# ANONYMOUS, NON-CONTACTABLE MEMBER OF THE PUBLIC v LEO

## Alleged promotion of Kyntheum to the public

**An anonymous, non-contactable complainant, who described themselves as a member of the public, complained about the promotion of Kyntheum (brodalumab) to the public by Leo Pharma. Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adults who were candidates for systemic therapy.**

**The complainant stated that he/she went for a job interview at Leo for a role which would involve working on Kyntheum and the complainant was surprised by the amount of advertising for the product in the open waiting room. The complainant stated that he/she took a photograph of an advertisement which depicted a naked man and a number of claims. The indication was also included which the complainant did not think was licensed at the time of interview.**

**There was also a billboard upon which was stated 'The future is clear the future is Kyntheum'.**

**The complainant stated that he/she worked in the field and was not an expert on the Code but did not think a company could advertise to the public before the product had been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or state 'well tolerated' when a number of patients in trials in the United States committed suicide.**

**The detailed response from Leo is given below.**

**The Panel noted Leo's submission that the materials referred to by the complainant were intended solely for the purpose of internal communications, as part of an internal campaign to engage staff in the launch of Kyntheum. Leo had submitted that the materials at issue were displayed within Leo's private, secure countryside-based offices within the staff coffee/ breakout area only. The Panel noted that Leo's offices were on the second floor and access to its offices was controlled; the only people who had access were Leo staff and visitors accompanied by a Leo staff member. The Panel noted Leo's submission that visitors would be shown to a room in the meetings area, away from the open-plan office and staff coffee area where the materials at issue were displayed.**

**The Panel considered that it was not necessarily unacceptable for a company to display product material within the confines of its offices, but such displays in areas routinely accessed by visitors, or even viewed by passers-by, needed to be appropriate. In the Panel's view, companies had to be aware of the impact and impression such material could have on visitors and the messages that might be conveyed. The Panel considered that if a visitor had seen the material at issue, they would be very aware that the company was shortly to launch a new product.**

**The Panel noted that the complainant had attended Leo's office to interview for a role working on Kyntheum. The Panel noted that the supplementary information stated that information about pharmaceutical companies provided to current or prospective employees might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The Panel noted Leo's submission that the materials at issue were only on display after Kyntheum's marketing authorization had been received. In these circumstances, it was not unreasonable for a prospective employee when interviewing for a position which involved working with Kyntheum to see internal communications on the product. In these circumstances, the Panel considered that there was no evidence to support the complainant's allegation that Leo had promoted Kyntheum to the public prior to the grant of its market authorisation as alleged. No breaches of the Code were ruled including Clause 2.**

**The Panel noted the complainant's concern that Kyntheum was described in the material at issue as 'well-tolerated' when a number of patients in trials in the US had committed suicide. The Panel noted that Section 4.4, Special Warnings and Precautions for use, of the Kyntheum SPC,stated that suicidal ideation and behaviour, including completed suicide, had been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The SPC advised that the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, care givers and families should be advised of the need to be alert for such and if a patient suffered from new or worsening symptoms of depression and/or suicidal ideation or behaviour was identified it was recommended to discontinue treatment with Kyntheum. The Panel noted that suicidal ideation/ behaviour was not listed as an adverse event in Section 4.8 of the SPC. The Panel further noted Leo's submission that in the Kyntheum development programme as a whole across five different therapeutic indications, six cases of completed suicide were identified during 10,438 patient-years of follow-up exposure in 6,243 patients. The Panel noted that the study authors in Farahik *et al* 2016, a**

**review of phase III trials, stated that two completed suicides in AMAGINE-2 did not necessarily constitute a causal relationship especially given that patients with psoriasis were already at higher risk for depression, suicidal ideation, attempt and completed suicide.**

**The Panel noted the narrow nature of the allegation and that the complainant bore the burden of proof. The Panel did not consider that the complainant had established, on the balance of probabilities, that describing Kyntheum as well-tolerated was misleading or could not be substantiated due to the number of trial patients that had committed suicide and no breaches of the Code were ruled.**

An anonymous, non-contactable complainant, who described themselves as a member of the public, complained about the promotion of Kyntheum (brodalumab) to the public by Leo Pharma. Kyntheum was indicated for the treatment of moderate to severe plaque psoriasis in adults who were candidates for systemic therapy.

**COMPLAINT**

The complainant stated that he/she went for a job interview at Leo's head office. The role would involve working on Kyntheum and the complainant was surprised by the amount of advertising for the product in the open waiting room. The complainant stated that he/she took a photograph of an advertisement which depicted a naked man and included the following claims:

> 'Confidence starts with clearance
>
> What does PASI 100 mean to Simon?
>
> Kyntheum targets the IL-17 pathway in a novel way, being the only biologic treatment for moderate to severe psoriasis that selectively targets the IL-17 receptor subunit A
>
> Patients achieving Pasi 100 are less likely to experience impairment to their health related quality of life than those with residual disease
>
> Kyntheum is superior to ustekinumab at achieving Pasi 100 at 12 weeks
> 44% vs 22% (Amagine 2) 37% vs 19% (amagine 3)
>
> Kyntheum has a simple induction schedule and is well tolerated.'

The complainant stated that the advertisement also included the indication which he/she did not think was licensed at the time of the interview.

There was also a billboard upon which was stated 'The future is clear the future is Kyntheum'.

The complainant stated that he/she worked in the field and was not an expert on the Code but did not think a company could advertise to the public before the product had been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or state 'well tolerated' when a number of patients in the trials in the United States committed suicide.

When writing to Leo, the Authority asked it to consider the requirements of Clauses, 2, 3, 9.1, and 26.1 in relation to the alleged promotion of an unlicensed product to the public, and Clauses 7.2 and 7.4 in relation to the claim 'well tolerated'.

**RESPONSE**

Leo submitted that it took its responsibilities for Code compliance very seriously and was committed to adhering to the Code and all applicable regulations in all its business activities. It was therefore disappointing that a prospective employee had complained anonymously to the PMCPA about information they had seen on Kyntheum when attending for an interview.

Leo strongly refuted the complainant's allegations. The materials viewed by the prospective employee were intended for internal employees only and were displayed so that they would become familiar with a product launch campaign. Leo submitted that displaying the product information to internal employees was a genuinely non-promotional activity and complied with the Code.

Leo explained that access to its offices was controlled and no visitor could enter the premises unattended as documented in the company's Site Security policy. In this specific instance, the complainant attended the Leo office as a prospective employee for a Kyntheum role and not as a member of the public. In that regard, it would not be inappropriate for that prospective employee to have access to internal product related materials relevant to his/her role. Leo denied a breach of Clause 26.1.

Leo submitted that based on email records and discussions with the cross-functional team, internal communication activities in relation to the materials in question were initiated after Kyntheum received its marketing authorization. Leo noted that there was a 'Kyntheum countdown clock' in the staff coffee area as part of the pre-launch internal activities. The complainant had not stated when he/she attended the Leo office. However, regardless of the date of attendance, given the materials at issue were on display after the grant of the marketing authorization, there had been no breach of Clause 3.

The claim that Kyntheum was 'well tolerated' was factual, balanced, in line with the marketing authorization and supported by clinical evidence. Leo noted that 'generally well tolerated' was included in certified materials that were pre-vetted by the MHRA and thus it denied breaches of Clauses 7.2 and 7.4.

Leo stated that it followed that there were no breaches of Clauses 9.1 and 2.

With regard to the allegation that it had promoted Kyntheum to the public, Leo reiterated that the materials at issue were displayed within the private, secure offices of Leo within the staff coffee/breakout area only. Leo did not consider that that area was 'an open waiting room' and it was not intended or designed for visitors. There was a small waiting area adjacent to the coffee area but Leo had no record of

Kyntheum materials being displayed in this space. Leo stated that it could not address the complainant's allegation on this point without the photograph taken but added that members of the public had never had unrestricted access to the secure Leo offices. It would be physically impossible for them to see the materials in the offices.

Leo explained that its offices were on the second floor of a building in the countryside with no form of unrestricted public access. The building housed different companies (including Leo) with a common reception/waiting area on the ground floor. Post, packages and the like were dropped off at reception and visitors would report to the reception staff at this initial entry point into the building. Any visitor with a legitimate pre-arranged business purpose within the Leo office was announced by telephone to their Leo contact. Visitors were then collected from reception by Leo staff and were accompanied to a specific area within the Leo offices on the second floor.

Leo noted that entry to its office was only possible through two doors, both of which required staff security passes to access. The offices were laid out such that the formal meeting rooms were grouped together at one end of the second floor with their own coffee/refreshment area. Most visitors would be shown to a room in the meetings area, away from the open plan office and staff coffee area which were not designed or intended primarily for the use of visitors. Therefore, there had been no promotion to the public and Leo denied a breach of Clause 26.1.

Leo submitted that the marketing authorization for Kyntheum was granted on 17 July 2017 and, according to email records and discussion with the cross-functional team, the internal communications activities relating to the materials in question were initiated on 25 July. Leo thus denied a breach of Clause 3.

Furthermore, the materials referred to by the complainant had never been intended for promotion to the public, as alleged. All materials on display were intended solely for the purpose of internal communications, as part of an internal Leo campaign to engage staff throughout the organisation in the forthcoming launch of Kyntheum.

Leo stated that it had maintained high standards as the materials at issue were submitted for technical review and certification, for internal display to office staff. Information stating 'for internal use only, not for distribution' was included on all pieces. The materials were part of an internal communications campaign; they and were not excessive in number and contained different information to fully reflect a complex new product.

Kyntheum was the first biologic medicine launched by Leo and so it was even more relevant that all employees had a reasonable technical understanding of this new complex medicine as part of building the company's capabilities and expertise. The purpose of the materials was to ensure staff understood, were engaged and educated in the work being undertaken by a cross-functional team in preparation for the Kyntheum launch. That ensured that all staff, regardless of function, recognised the need to prioritise support for the launch.

Leo submitted that the manner of internal communication was common and routine practice in the pharmaceutical industry. It was legitimate to provide business information to current employees which might relate to existing medicines and those not yet marketed. The material on display had never been exhibited to the public.

Leo noted that the complainant described him/herself both as a member of the public and as a prospective Leo employee for a Kyntheum related role. It was therefore clear that his/her visit to Leo's offices was for a defined purpose. Leo did not consider it unacceptable for a prospective employee to have access to a normal day in the life of Leo at its offices, including any internal displays at the time, in particular, those relevant to his/her prospective role. Leo submitted that was in line with Clause 26.2.

The material in question was neither intended nor deliberately shared with any member of the public.

In summary, Leo reiterated that the material at issue was displayed in a private and secure office and directed at Leo employees for the legitimate purpose of internal engagement and familiarisation with a product launch campaign. All the information in question was displayed after the UK marketing authorization had been granted and so for that reason, and the others stated above, Leo denied a breach of Clause 3.

The material at issue had never been visible to the general public and, as stated above, there were multiple safety checks to control access to Leo's offices. The complainant attended the Leo office as a prospective employee and thus he/she did not meet the definition of a general member of the public. For that reason and all the others stated above, the company did not accept a breach of Clause 26.1.

Signatory oversight was maintained over the content and audience for the material at issue, which were marked 'For Internal Use Only'. Leo standards had been sufficiently high with clear controls and policies over visitor access, as described to prevent such an occurrence as alleged. In this regard and for the detailed reasons set out above, Leo denied breaches of Clauses 9.1 and 2.

In relation to the claim that Kyntheum was 'well tolerated' and the occurrence of suicides in the clinical trials, Leo submitted that the claims included in the materials at issue were substantiated by extensive clinical trial data in the summary of product characteristics (SPC) and were not misleading. The claim 'well tolerated' was intended to convey that the adverse event profile of Kyntheum was acceptable for routine clinical use in indicated patients.
The efficacy and safety of Kyntheum was assessed in 4,373 adult plaque psoriasis patients across three multi-national, randomised, double-blind, phase 3, placebo-controlled clinical trials (AMAGINE-1,

AMAGINE-2, and AMAGINE-3 (Lebwohl *et al* 2015 and Papp *et al* 2016). AMAGINE-2 and AMAGINE-3 were also active comparator (ustekinumab)-controlled (Lebwohl *et al* 2015). All three trials included a 12-week placebo-controlled induction phase, a double-blind duration of 52 weeks, and an open-label long-term extension. The week 12 PASI 100 response rates were significantly higher with 210mg of brodalumab than with ustekinumab (44% vs 22% [AMAGINE-2] and 37% vs 19% [AMAGINE-3], P<0.001) (Lebwohl *et al* 2015).

In the AMAGINE-2 and 3 studies, 97% of patients completed the 12-week induction schedule which was comparable to the adherence rates of placebo (97.1%, 95.6%) (Lebwohl *et al* 2015).

A recent published systematic review and meta-analysis of the safety and efficacy of Kyntheum stated that there was 'an acceptable safety profile and a robust efficacy in the treatment of moderate-to-severe plaque psoriasis' (Attia *et al* 2017). Another review demonstrated that the pooled proportion of patients who experienced adverse events at 12 weeks in all three studies was 57.6% among patients taking Kyntheum 210mg and 51.0% among patients on placebo (Farahnik *et al* 2016).

The most commonly reported adverse reactions in all Kyntheum treated patients were arthralgia (4.6%), headache (4.3%), fatigue (2.6%), diarrhoea (2.2%) and oropharyngeal pain (2.1%) (SPC).

Leo stated that suicidal ideation and behaviour (SIB) was not a listed adverse event in the SPC. The SPC stated 'suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established'. Leo stated that psoriasis had profound psychosocial implications and suicidal ideation had been reported in as many as 17.3% of patients (Lebwohl *et al* 2017). Moreover, treatment with Kyntheum improved anxiety and depression scores significantly from baseline in 73% and 67% of patients with moderate to severe psoriasis respectively (Papp *et al*). A higher patient satisfaction and quality of life was observed with Kyntheum compared with placebo. As determined by DLQI [Dermatology Life Quality Index] response rate, 56-61% of patients receiving Kyntheum achieved a DLQI of 0 or 1 indicating that psoriasis no longer impacted their lives at week 12 compared with 5-7% of patients receiving placebo (Lebwohl *et al* 2017).

In the Kyntheum development programme as a whole across 5 different therapeutic indications, six cases of completed suicide were identified, during 10,438 patient-years of follow-up exposure in 6,243 patients (FDA briefing document and Valeant sponsor's briefing document 2016). Of the six completed suicides, four were in the psoriasis program (during 9161.8 patient-years of follow-up exposure, one of which was later adjudicated as an indeterminate case) and one each in the psoriatic arthritis and rheumatoid arthritis programs (FDA briefing document and Valeant sponsor's briefing document 2016). The rate of completed suicides in the psoriasis program for Kyntheum (0.04 in 100 patient-years) was comparable with the rate reported from clinical trials for apremilast (0.052-0.062), secukinumab (0.034) and across all psoriasis trials (0.028) (Valeant sponsor's briefing document 2016).

Leo considered that Kyntheum had demonstrated good efficacy and a clinically acceptable safety profile and so it denied a breach of Clauses 7.2 and 7.4.

Leo reiterated that the material at issue was reviewed and certified and it submitted that its standards had been sufficiently high in this regard and for the detailed reasons set out above, denied a breach of Clauses 9.1 and 2.

Leo provided details of the materials on display and referred to by the complainant which included a Kyntheum Stand (ref MAT-10201) and launch poster (ref MAT-10447).

**Summary**

Leo stated that it had demonstrated that it took its responsibilities for compliance with the Code very seriously and always remained committed to adhering to the Code and all applicable regulations in its business activities.

The activity in question was entirely for internal purposes with a view to educate and engage employees in the launch of a new medicine. This was a legitimate business activity and common place in the pharmaceutical industry.

The materials in question were on display after the marketing authorization had been granted and thus the company did not accept a breach of Clause 3. The entire activity was undertaken within a private and secure area of Leo's offices with no intent to promote to the public. The materials at issue were displayed in the staff coffee area. The complainant described him/herself as a prospective employee for a role working on Kyntheum. In the course of his/her interview related interactions with Leo it was not inappropriate for him/her to have had access to internal materials. Leo submitted that it had no evidence to suggest that a member of the public had been exposed to this information in its offices. Leo thus did not accept there had been a breach of Clause 26.1.

Based on clinical trial evidence, Leo considered that the claim that Kyntheum was 'well tolerated' was factually correct, not misleading and based on robust scientific evidence as outlined above. The company thus did not accept that there had been a breach of Clause 7.2 and 7.4.

Maintaining high standards and compliance with the Code and all applicable regulations was of utmost importance to Leo. Signatory oversight and copy approval process were applied to the material at issue in order to ensure their content and audience were appropriate. The company did not accept there

had been breaches of Clauses 9.1 and 2 in regard to this entirely legitimate internal business activity.

**PANEL RULING**

The Panel noted that the complainant was anonymous and non-contactable. The Constitution and Procedure stated that anonymous complaints would be accepted but that, like all other complaints, the complainant had the burden of proving his/her complaint on the balance of probabilities. All complaints were judged on the evidence provided by the parties. The complainant could not be contacted for more information.

The Panel noted Leo's submission that the materials referred to by the complainant were intended solely for the purpose of internal communications, as part of an internal campaign to engage staff throughout the organisation in the forthcoming launch of Kyntheum. Leo had submitted that the materials at issue were displayed within Leo's private, secure countryside-based offices within the staff coffee/breakout area only. The Panel noted that Leo's offices were on the second floor and access to its offices was controlled; the only people who had access were Leo staff and visitors accompanied by a Leo staff member. The Panel noted Leo's submission that visitors would be shown to a room in the meetings area, away from the open-plan office and staff coffee area where the materials at issue were displayed.

The Panel considered that it was not necessarily unacceptable for a company to display product material within the confines of its offices, but such displays in areas routinely accessed by visitors, or even viewed by passers-by, needed to be appropriate. In the Panel's view, companies had to be aware of the impact and impression such material could have on visitors and the messages that might be conveyed. The Panel considered that if a visitor had seen the material at issue, they would be very aware that the company was shortly to launch a new product.

The Panel noted that the complainant had attended Leo's office to interview for a role working on Kyntheum. The Panel noted that the supplementary information to Clause 26.2 stated that information about pharmaceutical companies provided to current or prospective employees might relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way. The Panel noted Leo's submission that the marketing authorization for Kyntheum was granted on 17 July 2017 and, according to email records and discussion with the cross-functional team, the internal communication activities relating to the materials in question were initiated on 25 July; the materials at issue were therefore only on display after Kyntheum's marketing authorization had been received. In these circumstances, it was not unreasonable for a prospective employee when interviewing for a position which involved working with Kyntheum to see internal communications on the product. In these circumstances, the Panel considered that there was no evidence to support the complainant's allegation that Leo had promoted Kyntheum to the public prior to the grant of its market authorisation as alleged. No breach of Clauses 3.1, 26.1, 9.1 and 2 were ruled.

The Panel noted its comments above with regard to Clause 26.2 that information provided to current or prospective employees must be factual and presented in a balanced way. The Panel noted the complainant's concern that Kyntheum was described in the material at issue as 'well-tolerated' when a number of patients in trials in the US had committed suicide. The Panel noted that Section 4.4, Special Warnings and Precautions for use of the Kyntheum SPC, stated that suicidal ideation and behaviour, including completed suicide, had been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour had not been established. The SPC advised that the risk and benefit of treatment with Kyntheum should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. Patients, care givers and families should be advised of the need to be alert for such and if a patient suffered from new or worsening symptoms of depression and/or suicidal ideation or behaviour was identified it was recommended to discontinue treatment with Kyntheum. The Panel noted that suicidal ideation/behaviour was not listed as an adverse event in Section 4.8 of the SPC. The Panel further noted Leo's submission that in the Kyntheum development programme as a whole across five different therapeutic indications, six cases of completed suicide were identified during 10,438 patient-years of follow-up exposure in 6,243 patients. The Panel noted that the study authors in Farahik *et al* 2016, a review of phase III trials, stated that two completed suicides in AMAGINE-2 did not necessarily constitute a causal relationship especially given that patients with psoriasis were already at higher risk for depression, suicidal ideation, attempt and completed suicide.

The Panel noted the narrow nature of the allegation and that the complainant bore the burden of proof. The Panel did not consider that the complainant had established, on the balance of probabilities, that describing Kyntheum as well-tolerated was misleading or could not be substantiated due to the number of trial patients that had committed suicide and no breach of Clauses 7.2 and 7.4 were ruled.

During its consideration of this case the Panel noted that one of the items at issue (ref MAT-10201) included an apparently naked man who was sitting on an underground train seat between other passengers and holding an A3 newspaper which covered his upper thigh to his mid-chest. The supplementary information to Clause 9.1 stated that the use of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose was unacceptable. The Panel did not consider that the imagery was sexual. It was of course not unacceptable to show bare skin when advertising

medicines for prescribing so long as the image was relevant and complied with the Code, including Clause 9.1. The quality and appearance of a patient's skin was relevant to the product. However the Panel considered that it was the subject's nakedness in a social setting which had the primary and immediate visual impact and was designed to draw attention to the material. The Panel queried whether the visual complied with the supplementary information to Clause 9.1 and requested that Leo's attention be drawn to this matter.

**Complaint received** **3 October 2017**

**Case completed** **8 February 2018**