CASE AUTH/2057/10/07

# GLAXOSMITHKLINE v GILEAD SCIENCES

## Promotion of Truvada

**GlaxoSmithKline complained about the promotion of Truvada (emtricitabine and tenofovir) by Gilead. The items at issue were two leavepieces, one describing the safety outcomes and the other describing the efficacy outcomes of the BICOMBO study. GlaxoSmithKline supplied Kivexa (abacavir and lamivudine).**

**GlaxoSmithKline explained that Kivexa and Truvada were both dual nucleoside backbones formulated as fixed dose combinations, licensed for the treatment of HIV infection. Currently there were no data available from robust, double blind, head-to-head studies directly comparing the efficacy and tolerability of Kivexa and Truvada, but studies were ongoing.**

**BICOMBO was an investigator sponsored, collaborative study jointly funded by GlaxoSmithKline and Gilead. In this open-label study, patients on a stable lamivudine-containing regimen were randomised to switch their nucleoside reverse transcriptase inhibitor (NRTI) backbone to either Truvada or Kivexa, whilst keeping the third agent of the regimen unchanged. The primary study endpoint was the proportion of patients with treatment failure for any reason through 48 weeks and was powered for non-inferiority with an upper limit of 95% confidence interval of estimated difference < 12.5%.**

**Secondary endpoints included the proportion of patients with virological failure at or before 48 weeks, CD4 changes and changes in fasting plasma lipids, body fat, bone mineral density and renal function. The 48 week data from this study were presented at an international conference in July 2007. The study concluded that for the primary parameter of treatment efficacy, the Kivexa group did not meet the non-inferiority endpoint compared with the Truvada group. For the secondary parameter of virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada.**

**GlaxoSmithKline noted in particular the following three claims in the efficacy outcomes leavepiece:**

- **'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'**
- **'Treatment failure rates for Kivexa were 6% higher than Truvada'**
- **'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'.**

**These claims of superiority, based on virological failures, were made despite the two therapies being statistically non-inferior for virological efficacy. This, with the lack of non-inferiority being proven for treatment failures as the primary parameter, was misleading as the study was not powered as a superiority study. GlaxoSmithKline alleged that these three claims were collectively in breach of the Code.**

**Additionally, given that there was a difference in the baseline regimens of the two groups, the randomisation had generated an inherent bias. More patients in the Truvada arm were on a tenofovir-containing regimen at baseline (34%) than patients continuing on an abacavir-containing regimen (7%) in the Kivexa arm. As such there would be an element of patients 'surviving' on existing therapy causing this bias as different proportions of patients in each arm had a therapy change.**

**The impression of superiority given by the bar chart should be corrected by explicitly stating the correct statistical interpretation as per the study design.**

**GlaxoSmithKline further noted that baseline resistance testing was not performed in this study and this could have affected the virologic endpoint. The authors reported that the 4 patients experiencing failure in the Kivexa arm had previously received 2 or more regimens for 1-5 years. Whilst they reported that these patients had not previously received abacavir, a number of NRTI-associated mutations could confer cross resistance to abacavir.**

**GlaxoSmithKline stated that baseline resistance testing would have allowed interpretation of these results, and stratification in the randomisation based upon this would have controlled for this factor. Because this was not done, no claim should be made on virological efficacy or failure rates without putting these facts in context. GlaxoSmithKline alleged that the claims were in breach of the Code for these reasons also and should not be made without an explicit qualification of this source of bias.**

**The issue was whether the virological failures emerged following therapy switch or were present prior to study commencement. Without this data, it was difficult to understand the clinical relevance of the virological failure. Any claims should reflect this uncertainty.**

**GlaxoSmithKline noted that the efficacy outcomes leavepiece also contained the wording 'Retrospective HLA-B5701 testing showed of 9 suspected HSR [hypersensitivity reactions] in the Kivexa arm, only 3 were HLA +ve. Clinical vigilance for HSR is essential during treatment' which implied that HLA-B*5701 screening was not an effective tool to reduce the**

**incidence of abacavir hypersensitivity and that if these subjects had been prospectively screened, then only three HSRs would have been prevented and the other six would still have occurred. This was extremely misleading in the light of all the available evidence and only referred to clinically-suspected HSRs rather than the more robust measure of immunologically-confirmed HSR.**

**When prospective screening was used, the diagnosis rate of HSR had been shown to reduce significantly if a clinician knew that a patient was HLA-B*5701 negative (Rauch *et al*). Indeed, in PREDICT-1 only 3.4% vs 7.8% of patients were diagnosed with a clinically-suspected HSR in the prospective screening arm vs the control arm. None of these subjects went on to have an immunologicially-confirmed HSR indicating that the majority of these diagnoses were misdiagnoses and not true HSR (Mallal *et al*, 2007).**

**Although factually correct, the statement could easily be misinterpreted as meaning that two-thirds of Kivexa HSR cases were in patients who did not possess the HLA-B*5701 allele. This ambiguity was due to the open-label design meaning that only patients in the Kivexa arm would have been suspected of being at risk of HSR and thus diagnosed as such in response to one or more symptoms raising clinical suspicion. In a blinded study suspected-HSRs could also have been diagnosed in the Truvada arm.**

**GlaxoSmithKline alleged that the statement at issue was ambiguous and misleading. Additionally the tone of the claim disparaged Kivexa. The statement cast doubt over the robustness of current evidence for the utility of HLA-B*5701 screening from the PREDICT-1 study.**

**Given the limitations of the BICOMBO study design, GlaxoSmithKline alleged that Gilead's interpretation of the data to support the promotion of Truvada was misleading.**

**The Panel noted that the BICOMBO study was the first to directly compare the efficacy and safety of Kivexa and Truvada. The study would run for three years but to date data was only available from the first 48 weeks of the study. The study had thus not run its course and there was limited data in the public domain with regard to study design, statistical methods etc. The study was designed to assess the non-inferiority of the two combinations with respect to treatment efficacy (primary endpoint) and virological efficacy (secondary endpoint). Kivexa failed to meet the primary non-inferior endpoint compared with Truvada. The authors suggested that this might have been because some patients had to discontinue Kivexa treatment due to abacavir hypersensitivity reactions (discontinuation of study therapy was regarded as treatment failure). In terms of virological efficacy Kivexa met non-inferiority criteria compared with Truvada however there were more failures with Kivexa than Truvada (2.4% vs 0% respectively).**

**The Panel noted that the efficacy leavepiece featured a bar chart detailing treatment failure and virological failure. The visual impression of the bar chart was that Truvada was superior to Kivexa although this had not been shown statistically. Although the results favoured Truvada, the study was not powered to show superiority; in any event only 48 week data was available from a study which still had over 2 years to run. The following claims appeared to the right of the bar chart: 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kivexa (2.4%) than Truvada (0%)'; 'Treatment failure rates with Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada.'**

**The Panel noted that although Kivexa had not been shown to the non-inferior to Truvada in terms of treatment efficacy, Truvada had not been shown to be superior. In terms of virological efficacy Kivexa was shown to be non-inferior to Truvada although there were more treatment failures with Kivexa than Truvada. The Panel considered that although the interim data from the BICOMBO study was of undoubted interest, but noted that the study had yet to run its full course. The Panel considered that the efficacy outcomes leavepiece implied that Truvada had been shown to be superior compared with Kivexa which was not so. The Panel considered that the claims detailed above were misleading as alleged. Breaches of the Code were ruled.**

**The Panel noted that the leavepiece at issue did not record the fact that no baseline resistance testing had taken place although it did state that at baseline patients had been virologically suppressed for at least 6 months. The definition of suppression (<200 copies HIV RNA per ml) was not stated although virological failure was stated to be ≥200 copies/ml. The Panel noted Gilead's submission that baseline resistance testing could not have been performed at study entry due to the viral load being undetectable.**

**Overall the Panel considered that whilst it might have been helpful for readers to know that baseline testing had not been carried out, the omission of such data was not misleading per se. Readers were told that patients were virologically suppressed at baseline. On balance the Panel considered that the claims 'For virological efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kinvexa (24%) than Truvada (0%)' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada' were not misleading on this point and ruled no breach of the Code.**

**The Panel considered that the claim 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA positive. Clinical vigilance for HSR is essential during treatment' clearly referred to suspected HSR and not immunologically-confirmed HSR. The Panel noted that the claim implied that 6 cases of suspected HSR were in patients who were HLA negative. Section 4.4 of the Kivexa SPC referred to the possibility of suspected HSR in**

**patients who did not carry HLA-B*5701. The Panel did not consider the claim at issue was misleading, ambiguous or incapable of substantiation nor did it disparage Kivexa. No breaches of the Code were ruled.**

**Although noting its comments above the Panel did not consider that high standards had not been maintained. No breach of the Code was ruled.**

**With regard to the safety outcomes leavepiece, GlaxoSmithKline noted the following:**

**'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile* than Kivexa, with no differences in renal function or bone mineral density'. (The asterisk referred to TG, TC and LDL and was shown as a footnote.)**

**GlaxoSmithKline had alleged that it was misleading to claim that Truvada had a significantly better lipid profile than Kivexa based on only three of the four parameters measured, as the fourth (HDL) was widely believed to be an important factor when evaluating cardiovascular risk, as in the Framingham calculator and the British Heart Foundation guidelines. Triglycerides were understood to play a minor role.**

**Furthermore GlaxoSmithKline alleged that the claim 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was misleading with regard to the safety of Truvada. The Truvada summary of product characteristics (SPC) listed hypertriglyceridaemia as a commonly reported adverse event, and cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 (with reference to section 4.4). This was likely to be in breach of the Code by not encouraging the rational use of the medicine.**

**Finally, GlaxoSmithKline alleged that the safety outcomes leavepiece was misleading in that it did not mention the primary outcomes of the study. This was not a safety study. Secondary parameter claims could not be made without presenting the primary parameter data from the study to allow clinicians to assess the relative efficacy and safety of the two components. Gilead's assertion that the primary efficacy parameters were presented elsewhere (ie in a separate leavepiece) did not allay GlaxoSmithKline's concerns, as it considered that each piece must be capable of standing alone.**

**The Panel noted that although Gilead had agreed to refer to all four lipid results (TG, TC, LDL and HDL) in its claims regarding lipid profile, it had not agreed to modify the claim 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile …'. The results shown to substantiate this claim were the absolute changes in lipid levels over 48 weeks and the lack of change in the TC/HDL ratio over the same time period. However, although, for instance, readers were told that LDL rose by 7mg/dL over 48 weeks there was no indication as to the clinical significance. The Panel considered that the information given was such that prescribers would be unable to form their own opinion as to the clinical significance of the results; the leavepiece was thus misleading in this regard. A breach of the Code was ruled.**

**The Panel noted that the leavepiece depicted a decrease in triglycerides (-16mg/dL) over 48 weeks. The Truvada SPC, however, listed hypertriglyceridaemia as a common side-effect. The Panel considered that it was misleading to refer to the observed decrease in triglycerides without noting the statement in the SPC regarding hypertriglyceridaemia. A breach of the Code was ruled.**

**The Panel did not consider that it was necessarily unacceptable to produce a leavepiece focussing only on the safety data when such data had come from secondary endpoints of a study. None of the primary end-points were safety-related and so in that regard the safety data was capable of standing alone. However the leavepiece at issue did not make it clear that the data presented was from secondary endpoints and that primary endpoints had related to efficacy. Some readers might assume that the BICOMBO study was primarily a safety study which was not so. The leavepiece was misleading in this regard. Breaches of the Code were ruled.**

GlaxoSmithKline UK Ltd complained about the promotion of Truvada (emtricitabine and tenofovir) by Gilead Sciences Limited. The items at issue were two leavepieces: describing the safety outcomes (ref 164/UKM/07-08/CM/510) and efficacy outcomes (ref 164/UKM/07-08/CM/505) of the BICOMBO study. GlaxoSmithKline supplied Kivexa (abacavir and lamivudine). There had been inter-company dialogue but agreement had not been reached on most of the issues.

GlaxoSmithKline explained that Kivexa and Truvada were both dual nucleoside backbones formulated as fixed dose combinations, licensed for the treatment of HIV infection and recommended in the BHIVA (British HIV Association) guidelines. Currently there were no data available from robust, double blind, head-to-head studies directly comparing the efficacy and tolerability of Kivexa and Truvada, but such studies were ongoing.

BICOMBO was an investigator sponsored, collaborative study jointly funded by GlaxoSmithKline and Gilead. In this open-label study, patients on a stable lamivudine-containing regimen were randomised to switch their nucleoside reverse transcriptase inhibitor (NRTI) backbone to either Truvada or Kivexa, whilst keeping the third agent of the regimen unchanged. The primary study endpoint was the proportion of patients with treatment failure for any reason through 48 weeks and was powered for non-inferiority with an upper limit of 95% confidence interval (CI) of estimated difference < 12.5%.

Secondary endpoints included the proportion of patients with virological failure at or before 48 weeks, CD4 changes and changes in fasting plasma lipids, body fat, bone mineral density and renal function. The 48 week data from this study were presented at the

International AIDS Society (IAS) conference in Sydney, July 2007. The study concluded that for the primary parameter of treatment efficacy, the Kivexa group did not meet the non-inferiority endpoint compared with the Truvada group. For the secondary parameter of virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada.

On 24 August, GlaxoSmithKline contacted Gilead about claims in the leavepiece; Study highlights: BICOMBO – safety outcomes. GlaxoSmithKline's initial concerns related to selective reference to lipid parameters that improved on Truvada (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL)), whilst ignoring the negative impact on high density lipoprotein (HDL). Additionally Gilead selectively ignored the neutral impact of Kivexa on HDL which was significantly different to that seen on Truvada.

GlaxoSmithKline noted Gilead's treatment of some non statistically significant differences in the piece whereby it claimed that there were no differences between the two treatment arms as regards changes in renal function, bone mineral density and limb fat. The small differences seen in favour of Kivexa failed to reach statistical significance. This contrasted with Gilead's treatment of other non statistically significant differences where the trend favoured Truvada.

GlaxoSmithKline also noted that flaws in the design of the BICOMBO study meant that the claims were not justified.

GlaxoSmithKline stated that Gilead considered that its presentation of the results from the BICOMBO study in the leavepiece at issue accurately reflected the study authors' conclusions. However, given that the fundamental principle of the Code when using a study to promote a product was that the claims must represent the balance of evidence available as well as being supportable by robust data, GlaxoSmithKline alleged that the leavepiece were misleading due to over interpretation and selective reporting of the study endpoints. There were additionally a number of design flaws in the BICOMBO study which cast doubt over the interpretation of the results and therefore the strength and nature of claims that could be made when using the data promotionally.

These flaws included: bias in randomisation, absence of baseline resistance testing, selective reporting of lipid endpoints, underpowered sub-analysis of other metabolic endpoints, retrospective HLA-B*5701 screening and open-label study design.

**1 Leavepiece entitled 'Study hightlights: BICOMBO – efficacy outcomes'.**

**COMPLAINT**

*Bias in randomisation*

GlaxoSmithKline stated in its initial letter, 24 August, about the safety outcomes leavepiece, that 'Additionally, we wish to point out that 34% of the patients assigned to the Truvada arm, were already taking tenofovir at baseline and hence had been controlled and tolerating tenofovir for 6 months. In contrast only 7% of patients assigned to the Kivexa arm were already on abacavir at baseline. Therefore, when using this data, it is important that you point out that the data will be skewed by inclusion of these patients.' and '… With no baseline resistance tests, 2 or more previous [antiretroviral therapy] regimens, small group numbers, and mismatched baseline [antiretroviral therapy] (17% on abacavir vs 34% on tenofovir in [the Truvada] arm), it is imperative that messages being used by your [representatives] do take account of all the facts, and accurately reflect the data'.

Gilead replied as follows: 'The only key message we are using is that contained within the box at the bottom of the Study Highlights: BiCombo Efficacy outcomes [leavepiece]. This states that 'switching to Truvada in virologically suppressed patients provides continued treatment efficacy with 0% virological failures over 48 weeks' and makes no reference to a switch to Kivexa'.

However, the efficacy outcomes leavepiece made three claims related to comparative data that could be seen to encourage switching in the bullet points on the right-hand side, stating:

- 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'
- 'Treatment failure rates for Kivexa were 6% higher than Truvada'
- 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'.

These claims of superiority, based on virological failures, were made despite the two therapies being statistically non-inferior for virological efficacy. This, with the lack of non-inferiority being proven for treatment failures as the primary parameter, was clearly misleading and in breach of the Code as the study was not powered as a superiority study. GlaxoSmithKline alleged that these three statements were collectively in breach of Clauses 7.2 and 7.3.

Additionally, given that there was a difference in the baseline regimens of the two groups, the randomisation had generated an inherent bias. More patients in the Truvada arm continued on a tenofovir-containing regimen (34%) than patients continuing on abacavir-containing regimen (7%) in the Kivexa arm. As such there would be an element of patients 'surviving' on existing therapy causing this bias as different proportions of patients in each arm had a therapy change.

GlaxoSmithKline requested that Gilead either change its leavepiece to include all of the baseline regimen data, pointing out the above mismatch of 7% vs 34%, or show only the unpowered analysis with the patients receiving baseline abacavir in the Kivexa arm and tenofovir in the Truvada arm removed. This would need to be labelled as under-powered for statistical analysis for clarity. Additionally GlaxoSmithKline insisted that the impression of superiority given by the

bar chart be corrected by explicitly stating the correct statistical interpretation as per the study design in the title of this graphic.

Gilead argued that it considered the claims were acceptable because they were the conclusions of the author. In GlaxoSmithKline's opinion, the fact that these might have been the conclusion of the author did not make them acceptable for use under the Code, as the two therapies were statistically non-inferior for virological efficacy.

When challenged on the point of randomisation bias at the late breaker session where these data were presented, the author presented an additional slide (slide 32 of the IAS presentation) showing an analysis of treatment failures but with all patients receiving baseline tenofovir or abacavir therapy removed. This analysis yielded similar results to the full data set. The decrease in patient numbers however meant that the statistical power was reduced which was likely to have widened the confidence intervals significantly, thus making any numerical treatment difference appear inflated. In this case the confidence intervals ranged from -1.4% to 16.8%, a range of 18.2%; encompassing zero and the non-inferiority margin. Given the lack of statistical rigour, the non- inferiority design and the expanding confidence intervals once the bias was corrected, the superiority claims made by Gilead were not balanced or supported by the evidence available and thus in breach as alleged.

Gilead implied that GlaxoSmithKline's criticism of the study was a criticism of the investigator. This was not so. This was simply a desire to correct misrepresentation of the data by Gilead by ensuring that issues with the study design were made clear to prescribers. As previously mentioned, the bias in the randomization of the study (regardless of the financial arrangements, the study being co-funded by GlaxoSmithKline and Gilead) was a fact that was self-evident based on the lack of baseline therapy stratification. This would inevitably affect the results and their interpretation. As explained above, removal of those patients randomised to continue on tenofovir or abacavir, as shown by the investigator in response to questions at the IAS conference, resulted in an underpowered analysis.

GlaxoSmithKline contrasted the position taken here by Gilead in making such strong claims of superiority based on a non-inferiority design, with its claims (referred to above) made of no difference on other parameters where no statistically significant difference was seen, but trends favoured Kivexa.

Although the BICOMBO study results demonstrated trends towards differences between Truvada and Kivexa as regards renal function and bone mineral density, these failed to reach statistical difference. Consequently GlaxoSmithKline considered that the statement regarding these parameters should read 'no significant differences' rather than 'no differences'. Gilead had agreed to make this amendment when reprinting the leavepieces, but did not define when that would be.

*Absence of baseline resistance testing*

With regard to the claims in the efficacy outcomes leavepiece:

- 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'
- 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'

Baseline resistance testing was not performed in this study and this could have affected the virologic endpoint. The authors reported that the 4 patients experiencing failure in the Kivexa arm had previously received 2 or more regimens for 1-5 years. Whilst they reported that these patients had not previously received abacavir, a number of NRTI-associated mutations could confer cross resistance to abacavir. Indeed, 2 of the 4 patients had multiple resistance mutations suggestive of possible prior resistance. Another patient had previous virological failure and wild-type virus, suggestive of poor adherence.

GlaxoSmithKline stated that baseline resistance testing would have allowed interpretation of these results, and stratification in the randomisation based upon this would have controlled for this factor. Because this was not done, no claim should be made on virological efficacy or failure rates without putting these facts in context. GlaxoSmithKline alleged that the claims were in breach of Clause 7.2 for these reasons also and should not be made without an explicit qualification of this source of bias.

In its response of 5 October, Gilead asserted that as baseline resistance testing was not the standard of care in the centres carrying out the study it was not included in the study protocol. Gilead assumed that baseline mutation in the Kivexa and Truvada arms would have been similar, but such an assumption could not be made.

GlaxoSmithKline pointed out to Gilead that whether the resistance testing was standard of care or not was irrelevant. The issue was whether the virological failures emerged following therapy switch or were present prior to study commencement. Without this data, it was difficult to understand the clinical relevance of the virological failure. Any claims should reflect this uncertainty. As mentioned above, the fact that the author presented these conclusions at the IAS did not make their use acceptable under the Code.

*Retrospective HLA-B*5701 screening and open-label study design*

The efficacy outcomes leavepiece contained the wording:

- 'Retrospective HLA-B5701 testing showed of 9 suspected HSR [hypersensitivity reactions] in the Kivexa arm, only 3 were HLA +ve. Clinical vigilance for HSR is essential during treatment'.

This statement implied that HLA-B*5701 screening was not an effective tool to reduce the incidence of abacavir hypersensitivity and that if these subjects had been prospectively screened, then only three HSRs would have been prevented and the other six would still have occurred. This was extremely misleading in the light of all the available evidence and only referred to clinically-suspected HSRs rather than the more robust measure of immunologically-confirmed HSR.

When prospective screening was used, the diagnosis rate of HSR had been shown to reduce significantly if a clinician knew that a patient was HLA-B*5701 negative (Rauch *et al*). Indeed, in PREDICT-1 only 3.4% vs 7.8% of patients were diagnosed with a clinically-suspected HSR in the prospective screening arm vs the control arm. None of these subjects went on to have an immunologicially-confirmed HSR indicating that the majority of these diagnoses were misdiagnoses and not true HSR (Mallal *et al*, 2007).

Although factually correct, the statement could easily be misinterpreted as meaning that two-thirds of Kivexa HSR cases were in patients who did not possess the HLA-B*5701 allele. This ambiguity was due to the open-label design meaning that only patients in the Kivexa arm would have been suspected of being at risk of HSR and thus diagnosed as such in response to one or more symptoms raising clinical suspicion. In a blinded study suspected-HSRs could also have been diagnosed in the Truvada arm. Clinical diagnosis of HSR had occurred in non-abacavir arms in blinded studies eg CNA30024 where 3% abacavir HSR was reported in the zidovudine arm (DeJesus *et al*, 2004).

GlaxoSmithKline alleged that the statement at issue was ambiguous and misleading in breach of Clause 7.2. Additionally, GlaxoSmithKline alleged that the tone of the claim disparaged Kivexa in breach of Clause 8.1. The statement cast doubt over the robustness of current evidence for the utility of HLA-B*5701 screening from the PREDICT-1 study, which was a highly regarded and robust study also presented at the IAS conference.

In its response of 5 October, Gilead correctly noted that HLA-B*5701 screening was not standard care when the study was initiated, hence the use of retrospecting screening. However, Gilead refused to accept any disparagement on its part of the use of HLA screening.

Given the limitations of the BICOMBO study design, GlaxoSmithKline alleged that Gilead's interpretation of the data to support the promotion of Truvada was misleading in breach of Clauses 7.2, 7.3, 7.4, 8.1 and 9.1.

Since writing to Gilead, GlaxoSmithKline received a copy of a report issued by the IAS entitled 'New research and its implications for policy and practice', in which it praised the validation of genetic screening in the PREDICT-1 study and contrasted this against the study design issues regarding use of genetic screening encountered in the BICOMBO study:

> 'For clinical investigators, BICOMBO trial results underscore difficulties in planning and interpreting comparisons of two regimens in a rapidly evolving treatment environment. Had the trial incorporated HLA-B*5701 screening for abacavir hypersensitivity (instead of using it retrospectively), a small but perhaps critical number of participants may not have stopped abacavir for feared hypersensitivity and thus would not have been counted as 'failures'. Treatment advocates must ensure their constituencies are provided with fastidious and objective appraisals of such trial results in terms understandable to the layperson.'

## RESPONSE

Gilead noted that current treatment of HIV patients naïve to therapy was based mainly on a backbone of two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) as recommended by most national and international guidelines.

In randomised controlled trials this combination of 2NRTIs + 1NNRTI had provided the best efficacy and safety results. Currently in Europe, the most commonly prescribed NRTIs in naïve patients were the new fixed dosed combination tablets of either Truvada or Kivexa. The older combination Combivir (zidovudine and lamivudine) was now less frequently recommended in guidelines for naïve patients due to its toxicity profile compared to the newer combinations, so that patients stable on treatment were increasingly being switched to Kivexa or Truvada.

At present, comparative assessments of efficacy and toxicity between Kivexa and Truvada in naïve patients could only be drawn indirectly from results of randomised clinical trials of Kivexa or Truvada vs Combivir or other NRTIs with efavirenz. A large independent randomised clinical trial (ACTG5202) had recently been set up to compare Kivexa and Truvada head-to-head in naïve patients, however data from this long term trial was not expected for another 2 years.

The BICOMBO study was a robust independent, investigator-led study to compare the efficacy and safety of a switch to either Kivexa or Truvada in virologically controlled patients. This was an important study because it was the first randomised comparison of Kivexa and Truvada and provided the first head-to-head results allowing comparisons to be drawn between these two NRTI combinations in this setting. The study would run for 3 years and the first 48 week results were recently presented at a major HIV conference. Because of its uniqueness, the BICOMBO study results were likely to generate valuable scientific debate until ACTG5202 reported in 2009. As with all science, Gilead welcomed discussion and debate of this valuable new data.

Gilead agreed with GlaxoSmithKline that one of the fundamental principles of the Code when using a study to promote a product was that claims made must represent the balance of evidence available as well as being supportable by robust data. The leavepieces at issue were an accurate summary of the BICOMBO

study results and conclusions as presented at IAS 2007 and Gilead believed that sufficient information was presented to allow the reader to make a fair assessment of the study.

The BICOMBO study was first proposed to Gilead and GlaxoSmithKline in 2004 by an international group of HIV experts. The investigators were all based in Spain, where the study was exclusively conducted. The study proposal and protocol were submitted to each company by the investigators. The study proposal and all components of the protocol including study design, efficacy endpoints, safety analysis, randomisation procedures and the statistical methodology were assessed by Gilead before March 2005 when the company finally agreed to support the study. Gilead understood that both it and GlaxoSmithKline believed that the study had merit and import and had therefore agreed to co-fund it. The investigators shared the 48 week data with both companies prior to presenting it as a 'late-breaker' oral presentation at the IAS meeting in July, 2007.

With regard to inter-company dialogue, Gilead refuted GlaxoSmithKline's implication that Gilead had not responded in a timely and adequate manner to its concerns; Gilead had entered into dialogue in good spirit in a timely and constructive fashion. Gilead had responded to GlaxoSmithKline's concerns in a positive manner with a view to maintaining the highest scientific standards and complying with all applicable regulations, law and the Code.

Gilead did not agree with GlaxoSmithKline's allegations, however Gilead had agreed to amend the promotional materials at certain points by 30 October 2007, to improve clarity and enhance clinical discussion. All such proposed amendments were accurate and in line with the results and conclusions of the lead investigator's presentation. GlaxoSmithKline has rejected Gilead's offer for representation of the two companies to meet to further discuss the materials in an attempt to resolve the ongoing dispute.

*Bias in randomisation*

As stated by GlaxoSmithKline and clearly indicated at the top of both leavepieces, the BICOMBO study was an investigator-initiated and managed study, jointly funded by Gilead and GlaxoSmithKline. Throughout Gilead's dialogue with GlaxoSmithKline, Gilead had made it very clear that the contents of both leavepieces were accurate summaries of the results and conclusions presented at IAS 2007.

In BICOMBO, full randomisation of study subjects was performed by the investigator team in the manner approved by an independent statistician under the terms of the study protocol (randomisation was centralised and random numbers generated by means of a computer programme). The data was analysed by the Epidemiology and Statistics Unit, Hospital Clinic in Barcelona. In addition the results of the BICOMBO study had been peer-reviewed by the IAS faculty before the data was accepted as an oral presentation at its 2007 meeting.

GlaxoSmithKline had alleged that the BICOMBO study was flawed as 34% of patients assigned to the Truvada arm were already taking tenofovir at baseline and that only 7% of patients assigned to the Kivexa arm were already on abacavir at baseline. Market share data for the two combinations in Spain and the rest of Europe would have been readily available to any pharmaceutical company at the time of study review. The baseline imbalance in the two arms of the study could be anticipated because of the different market share of the two products in Spain. At IAS 2007, in response to a question from the floor, a subgroup analysis of the results with the prior drug exposure imbalance corrected, was presented and this demonstrated that there was no effect on the study conclusions.

Since the IAS presentation in July 2007, a further more complete analysis of the effects of this difference in prior product exposure had been formally analysed and presented at the EACS 2007 conference (Sanz *et al*) and this confirmed the results of the full study group that was previously presented at IAS 2007. This sub-analysis, excluding patients previously exposed to tenofovir or abacavir reached the same conclusions as the IAS presentation.

GlaxoSmithKline had agreed to continue funding of the BICOMBO study for 2008 and had been able to comment on the results before making this decision. Moreover, GlaxoSmithKline accepted the study design in providing its initial funding support in 2005.

However, it was important to note that there was no significant bias in the numbers of patients taking tenofovir at baseline who were then assigned to Truvada arm (34%) or Kivexa (26%) and also in the proportion of patients taking abacavir at baseline who were then assigned to Truvada (11%) or Kivexa (7%). The arms were well-balanced at baseline for these and other factors, with the exception that more Kivexa patients were still on their first antiretroviral regimen (29%) compared to the Truvada arm (17%), (p=0.01) over a similar median time of previous antiretroviral exposure (4.2 years, Kivexa; vs 3.7 years, Truvada). This greater treatment experience in terms of changes of antiretroviral regimen prior to study entry was likely to have benefited Kivexa rather than Truvada, as there would be greater risk of resistance and treatment failure in those that had changed treatments more frequently.

Gilead noted that as a condition of inclusion, patients had to be virologically suppressed and stable on treatment ie HIV RNA,< 200 copies per mL for six months or longer prior to randomisation. Such a stable viral treatment picture indicated that the likelihood of virological failure during the study was unlikely and was a general requirement of studies involving the switch of anti-retroviral drugs. The design of the study tested whether switch to either Kivexa or Truvada in stable and virologically suppressed patients maintained both virological control and a favourable safety profile.

Gilead therefore believed that the presentation of the

BICOMBO results was fair and balanced with sufficient information to allow readers to reach their own conclusions.

*Baseline resistance testing*

Baseline resistance testing was now generally regarded as necessary prior to starting treatment in naïve patients. However in the UK, this requirement had only recently been incorporated into guidelines for all naïve patients (BHIVA 2006) and adoption of these guidelines varied widely in Europe. Patients started on treatment prior to 2006 generally did not have baseline resistance tests performed and fully suppressed patients could not have resistance tests done at study entry, because their viral load was undetectable.

In the BICOMBO study, patients had been treated for a median of 4.2 years (Kivexa) and 3.7 years (Truvada). Baseline resistance testing was not undertaken at study entry as patients were already on treatment and this had not been a common practice in Spain when the BICOMBO study was planned or started and as such was not included within the protocol. Indeed baseline resistance testing was reserved for studies in treatment-naïve patients or for patients failing on treatment, neither of which applied here. There were several other examples of treatment-switch studies that had not required the availability of baseline resistance test as inclusion criteria, for example the RAVE study and the SWEET study, as the study population was treatment experienced. A requirement that there was no known previous virological failure and no documented resistance, was generally considered adequate in these studies.

*Endpoints*

BICOMBO was a non-inferiority study of Kivexa vs Truvada with an upper limit of 95% CI of estimated difference < 12.5%. This study design had been widely used to compare both naïve and experienced patients in various settings.

The primary endpoint of the BICOMBO study was the proportion of patients with treatment failure for any reason through week 48. This included virological rebound (> 200 copies/mL), discontinuation of study therapy or patients lost to follow-up, progression to a new late stage event or death.

The secondary endpoints were: the proportion of patients with virological failure at or before week 48 confirmed on-study HIV RNA ≥ 200 copies/mL or last on-study HIV RNA ≥ 200 copies/mL followed by discontinuation; time to treatment failure and to virological failure; CD4 changes; safety; and changes of fasting plasma lipids, body fat, bone mineral density and renal function.

With regard to the efficacy outcomes leavepiece, Gilead submitted that the primary endpoint of treatment failure was visually displayed as the first bar chart with the statistical data above in the graphics window and showed that Kivexa did not meet the non-inferiority endpoint compared to Truvada. The bullet points 'Treatment failure rates for Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada',

These were statements of fact supporting the primary endpoint bar chart on the left of the panel. One of the secondary endpoints, the proportion of patients with virological failure, was addressed to the left of the primary endpoint in the panel with two supporting bullet points 0% virological failure for patients switched to Truvada' and 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada: however, there were more failures with Kivexa (2.4%) than Truvada (0%)'.

The second bullet point stated that non-inferiority was met but that there were more failures in the Kivexa arm. This again was a statement of fact relating specifically to this study.

Gilead denied that the efficacy outcomes leavepiece breached Clauses 7.2 and 7.3. The study was powered for non-inferiority for treatment failures, the primary efficacy endpoint. Kivexa did not meet this endpoint compared to Truvada. The efficacy leavepiece did not mention 'superiority' as the study was not powered for superiority and therefore Gilead denied a breach of Clauses 7.2 and 7.3.

The efficacy outcomes leavepiece addressed the primary endpoint (visually displayed as the first bar chart) and then went onto highlight important secondary efficacy endpoint areas. The claims made in the three bullet points accurately represented the conclusions of the the BICOMBO study as presented to IAS. GlaxoSmithKline then complained that '...there was a difference in the baseline regimens of the two groups, the randomisation has generated an inherent bias'. As stated previously, GlaxoSmithKline would have reviewed the protocol before deciding to fund the study and any areas of concern should have been raised then. The fact that GlaxoSmithKline failed to raise such concerns at this point must indicate that it was satisfied with the study design, or accepted such concerns as inconsequential on approving provision of continued funding to the study. In Gilead's opinion, these points were being raised now in order to explain study results and conclusions that were not favourable to GlaxoSmithKline. In addition Gilead believed that any potential bias in randomisation was part of the study design and would actually favour Kivexa. Gilead believed that the study was powered appropriately and any suggestion to remove data relating to patients receiving abacavir in the Kivexa arm and tenofovir in the Truvada arm was disingenuous.

The efficacy outcomes leavepiece was, as stated prominently at the top, intended to discuss 'Study Highlights'. It related solely to a study pre-examined and co-funded by the two companies. In faithfully representing the data as presented at the IAS conference, the leavepiece addressed the primary and main secondary efficacy endpoints. However for clarity, Gilead had agreed to add the table on baseline therapy from the IAS presentation to the leavepiece in

order that any baseline bias that could potentially favour Kivexa might be discussed with clinicians. In addition, Gilead had agreed to include the statistical bars from the presentation to replace the statistical figures which appeared above the bar charts in the first version of the leavepiece for visual simplicity.

*Absence of baseline resistance testing*

As stated above, baseline resistance testing was not performed in this study and it was not common practice to perform this in stable treatment-experienced patients. GlaxoSmithKline's concerns about baseline resistance testing could have been aired or would have been accepted by GlaxoSmithKline before it decided to fund the BICOMBO study. The presentation at the IAS included a slide showing that none of the four patients with virological failure in the Kivexa arm had been exposed to abacavir prior to the study, and that virological failure developed between months 4-8 of the study. The four patients had therefore been treated with an alternative lamivudine-based regimen (according to protocol) on which they had exhibited virological stability 'for 1-5 years', before entry to the study. That was, an HIV RNA viral load of < 200 copies /mL had been maintained for ≥ 6 months and that on change to Kivexa (also a lamivudine-based regimen), these patients failed virologically. This might point to a relative weakness of Kivexa compared to Truvada in the setting of treatment switch, however, the number of failures was few in number so that the non-inferiority criteria for this end point was met.

There were more patients in the Truvada arm who were more treatment experienced in that more patients had had more than one course of antiretroviral therapy. Previous treatment failure might theoretically predispose to viral resistance developing, as breaks and gaps in effective treatment might possibly have occurred in changes of antiretroviral regimen. Counter to GlaxoSmithKline's claim, it could therefore be argued that given the baseline data, patients in the Truvada arm were at greater risk of virological failure than those on Kivexa. However there were no failures on Truvada in this study.

As stated in inter-company communication, Gilead proposed to include the relevant baseline data table in the efficacy leavepiece in order to improve its clarity. Gilead also proposed to add a cartoon of the relevant statistics to ensure that those unfamiliar with non-inferiority trial designs and interquartile range statistics might better understand the non-inferiority test. Gilead denied breaches of Clauses 7.2 and 7.3.

*Retrospective HLA-B*5701 screening and open-label study design*

The efficacy outcomes leavepiece contained the wording 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA +ve'.

This was a statement of fact from the conduct of the study as presented by the principal investigator. HLA testing had not been part of standard clinical practice in the great majority of countries of the world and was not standard practice when the study protocol was designed. Indeed, other GlaxoSmithKline-sponsored studies (HEAT, ALOHA and SHARE which were currently running) initiated at the same time as BICOMBO did not include baseline HLA testing.
As an open label design, the BICOMBO study reflected 'real life' clinical practice and therefore under such circumstances a higher degree of suspicion of abacavir-related hypersensitivity was likely to exist, as this reaction could be confused with other symptoms and signs. Gilead noted that Section 4.4 of the Kivexa SPC stated:

> 'In clinical studies approximately 5% of subjects receiving abacavir develop a hypersensitivity reaction. Some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions.' 'It is estimated that approximately 50% of patients with the HLA-B*5701 allele develop a suspected hypersensitivity reaction (HSR) during the course of abacavir treatment versus less than 3% of patients who do not have the HLA-B*5701 allele in the Caucasian population.' 'However, it is noteworthy that among patients with a suspected hypersensitivity reaction, 50% did not carry the HLA-B*5701 in the Caucasian population. Therefore, the clinical diagnosis of suspected hypersensitivity to abacavir must remain the basis for clinical decision-making.
> '

Of the 167 patients randomised to Kivexa, nine were suspected of developing abacavir hypersensitivity. This equated to 5% of the Kivexa study arm and accorded very well with data from other studies and the statement on HSR in the Kivexa SPC, mentioned above. Of these nine patients, six were shown retrospectively to be HLA-B*5701 negative, a proportion similar to that noted in the Kivexa SPC 'among patients with a suspected hypersensitivity reaction, 50% did not carry HLA-B*5701 in the Caucasian population'. As the BICOMBO study was conducted entirely in Spain, then the data were congruent with this prevalence statement about a Caucasian population.

In addition, the PREDICT study presented by GlaxoSmithKline at the 2007 IAS meeting concluded that 'GlaxoSmithKline continues to recommend the role of ongoing clinical vigilance in the management of HIV patients, regardless of the effectiveness of other tools available'. This was consistent with Gilead's statement in the efficacy leavepiece that 'clinical vigilance for HSR is essential during treatment'. It was incumbent upon the pharmaceutical industry to maintain awareness amongst health professionals of potentially serious issues associated with the use of medicines, as GlaxoSmithKline did with its Kivexa promotional materials regarding HSR. As Kivexa was mentioned in the efficacy leavepiece, Gilead had a duty to address HSR as part of overall safety concerns.

The detailed explanation by GlaxoSmithKline's detailed explanation of HLA-B*5701 and HSR testing in its letter of 21 September to Gilead represented a misinterpretation of the leavepieces. Gilead's statement

on the study numbers who underwent retrospective HLA-B5701 testing was not ambiguous or misleading in nature and was not in breach of either Clause 7.2 or 9.1. At no point had Gilead denigrated HLA testing. Gilead strongly denied that the efficacy leavepiece disparaged Kivexa or HLA-B*5701 testing and Gilead denied breaches of Clauses 7.2, 7.3, 8.1 and 9.1.

### PANEL RULING

The Panel noted that the BICOMBO study was the first to directly compare the efficacy and safety of Kivexa and Truvada. The study would run for three years but to date data was only available from the first 48 weeks of the study and this had been presented in abstract form and orally at the IAS in July 2007. The study had thus not run its course and there was limited data in the public domain with regard to study design, statistical methods etc. The study was designed to assess the non-inferiority of the two combinations with respect to treatment efficacy (primary endpoint) and virological efficacy (secondary endpoint). Kivexa failed to meet the primary non-inferior endpoint compared with Truvada. The authors suggested that this might have been because some patients had to discontinue Kivexa treatment due to abacavir hypersensitivity reactions (discontinuation of study therapy was regarded as treatment failure). In terms of virological efficacy Kivexa met non-inferiority criteria compared with Truvada however there were more failures with Kivexa than Truvada (2.4% vs 0% respectively).

The Panel noted that the efficacy leavepiece featured a bar chart detailing treatment failure and virological failure. The visual impression of the bar chart was that Truvada was superior to Kivexa although this had not been shown statistically. Although the results favoured Truvada, the study was not powered to show superiority; in any event only 48 week data was available from a study which still had over 2 years to run. The following claims appeared to the right of the bar chart: 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kivexa (2.4%) than Truvada (0%)'; 'Treatment failure rates with Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada.'

The Panel noted that although Kivexa had not been shown to the non-inferior to Truvada in terms of treatment efficacy, Truvada had not been shown to be superior. In terms of virological efficacy Kivexa was shown to be non-inferior to Truvada although there were more treatment failures with Kivexa than Truvada. The Panel considered that although the interim data from the BICOMBO study was of undoubted interest, but noted that the study had yet to run its full course. In that regard the Panel noted the supplementary information to Clause 7.2 of the Code which stated that where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material.

The Panel considered that the efficacy outcomes leavepiece implied that Truvada had been shown to be superior compared with Kivexa which was not so. The Panel considered that the claims detailed above were misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the leavepiece at issue did not record the fact that no baseline resistance testing had taken place although it did state that at baseline patients had been virologically suppressed for at least 6 months. The definition of suppression (<200 copies HIV RNA per ml) was not stated although virological failure was stated to be ≥200 copies/ml. The Panel noted Gilead's submission that baseline resistance testing could not have been performed at study entry due to the viral load being undetectable.

Overall the Panel considered that whilst it might have been helpful for readers of the leavepiece to know that baseline testing had not been carried out, the omission of such data was not misleading per se. Readers were told that patients were virologically suppressed at baseline. On balance the Panel considered that the claims 'For virological efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kinvexa (24%) than Truvada (0%)' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada' were not misleading on this point and ruled no breach of Clause 7.2.

The Panel considered that the claim 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA positive. Clinical vigilance for HSR is essential during treatment' clearly referred to suspected HSR and not immunologically-confirmed HSR. The Panel noted that the claim implied that 6 cases of suspected HSR were in patients who were HLA negative. Section 4.4 of the Kivexa SPC referred to the possibility of suspected HSR in patients who did not carry HLA-B*5701. The Panel did not consider the claim at issue was misleading, ambiguous or incapable of substantiation nor did it disparage Kivexa. No breach of Clauses 7.2, 7.3, 7.4 and 8.1 was ruled.

Although noting its comments above the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

### 2 Leavepiece entitled 'Study highlights: BICOMBO – safety outcomes'.

### COMPLAINT

GlaxoSmithKline was concerned that Gilead had not properly considered its complaints regarding the following claim made in the safety outcomes leavepiece:

> 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile* than Kivexa, with no differences in renal function or bone mineral density'. (The

asterisk referred to TG, TC and LDL and was shown as a footnote.)

In its letter of 24 August, GlaxoSmithKline alleged that it was misleading to claim that Truvada had a significantly better lipid profile than Kivexa based on only three of the four parameters measured, as the fourth (HDL) was widely believed to be an important factor when evaluating cardiovascular risk, as in the Framingham calculator and the British Heart Foundation guidelines. TGs were understood to play a minor role.

Use of the asterisk and footnote were inappropriate. Clearly Gilead's representation of these data was selective and misleading and should report all four lipid results in a balanced manner, rather than excluding the clinically relevant parameter of HDL which improved significantly in the Kivexa arm of the study.

In its response Gilead argued that the lipid profiles demonstrated in the BICOMBO study were entirely consistent with the findings of a number of other studies, but only one of these (RAVE) directly compared tenofovir and abacavir. The RAVE study demonstrated small but statistically significant differences in favour of tenofovir for TC, LDL and TG (Moyle GJ *et al*). HDL did not change from baseline in the abacavir arm of the RAVE study but fell slightly in the tenofovir arm; the difference between the two treatment arms as regards HDL did not reach statistical significance. Importantly, the clinical relevance of the lipid changes reported in the RAVE study with regard to cardiovascular risk remained uncertain. The RAVE study had its limitations too, as there were only around 50 patients in each arm of the study and the tenofovir and abacavir arms in this study were not balanced as regards use of stavadine and zidovadine at baseline – proportionately more patients in the Truvada arm were on stavadine at baseline compared with the Kivexa arm (77% v 59%) and this constituted a major criticism of the study.

BICOMBO was the first comparative study between Truvada and Kivexa to provide TC/HDL ratios as the RAVE study did not do so.

In BICOMBO, HDL worsened on Truvada and the TC:HDL ratio remained unchanged for both Truvada and Kivexa. Following the dialogue, Gilead had agreed to amend 'the text of the first bullet point of the Gilead safety leavepiece to report on all four lipid results'. Gilead subsequently confirmed that it would remove the asterisk and qualified claim that would otherwise be in breach of the supplementary information to Clause 7. GlaxoSmithKline thus expected that Gilead would qualify the broad lipid claim made to provide the appropriate balance as given by the HDL data.

Despite these concessions, Gilead had not agreed to modify the claim 'switching to Truvada provides a significantly more favourable lipid profile than Kivexa'. This was clearly misleading and all embracing even with Gilead's proposed concessions. Thus GlaxoSmithKline believed that on this point inter-company dialogue had failed (as per Gilead's letters of 5 and 10 October) and that this claim was in breach of Clause 7.2.

Furthermore GlaxoSmithKline was concerned that the claim 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was misleading with regard to the safety of Truvada. The Truvada summary of product characteristics (SPC) listed hypertriglyceridaemia as a commonly reported adverse event, and cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 (with reference to section 4.4). This was likely to be in breach of Clause 7.10 by not encouraging the rational use of the medicine.

GlaxoSmithKline did not find Gilead's response to the fact that hypertriglyceridaemia was present as an adverse event in the Truvada SPC satisfactory as the leavepiece clearly implied an improvement in triglycerides at variance with this important safety statement in the SPC. Gilead claimed that it was acceptable to cite such study conclusions when made by the investigator. Any results in relation to this study should be offset by reference to this important statement. GlaxoSmithKline alleged a breach of Clause 7.10. As above, statements made by investigators were not automatically suitable for inclusion in promotional material.

Finally, GlaxoSmithKline alleged that the Study highlights – safety outcomes leavepiece was misleading in that it did not mention the primary outcomes of the study. This was not a safety study. Secondary parameter claims could not be made without presenting the primary parameter data from the study to allow clinicians to assess the relative efficacy and safety of the two components. Gilead's assertion that the primary efficacy parameters were presented elsewhere (ie in a separate leavepiece) did not allay GlaxoSmithKline's concerns, as it considered that each piece must be capable of standing alone. GlaxoSmithKline reasserted its belief that this element was in breach of Clauses 7.2 and 7.10.

## RESPONSE

Gilead explained that dyslipidaemia was common in HIV-infected and HIV-treated patients but the implications of dyslipidaemia in these patients were not fully known. At present there were no UK guidelines for the management of dyslipidaemia in HIV patients. To Gilead's knowledge, the only guidelines relating to the evaluation and management of dyslipidaemia in HIV patients emanated from the US.

The guidelines used as their basis the US National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP III]) criteria and algorithm. The NCEP ATP III identified five risk factors that modified the target levels to which LDL cholesterol should be brought, ie smoking, age, a family history of premature coronary heart disease, hypertension and a low HDL (< 1mmol/L) level

(diabetes was considered equivalent to the presence of coronary heart disease). If no or only one risk factor was present, then the goal to which LDL should be reduced to, if elevated, was 4.10mmol/L. If two or more risk factors were present then the goal was reduced to 3.33mmol/L. As low HDL cholesterol was one of the five risk factors, then it might not be important in the management of an elevated LDL cholesterol if, for example, two of the other risk factors were present, such as hypertension and a family history. The level of LDL cholesterol was considered the primary parameter on which to base management decisions by these guidelines, the HDL cholesterol level was secondary. As these guidelines represented the present state of management of dyslipidaemia in HIV patients then Gilead believed that the bullet point on the safety leavepiece 'Truvada showed a significantly more favourable lipid profile compared to Kivexa' was factually justified and did not breach Clauses 7.2 and 7.10.

The DAD (Data collection on Adverse events of anti-HIV Drugs) study was the largest prospective cohort of HIV patients worldwide, assessing morbidity and mortality due to cardiovascular disease, as well as liver failure and related death. As the factors contributing to cardiovascular risk in the HIV population were not well understood, the CHMP had recently recommended that the DAD cohort be continued to help in elucidating the role of antiretroviral therapy in cardiovascular risk.

Gilead had always accepted the value of the Framingham calculation for the non-HIV infected population. Gilead had never argued that HDL was not an important factor in cardiovascular risk; it had merely asserted that according to the published study results triglycerides, total cholesterol and low density lipoprotein indices improved on Truvada administration. In the interests of clarity, Gilead had already informed GlaxoSmithKline that the text of the first bullet point of the safety outcomes leavepiece would be amended to report on all four lipid results (TG, TC, LDL and HDL) in the bulleted text, to accompany the visual representation of the results, already prominently displayed in the piece, adjacent to the bullet. Gilead suggested that the following be added to its leavepiece to enable clinician discussion: 'The median fasting HDL level fell by 4 mg/dL (0.1 mmol/l) in the Truvada arm, and remained the same in the Kivexa arm, $p<0.0001$)'.

The BICOMBO study showed no change with respect to HDL on Kivexa treatment – this was not an improvement. On the contrary, treatment with Kivexa resulted in deteriorations in both TC and LDL whilst HDL and TG remained unchanged. For those on Truvada, according to the data, each of TG, TC and LDL improved but HDL declined in comparison with Kivexa.

The claim that 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was a comparative statement made by the investigators from their analysis of the results and not from a review of the SPCs of each of Truvada and Kivexa. The statement fell within the investigators' remit of being able to fairly report the results of their study and their analysis of them.

Whilst GlaxoSmithKline had correctly observed that the Truvada SPC listed hypertriglyceridaemia as a commonly reported adverse event, and had cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 of the SPC (with reference to section 4.4. of the SPC) this did not prevent independent study reporting and analysis. Furthermore, the statement in the Truvada SPC related to naïve patients that were started on tenofovir, not experienced patients who were switched from an existing NRTI backbone.

The comparative statement made by the investigators and repeated by Gilead arose from the comparison of the lipid profiles of Truvada and Kivexa from the results of the BICOMBO study. The BICOMBO study was a switch study in which patients had previously been on a variety of previous NRTI backbones which might have had unfavourable lipid profiles. Previous studies that had involved switching from one NRTI backbone to Truvada or to its component tenofovir, had consistently shown benefits in lipid profiles, including triglycerides.

There was no breach of Clause 7.10 as Gilead had presented the lipid data objectively, in context and without exaggerating Truvada's properties. In making such a statement, Gilead was fairly reporting the peer-reviewed clinical study results of an independent investigator.

The safety outcomes leavepiece did not mention the primary outcomes of the BICOMBO study. The safety data were secondary endpoints and the leavepiece was used in conjunction with the efficacy outcomes leavepiece by the representatives. The Code did not prevent the production of leavepieces which only discussed a secondary endpoint although conventionally both primary and secondary outcomes to a study could be presented at the same time. The supplementary information to Clause 4.1 stated that the material should be able to stand alone for example, and this could be achieved by having the prescribing information included within the piece. Whilst Gilead accepted that this was not a safety study per se, Gilead had presented the primary endpoint data from the BICOMBO study elsewhere, to allow clinicians to assess the relative efficacy and safety of the two components and Gilead representatives would continue to present both leavepieces to describe both the primary and secondary outcomes. When displayed, the leavepieces had also been displayed together to represent all the main findings of the study. Gilead proposed that it also added the words 'Primary endpoint' and 'Secondary endpoints' to the leavepieces as appropriate, to make this information clearer.

In summary, the BICOMBO study was an important study because it was the first head-to-head randomised trial to compare the performance of Kivexa and Truvada in the setting of virologically controlled HIV positive patients, who required switching their

medicines. Gilead believed that the BICOMBO study was a robust independent investigator-led study worthy of summary and discussion and it welcomed discussion and debate of this valuable new data.

Gilead firmly believed that the leavepieces accurately summarised the BICOMBO results and conclusions as presented at IAS 2007 and that sufficient information was presented to allow the reader to make a fair assessment of the study results and conclusions.

## PANEL RULING

The Panel noted that although Gilead had agreed to refer to all four lipid results (TG, TC, LDL and HDL) in its claims regarding lipid profile, it had not agreed to modify the claim 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile …'. The results shown to substantiate this claim were the absolute changes in lipid levels over 48 weeks and the lack of change in the TC/HDL ratio over the same time period. However, although, for instance, readers were told that LDL rose by 7mg/dL over 48 weeks there was no indication as to the clinical significance of this. The Panel considered that the information given was such that prescribers would be unable to form their own opinion as to the clinical significance of the results; the leavepiece was thus misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that the leavepiece depicted a decrease in triglycerides (-16mg/dL) over 48 weeks. The Truvada SPC, however, listed hypertriglyceridaemia as a common side-effect. The Panel considered that it was misleading to refer to the observed decrease in triglycerides without noting the statement in the SPC regarding hypertriglyceridaemia. A breach of Clause 7.10 was ruled as alleged.

The Panel did not consider that it was necessarily unacceptable to produce a leavepiece focussing only on the safety data when such data had come from secondary endpoints of a study. None of the primary end-points were safety-related and so in that regard the safety data was capable of standing alone. However the leavepiece at issue did not make it clear that the data presented was from secondary endpoints and that primary endpoints had related to efficacy. Some readers might assume that the BICOMBO study was primarily a safety study which was not so. The leavepiece was misleading in this regard. Breaches of Clauses 7.2 and 7.10 were ruled.

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| **Complaint received** | **12 October 2007** |
| **Case completed** | **7 January 2008** |