* even though, according to Amgen that was the most clinically relevant cohort for UK clinical practice. In that regard, however, the Panel noted that Repatha could be used in combination with other statins or alone or in combination with other lipid lowering therapies in patients who were statin intolerant, or for whom a statin was contraindicated. Section 5.1 of the Repatha SPC referred to LDL-C reductions of approximately 55% to 75%. In addition, the Panel noted that the more favourable result vs placebo had been used in the leavepiece not the results vs baseline. Overall the Panel did not consider that the information in the leavepiece was sufficiently complete, or set out in such a way as to ensure that readers could form their own opinion of the clinical significance of Robinson *et al* and the impact that it might have on their use of Repatha. A breach of the Code was ruled. The Panel considered that the prominence given to the 75% additional LDL-C reduction vs placebo in a small patient cohort, exaggerated the general efficacy of Repatha. The result would not apply to all patients eligible for Repatha therapy. A breach of the Code was ruled.

The Panel noted its ruling above and considered that high standards had not been maintained. A breach of the Code was ruled.

Sanofi complained about a Repatha (evolocumab) leavepiece (ref UKIE-P-145-0715-110865 and EUHQ-P-145-0715-110847, August 2015) distributed by Amgen at the European Society of Cardiology (ESC) Congress, London, 29 August – 2 September 2015.

Repatha was indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C (low density lipoprotein cholesterol) goals with the maximum tolerated dose of a statin; or alone or in combination with other lipid-lowering therapies in patients who were statin-intolerant, or for whom a statin was contraindicated. It was also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Claim '75% additional LDL-C reduction vs placebo'.

The claim '75% additional LDL-C reduction vs placebo' appeared on the front cover of the six page, gate-folded leavepiece beneath the heading 'Repatha (evolocumab). The first licensed PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitor in the EU, delivering consistent, intensive LDL-C reductions'. The claim was followed by 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg. Repatha 140mg Q2W [every two weeks] delivered an additional 75% LDL-C reduction vs placebo' which was referenced to Robinson *et al* (2014).

COMPLAINT

Sanofi alleged that the claim was misleading and had been 'cherry-picked' from Robinson *et al*. It was clear from reading Robinson *et al* that the 75% efficacy claim vs double-placebo was not a primary endpoint nor was it likely to be a secondary

endpoint. The authors stated that the primary endpoint was percentage change from baseline in LDL-C level while the secondary endpoints included change from baseline in LDL-C level, percent change from baseline in additional lipid parameters and the proportion of patients achieving LDL-C levels < 70mg/dL. The leavepiece should, at the very least, state the results of the primary endpoint in addition to the 75% claim. A breach of Clause 7.2 was alleged.

Sanofi further noted the complex study design of Robinson *et al*. The 75% efficacy claim was derived from only one of the 24 treatment groups, ie the group (n=109) of Repatha 140mg every two weeks and atorvastatin 80mg every two weeks [sic, atorvastatin was taken each day]. Sanofi noted that 1,896 patients were involved in the study but the 75% efficacy claim was derived from only 109. Nowhere in the leavepiece was the 109 patient number mentioned. The only place any patient number was stated was in a footer which mentioned that 1,896 patients were involved in the entire study. Sanofi alleged that readers would be misled into thinking that the 75% efficacy claim was derived from the entire study rather than just one of the 24 groups comprised of only 109 patients. Clinicians would naturally give the 75% efficacy claim less credibility if they realised that it was based on fewer patients than the 1,896 patient number quoted.

Sanofi stated that the group (n=109) taking Repatha 140mg every two weeks and atorvastatin 80mg was one of two groups stratified under the 'high-intensity statin' category; the other group (n=111) in this category were on Repatha 140mg every two weeks and rosuvastatin 40mg. The corresponding result for the latter group was lower at 66% vs double-placebo (59% vs baseline). Sanofi submitted that in order not to mislead, the lower result from the Repatha and rosuvastatin group should also be stated in the leavepiece. Therefore, instead of stating the 75% efficacy claim in isolation, Amgen should have given a range of results, ie 66%-75% under the 'high-intensity statin' category. By not doing so Amgen had 'cherry-picked' the higher efficacy result while ignoring the lower associated figure, thereby misleading readers into thinking that Repatha had a higher efficacy figure than the range demonstrated in the study. As such, prescribers would be misled into prescribing Repatha for a wider group of patients than would be done otherwise. Sanofi alleged breaches of Clauses 7.2 and 7.10.

Sanofi stated that when using the 75% efficacy claim, Amgen should also have added that the double-placebo arm (who were not on any form of lipid-lowering therapy) had an increase of LDL-C of 13%. Hence, the actual efficacy result vs baseline was much lower at 62%. Readers should be told about the 13% increase so that an informed assessment could be made about the true efficacy of Repatha from baseline. Sanofi noted that Robinson *et al* stated that the primary endpoint was percentage change from baseline in LDL-C. Therefore, headlining a result of Repatha plus a high intensity statin vs double-placebo implied a larger efficacy effect and was clinically misleading. Sanofi alleged breaches of Clauses 7.2 and 7.10.

Sanofi further stated that the 75% efficacy claim was positioned above text in the lower half of the first page which outlined Repatha's therapeutic indications thereby implying that the claim applied to all adult patient types with primary hypercholesterolaemia and mixed dyslipidaemia, which was clearly not so. Sanofi alleged that positioning the 75% efficacy claim above the therapeutic indications was both misleading and inconsistent with the Repatha summary of product characteristics (SPC), in breach of Clauses 3.2 and 7.10.

Sanofi noted that the 75% efficacy claim was made at one of the world's largest cardiology scientific congresses with about 30,000 delegates in attendance. In that regard Sanofi alleged a breach of Clause 9.1 as Amgen had not upheld high standards by misleading so many health professionals and scientists.

RESPONSE

Amgen confirmed that the co-primary endpoint of the pivotal Robinson *et al* study was percentage change in LDL-C from baseline vs placebo. Robinson *et al* was a phase 3, multicenter, double-blind, randomized, double-dummy, placebo- and ezetimibe-controlled study to evaluate the efficacy and safety of 12 weeks of subcutaneous (SC) evolocumab compared with placebo when administered in combination with statin therapy in hyperlipidaemic subjects. After the screening period, eligible subjects were randomized to 1 of 5 statin cohorts (atorvastatin 10mg or 80mg, rosuvastatin 5mg or 40mg, or simvastatin 40mg) for a 4 week lipid stabilization period. Following the lipid stabilization period, eligible subjects were randomized within each statin dose cohort to blinded investigation product (evolocumab, placebo or ezetimibe). The study had two co-primary endpoints, percent change from baseline in LDL-C at week 12 and mean percent change from baseline in LDL-C at weeks 10 and 12 (averaging of weeks 10 and 12, ie the LDL reduction at week 12 and the LDL reduction at 10/12 weeks). Amgen submitted that in order to calculate the treatment difference between the two arms, the following was performed to determine the outcome:

1 Determine the LDL reduction for each subject in the study vs baseline (at 12 weeks and weeks 10/12)
2 Derive a mean for the LDL reduction on each group (ie evolocumab plus statin and placebo plus statin)
3 Compare the mean LDL-C reduction in the evolocumab plus statin treatment group with that in the placebo plus statin treatment group.

Amgen submitted it was standard statistical practice that the endpoint was written at the subject level ie what was assessed in the patient. The main outcomes measure (LDL percent change from baseline) referred to the patient level data from which efficacy claims might be made depending on the objective of the study which, in this case, was the effect of evolocumab on LDL-C lowering compared with the control groups (placebo or ezetimibe). In addition to being standard statistical

practice, this was one of the key reasons why control arms were used in studies in order to obtain robust efficacy data. For the avoidance of doubt, this was specifically mentioned in the rationale and design of the study (Robinson *et al* 2014b) as follows:

> 'The aim of this phase 3 study is to evaluate the efficacy of 12 weeks of subcutaneous evolocumab (vs placebo) administered every 2 weeks or every month in combination with a statin in patients with hypercholesterolemia and mixed dyslipidemia' (emphasis added).
>
> '[Robinson *et al*] is a phase 3 trial designed to assess LDL-C response to evolocumab compared with placebo in subjects randomized to 1 of 3 commonly prescribed statins while providing comparative data against ezetimibe' (emphasis added).
>
> 'The expected number of subjects randomized to IP [investigational product] for this study was 1700, which will provide ≥98% power for testing the superiority of each evolocumab dosing regimen over placebo on the co primary endpoints within each background statin therapy group and SC dose-frequency group' (emphasis added).

The treatments difference results (vs placebo), including those for the atorvastatin 80mg arm, were shown in table 4 of Robinson *et al*. Amgen explained this in detail to Sanofi both in its written response and during the teleconference and provided it with the study design paper (Robinson *et al* 2014b). Therefore, Amgen submitted that Sanofi was wrong to infer that the claim was not based on the primary endpoint and Amgen refuted a breach of Clause 7.2.

Amgen submitted that each statin cohort could be considered as its own stand-alone study (ie 5 studies in one). Each cohort was the same, as if different studies had been run among subjects with a particular fixed stable background statin under different protocol numbers. The same held for the dose frequencies of evolocumab. The sample size and power of the study was designed such that each cohort could be evaluated on its own. The co-primary endpoints were evaluated within the statin dose groups and evolocumab dose frequency groups separately (Robinson *et al* 2014b). Multiplicity adjustments within each dose-frequency group and against each control arm were made to correct for multiple endpoints.

Thus, the 75% LDL-C reduction vs placebo was based on a statistically robust study design where each statin cohort was compared with the corresponding placebo group and considered a statistically significant primary efficacy endpoint result in its own right. The results for the atorvastatin 80mg cohort were highly significant for both of the co-primary endpoints and the 75% claim represented a pre-specified co-primary endpoint. Amgen denied a breach of Clause 7.2.

Amgen submitted that the design of the study was rigorous to ensure robust results could be achieved with regards to the efficacy of evolocumab when added to 5 different statin regimens and compared with both placebo and, in the case of the atorvastatin arms, with ezetimibe as well, at two different evolocumab doses. The 75% efficacy claim came from the evolocumab once every two weeks arm, when added to atorvastatin 80mg, vs placebo (109+55, n=164). The results for the atorvastatin 80mg cohort were highly significant for both of the co-primary endpoints. As detailed above, the 75% efficacy result represented a primary endpoint and it was therefore reasonable to use it as a headline claim. It was clearly stated in the leavepiece, below the 75%, that the claim referred to patients taking atorvastatin 80mg. Amgen submitted that the footnote clearly stated that the data had been taken from Robinson *et al*, which involved 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia. It was clear that the numbers related to the total study; '… international trial [(Robinson *et al*)] involving 1,896 patients …'. The footnote outlined all the different statin baseline regimens used and the range of LDL-C reductions achieved, within the overall 1,896 patient study. It was wrong to argue that readers would be confused and believe that the claim '75% additional LDL-C reduction vs placebo' was based on 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia. The indication, as per the Repatha SPC, was in combination with a maximum tolerated dose of a statin. Atorvastatin 80mg was the maximum licensed dose of atorvastatin. Furthermore, the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice as it was specifically recommended in the National Institute for Health and Care Excellence (NICE) guideline on lipid modification (CG181) in secondary prevention. Rosuvastatin was not included in the NICE guidelines. It would not be appropriate to base a claim on the results of alternative statins and/or lower doses as these did not reflect the clinical guidelines which clinicians would follow. Importantly Amgen noted that, as part of the pre-vetting process for new medicines, the claim had been pre-vetted by the Medicines and Healthcare products Agency (MHRA) and no objections were raised and the claim was consistent with the Repatha SPC.

In summary, Amgen strongly refuted that the claim was misleading, it was therefore not in breach of Clause 7.2 as it was based on the following points as detailed above:

- This was a pre-specified primary end-point of the study
- Each statin cohort was analysed separately with sufficient sample size and power
- It reflected NICE guidelines on lipid modification (CG181) as well as UK clinical practice
- The claim had been pre-vetted by the MHRA
- It was consistent with the Repatha SPC.

Amgen submitted that as explained previously, the design and scale of the study were such that each arm could be considered a statistically significant result in its own right and therefore the 75% referred to a valid primary efficacy result. The 75% result was selected as it reflected the group on atorvastatin

80mg at baseline. Of the individual primary efficacy results, it was chosen as it was deemed most relevant to UK clinicians, given 80mg atorvastatin was recommended as the high intensity statin of choice in the relevant NICE clinical guideline (CG181). Rosuvastatin was not mentioned in the NICE guidelines. The range 66-75% was included in the footnotes. In discussion with Sanofi, Amgen offered to make the range more prominent underneath the claim although it continued to believe that it was unnecessary and that offer was rejected by Sanofi. Amgen was extremely disappointed to find that what it had proposed was now the subject of a complaint. Amgen had now added the range to the 75% claim, a copy of the updated leavepiece (ref UKIE-P-145-0715-110865(1)) was provided. Amgen voluntarily offered to make the 66-75% range more prominent underneath the 75% claim, and Sanofi had agreed to this compromise in other countries.

Amgen submitted that as described earlier, the primary efficacy results of the study were vs placebo or ezetimibe thus the resultant efficacy claims reflected this. Again, this was a key reason as to why trials were conducted with control arms. With regard to the comment 'who were not on any form of lipid lowering therapy', Amgen did not understand the point at issue and confirmed that all patients were randomized to one of 5 statin regimens, before being randomized to evolocumab, ezetimibe or placebo. As mentioned in the design paper (Robinson *et al* 2014b)), 'To obtain stable baseline lipid values and ensure subjects were able to tolerate statins, all subjects (irrespective of prior statin usage) entered a 4-week lipid-stabilization period on their assigned statin'. Amgen submitted that such matters indicated that Sanofi did not understand the conduct of the trial and had therefore made an unfounded complaint. The claim was based directly on the primary endpoint of the trial and Amgen therefore refuted breaches of Clauses 7.2 and 7.10.

The context of the claim and nature of the study from which it was derived were made clear in the wording around the claim and in the footer. Amgen considered that it was good practice to make the licensed therapeutic indication of the product clear on the first page of the leavepiece (which was taken verbatim from the SPC). This was explicitly stated on the leavepiece under the heading 'Therapeutic indications'. Such detail was what one would expect when a new medicine came to the market and also one of the MHRA's requirements. In Amgen's view, Sanofi appeared to have asserted that the therapeutic indications should always be placed in isolation on a page. This was incorrect and not required by the Code. Amgen submitted that that complaint was unfounded and it denied a breach of Clauses 3.2 and 7.10.

For the detailed reasons outlined above, Amgen did not consider that ESC delegates had been misled and it therefore denied a breach of Clause 9.1. Amgen had applied its usual high standards throughout the process and noted that all promotional materials used at the ESC had been pre-vetted and approved by the MHRA and no claims had been made that were inconsistent with the Repatha SPC.

PANEL RULING

The Panel noted that Robinson *et al* was a randomized, double-blind, placebo- and ezetimibe-controlled trial to evaluate the efficacy of evolocumab (dosed either once every two weeks or once a month) in patients with hypercholesterolaemia on background statin therapy. In that regard Sanofi was incorrect to state that patients in the double-placebo arm were not on any form of lipid-lowering therapy; they were on background statin therapy. The study consisted of 24 different treatment arms and so although 1,896 patients received at least one dose of the study medicines, the number of patients in each treatment arm ranged from 55 to 115. The co-primary endpoints were the percentage change from *baseline* in LDL-C level at the mean of weeks 10 and 12 and at week 12. The Panel noted that although a footnote on the front page of the leavepiece gave a brief description of the study at issue, it stated that 1,896 patients were involved without explaining that the numbers of patients in the treatment groups were considerably fewer.

The results section of Robinson *et al* stated that at the mean of weeks 10 and 12, percent reduction from baseline in LDL-C (one of the co-primary endpoints) was 59-66% with every two week dosing of evolocumab and 62-65% with monthly dosing. It was stated that these reductions corresponded to changes vs *placebo* of 66-75% and 63-75% respectively; it was from these higher figures that the claim in question was derived. The study result highlighted in the leavepiece ('75% additional LDL-C reduction vs placebo') was that obtained from patients on atorvastatin 80mg plus evolocumab given every two weeks (n=109) vs patients on atorvastatin 80mg and double-placebo. In that regard the Panel noted Amgen's submission that the atorvastatin 80mg cohort was the most clinically relevant cohort for UK clinical practice. For patients on other background statins the treatment differences vs placebo for evolocumab dosed every two weeks were 66% (rosuvastatin 40mg, n=111), 70% (atorvastatin 10mg, n=110), 69% (simvastatin 40mg, n=112) and 67% (rosuvastatin 5mg, n=113). In that regard the Panel noted that the headline figure of 75% applied only to patients on atorvastatin 80mg and the treatment differences were otherwise no more than 70%. In the study arms which included evolocumab dosed monthly then the treatment differences vs placebo were similar ie 75% (atorvastatin 80mg, n=110), 63% (rosuvastatin 40mg, n=112), 63% (atorvastatin 10mg, n=110), 68% (simvastatin 40mg, n=115) and 67% (rosuvastatin 5mg, n= 115). The Panel noted that although a footnote gave brief details of the design and outcome of Robinson *et al* (including the range (66-75%) of additional LDL-cholesterol lowering vs placebo), it was an established principle under the Code that footnotes should not be used to qualify otherwise misleading headlines. The Panel further noted that the discussion section of Robinson *et al* it stated that the limitations of the study included, *inter alia*, the small sample sizes in some of the groups. In conclusion the authors stated that further studies were needed to evaluate the longer-term clinical outcomes of adding evolocumab to background statin therapy.

The Panel noted that the claim '75% additional LDL-C reduction vs placebo' appeared prominently on the front cover of the leavepiece. The claim was qualified below, in smaller print, with 'In patients with primary hypercholesterolaemia or mixed dyslipidaemia receiving atorvastatin 80mg, Repatha 140mg [every two weeks] delivered an additional 75% LDL-C reduction vs placebo'. The Panel noted, however, that the headline claim was that Repatha delivered consistent LDL-C reductions and in that regard it noted its comments above about the range of percentage reductions vs placebo. The Panel further noted that the 75% additional reductions in LDL-C levels were vs placebo. Although this figure was *based* on the co-primary endpoint it was not the co-primary endpoint *per se* which, according to the study, was vs baseline and which was a lower percentage.

The Panel further noted that below the claim in question, the leavepiece detailed the therapeutic indications for Repatha. In that regard the Panel considered that some readers might assume that the clinical results referred to ('75% additional LDL-C reduction vs placebo') could be achieved in all patients eligible for Repatha therapy. This was not so; that result was achieved in a very specific treatment group ie those taking atorvastatin 80mg. The Panel noted the alleged breach of Clause 3.2 with regard to the positioning of the 75% efficacy claim above the therapeutic indications. The Panel did not consider that the relative position of the claim to the therapeutic indications meant that the claim was inconsistent with the particulars listed in the Repatha SPC. No breach of Clause 3.2 was ruled.

The Panel did not consider that the claim at issue, by emphasising the results from just one study arm, represented the balance of the evidence from Robinson *et al* even though, according to Amgen that was the most clinically relevant cohort for UK clinical practice. In that regard, however, the Panel noted that Repatha could be used in combination with other statins or alone or in combination with other lipid lowering therapies in patients who were statin intolerant, or for whom a statin was contraindicated. Section 5.1 of the Repatha SPC referred to LDL-C reductions of approximately 55% to 75%. In addition, the Panel noted that the more favourable result vs placebo had been used in the leavepiece not the results vs baseline. Overall the Panel did not consider that the information in the leavepiece was sufficiently complete, or set out in such a way as to ensure that readers could form their own opinion of the clinical significance of Robinson *et al* and the impact that it might have on their use of Repatha. A breach of Clause 7.2 was ruled. The Panel considered that the prominence given to the 75% additional LDL-C reduction vs placebo in a small patient cohort, exaggerated the general efficacy of Repatha. The result would not apply to all patients eligible for Repatha therapy. A breach of Clause 7.10 was ruled.

The Panel noted its ruling above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaint received **20 October 2015**

Case completed **11 January 2016**