CASE/0409/12/24

PFIZER v ALNYLAM

Alleged promotion at the European Society of Cardiology (ESC) 2024 congress in London

CASE SUMMARY

This case was in relation to activities undertaken by Alnylam at a European cardiology congress in 2024, including its exhibition booth material, two "tutorials" held by Alnylam, and an Alnylam-organised evening meeting ("ATTR Meeting"). Pfizer alleged that Alnylam had presented off-label information at the ATTR meeting, that the London venue at which the meeting was held was inappropriately lavish, that the congress booth material was directed to an inappropriate audience and that the two tutorials promoted its medicine outside the terms of its marketing authorisation.

There was an appeal by Alnylam of four of the Panel's rulings.

The outcome under the 2021 Code was:

Breach of Clause 5.1 [Panel's breach ruling upheld at appeal]	**Failing to maintain high standards**
Breach of Clause 11.2 [Panel's breach ruling upheld at appeal]	**Promoting a medicine for an unlicenced indication**

No Breach of Clause 2 [Panel's breach ruling overturned at appeal]	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 3.6	**Requirement that materials and activities must not be disguised promotion**
No Breach of Clause 5.6	**Requirement that material should only be provided or made available to these groups of people whose need for or interest in it can reasonably be assumed**
No Breach of Clause 6.1	**Requirement that information, claims and comparisons must not be misleading**
No Breach of Clause 10.1	**Requirement that lavish, extravagant or deluxe venues must not be used for events or meetings**
No Breach of Clause 11.2 (x2)	**Requirement that promotion of a medicine must be in accordance with the terms of its marketing authorisation**
No Breach of Clause 11.2 [Panel's breach ruling overturned at appeal]	**Requirement that promotion of a medicine must be in accordance with the terms of its marketing authorisation**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from Pfizer Limited about Alnylam UK Ltd.

COMPLAINT

The complaint wording is reproduced below:

> "Dear PMCPA
>
> I am writing to you regarding a number of potential breaches of the ABPI Code of Practice by Alnylam, that were noted by Pfizer at the recent European Society of Cardiology (ESC) congress 2024 in London. Our understanding is that Alnylam Pharmaceuticals UK has voluntarily agreed to abide by the ABPI Code of Practice, and our concerns remain unresolved despite a thorough intercompany dialogue process.
>
> **Potential promotional meeting where off-label information was presented**
>
> Pfizer has concerns about an Alnylam organised meeting on the [date] August 2024, during the ESC 2024 congress. The social media post shown below indicates that the meeting was held at Banking Hall in London and the photograph on the post shows the publication of the HELIOS-B data being presented on a screen.
>
> We note that the top line results of the Alnylam sponsored HELIOS-B phase 3 study were communicated as part of the main ESC scientific programme at a late breaker Hot Line session as well as at an Alnylam a press conference. The HELIOS-B study evaluated the efficacy and safety of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM). Vutrisiran is currently not indicated for the treatment of ATTR-CM. It is indicated for 'the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy'. Alnylam has confirmed through the intercompany dialogue process that the regulatory submissions to FDA and EMA to gain an indication for patients with ATTR-CM were made approximately 6 weeks after the Alnylam organised meeting took place at the ESC congress.
>
> During intercompany dialogue, Alnylam maintained that the Alnylam-organised meeting on the [date] August 2024, held at Banking Hall was a legitimate exchange of medical and scientific information (LEMS) meeting.
>
> The ABPI Code allows for LEMS during the development of a medicine. The exchange of information with the scientific community is expected to help guide companies in the development of investigational molecules. As noted in previous PMCPA rulings, although the term 'investigational' is not defined in the Code, it is questionable whether a product going through the EMA and FDA submission process for a new indication approximately 6 weeks after a LEMS meeting could be

considered an 'investigational molecule' or being 'in development'. Indeed, Alnylam explained to us that it was not relevant whether the insights gained from the LEMS meeting would influence their clinical development program.

Pfizer is aware that this was a large meeting, and we therefore question whether each delegate had a meaningful opportunity to contribute to the scientific exchange. From the intercompany dialogue, Pfizer understand that interactive country workshops took place during this meeting, which explored local needs and challenges, and considered the necessary steps for optimising ATTR amyloidosis management both now and in the future. However, this gives the impression that these were practical discussions about implementation into clinical practice, rather than scientific exchange about the development of a medicine.

Alnylam stated that there was no heavy weighting towards vutrisiran data and HELIOS B at the LEMS meeting, and without seeing the actual presentations Pfizer is unable to comment on whether they were appropriately fair and balanced. That said, given that HELIOS-B was presented at the ESC congress as part of the scientific programme as a late breaker hot topic session with an associated press conference, and given that the lead investigator for HELIOS-B was at the LEMS meeting (as shown in the social media post), this makes it highly likely that there would have been great interest in vutrisiran and HELIOS-B data at the LEMS meeting with a heavy weighting towards it.

[Screenshot of social media post provided].

Taking all these points together, we do not believe that this was a bona fide LEMS meeting as required by the Code. Instead, Pfizer maintain that this was a pre-licence promotional meeting designed to promote vutrisiran off-label for ATTR-CM and to promote the HELIOS-B trial results. Given that vutrisiran does not have a licence to treat ATTR-CM, this represents promotion that is not in accordance with terms of vutrisiran’s marketing authorisation - a breach of Clause 11.2, fails to maintain the high standards expected of our industry - a breach of clause 5.1 and reduces confidence in the industry – a breach of clause 2.

Inappropriately lavish venue for Alnylam-organised meeting on the [date] August 2024

As shown in the above social media post, the Alnylam-hosted meeting on the [date] August 2024, during the ESC congress was held at Banking Hall in London. This venue is described as a stunning art deco gem dripping in grandeur, an iconic Grade II listed landmark, with a sweeping marble staircase, towering columns and marble floor. A venue full of sophistication, luxury and elegance.

Alnylam maintains that the travel time from the ESC conference at the London ExCel to the Banking Hall was 30 minutes or less and was therefore a reasonable choice for their meeting venue. However, Pfizer asserts that a venue of this nature that is at least 30 minutes travel by taxi or public transport from the ESC conference site, cannot be considered an appropriate venue when there must have been a wide selection of business-style venues in much closer proximity to the London ExCel centre. Pfizer questions the level of subsistence provided to each attendee at this

event and the number and roles of Alnylam employees in attendance, in particular if commercial colleagues were present, given that Alnylam maintains this was a LEMS meeting.

Pfizer cannot see how Banking Hall meets the requirement for venues to be appropriate and not lavish, extravagant or deluxe and we therefore believe that the selected venue is not consistent with the requirements of clause 10.1 of the Code.

Ambiguous, misleading and incomplete claims in booth material

Pfizer has additional concerns about the Alnylam exhibition booth, where ESC congress attendees walking past could have incorrectly assumed Amvuttra (vutrisiran) has an indication for the treatment of ATTR-CM. The details of the actual licensed indication for vutrisiran 'the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy' was missing from the most prominent overhead panel for a significant proportion of the video loop. Please see photograph examples below.

During intercompany dialogue, Alnylam confirmed that the indication statement was displayed on this overhead booth panel for 14 seconds out of the 53 second video loop. If the licenced indication was only displayed for approximately 25% of the loop, then Pfizer maintains that this is very likely to have been missed by busy healthcare professionals at the congress. Given the overall context of Alnylam's activities at ESC, this could have incorrectly given prescribing HCPs the impression that vutrisiran has a cardiac licence in ATTR-CM, particularly given that ESC is a specialist cardiology conference.

The Code requires information and claims to be accurate and unambiguous. We believe the prominent overhead signage at the Alnylam booth was deliberately ambiguous and misleading representing a breach of clause 6.1 of the Code which resulted in vutrisiran being promoted for an unlicensed indication, a breach of clause 11.2.

[Images of vutrisiran congress booth provided].

Promotional material directed to an inappropriate audience at ESC 2024 congress

Both the Alnylam exhibition booth and the 2 large advertising boards in the main walkway of the ExCel Centre , were promoting Amvuttra (vutrisiran), which as stated above is indicated for 'the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy'. The ESC congress is directed at cardiologists and cardiology experts and so we question the relevance of promoting a medicine indicated for the treatment of hATTR polyneuropathy (hATTR-PN) at this conference.

Through intercompany dialogue, Pfizer have accepted that cardiologists may have an interest in hATTR with mixed phenotype, but we note that vutrisiran use is off-label for ATTR-CM. We maintain that the overall intent and impression given was that vutrisiran could be used in ATTR-CM. We therefore maintain that it was

inappropriate to promote vutrisiran to a cardiology audience at this ESC congress and that Alnylam's activity was inconsistent with the requirements of Clause 5.6 of the Code.

Promotion of a medicine not in accordance with the terms of its marketing authorisation

At the ESC conference, Alnylam held what they describe as a non-promotional tutorial session entitled *'Unveil the unseen: monitoring disease progression and treatment response in ATTR-cardiomyopathy'*. Alnylam maintain that treatments like vutrisiran were not discussed, but it does not seem credible to say that 'treatment response in ATTR-CM' was discussed but treatments were not. A discussion about treatment response would surely solicit questions about use of vutrisiran in ATTR-CM which would be an off-label indication.

Alnylam held a second tutorial session at ESC entitled *'Expert Exchange: Treating hATTR Polyneuropathy Patients with a Mixed Phenotype (Polyneuropathy and Cardiomyopathy)',* which was promotional in nature. The second tutorial session mentioned vutrisiran for the treatment of patients with hATTR-PN with mixed phenotype and cardiac manifestations. Pfizer accepts that Alnylam made the licensed indication in hereditary ATTR polyneuropathy clear in the tutorial but remain concerned that ATTR-CM was discussed in this promotional tutorial, which is an off-label indication, given that cardiac manifestations were covered.

We note again that the results of the HELIOS-B phase 3 study in ATTR-CM were presented as a late breaker hot line session with an associated press conference. This is highly likely to have raised awareness and interest in data for vutrisiran in ATTR-CM, and therefore Alnylam should have taken extra care in their other activities at ESC not to discuss ATTR-CM given that it is an off-label indication. With submissions to FDA and EMA made approximately 6 weeks after the ESC congress, the Alnylam activities at ESC were very close to a potential new indication which makes them all the more concerning. It is even more problematic because the formulation, dosage and frequency of administration are the same for the on-label and off-label use of vutrisiran.

Pfizer maintains that the overall perception of vutrisiran at this conference was misleading and we assert that the Alnylam activities at the Banking Hall meeting and at the ESC itself were designed to give the impression that vutrisiran is licenced for ATTR-CM. Through these activities we believe Alnylam promoted vutrisiran for an indication not covered by its marketing authorisation. As such we believe that Alnylam breached clauses 3.6 and 11.2 of the Code.

Pfizer maintains that Alnylam's ESC activities constituted a deliberate attempt to promote a potential new indication ahead of licensure. We believe that this does not uphold the high standards expected of our industry (in breach of Clause 5.1) and that it also reduces confidence in the industry (in breach of Clause 2)."

When writing to Alnylam, the PMCPA asked it to consider the requirements of the following clauses of the 2021 Code:

Allegation	Clauses raised by Pfizer
Potential promotional meeting where off-label information was presented	11.2 5.1 2
Inappropriately lavish venue for Alnylam-organised meeting on the [date] August 2024	10.1
Ambiguous, misleading and incomplete claims in booth material	6.1 11.2
Promotional material directed to an inappropriate audience at ESC	5.6
Promotion of a medicine not in accordance with the terms of its marketing authorisation	3.6 11.2

Alnylam were overall asked to bear in mind the requirements of Clauses 5.1 and 2 of the 2021 Code.

ALNYLAM'S RESPONSE

The response from Alnylam is reproduced below, with some typographical errors corrected:

> "Alnylam is fully committed to strict adherence to the Code and all applicable laws and regulations. As a non-member of the ABPI which has agreed to adhere to the Code, Alnylam is dedicated to applying high standards at all times across all areas of its business and carefully considered the principles of the Code when preparing for the ESC Congress.
>
> Alnylam takes any concern raised regarding compliance with the Code seriously. As such, Alnylam has cooperated with the Complainant, responding fully to each of their concerns in a timely way through intercompany dialogue.
>
> **Background**
>
> Alnylam and the Complainant both operate within the transthyretin amyloidosis ('ATTR') therapy area. ATTR is a rapidly progressive, debilitating disease caused by misfolded transthyretin (TTR) protein, which accumulates as amyloid deposits in various parts of the body, including the nerves, heart and digestive system. There are two different types of ATTR amyloidosis: (i) hereditary ATTR ('hATTR'), caused by a TTR gene variant, and (ii) wild-type ATTR amyloidosis, which occurs without a TTR gene variant but naturally through the aging process. The most common manifestations of hATTR are polyneuropathy (hATTR-PN), cardiomyopathy (hATTR-CM), or both (mixed phenotype).
>
> Alnylam's therapy, vutrisiran, is authorised by the MHRA and prescribed by both neurologists and cardiologists for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. The Complainant's therapy,

tafamidis (61mg), is the only therapy authorised by the MHRA specifically for treatment of ATTR patients with cardiomyopathy. Since the ESC congress [2024], Alnylam made submissions to the FDA (9 October 2024) and EMA (16 October 2024) for authorisation of the use of vutrisiran for the treatment of ATTR patients with cardiomyopathy. Alnylam is concerned that the Complainant's approach in this case could be driven by this commercial background rather than scientific, medical or compliance concerns.

Over the last 6 months the parties have had multiple rounds of intercompany dialogue and the Complainant has continually repeated its allegations notwithstanding the fulsome responses provided by Alnylam. Several of those letters were omitted in the Complaint so we rectify that in our Response to give the PMCPA the full picture. You will notice from these letters that as Alnylam extinguished some alleged concerns conveyed by the Complainant, the Complainant searched for new ones. Some of our key concerns with the Complainant's approach are summarised below.

ATTR has a severe impact on a patient's life (mean survival after diagnosis for patients with hATTR-PN being 4-12 years and for patients with ATTR-CM being 2-4 years) and is an under-diagnosed disease. Medical education is critical in this area. Despite acknowledging in its own published scientific and medical literature the multisystemic nature and under-diagnosis of this rare disease requiring a multidisciplinary approach, something which is also recognised in the NICE assessment of the Complainant's tafamidis therapy, it appears that the Complainant is seeking to prevent Alnylam from organising medical education. This is clinically unsound, detrimental to patient health and wholly inappropriate. Indeed in our Response we identify several countries (including the UK) in which cardiologists prescribe for hATTR-PN and/or patients with mixed phenotype. All of this goes to justify the relevance and importance of Alnylam's attendance and activities at the ESC congress.

For the purposes of their Complaint, the Complainant has cherry-picked information, conflated issues and pulled Alnylam's activities out of context to create an impression which was neither intended by Alnylam nor experienced by cardiologists at the ESC congress or ATTR Meeting. For example, (i) the Complainant is basing its Complaint on a single and unrepresentative image from our LEMS event which an independent attendee posted on social media and which the Complainant would have had to have searched for, (ii) the Complainant has selected a still photograph identifying a single frame of a dynamic video that was played at the ESC congress on loop, (iii) the Complainant has referenced an irrelevant and exaggerating excerpt of the Banking Hall venue's promotional website found during their cursory desktop review, and (iv) the Complainant is artificially seeking to create a nexus (when that nexus never existed) between Alnylam's activities and the hotline where the ESC congress Secretariat independently chose to feature HELIOS-B, the presentation for which was made by the principal investigator as well as an independent discussant chosen by the ESC.

We assert that had there been any wrongdoing by Alnylam, the Complainant's staff would surely have presented good evidence of it. The PMCPA may be interested to learn that we have on record that 30 of the Complainant's employees attended one

of our HCP-only tutorials (Tutorial 1 '*Unveil the unseen: monitoring disease progression and treatment response in ATTR-cardiomyopathy'*, attended by around 120 conference goers in total), and that this delegation included the Complainant's senior team members such as its [job titles provided]. That is after Pfizer warned us that they '*will continue to monitor Alnylam activities and statements*' in relation to the ESC congress. This senior delegation, and particularly the Complainant's [job title] who was also in copy in the intercompany dialogue between the Complainant and Alnylam during the ESC congress, witnessed Tutorial 1 first-hand. Notwithstanding this, the Complainant has not provided any meaningful evidence to substantiate its claims, and despite Alnylam explaining the position and confirming in the dialogue that it took all reasonable steps and precautions to comply with the Code, the Complainant has progressed the matter to the PMCPA with nothing more than several bare allegations made on assumptions without credible basis.

In our Response Alnylam has addressed the allegations in a more logical order than presented by the Complainant, and which is closer to the way they were raised by the Complainant during intercompany dialogue, delineates the promotional from the non-promotional elements, and separates out what others (notably the ESC Secretariat) were in control of and responsible for at the ESC congress

We make these points in accordance with the overriding objective of the Code to assist the PMCPA to deal with cases fairly and justly while protecting patient safety.

Response

Against this background we attach Alnylam's response to the Complaint. Alnylam maintains that its activities in and around the ESC Congress were in full compliance with the Code at all times.

Alnylam's Response to the Complainant's allegations

Promotional material directed to an inappropriate audience at ESC 2024 congress

The Complaint alleges that the promotion of Alnylam's vutrisiran to a cardiology audience at the ESC congress was inconsistent with Clause 5.6 of the Code. Clause 5.6 of the Code prohibits the provision of material to groups of people whose need for or interest in it cannot reasonably be assumed.

Transthyretin amyloidosis (ATTR) is a systemic, progressive disease, which results from the deposition of misfolded transthyretin (TTR) protein in multiple organs and tissues. The misfolded TTR can build up as amyloid in organs and tissues such as the heart and nerves. This results in a variety of manifestations of the disease including cardiac (CM), polyneuropathy (PN), gastrointestinal (GI) and central nervous system (CNS). All patients will develop multisystem disease, regardless of variant or predominant symptomatology. There are two different types of ATTR amyloidosis: (i) hereditary ATTR (hATTR), caused by a TTR gene variant, and (ii) wild-type ATTR amyloidosis, which occurs without a TTR gene variant but naturally through the aging process.

The European Medicines Agency (EMA) has acknowledged that frequently hATTR patients have multiple simultaneous manifestations. A significant proportion of patients develop a mixed phenotype of both PN and CM as a result of the disease. This possibility is noted on the Complainant's website: "*because amyloid fibrils can deposit in different parts of the body, including in the heart and nerves, some patients may present with mixed phenotype, namely, symptoms of both cardiomyopathy and polyneuropathy*" alongside which Adams et al (2021) is cited.

It follows that ATTR Amyloidosis, being a multi-system disease, medically requires a multi-disciplinary approach.

In fact we note that the Complainant's website referenced above emphasises the medical need for multidisciplinary team diagnosis and management of ATTR amyloidosis ("*a well-coordinated multidisciplinary health care team can increase early and accurate diagnosis of ATTR-CM*").

This is also supported by a publication by Transthyretin Amyloidosis Outcomes Survey (THAOS - a Pfizer-supported registry): "*these data reinforce the need for multidisciplinary evaluation at initial assessment and follow-up of all patients with ATTR amyloidosis*" and "*these THAOS data represent the largest analysis of a real-world mixed phenotype ATTR amyloidosis population to date and suggest that a mixed phenotype may be more prevalent than previously thought. Patients may also migrate from a primarily neurologic or cardiologic presentation to a mixed phenotype over time. These data reinforce the need for multidisciplinary evaluation at initial assessment and follow-up of all patients with ATTR amyloidosis"*. This publication noted that a significant portion of over 3,500 patients involved in the study were classified as mixed phenotype ("*approximately one-third of symptomatic patients… were classified at enrolment or follow-up as mixed phenotype*").

The Complainant also agrees in intercompany dialogue that "*cardiologists may have an interest in hATTR with mixed phenotype with ATTR cardiomyopathy*". This is supported by the number of requests from cardiologists at the booth for the HELIOS-A study manuscript which concerns a study of vutrisiran for patients with hATTR-PN.

The NICE technology appraisal of Complainant's drug tafamidis (61mg), recognised that vutrisiran is a treatment option for mixed phenotype patients with ATTR-CM and hereditary ATTR-PN (stage 1 or 2):

[Screenshot of relevant section of tafamidis NICE technology appraisal provided]

Moreover, the scope of the vutrisiran SmPC is clear and unambiguous and does not exclude hATTR-PN patients who have other concomitant symptoms (i.e. other hATTR manifestations).

Accordingly, it is appropriate and necessary to approach all HCPs treating hATTR patients with a variety of symptoms, including cardiologists who not only see patients with polyneuropathy but are also authorised prescribers of vutrisiran or referring physicians, to ensure that they know to check whether their patients might have the PN phenotype and might therefore need/benefit from Alnylam's treatment.

Alnylam is aware of numerous cases where cardiologists are involved in treatment of hATTR-PN and/or mixed phenotype including in the UK, Germany, Sweden, Spain, Canada and Japan, and we confirm that cardiologists from those countries attended the ESC congress.

We confirm that Alnylam has attended cardiac conferences similar to the ESC congress across the world for a number of years without the Complainant's concerns around appropriate audience being raised by other companies, organisers of those conferences or attendees.

For all these reasons, the need or interest of cardiologists in the material provided at the ESC congress is beyond doubt, such that there can be no breach of Clause 5.6.

The Complainant also alleges in this part of their Complaint that by promoting vutrisiran to a cardiology audience the overall intent and impression given was the vutrisiran can be used in ATTR-CM. We wish to state clearly upfront that this was not Alnylam's intention and nor was that impression given. This point is specifically addressed below in relation to further allegations made by the Complainant.

Ambiguous, misleading and incomplete claims in booth material

The Complaint alleges that the overhead signage at the Alnylam ESC congress booth was deliberately ambiguous and misleading representing a breach of Clause 6.1 of the Code which resulted in vutrisiran being promoted for an unlicensed indication, a breach of Clause 11.2 of the Code.

Alnylam strongly disagrees. Vutrisiran is indicated for the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy, and this authorised indication was prominently and clearly displayed in the overhead panel of Alnylam's booth at the ESC congress as well as other parts of the booth.

The video on the overhead panel was short (53-seconds total) and was repeated on loop, so the licensed indication was displayed at a high frequency. In total, vutrisiran's indication was displayed clearly on the overhead panel for 14 seconds as part of the 53-second cycle of the video. This was sufficient to communicate the licensed indication to attendees. The Complainant's assertion that the licensed indication was "missing" for a significant proportion of the video loop is incorrect and misleading. We note that the Complainant has not presented any evidence that anyone missed it or was in any way misled.

Alnylam also wishes to point out the authorised indication was displayed prominently across the booth. This included printed copies of prescribing information available at the booth, information available for viewing on Alnylam staff's iPads for discussions at the booth, a sticker affixed to the booth itself, the four large interactive touchscreens and a free-standing sign displaying the indication within the booth that were readily accessible by attendees at the booth, all of which clearly stated:

"*AMVUTTRA® (vutrisiran) is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. The decision to continue treatment in those patients whose disease*

progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment."

"*Prescribing Information can be provided upon request*."

We also confirm that all booth material available to HCPs was focused on hATTR-PN, HELIOS-A clinical data and vutrisiran's authorised indication, and so healthcare professionals present were fully capable of understanding vutrisiran's authorised indication.

Alnylam's compliance briefing for Alnylam's staff at the conference was also clear that any promotional communications during the congress must never be off-label ("*commercial colleagues must not engage in any off-label discussions at all*"). Alnylam's staff had prescribing information readily available ("*up-to-date PI needs to be easily accessible*") and that commercial colleagues must not engage in any off-label discussions ("*off-label information must not be discussed*").

Taking all of this into account, the claims in booth material were in no way ambiguous, misleading or incomplete, nor was vutrisiran promoted for an unlicensed indication. There was no breach of Clauses 6.1 or 11.2.

Promotion of a medicine not in accordance with the terms of its marketing authorisation

Tutorial 2 (promotional): Expert Exchange: Treating hATTR Polyneuropathy Patients with a Mixed Phenotype (Polyneuropathy and Cardiomyopathy) with the following speakers:

[Names of speakers and disclosures provided]

The Complaint alleges that Alnylam's tutorial 2 resulted in the promotion of vutrisiran for treatment of ATTR-CM and so alleges a breach of Clauses 3.6 (disguised promotion) and 11.2 (promotion not in accordance with the marketing authorisation) of the Code.

Alnylam strongly disagrees. This was a promotional tutorial with objectives of understanding the heterogeneous nature of hATTR-PN patients with a mixed phenotype (polyneuropathy and cardiomyopathy), and examining the real-world experience of treating mixed phenotype hATTR patients (polyneuropathy and cardiomyopathy) and the considerations for clinical practice.

The promotional nature of the session was clearly communicated to attendees and Alnylam made clear throughout that vutrisiran is authorised only for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

The following notice was displayed for a prolonged period at the beginning of the session and repeated four times throughout the session:

"Vutrisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy."

During the briefing provided by Alnylam to speakers in advance of the session Alnylam made clear that "*vutrisiran is not approved for the treatment of ATTR-cardiomyopathy (ATTR-CM), and therefore vutrisiran in the context of treating ATTR-CM, including information around the HELIOS-B trial results, should not be discussed at this meeting*". Similarly, the speakers were told that "*content should not include mention of any disease-modifying treatment for ATTR-CM*".

Alnylam emphasised to the speakers that the focus of the session must be on patients with hATTR-PN. During tutorial 2, Alnylam presented two case studies involving evaluation of patients with hATTR-PN mixed phenotype (with cardiac manifestations) treated with vutrisiran. This included review of ECG data, bone scans, cine-CMR images and other cardiac scans. It is important to note that these studies were presented in order to inform cardiologists how to monitor the progression of the cardiac manifestations of the disease in patients with hATTR-PN. HELIOS-A study cardiac data was also presented. Cardiac biomarkers are identified in vutrisiran's SmPC, and in line with the SmPC it was made clear that that the clinical benefit of vutrisiran in regard to cardiomyopathy is yet to be confirmed: "*Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed*". Accordingly other treatment options may need to be considered. The Complainant knows this because its personnel (including the Complainant's [job titles of three senior employees provided]) were present at this promotional tutorial, and if there were any evidence of a breach they surely would have provided it. Instead their allegations remain wholly unsupported.

Alnylam took great care to comply with the Code at all times, there was no disguised promotion, and at no point did Alnylam promote vutrisiran outside the scope of its marketing authorisation.

Tutorial 1 (non-promotional): Unveil the unseen: monitoring disease progression and treatment response in ATTR-cardiomyopathy with [named speaker]

[Disclosures for named speaker provided]

Again the Complaint alleges that Alnylam's Tutorial 1 resulted in the promotion of vutrisiran for treatment of ATTR-CM and as such resulted in a breach of Clauses 3.6 (disguised promotion) and 11.2 (promotion not in accordance with the marketing authorisation) of the Code.

This was a non-promotional tutorial with the objectives of exploring a multiparametric approach to monitoring disease progression in patients with ATTR-CM focusing specifically on the tools for monitoring such progression, and analysing patient cases to determine the impact of such tools in monitoring disease progression. It is well-recognised that there are inconsistencies with, and a lack of availability of, appropriate tools used to evaluate and monitor ATTR-CM.

The non-promotional nature of this Tutorial 1 was made clear to participants. No materials advertising or content used in Tutorial 1 were available at Alnylam's ESC congress booth and therefore there was no nexus between the tutorial and the booth.

Alnylam did not mention any specific therapeutic (whether Alnylam's vutrisiran or patisiran, Pfizer's tafamidis or otherwise) during the session either directly or indirectly. During the speaker briefing provided by Alnylam prior to the session Alnylam emphasised that "*there must be no reference, directly or indirectly, to Alnylam therapies (both approved and those in development), including vutrisiran and patisiran*". These instructions were strictly adhered to throughout the session.

The reference to "treatment response" in the title relates to discussion and presentation of data showing how earlier diagnoses of ATTR-CM over the last ~20 years have contributed to improved survival, without reference to any specific treatments. We can also confirm that no questions on use of vutrisiran to treat ATTR-CM were asked by attendees demonstrating that Alnylam did not solicit questions around off-label use of vutrisiran.

Again the Complainant knows this because 30 of its personnel (including the Complainant's [list of job titles provided]) were present at this non-promotional tutorial, and if there were any evidence of a breach they surely would have provided it. Instead their allegations remain wholly unsupported.

Alnylam took great care to comply with the Code at all times, there was no disguised promotion, and at no point did Alnylam promote vutrisiran outside the scope of its marketing authorisation.

ESC Secretariat's late breaker hotline session

The Complainant seems to be hinging its Complaint on the so-called "HELIOS-B" study, a phase 3 study of vutrisiran for the treatment of ATTR-CM. However, the Complaint fails to recognise critical factors when seeking to make that unjustified connection.

First, this session was not an Alnylam sponsored session. Instead, the ESC congress Secretariat independently chose to feature the study as a "hotline" session. The presentation was made by the principal investigator as well as an independent discussant, chosen by the ESC.

Secondly, at the time when Alnylam made a request to the ESC Secretariat to organise and fund activities at the ESC congress (specifically to have a booth and host the two tutorial sessions), the HELIOS-B study results and ESC 's decision to present the HELIOS-B study in a hotline session were not known to Alnylam (or the ESC). Alnylam's decision to attend and present at the ESC congress was made prior to, independent of and irrespective of the HELIOS-B results and the hotline presentation.

Thirdly, to accompany the ESC's decision, a press conference was organised with the principal investigator. It is important to note that the press conference addressed

journalists and so the audience was totally different to the attendees of ESC congress (cardiologists), and the content was informational, not promotional in nature.

Fourthly, the Alnylam non-promotional tutorial (Tutorial 1) and promotional tutorial (Tutorial 2) organised by Alnylam were totally distinct from the ESC Secretariat's late breaker hotline session and the press conference.

Fifthly, the content of the tutorials were wholly unrelated to the HELIOS-B study. Each tutorial provided information relevant to the ESC congress attendees' interests and speciality, without any mention, discussion or enquiries regarding HELIOS-B, or vutrisiran and ATTR-CM. Similarly, no HELIOS-B data was presented at Alnylam's ESC congress commercial booth.

As such, contrary to the Complainant's accusations, there was no nexus between Alnylam's activities at the ESC congress and this hotline session.

For all of these reasons we feel strongly that Alnylam's activities throughout the ESC congress were conducted with great care to avoid the possibility of off-label promotion or disguised promotion and we reject the allegations that Alnylam breached the Code.

Inappropriately lavish venue for Alnylam-organised meeting on the [date] August 2024

The Complaint alleges that the Banking Hall does not meet the requirement for venues under Clause 10.1 of the Code.

Alnylam strongly disagrees. Alnylam carefully considered the suitability of the venue and deliberately steered away from lavish, extravagant or deluxe venues.

Alnylam engaged a third party agent in March 2024 to identify potential venues for the ATTR Exchange Meeting held on [date] August 2024 ("ATTR Meeting"). Alnylam asked for a 4 star venue or equivalent for a pharmaceutical company sponsored event with a suitable set up close to the Canary Wharf area, the site of the ESC congress (ExCel London). Availability was limited and the agent identified three potential venues – [two named hotels] and the Banking Hall. Alnylam considered the [two other named hotels] unsuitable for various reasons, including lack of privacy, city views and not being conducive to workshop discussions. Alnylam chose the Banking Hall for its functional and professional setting, making it appropriate and conducive to the educational purpose of the meeting. The Banking Hall is a good quality business conference facility suitable space for both round-table discussions as well as panel/audience discussion, with unobstructed views to the screens/stage, good audio set-up allowing attendees to discuss a number of complex topics amongst themselves as well as with a panel of experts. It had capacity to accommodate the number of expected attendees and there was no access for the public.

The venue is offered on the corporate website as a "blank canvas" with a simple setup comprised mostly of a large open hall and suitable for a conference:

"Banking Hall is designed to adapt to your corporate needs, whether it's a focused meeting or a collaborative team-building day. Equipped with cutting-edge AV

technology and breakout spaces, the venue offers a professional yet flexible environment."

"The venue offers flexibility with breakout spaces that ensure your event flows smoothly. Our team works closely with you to bring your ideas to life, delivering professional service and attention to detail at every step."

The photo below shows this set up during the ATTR Meeting.

[Photograph of ATTR meeting provided]

The venue's features, such as the absence of windows in and views from the main room, ensured privacy and minimised distractions, creating an environment suitable for focused discussions. No additional activities or facilities were available at the venue. The venue was not an attraction, nor a 5 star venue.

To the extent Alnylam saw any potential concern, it dealt with it. On its site visit prior to the ATTR Meeting, Alnylam noted 3 small windows on the side of the venue (in the reception area and not where the main event of the ATTR Meeting would take place) and so for the ATTR Meeting these windows were blocked off – see the covered window to the left of the image below.

[Photograph from ATTR meeting showing blocked off windows provided]

The venue's location in the business/financial district of London, rather than a tourist area. The journey from the ExCel London to the Banking Hall took less than 30 minutes and so is near-by for London standards, particularly given that the docklands is a mostly residential area, which was similar to the other two venues identified by the agent. The venue's proximity to public transport links was also a factor in its selection, ensuring convenience for attendees.

Meanwhile the descriptions of the venue mentioned by the Complainant have been pulled out of all context and do not represent the reality. They appear to be based on a cursory desktop review. The venue hires out its space for a variety of events. The exaggerated marketing descriptions to which the Complaint refers are not relevant since they are based on parts of the website targeting wedding planners rather than serious, professional conference organisers. We also wish to point out that those descriptions did not appear on the venue website when Alnylam booked the Banking Hall for the ATTR Meeting. In any event, those descriptions are not reflective of the venue in which the educational event was held by Alnylam and instead they create a false impression.

We can also confirm that the venue was not in any event a draw for attendees. Invitations to the ATTR Meeting were sent out in advance to a closed recipient list. No invitations were extended to attendees verbally. A good proportion of invitees (34) accepted the invitation without knowledge of the venue location, indicating their interest in the event's educational content rather than the venue. Even when the venue name was disclosed to attendees, after 26 June 2024, they are unlikely to have known it and no description of the venue was provided by Alnylam. Accordingly, Alnylam sees no basis for the suggestion that the venue was an attraction for attendees.

We also confirm that cost of subsistence was £70 per person. This comprised a welcome drink and canapes, a three course dinner, half a bottle of house wine, half a bottle of filtered water, and tea or coffee. This is well understood to be an acceptable level in accordance with the Code.

Taking all of these facts into account, there can be no breach under Clause 10.1 of the Code.

We note that the Complainant confuses its allegation under Clause 10.1 by referring to Alnylam attendees which is irrelevant to the nature of the venue. Nonetheless we specifically address attendees below.

Potential promotional meeting where off-label information was presented

The Complainant alleges that Alnylam's ATTR Meeting was a promotional meeting of vutrisiran off-label for ATTR-CM and of HELIOS-B trial results constituting a breach of Clause 11.2 (promotion that is not in accordance with terms of vutrisiran's marketing authorisation). This allegation is based on a single social media post from an independent attendee from Singapore which shows an image of the ATTR Meeting, without context.

Again Alnylam strongly disagrees that there been any breach. The ATTR Meeting was not a promotional meeting. The ATTR Meeting was a medically-led international LEMS (legitimate exchange of medical and scientific information) event, permitted by the Code. This was made clear to attendees and Alnylam personnel.

Alnylam took great care to ensure compliance with Code and PMCPA guidance concerning LEMS meetings.

The Code provides: "*The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited, provided that any such information or activity does not constitute promotion which is prohibited under this or any other clause*".

The PMCPA's Guidance on Clause 3 at the time expands on this for a situation where a company, such as Alnylam, has an authorised product and is seeking to expand the label: "*If a company is producing information on an as yet unlicensed indication for a product that has a marketing authorization, for example at a company symposium at a learned society's meeting, this must be a genuine legitimate exchange of medical and scientific information during the development of that medicine, involving debate which would enhance the state of scientific knowledge. To avoid being seen as the dissemination of data to expand the product's use, ie promotional and in breach of the Code, the activity must not be a one way flow of information.*"

Moreover, it is well-understood that interpretation of the Code requires a principle-based approach, which in this case requires consideration of the LEMS meeting in the context of a rare, complex, multi-disciplinary and underdiagnosed disease area, ATTR.

Genuine legitimate exchange of medical and scientific information

This LEMS ATTR Meeting was not product-focused but disease-focused. The primary objective of this LEMS meeting was to provide a platform for the legitimate exchange of medical and scientific information and to enhance the learning in ATTR amongst the medical community in a fair, balanced and accurate manner, a goal which is critically important in this rare disease area. hATTR is a rare disease (the prevalence of hATTR is estimated to be less than 1 in 100,000 people in the general European population). Since hATTR may present as different manifestations of the disease e.g., GI dysfunction, polyneuropathy, cardiomyopathy as well as overlapping symptoms/signs with other forms of amyloidosis, it is very challenging to diagnose and as a result it is suspected that there are a significant number of undiagnosed patients with hATTR. The NICE technology appraisal of Complainant's drug tafamidis (61mg) acknowledges that "*the prevalence of ATTR-CM in the UK is currently unknown. It is difficult to reliably estimate due to potential under-diagnosis and under-reporting of the condition*."

Accordingly, the ATTR Meeting was a forum for exchanging knowledge on the challenges, needs and gaps in the understanding of the diagnosis, management and treatment of ATTR Amyloidosis for HCPs from across the globe. This knowledge exchange is key (even amongst experts in the field) for this poorly understood and rare disease area.

During development of a medicine

The Complainant questions whether Alnylam has a product in development and how Alnylam benefitted from organising this meeting.

Although secondary to the primary purpose of the ATTR Meeting (as mentioned above), we confirm that the information it obtained from the ATTR Meeting will help to inform Alnylam's continuing development of vutrisiran as well as nucresiran, Alnylam's next generation innovative RNAi based therapy in development (phase 1 trials) for ATTR.

Through the medical and scientific discussions at the ATTR Meeting, Alnylam sought to understand different countries' and clinician needs in relation to diagnosis, management and treatment of patients with ATTR. This can better inform Alnylam's research and project plans and clinical study design to help ensure that these studies (and data generated from them) are relevant and applicable to those specific countries. The points discussed during the ATTR Meeting could also help Alnylam determine further analysis of data available from its prior clinical trials. In addition, the ATTR Meeting was designed to help Alnylam understand the unmet need which could shape its reimbursement/approval discussions in relation to vutrisiran in the years to come.

Debate

The entire ATTR Meeting was carefully structured to ensure dedicated interactive discussion and debate throughout. This was achieved through:

i. an interactive faculty panel fireside chat (~1hr5) which comprised of:

a. debate and discussion on key topics amongst the faculty with opportunity for questions from and interaction with the audience, and audience polling (three questions) (~55mins). The set-up was conducive to a two-way discussion rather than a traditional presentation;
b. audience Q&A session (~10mins); and

ii. interactive in depth country-level workshops (where attendees discussed amongst their tables their thoughts on a number of scientific and medical questions) and feedback discussion (~1hr15),

iii. with the remaining time being a short introduction and conclusion (~15min).

This was preceded by a 30 minute arrival and registration period. There were no separate networking sessions in the agenda.

We can therefore confirm that there was significant discussion throughout the ATTR Meeting, consistent with the PMCPA's ruling in AUTH/3469/2/21 - Complainant v Takeda.

Faculty panel session

The faculty panel explored a variety of topics, one of which was the evolving treatment landscape in ATTR amyloidosis where faculty discussed current trends, unmet needs, and challenges. This segment represented about a third of the time allocated to the faculty panel session (approximately 20 minutes). We confirm that there was no heavy weighting towards HELIOS-B or vutrisiran:

Only four slides in the forty slide, one-hour long, discussion slide-deck addressed HELIOS-B:

- The social media photograph featured in the Complaint shows the single slide where HELIOS-B was mentioned briefly the first time in the context of explaining Alnylam's history and interest in ATTR amyloidosis. This slide referred to the image of a simultaneous publication of HELIOS-B published in The New England Journal of Medicine but did not provide any substantive content from the publication nor any data from the study. It contained the following notice: "*Vutrisiran is an investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis with cardiomyopathy (ATTR-CM)*".

- The "*evolving treatment landscape and patient management strategies*" segment of the session involved a balanced discussion on ATTR-CM clinical trials. In addition to HELIOS-B, other ATTR-CM clinical trials concerning other non-Alnylam therapies either available or in development were discussed in a balanced way (including APOLLO-B, ATTR-ACT, ATTRibute-CM and CARDIO-TTRansform). One of these slides specifically focused on HELIOS-B as the results were reported the previous day and so it was important for the attendees to understand the context of the HELIOS-

B results alongside the other ATTR-CM clinical trials. These 3 slides represented approximately 9 minutes of the session.

In addition to vutrisiran, other treatments were mentioned (including non-disease modifying therapies) in a fair and balanced way.

The points discussed by the faculty presenters during the evening faculty panel session were scientific, medical and educational, including:

- Looking at patients with established heart failure, what are some of the main signs or symptoms that might make you think about cardiac ATTR amyloidosis as a possible diagnosis?

- What are some easy and practical strategies that physicians can implement to diagnose ATTR amyloidosis?

- With a progressive disease like ATTR-CM, early intervention is always better. How do we identify the right time to initiate treatment during disease progression?

The speakers on the panel were selected on basis of expertise and experience in area across the globe. Three of the speakers are from [named specialist centre] which is a world-renowned centre. Others were leading experts from France and Spain.

Workshop session

The workshop involved discussion on four topics:

1. What is the top challenge with timely diagnosis of patients with ATTR amyloidosis? What would you describe as the biggest challenge to early detection and diagnosis of ATTR amyloidosis?

2. Does the model of care in your region/country work well for patients with ATTR amyloidosis?

3. What are the key gaps in the management and treatment of patients with ATTR amyloidosis in your region/country? What tools or resources would best address the key gaps in the management and treatment of patients with ATTR amyloidosis in your region/country?

4. What are your key recommendations given the evolving landscape in ATTR amyloidosis in your region/country?

Only one of the four topics of conversation for the workshop discussions explored the local implications of the evolving treatment landscape. This segment lasted about 10 minutes out of a total of 75 minutes.

The briefing to workshop facilitators, who were stationed on tables with attendees, made clear what the role of a facilitator is (i.e. a guide, monitor/manager, impartial,

timekeeper and observer) and is not (i.e. a mediator, speculator, cheerleader or contributor). In addition, the facilitators were directed to allow 3 minutes for individual consideration before moving to a round table discussion for the following 7 minutes. Speakers from the faculty panel session did not join the workshop discussions.

Like the faculty panel session, the topics of discussion amongst the attendees at the workshop session were scientific, medical and educational.

Invitees and attendees

The roughly 70 attendees (excluding Alnylam attendees and faculty) were divided up into small interactive country-level groups (roughly 9 individuals per group) to enable a meaningful exchange of information. Delegates were selected based on their expertise in ATTR amyloidosis, ensuring they were well-placed to contribute to and benefit from the scientific exchange.

31 Alnylam individuals participated in the ATTR Meeting. This included country medical team members (20), general managers (7), executive head of international region (1) and global executive leadership members (3).

Each Alnylam individual received detailed briefings. It was made clear during those briefings that "*all discussions should be led by the medical team"* and *"non-medical attendees are present in a listening role"*

General managers have broad responsibilities and they were instructed to "*remain passive during discussions, with no direct involvement in the table workshop*" and "*not participate in, or respond to, any off-label questions should they arise*". They were in attendance simply to learn about ATTR, a rare, complex, multi-disciplinary and underdiagnosed disease.

In addition, those global executive leadership members and the executive head of international who were in attendance did not participate in the workshop session.

For all these reasons we confirm that the ATTR Meeting was a non-promotional bona fide LEMS and was delivered in accordance with the Code and we firmly reject the Complainant's unsubstantiated allegations. Throughout the ATTR Meeting Alnylam ensured that there was no off-label promotion of vutrisiran.

Final remarks

In addition to the clauses of the Code set out in the sections above, the Complainant alleged a breach of Clause 2 (upholding confidence in the industry) and Clause 5.1 (high standards must be maintained at all times).

Alnylam has provided a full and transparent explanation of its activities in the face of sweeping and unsubstantiated allegations from a competitor. We remain confident that Alnylam has maintained high standards at all times and has not brought any discredit on the pharmaceutical industry. We note that the Complainant has provided no convincing evidence to the contrary and we question their motivations when it seems that they are seeking to create a misleading impression.

We hope that the information provided in this response, together with its enclosures, demonstrates to the PMCPA Alnylam's full commitment to comply with the spirit and letter of the Code."

PANEL RULING

This intercompany complaint related to activities undertaken by Alnylam at a European cardiology congress in 2024, including its exhibition booth material, two "tutorials" held by Alnylam, and an Alnylam-organised evening meeting ("ATTR Meeting"). Pfizer alleged that Alnylam had presented off-label information at the ATTR meeting, that the London venue at which the meeting was held was inappropriately lavish, that the congress booth material was directed to an inappropriate audience and that the two tutorials promoted its medicine outside the terms of its marketing authorisation.

The Panel noted that at the time of the congress Amvuttra (vutrisiran) was indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. At the time of the event, Pfizer's medicine, tafamidis, was the only therapy authorised in the UK for the treatment of ATTR patients with cardiomyopathy (ATTR-CM). Vutrisiran was due to be submitted for an indication for ATTR-CM to regulatory authorities, including the FDA and EMA.

The Panel noted Pfizer's comment that Alnylam should have taken extra care in their activities at the congress given the HELIOS-B phase 3 study results in ATTR-CM were presented as a late breaker hotline session with an associated press conference, which was highly likely to have raised awareness and interest in data for vutrisiran in ATTR-CM, an off-label indication.

Alnylam submitted it had not sponsored this session and that the congress secretariat independently chose to feature the study as a "hotline" session delivered by the principal investigator as well as an independent discussant. According to Alnylam, when it made a request to the secretariat to have a booth and host the two tutorial sessions at the congress, the HELIOS-B study results and congress' decision to present the HELIOS-B study in a hotline session were not known to Alnylam or the congress organisers. Alnylam's decision to attend and present at the congress was made prior to, independent of and irrespective of the HELIOS-B results and the hotline presentation. Alnylam further submitted that to accompany the congress' hotline session, a non-promotional press conference was organised with the principal investigator which addressed journalists, an audience that differed to the cardiology audience of the conference. The Panel noted that Pfizer's allegations related to the appropriateness of Alnylam's activities at the cardiology congress given the context of the HELIOS-B hotline session. The Panel did not consider that Pfizer had made any allegations about the hotline session itself and therefore made no rulings on this point.

Promotion of vutrisiran at the cardiology congress

Pfizer raised concerns regarding Alnylam's promotion of vutrisiran at the cardiology congress. The Panel considered that the allegations in this part of the complaint related to two related but distinct matters. Firstly, whether the promotion of vutrisiran, which was licensed for ATTR-PN, to a cardiology audience was appropriate and secondly whether the content of the booth materials misleadingly implied that vutrisiran was indicated for ATTR-CM.

The Panel noted that Amvuttra (vutrisiran) was indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. The Panel took account of Alnylam's submission that the vutrisiran SmPC did not exclude hATTR-PN patients with other concomitant symptoms (i.e. other hATTR manifestations).

The Panel understood that the multisystem presentation of amyloidosis was not in dispute between the parties and that it formed relevant scientific context for the Panel's consideration. The Panel took account of Alnylam's submission that a mixed phenotype including polyneuropathy and cardiomyopathy could be found in the majority of patients with hATTR, and that transthyretin amyloidosis was a progressive, multisystem disease that required a multidisciplinary approach to monitoring and treatment. The Panel made its rulings on this basis.

Allegation 1 - Promotional material directed to an inappropriate audience

Pfizer alleged that Alnylam's promotion of vutrisiran at the congress to a cardiology audience, by means of its exhibition booth and advertising boards in the main walkway of the venue, was inappropriate and inconsistent with Clause 5.6 of the Code.

Clause 5.6 required that "*Material should only be provided or made available to those groups of people whose need for or interest in it can reasonably be assumed. Material should be tailored to the audience to whom it is directed*."

The Panel took account of Alnylam's submission that all patients will develop multisystem disease, regardless of variant or predominant symptomatology, and noted its observation above that, while vutrisiran's indication was limited to treatment in patients with polyneuropathy, a mixed phenotype including polyneuropathy and cardiomyopathy could be found in the majority of patients with hATTR, resulting in progressive, multisystem disease that required a multidisciplinary approach to monitoring and treatment.

Alnylam submitted that the scope of the vutrisiran SPC did not exclude hATTR-PN patients with other concomitant symptoms (i.e. other hATTR manifestations) and that it was therefore appropriate to approach all health professionals treating hATTR patients with a variety of symptoms, including cardiologists who not only saw patients with polyneuropathy but were also authorised prescribers of vutrisiran. Alnylam further submitted that cardiologists were involved in the treatment of and prescribed for hATTR-PN and/or mixed phenotype in several countries including the UK. In this regard, the Panel noted that the vutrisiran SPC stated *"therapy should be initiated under the supervision of a physician knowledgeable in the management of amyloidosis*", without restriction to a particular speciality.

The Panel observed that both parties appeared to accept that cardiologists may have an interest in hATTR with mixed phenotype. However, the Panel did not have before it any evidence regarding the extent or prevalence of cardiologist involvement or prescribing in hATTR-PN with cardiac manifestations. The Panel considered that Pfizer had not established that Alnylam's promotion of vutrisiran at the congress was directed to an audience whose need for, or interest in, the material could not be reasonably assumed. On the evidence before it, the Panel therefore ruled **no breach of Clause 5.6**.

Allegation 2 - Ambiguous, misleading and incomplete claims in booth material

Pfizer further alleged that the Alnylam exhibition booth resulted in vutrisiran being promoted for an unlicensed indication as congress attendees walking past could have incorrectly assumed Amvuttra (vutrisiran) was indicated for the treatment of ATTR-CM. In this regard, Pfizer referred to the overhead video panel and alleged that health professionals would have missed the licensed indication as it only displayed the licensed indication for vutrisiran for approximately 25% of the loop.

The Panel observed that the 53-second long canopy video displayed the brand name, and adjacent generic name on the left side, followed by smaller text underneath stating “References, AE reporting information and Prescribing Information are available on the booth”.

The following prominent promotional claims appeared as the video played:

1. Frame 1: “RAPID KNOCKDOWN OF TOXIC TTR” in the centre of the video
2. Frame 2: “RAPID KNOCKDOWN OF TOXIC TTR from baseline as early as day 22” appearing as a speech bubble adjacent to a graph in the centre of the video, illustrating mean % reduction from baseline in serum TTR versus time in weeks, and “88% REDUCTION IN SERUM TTR FROM BASELINE AT 18 MONTHS” to the right of the graph.
3. Frame 3: “AMVUTTRA DELIVERS RAPID KNOCKDOWN OF TOXIC TTR FROM BASELINE AS EARLY AS DAY 22” in the centre of the video, with the statement about 88% reduction in serum TTR appearing to the right.
4. Frame 4: “AMVUTTRA DELIVERS RAPID KNOCKDOWN OF TOXIC TTR FROM BASELINE AS EARLY AS DAY 22. TOXIC TTR IS CIRCULATING MISFOLDED TTR AND THE AGGREGATES IT FORMS WHICH ACCUMULATE IN MULTIPLE ORGANS AND TISSUES.”
5. Frame 5: “AMVUTTRA IS INDICATED FOR THE TREATMENT OF HEREDITARY TRANSTHYRETIN AMYLOIDOSIS (hATTR) IN ADULT PATIENTS WITH STAGE 1 OR STAGE 2 POLYNEUROPATHY” in the centre of the video, with the statement about 88% reduction in serum TTR appearing to the right.

Frame 5, which contained the indication for vutrisiran, appeared at 40 seconds and remained on screen for 13 seconds, which was the longest single frame of the video, and was repeated on a loop every 39 seconds.

Alnylam submitted that the authorised indication for vutrisiran was displayed prominently across the booth which included printed copies of prescribing information available at the booth, information available for viewing on Alnylam staff’s iPads for discussions, a sticker affixed to the booth itself, four large interactive touchscreens and a free-standing sign displaying the indication. Alnylam further submitted that all booth material focused on hATTR-PN, HELIOS-A clinical data (a study for patients with hATTR-PN) and vutrisiran’s authorised indication.

The Panel noted it appeared from Alnylam’s submission that its other promotional materials at the congress included:

1. Commercial booth indication sticker which included the indication of vutrisiran along with the statement “The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of

the physician based on the overall benefit and risk assessment" and that prescribing information was available from the booth
2. Booth back wall printed circles
3. Four large interactive touchscreens
4. Booth counter/bar screen and back wall printed circle
5. iPad: sales aid and pathophysiology video [not provided by Alnylam]
6. Booth arches with the Amvuttra logo
7. Free-standing sign including vutrisiran's indication, the same statement as in material 1 above and a QR code to access prescribing information

It appeared to the Panel that there were 5 backwall printed circles, of which four seemed to be accompanied by interactive touchscreens and one with a booth counter/bar screen.

The first printed circle included the prominent claim "~50% OF PATIENTS EXPERIENCED REVERSAL OF NEUROPATHY AND QoL IMPAIRMENT FROM BASELINE* PRIMARY AND SECONDARY ENDPOINTS". The asterisk for the claim read "*mNIS+7 and Norfolk QoL-DN scores improved vs baseline in 48% (n=57/118) and 57% (n=67/118) of patients with hATTR-PN, respectively, at 18 months" and the circle included reference to "AE reporting information and Prescribing Information are available to the left of the first booth arch". The contents of the associated touch screen included a page headed "hATTR is a rapidly progressive disease" with the text "AMVUTTRA transformed outcomes in hATTR-PN, reversing neuropathy and QoL impairment from baseline in approximately 50% of patients" and icons of a neuron, a heart and a GI tract. The next page headed "The HELIOS-A trial included a broad population of patients with hATTR-PN (N=164)" included sections for baseline demographics and disease characteristics along with the HELIOS-A study design. The study design section included the inclusion and exclusion criteria, patient disposition, outcome measures (listed by primary, secondary and exploratory cardiac endpoints) along with the wording "Non-inferiority in serum TTR reduction through Month 18" under the heading "AMVUTTRA vs patisiran". This was followed by illustrations of the primary endpoint outcome and a secondary endpoint outcome (change from baseline to Month 18 in Norfolk QoL-DN score).

The second printed circle was of the prominent claim "TOXIC TTR CAUSES MULTISYSTEM DEVASTATION IN hATTR". The contents of the 5 pages of the associated touch screen explained that hATTR resulted from the deposition of toxic TTR and that all patients would develop multisystem disease including autonomic symptoms, cardiomyopathy and sensory-motor neuropathy. Subsequent focussed on hATTR progression being rapid with the final page stating that early identification and intervention was vital; red flags for hATTR for polyneuropathy was stated to be any patient with progressive symmetric neuropathy plus at least 1 of the following: autonomic neuropathy, GI complaints, bilateral carpal tunnel syndrome, cardiomyopathy.

The third printed circle stating "RAPID KNOCKDOWN OF TOXIC TTR AS EARLY AS DAY 2 SECONDARY ENDPOINT" appeared to be accompanied by a touch screen that included illustrations of the reduction from baseline in serum TTR at 18 months and the change from baseline to Month 18 in mBMI score (nutritional status) which were secondary endpoints.

The touch screen for the fourth printed circle "REINFORCED BY 3,347 PATIENT-YEARS OF EXPOSURE AND DOSED 4 TIMES A YEAR" included information relating to dosing, adverse events, special warnings and precautions for vutrisiran.

The fifth printed circle, on the back wall, stated “RAPID KNOCKDOWN OF TOXIC TTR POWERED BY AMVUTTRA” with reference to adverse event reporting and prescribing information being available to the left of the first booth arch. It appeared that the accompanying screen included the indication and five summary slides stating:

1. hATTR is a rapidly progressive, multisystem disease that results from the deposition of toxic TTR, which causes irreversible multisystem damage and premature death
2. AMVUTTRA uses RNAi to provide rapid knockdown of serum TTR from baseline as early as Day 22 after the first dose, to substantially reduce deposition of toxic TTR
3. Rapid knockdown of toxic TTR powered by AMVUTTRA transformed outcomes, reversing neuropathy and QoL impairment from baseline in ~50% of patients with hATTR-PN
4. The most frequently occurring adverse reactions reported in patients treated with AMVUTTRA were pain in extremity (15%) and arthralgia (11%)
5. With subcutaneous administration, AMVUTTRA is the first and only hATTR treatment dosed 4 times a year

Alnylam’s pre-congress compliance briefing for staff attending the congress included for messaging to be consistent with the approved product label and for questions outside of the indication to be referred to the medical booth. Guidance related to Helios-B results, a vutrisiran trial for patients with ATTR-CM, stated:

- “If you receive questions from HCPs regarding the results of the study or the potential future use of vutrisiran in this patient population, do not comment/discuss or share information. Any questions outside of the licensed indication refer these questions to the Medical booth for response
- Reconfirm with the HCP that we are licensed for hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy referencing your approved materials and offer to go through the on-label data
- Focus on licensed indication: All discussions should be centred on the treatment of polyneuropathy (PN) in patients with hATTR, including those patients with hATTR-PN that also have cardiac manifestations. Ensure that any mention of the product does not imply efficacy for cardiomyopathy (CM), which is outside the licensed indication”.

The Panel noted its ruling of no breach of Clause 5.6 under allegation 1, having concluded it had not been established that promotional material for vutrisiran was directed to an audience whose need for, or interest in, the material could not be reasonably assumed. The matter for the Panel under this allegation was whether the content of the exhibition booth, particularly the overhead canopy video which Pfizer’s allegations specifically related to, misleadingly implied vutrisiran was for the treatment of ATTR-CM for which it was not licensed.

The Panel took into account the duration and repetition of the licensed indication within the video loop, the presence of the indication across other booth materials and the associated briefing for commercial employees in attendance. In the Panel’s view, Pfizer had not established that the Alnylam booth material, including the overhead signage, was ambiguous, misleading or incomplete such that they promoted vutrisiran for an unlicensed indication. The Panel ruled **no breaches of Clauses 6.1 and 11.2**.

Alnylam tutorials at the cardiology congress

Allegation 3 - Promotion of a medicine not in accordance with the terms of its marketing authorisation

Pfizer alleged that two tutorials held at the congress by Alnylam promoted vutrisiran for an off-label indication. Alnylam submitted each tutorial was held twice during the course of the congress.

Tutorial 1: Unveil the unseen: monitoring disease progression and treatment response in ATTR-cardiomyopathy

Pfizer alleged it did not seem credible that treatment response in ATTR-CM was discussed and treatments were not. Pfizer further alleged that the discussion about treatment response would have solicited questions about use of vutrisiran in ATTR-CM, which would be an off-label indication.

The Panel noted that the title slide for tutorial 1 included the heading "Unveil the unseen: monitoring disease progression and treatment response in ATTR-cardiomyopathy". A footnote in small font stated, "This tutorial is organised and funded by Alnylam Pharmaceuticals; for healthcare professionals only. Alnylam medicinal products will not be discussed during this tutorial".

The introductory slides included details of ATTR being a progressive, fatal disease, caused by toxic TTR deposition and emphasised the importance of fast recognition of ATTR-CM disease progression to minimise the risk of cardiovascular damage. Poll questions for the attendees included questions on which markers they consider to be the most important when identifying ATTR-CM disease progression, and questions related to a patient case study, such as which initial testing they would conduct for this patient, next steps in the diagnosis pathway, which patients they would consider for TTR genetic testing and what has enabled earlier diagnosis in recent years.

Alnylam submitted that tutorial 1 was non-promotional and the objectives were to explore a multiparametric approach to monitoring disease progression in patients with ATTR-CM focusing specifically on the tools for monitoring such progression and analysing patient cases to determine the impact of such tools in monitoring disease progression. No materials advertising, or content used in, tutorial 1 were available at Alnylam's congress booth.

The Panel noted that the speaker briefing slides for tutorial 1 stated, "As a non-promotional meeting, there must be no reference, directly or indirectly, to Alnylam therapies (both approved and those in development), including vutrisiran and patisiran. If there are any questions relating to Alnylam therapies during the meeting, it must be made clear that, as this is a non-promotional meeting, these cannot be discussed. Please respond to advise the individual to follow up with Alnylam Medical Information if they require further information or support, whilst reminding that the objective of this meeting is to share learnings about the importance and modalities of monitoring disease progression in ATTR-cardiomyopathy (ATTR-CM) and not to discuss treatment options".

The 'desired outcomes' included:

- “Drive awareness around the rapidity of ATTR-CM disease progression, and the increased risk of irreversible damage to cardiac tissue and quality of life.
- Educate on the need for a comprehensive approach to evaluating disease progression
- Use anonymised real-world case studies to reinforce learnings on tools for monitoring disease progression”

The briefing slides further stated, “Please note that any discussion on treatment options should not include mention of any disease-modifying therapy, rather to focus on monitoring patients on non-disease-modifying therapy”.

The Panel noted Alnylam’s submission that Alnylam did not mention any specific medicine during the session either directly or indirectly, and the reference to “treatment response” in the title related to discussion and presentation of data showing how earlier diagnoses of ATTR-CM over the last ~20 years contributed to improved survival, without reference to any specific treatments.

The Panel observed that the slides did not include any information on medicines or treatment and that the focus of the presentation appeared to be on monitoring disease progression using various markers.

While the Panel recognised Pfizer’s concerns that the title and focus of the tutorial could have reasonably prompted interest in treatment options for it amongst attendees, the Panel took account of Alnylam’s submission that no questions on the use of vutrisiran to treat ATTR-CM were asked by attendees.

The complainant bore the burden of proof. In the Panel’s view, Pfizer had not established that treatments, including vutrisiran, were discussed during the tutorial or that it had solicited questions about the use of vutrisiran in ATTR-CM, which was off-label. On the evidence before it, the Panel ruled **no breach of Clause 11.2**.

Tutorial 2: Expert Exchange: Treating hATTR Polyneuropathy Patients with a Mixed Phenotype (Polyneuropathy and Cardiomyopathy)

The Panel noted that Alnylam’s speaker brief for tutorial 2 stated:

> “This meeting is labelled as promotional; all content and discussion on treatments must be fair, balanced, not misleading and on label:
>
> - Vutrisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.
>
> Vutrisiran is not approved for the treatment of ATTR-cardiomyopathy (ATTR-CM), and therefore vutrisiran in the context of treating ATTR-CM, including information around the HELIOS-B trial results, should not be discussed at this meeting. Content should not include mention of any disease-modifying treatment for ATTR-CM. If there are any questions regarding the above during the meeting, please advise the individual to follow up with Alnylam Medical Information”.

The ‘overall objectives’ slide stated that the anticipated audience included:

"General cardiologists with limited experience in managing hATTR polyneuropathy patients with a mixed phenotype, who therefore:

- Lack an understanding of the spectrum of multisystemic involvement in these patients
- Seek to understand optimal approaches to treating these patients."

The 'desired outcomes' included:

- "Reinforce knowledge on the multisystemic nature of hATTR polyneuropathy.
- Drive awareness of potential therapeutic strategies for treating hATTR polyneuropathy patients.
- Highlight the opportunity to treat hATTR polyneuropathy patients with a mixed phenotype with vutrisiran, and the rapid knockdown of toxic transthyretin (TTR)
- Examine real-world experience of treating mixed phenotype hATTR polyneuropathy patients with vutrisiran."

Further, a slide on 'key elements to include' stated:

- "Highlight the evolution of hATTR patient profiles and the critical need for recognising multisystemic involvement (polyneuropathy and cardiomyopathy).
    - Discuss the reclassification of patients from predominantly cardiomyopathy or polyneuropathy to mixed phenotype, thereby reinforcing the need for multidisciplinary evaluation at initial assessment
- Provide a brief overview of treatment options in the hATTR polyneuropathy landscape and highlight RNAi therapy.
- Underscore the role of vutrisiran in treating mixed phenotype hATTR polyneuropathy patients by showcasing HELIOS-A results, including the polyneuropathy and cardiac endpoints.
- Share practical insights, via patient cases, on treating mixed phenotype hATTR polyneuropathy patients with vutrisiran, and the rapid knockdown of toxic TTR."

The opening title slide of the promotional tutorial, which comprised of 56 slides, included the prominent heading "Expert Exchange: Treating hATTR Polyneuropathy Patients with a Mixed Phenotype (polyneuropathy and cardiomyopathy)", followed by a sponsorship statement in small font: "This is an Alnylam-sponsored promotional event; organised and funded by Alnylam Pharmaceuticals. The tutorial will include information on Alnylam medicinal products; for healthcare professionals only. Prescribing information is available at the Alnylam Tutorials Registration Desk". The bottom of the slide included, in small font, the licensed indication for vutrisiran, an additional monitoring statement and an adverse event reporting statement.

A subsequent slide included the learning objectives:

"1. Understand the heterogeneous nature of hATTR polyneuropathy patients with a mixed phenotype (polyneuropathy and cardiomyopathy)

2. Examine real-world experience of treating mixed phenotype hATTR patients (polyneuropathy and cardiomyopathy) and the considerations for clinical practice"

The introductory slides explained the patient profile and disease progression in clinical practice, stating that hATTR is a progressive, multisystem, debilitating and ultimately fatal disease with great genotype and phenotype heterogeneity. An infographic illustrating the clinical manifestations of hATTR included CNS and cardiovascular manifestations, among others, such as ocular and gastrointestinal manifestations.

The presentation included two patient case studies. Patient A had hATTR-PN mixed phenotype with cardiac manifestations and was treated with vutrisiran and an SGLT2-inhibitor and a diuretic. Electrocardiogram (ECG), cine CMR images of the patient's heart and LGE CMR images of the heart with contrast were included. Subsequent poll questions for the attendees focussed on the evaluation of the patient, who had a mixed phenotype with cardiac manifestations. These were followed by treatment options for hATTR polyneuropathy patients with mixed phenotype (polyneuropathy and cardiomyopathy). The Panel noted that there was a single slide which illustrated therapeutic options for hATTR in the form of an infographic which listed the options but did not go into any detail about these. This was followed by six slides which discussed HELIOS-A data in patients with hATTR-PN, in which patients were randomised 3:1 to receive 25mg of vutrisiran once every 3 months or 0.3mg/kg patisiran once every 3 weeks. The slides focussed on vutrisiran's efficacy outcomes as well as special warning and precautions.

The second case study for Patient B looked at the RNAi treatment journey of a patient with hATTR-PN mixed phenotype (including cardiac manifestations), who started treatment with patisiran and recently switched to vutrisiran. The case study included an image of a 2D echo showing wall thickness of the heart and an ECG. The associated poll questions for the attendees included, among others, a question on the importance of collaboration between cardiologists and neurologists for the treatment of patients with hATTR-PN mixed phenotype with cardiac manifestations.

The Panel noted Alnylam's submission that the patient case studies were presented to inform cardiologists how to monitor the progression of the cardiac manifestations of the disease in patients with hATTR-PN, and that cardiac biomarkers were identified in vutrisiran's SPC.

Section 5.1 of the vutrisiran SPC, Pharmacodynamic properties - Clinical efficacy and safety stated;

> "*The N-terminal prohormone-B-type natriuretic peptide (NT-proBNP) is a prognostic biomarker of cardiac dysfunction. NT-proBNP baseline values (geometric mean) were 273 ng/L and 531 ng/L in Amvuttra-treated and placebo-treated patients, respectively. At month 18, the geometric mean NT-proBNP levels decreased by 6% in Amvuttra patients, while there was a 96% increase in placebo patients.*
>
> *Centrally-assessed echocardiograms showed changes in LV wall thickness (LS mean difference: -0.18 mm [95% CI -0.74, 0.38]) and longitudinal strain (LS mean difference: -0.4% [95% CI -1.2, 0.4]) with Amvuttra treatment relative to placebo.*
>
> *Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed.*"

The slides on HELIOS-A data included two slides illustrating, in the form of two graphs, a decrease in NT-proBNP levels versus external placebo in patients with hATTR-PN who were treated with vutrisiran. The first graph illustrated a decrease in baseline in NT-proBNP levels versus time in the modified intent-to-treat population, and the second graph illustrated a decrease in baseline NT-proBNP levels versus time in a cardiac subpopulation. The slide stated, “Vutrisiran* achieved improvement in NT-proBNP at Month 9, with continued improvement to Month 18 in both the mITT population and cardiac subpopulation compared with the external placebo group (exploratory endpoint)”. The asterisk led to a footnote in small font, which stated, “Vutrisiran is indicated for the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy”.

The second slide stated, “Vutrisiran showed benefits in exploratory measures of cardiac stress vs external placebo at Month 18 in patients with hATTR-PN”. Two graphs illustrated change in LV wall thickness in the modified intent-to-treat population and the cardiac subpopulation. A footnote in small font, beneath the graphs, stated, “Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed. *Vutrisiran is indicated for the treatment of hATTR in adult patients with stage 1 or stage 2 polyneuropathy”.

The Panel noted its observations under Allegation 1 above, that while vutrisiran’s indication was limited to treatment in patients with polyneuropathy, a mixed phenotype including polyneuropathy and cardiomyopathy could be found in the majority of patients with hereditary transthyretin amyloidosis, resulting in progressive, multisystem disease that required a multidisciplinary approach to monitoring and treatment.

However, the Panel considered the overall impression created by the presentation. In the Panel’s view, the repeated emphasis on cardiac manifestations, cardiac subpopulation analyses and treatment-related cardiac endpoints, when taken together, would have, on the balance of probabilities, created the impression that vutrisiran was being positioned as a treatment option primarily for patients with cardiac manifestations. In the Panel’s view, the footnotes stating the licensed indication on the two slides about decrease in NT-proBNP levels and the benefits of vutrisiran in cardiac stress did not negate the misleading impression created that vutrisiran would be suitable for ATTR-CM patients regardless of whether they presented with a mixed phenotype or not.

Taking account of its comments, along with the broader context that Alnylam was due to make regulatory submissions for an indication related to ATTR-CM in the near future for vutrisiran, the Panel considered, on balance, that vutrisiran had been promoted in a manner that was inconsistent with the terms of its marketing authorisation. The Panel ruled a **breach of Clause 11.2**.

ATTR evening meeting at the Banking Hall

The Panel noted that Pfizer raised two allegations in relation to an ATTR meeting held by Alnylam one evening at the Banking Hall, during the course of the congress.

Pfizer submitted a screenshot of a social media post, which was dated the day after the meeting and included a photograph of the principal investigator with the person who made the post along with a second photograph showing HELIOS-B trial results being presented. The post stated,

> “Grateful to meet the humble and inspiring [named professor], HELIOS-B trial PI [Principal Investigator], in a beautiful Banking Hall surrounded by international experts on cardiac amyloidosis [heart emoji] Thankful to [named doctor] for the opportunity @[named professor] @[named doctor] @Alnylam”

The Panel considered there were broadly two allegations. Pfizer firstly alleged that the venue was inappropriately lavish and questioned the level of subsistence provided to each attendee at the event. Pfizer further alleged it did not constitute a bona fide legitimate exchange of medical and scientific information (LEMS) meeting but was instead a pre-licence promotional meeting.

Allegation 4: Inappropriately lavish venue for Alnylam-organised meeting

Alnylam submitted that it had engaged a third party to identify potential venues for the ATTR meeting that were 4-star or equivalent with suitable meeting facilities close to the site of the congress. Alnylam submitted it chose the Banking Hall for its functional and professional setting, making it appropriate and conducive to the educational purpose of the meeting, with no access for the public, and no additional activities or facilities available at the venue.

The Panel noted that Alnylam’s screenshot of the corporate events webpage for the Banking Hall venue, taken in January 2025 following an update to its website, described the venue as an “inspiring venue with Advanced Technology in Central London … rich with 1930s Art Deco character … the space can be tailored to suit your specific needs, whether it’s a conference, gala, or product launch”. The Panel considered the majority of the descriptions, however, focussed on the venue being suitable for corporate needs, meetings and team-building events.

The Panel noted Alnylam’s submission that the marketing descriptions to which the complainant referred to were based on parts of the website that targeted wedding planners rather than professional conference organisers and that those descriptions did not appear on the venue website when Alnylam booked the Banking Hall for the ATTR Meeting.

The Panel noted that Pfizer’s description of the venue, as “a stunning art deco gem dripping in grandeur, an iconic Grade II listed landmark, with a sweeping marble staircase, towering columns and marble floor. A venue full of sophistication, luxury and elegance” did not appear on the website screenshots before the Panel.

The Panel noted the ATTR meeting Save the Date referred to the heading “International Deep Dive into ATTR Amyloidosis, organised by Alnylam” and provided the date and time of the meeting, with the location described only as “London | near ExCel Convention Centre (TBC)”. The calendar invitation similarly referred to the meeting location as such and described the purpose of the event as an evening of scientific discussion and peer exchange. Neither the Save the Date nor the calendar invitation named the Banking Hall venue.

The email invitation subsequently sent out included the name and address of the Banking Hall but did not include any descriptive language regarding the venue itself. Alnylam submitted that a "good proportion" of invitees (34) accepted the invitation without knowledge of the venue location, indicating their interest in the event's educational content rather than the venue.

In relation to Pfizer’s comment about the level of subsistence provided by Alnylam, the Panel noted Alnylam’s submission that the cost of subsistence was £70 per person, which comprised

a welcome drink and canapes, a three course dinner, half a bottle of house wine, half a bottle of filtered water, and tea or coffee.

Taking account of the above, and on the evidence before it, the Panel considered that Pfizer had not established that the Banking Hall venue was inappropriate nor that the level of subsistence was excessive. The Panel ruled **no breach of Clause 10.1** accordingly.

Allegation 5: Potential promotional meeting where off-label information was presented

The Panel noted Pfizer referred to the screenshot of the social media post described above, which showed the HELIOS-B trial results being presented, a study that evaluated the efficacy and safety of vutrisiran in patients with ATTR-CM. In this regard, Pfizer alleged that the ATTR evening meeting organised by Alnylam did not constitute a bona fide legitimate exchange of medical and scientific information, but instead was a pre-license promotional meeting designed to promote vutrisiran off-label for ATTR-CM.

Pfizer raised a number of concerns in support of this allegation, including:

1. Whether vutrisiran could be considered an 'investigational molecule' or being 'in development' given that Alnylam was going through the EMA and FDA submission process for a new indication approximately 6 weeks after the meeting
2. Whether each delegate had a meaningful opportunity to contribute to the scientific exchange given it was a large meeting
3. That the interactive country workshops explored local needs, challenges, and considered the necessary steps for optimising ATTR amyloidosis management, both now and in the future, giving the impression that these were practical discussions about implementation, rather than scientific exchanges about the development of a medicine
4. That the presence of the given HELIOS-B principal investigator made it highly likely that there would have been great interest in vutrisiran and HELIOS-B data at the meeting, with a heavy weighting towards it
5. Whether the number of Alnylam employees in attendance, and their roles, were appropriate.

Alnylam submitted that the ATTR meeting was a medically led international LEMS event which was not product-focused but disease-focused. Alnylam submitted the meeting was a forum for exchanging knowledge on the challenges, needs and gaps in the understanding of the diagnosis, management and treatment of ATTR Amyloidosis for health professionals from across the globe.

The Panel noted Alnylam's submission that approximately 70 individuals attended the meeting and were divided into country-level groups of around nine participants. 31 Alnylam employees were in attendance, including 20 country medical team members, seven general managers and four senior leaders.

The agenda for the ATTR meeting was as follows:

19:45-19:55 Opening Session

19:55-21:00	Faculty-led discussion *The evolving landscape in ATTR amyloidosis, including current trends, unmet needs and challenges*
21-00-22:00	Breakout group discussions *Workshop over dinner*
22:00-22:15	Feedback session *Synergising thoughts, Group reflections and future strategies*
22:15-22:20	Meeting close

The meeting comprised approximately 40 slides, including title, holding and audience poll slides. The opening slide, "International Deep Dive into ATTR Amyloidosis", included the following text in small font:

> "This legitimate exchange of medical and scientific information (LEMS) event is organised and funded by Alnylam Pharmaceuticals. The meeting, as part of the wider agenda, will include discussions on unapproved therapies in the pipeline, including those in development by Alnylam amongst others in development by third parties. Therapies in development for ATTR-CM will be discussed during this presentation."

The title slide further included:

> "Note: Patisiran does not have marketing authorization for the treatment of ATTR-CM. Vutrisiran▼ is in development for treating ATTR-CM. Patisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. Vutrisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy."

The meeting started with a welcome from a global senior medical leader from Alnylam. The slides in this session included a timeline of RNAi therapeutics, setting out Alnylam's history and involvement in the field, the mechanism of action of RNAi therapeutics and a slide titled "Primary Analysis of HELIOS-B Published Today in The New England Journal of Medicine". This slide, which appeared in the social media post provided by Pfizer, contained a screenshot of the publication and the boxed statement that "Vutrisiran is an investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis with cardiomyopathy (ATTR-CM)."

The Panel noted that the faculty comprised an Alnylam global employee and four key opinion leaders who collectively delivered sessions on disease awareness, diagnosis, monitoring in ATTR amyloidosis and treatment. The treatment session, titled "Advancing care in ATTR amyloidosis: Evolving treatment landscape and patient management strategies", was delivered by two key opinion leaders and, according to Alnylam, represented a third of the time (20 minutes) allocated to the faculty's presentation.

The first slide of the evolving treatment session was titled "Therapeutic opportunities in ATTR amyloidosis" and included a graphical representation of the pathophysiology of ATTR amyloidosis highlighting the potential targets across the disease pathway for disease-modifying therapies. These included targeting transthyretin synthesis (including RNA interference therapies, antisense oligonucleotides, gene editing and liver transplantation), transthyretin tetramer stabilisation (TTR stabilisers), and transthyretin degradation (anti-TTR monoclonal

antibodies). The next slide, titled “Drug therapies for heart failure – what do the guidelines say?”, illustrated non-disease modifying drug classes used in the management of heart failure and whether there was expert consensus opinion across various cardiology societies and guidelines across the world. Neither slide referenced specific product names within each category highlighted.

The following slide, titled “Timeline of key clinical trials in ATTR-CM”, presented a chronological overview of major ATTR-CM clinical trials. These included ATTR-ACT, ATTRibute-CM, APOLLO-B, HELIOS-B and CARDIO-TTRansform (Alnylam and non-Alnylam trials) with brief details of each. A subsequent slide titled “Clinical trial endpoints” listed primary and secondary endpoint results for the ATTR-CM trials shown on the timeline, with brief summaries of outcomes. In relation to one of Alnylam’s trials, APOLLO-B, the slide included a statement that patisiran was not licensed for the treatment of ATTR-CM.

The Panel noted the final slide with substantive content illustrated an overview of the results from the HELIOS-B study. The slide was headed with the statement “Vutrisiran met all 10 primary and secondary endpoints, in both overall and monotherapy populations” and included graphical representations of clinical outcomes. The slide further stated “Vutrisiran showed acceptable safety and tolerability profiles as previously established”.

Alnylam submitted that the ATTR-CM clinical trials were discussed in a balanced way and that one slide specifically focused on HELIOS-B as the results were reported the previous day and so it was important for the attendees to understand the context of the HELIOS-B results alongside the other ATTR-CM clinical trials. The Panel observed no other ATTR-CM clinical trial results were presented in similar detail.

The Panel noted that three questions were planned to be posed to the faculty panel about their thoughts on new therapies or investigational approaches, biggest unmet needs in ATTR-CM and how they envisaged treatment protocols evolving. This was followed by an “Ask the experts” Q&A session along with breakout group discussions that took place over dinner and a feedback session.

The breakout sessions took place over dinner and lasted approximately 45 minutes followed by a 15-minute feedback session from the Alnylam facilitators to the faculty. According to the discussion slides, attendees were to be encouraged to explore local needs and challenges, and to consider the necessary steps for optimising ATTR amyloidosis management both now and in the future. Alnylam submitted that medical team members facilitated the breakout sessions and shared feedback with the faculty whereas the country general managers were in attendance to “simply learn” about ATTR with no direct involvement; the four senior leaders did not participate in the breakout sessions.

The facilitator guide included the following:

> “1a) What is the top challenge with timely diagnosis of patients with ATTR amyloidosis? (3 minutes for individual thinking and note of question 1a)
>
> 1b) What would you describe as the biggest challenge to early detection and diagnosis of ATTR amyloidosis? (7 minutes of round-table discussion)

Please ask one attendee to share the model of care most commonly used in their region, and confirm this consensus with other table attendees. Then discuss question 2.

2) Does the model of care in your region/country work well for patients with ATTR amyloidosis? Would this model of care work in the future? What changes would help improve patient care? (10 minutes of round-table discussion)

3a) What are the key gaps in the management and treatment of patients with ATTR amyloidosis in your region/country? (3 minutes for individual thinking and note of question 3a)

3b) What tools or resources would best address the key gaps in the management and treatment of patients with ATTR amyloidosis in your region/country? (7 minutes of round-table discussion)

4) What are your key recommendations given the evolving landscape in ATTR amyloidosis in your region/country? (10 minutes of round-table discussion)"

The matter for the Panel to consider was whether, taking all the circumstances into account, the ATTR meeting could be regarded as a bona fide legitimate exchange of medical and scientific information.

The Panel noted the Code stated the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited, provided that any such information or activity did not constitute promotion.

In this regard the context in which the exchange took place and the audience would be important factors in determining whether the activity was acceptable under the Code. The proactive provision of information by a pharmaceutical company about the unauthorised use of a medicine was very likely to be seen as promotion.

The Panel considered for the legitimate exchange of medical and scientific information during the development of a medicine, data presented should be new and pivotal and should enhance current medical or scientific knowledge. Delegates must be able to adequately participate in the debate. It must not be a one-way flow of information. This facilitates the possibility of genuine challenge and exchange of views on the data being presented. There should be no connection or overarching theme between the promotional and non-promotional activities.

The legitimate exchange of medical and scientific information is carried out during the development of a medicine. Whether a medicine is still 'in development' is decided on a case-by-case basis. There is no defined time period in the Code, however, if a marketing authorisation has been applied for in any country, the medicine is unlikely to be seen as still 'in development'. Companies should also take particular care when an unlicensed medicine is already available for use, for example, in a compassionate use programme. Each case would be considered on its individual merits. The legitimate exchange of medical and scientific information during the development of a medicine is not limited to medicines without a marketing authorisation. However, it would be more difficult for a company to establish that a medicine with a marketing authorisation is 'in development' in relation to an unlicensed

indication being discussed, particularly if the licensed medicine was available in a dosage form that could be used for the unlicensed indication.

It was for the Panel to consider whether the structure and arrangements for the meeting facilitated a genuine exchange. The meeting involved in excess of 100 attendees (approximately 70 external) with delegates seated with others from the same country in a banquet-style layout.

The 65-minute faculty-led session involved structured presentations, which included polling questions to be answered online. Attendees could submit questions via a link at any time, which would be answered during the Q&A session along with any questions that were asked on the microphone during that slot. The subsequent breakout group discussions were facilitated by Alnylam medical team members who collated feedback and returned this to the faculty to share as part of the group reflection session.

The Panel took into account that the sessions were delivered to a large audience and that the breakout sessions appeared to be a mechanism to gather insights from attendees. The nature and depth of discussion was fundamental to the legitimate exchange of medical and scientific information. In the Panel's view, neither format would have facilitated a meaningful two-way medical or scientific debate or exchange.

In reaching its view, the Panel noted that the breakout sessions took place for 45 minutes over a three-course dinner and that the role of Alnylam medical team members in the breakout sessions was to facilitate and collate feedback. The Panel particularly took into account that the focus was primarily on practical challenges, models of care and future optimisation of ATTR management. In this regard, the Panel questioned Alnylam's submission that the meeting sought to inform future research and queried whether the sessions, in context, constituted scientific debate about the development of a medicine.

Notably, the Panel considered whether vutrisiran could reasonably be regarded as still 'in development' for ATTR-CM at the time of the meeting. The Panel took into account that the product was available in the same dosage form to be used in ATTR-CM and considered this heightened the need for particular caution. The closer the activity to the grant of the marketing authorisation for a product, the more difficult it was to argue that activities were a legitimate exchange of medical and scientific information during the development of a medicine.

While the Code did not define any timepoints, the Panel acknowledged Pfizer's concerns regarding the proximity of regulatory submissions. There was limited time for Alnylam to act upon any information for vutrisiran to be used in ATTR-CM.

In the Panel's view, a product which already had a license for ATTR-PN and for which regulatory submissions were due in the near future for another indication, ATTR-CM, could not be considered to be in development. The Panel considered this, along with the cumulative effect of the nature of the content, format and scale of the event, meant that the ATTR meeting could not benefit from being a legitimate exchange of medical and scientific information.

The Panel therefore considered that the presentation of the HELIOS-B data, which outlined the results for vutrisiran for ATTR-CM, meant that vutrisiran had been promoted for an unlicenced indication at the time of the complaint. The Panel **ruled a breach of Clause 11.2**.

Allegation 6 – Disguised promotion

The next matter for the Panel to consider was whether the meeting constituted disguised promotion.

The Panel noted that the save the date PDF, save the date calendar invite and email invitation labelled the meeting as being an "international deep dive into ATTR amyloidosis" organised by Alnylam.

The two save the date materials invited recipients to join *"for an evening of sharing insights, engaging in scientific debate and fostering discussion with peers, with the aim of advancing our understanding of the field and shaping the future of ATTR amyloidosis management*". Among other things, the save the date PDF included an agenda which listed the following: *"The evolution of ATTR amyloidosis through the years; Diagnostic challenges and complexities of this heterogeneous condition; The unmet need in care management and strategies to improve the status quo; and Early diagnosis, progression mapping, and patient monitoring".*

The email invitation stated that the evening would begin with an opening on the evolution of ATTR amyloidosis, followed by faculty-led discussion introducing key "hot topics" in ATTR amyloidosis faced across the globe including:

- *"Innovation over time: The evolution of knowledge and understanding of ATTR amyloidosis*
- *Navigating the diagnostic challenges and multisystemic nature of ATTR amyloidosis*
- *Awareness to action: Optimising approaches for patient monitoring in ATTR-CM management*
- *Advancing care in ATTR amyloidosis: Evolving treatment landscape and patient management strategies"*

It included that attendees would have the opportunity to participate in scientific debates and to engage with peers in order to deepen and enhance shared knowledge of ATTR amyloidosis.

At the bottom of the email (beneath the registration link) and also in the footer of the save the date PDF, in small font, was the wording:

> *"This legitimate exchange of medical and scientific information (LEMS) event is organised and funded by Alnylam Pharmaceuticals. The meeting, as part of the wider agenda, will include discussing therapies currently in the pipeline, including those developed by Alnylam amongst others in development. For healthcare professionals only."*

The Panel noted that the meeting was labelled as a LEMS event and while the Panel considered its determination above that the ATTR meeting did not constitute the legitimate exchange of scientific and medical information during the development of a medicine, its concerns that vutrisiran had been promoted for ATTR-CM were covered by its ruling of Clause 11.2 above.

The Panel noted that promotional material did not need to be labelled as such, however, it must not be disguised. The Panel considered it was clear from the materials that the meeting was organised by Alnylam. The Panel further took into account that the save the date PDF and email

invitation included, albeit in small font in the footer, that there would be discussion of "*therapies currently in the pipeline, including those developed by Alnylam amongst others in development".*

The Panel noted that the definition of promotion in Clause 1.17 was broad. In the Panel's view, attendees would have reasonably foreseen from the materials that Alnylam's medicines would be discussed at the meeting and, on balance, the Panel ruled **no breach of Clause 3.6**.

Overall

Allegation 7-8: High standards and confidence in the industry

The Panel noted Pfizer alleged that Alnylam had failed to maintain high standards and had reduced confidence in the industry in relation to the ATTR-meeting not being a bona fide legitimate exchange of medical and scientific information. Pfizer further stated at the conclusion of its letter of complaint to the PMCPA that it maintained that Alnylam's activities constituted a deliberate attempt to promote a potential new indication ahead of licensure, in breach of Clauses 5.1 and 2.

The Panel observed that the case preparation manager had included Clauses 5.1 and 2 among the clauses raised in relation to the ATTR-meeting while later asking Alnylam to bear in mind the requirements of Clauses 5.1 and 2 overall. In this regard, the Panel observed that the clauses had been raised once by Pfizer during intercompany dialogue in relation to the overall complaint and that Alnylam had responded on that basis throughout its correspondence, including in its response to the PMCPA. Noting there did not appear to be any additional allegations, the Panel considered the allegations raised applied to the overall circumstances of this case, albeit with particular emphasis on the ATTR-meeting. The Panel accordingly determined it would solely rule on Clauses 5.1 and 2 in relation to the overall circumstances of the meeting.

The Panel considered its view above that it was not unacceptable for Alnylam to promote vutrisiran for ATTR-PN to cardiologists given the multisystem nature of amyloidosis and the role of cardiologists in treatment pathways. However, the Panel took account of its rulings that Alnylam had promoted vutrisiran at Tutorial 2 and the ATTR-meeting in a manner that was not in accordance with its marketing authorisation at the time of the complaint. The Panel considered Alnylam had failed to maintain high standards in this regard and ruled a **breach of Clause 5.1**.

Clause 2 was a sign of particular censure and was reserved for such use. In considering Clause 2, the Panel took account of the seriousness and context of the activities ruled in breach. The Panel particularly noted its view that vutrisiran could not reasonably be regarded as still 'in development' at the time of the ATTR meeting, taking account that it was available and licensed in the same dosage form for ATTR-PN, and that regulatory submissions for the ATTR-CM indication were due to be made shortly thereafter. The Panel considered this context heightened the need for particular care. The Panel further noted that the promotion of an unlicensed indication had also been determined to have taken place at Tutorial 2. Taking all the circumstances into account, the Panel considered that Alnylam's conduct was such as to reduce confidence in the pharmaceutical industry. The Panel **ruled a breach of Clause 2.**

APPEAL BY ALNYLAM

Alnylam's written basis for appealing is reproduced below:

"Breaches appealed by Alnylam
We refer to the PMCPA's letter dated 14 January 2026 containing the Panel's ruling in the above case. Further to Alnylam's notice of appeal, Alnylam is appealing the following parts of the ruling in which the Panel found breaches of the Code:

- Breach of Clause 11.2 in relation to allegation 3 (Promotion of a medicine not in accordance with the terms of its marketing authorisation) in relation to promotional Tutorial 2;
- Breach of Clause 11.2 in relation to allegation 5 (Potential promotional meeting where off-label information was presented) in relation to the ATTR Meeting; and
- Breach of Clause 5.1 and Clause 2 in relation to allegations 7-8 (High standards and confidence in the industry).

We ask that the Appeal Board re-evaluate the Panel's ruling and the evidence submitted by Alnylam in the context of additional and important medical background, some further detail of the two events and the independent witness statements which we provide in this response.

Pfizer has not provided sufficient evidence to prove their complaint for either event

As described in the Introduction to the PMCPA Constitution and Procedure, the **complainant has the burden of proving their complaint on the balance of probabilities.** The burden of proof means that a complainant's allegations should not be upheld if they cannot provide sufficient evidence to convince the Appeal Board that a breach of the Code has occurred.

For the **ESC Alnylam sponsored Tutorial 2** (Allegation 3), Pfizer has alleged that Alnylam promoted vutrisiran in a manner not in accordance with its marketing authorisation (Clause 11.2). However, they have not submitted any evidence to support their allegation, which is noteworthy as Pfizer staff members were in attendance at both sessions of the tutorial. In their complaint, Pfizer accepts that Alnylam made the licensed indication of hereditary ATTR Amyloidosis polyneuropathy (defined below) clear in the tutorial and Pfizer failed to put forward any content from the presentation which could be viewed as off-label promotion for vutrisiran. Pfizer has not provided evidence that any attendee had or could have concluded that vutrisiran was licensed or being promoted for ATTR-CM (defined below), and nobody attending the tutorial (other than Pfizer, a competitor of Alnylam) has complained. Further, Pfizer has not shown that the content is not relevant to a cardiologist reviewing a hereditary ATTR Amyloidosis polyneuropathy patient in their clinic. Again, without such evidence, it is difficult to understand how Pfizer has proven beyond the balance of probabilities that the tutorial was not in accordance with the marketing authorisation or inconsistent with the Summary of Product Characteristics ("**SmPC**"). On the contrary, the information presented was in accordance with the vutrisiran marketing authorisation and consistent with the SmPC.

For the **Alnylam organised ATTR Amyloidosis evening meeting** (Allegation 5), Pfizer submitted a single photo from an ex-UK cardiologist attendee's personal Twitter

account in which [they] stated that [they were] "*grateful to meet the humble and inspiring [named health professional], Helios-B trial PI, in a beautiful Banking Hall surrounded by international experts on cardiac amyloidosis*", thanking [their] supervisor for enabling [their] attendance. Alnylam were not responsible for the social media post. Pfizer submitted no evidence that Alnylam had promoted vutrisiran (whether or not in a manner in accordance with its SmPC). Pfizer were not present at the meeting and did not provide credible evidence of a breach regarding its content or conduct. Their complaint is therefore based on speculation rather than substantiated evidence, and, as with Tutorial 2, no other party raised any concerns about the meeting. In fact, statements from attending clinicians are clear that they felt the contrary (see section below titled "*Faculty and Attendee perception of the meeting was scientific and medical, not promotional*"). Again therefore, Alnylam do not understand how Pfizer has discharged its burden of proof. This meeting did not promote the use of vutrisiran; it included mention of new data for vutrisiran along with data on other authorised and unauthorised products in a manner that was factual, balanced and non-promotional.

Medical background and context - Transthyretin Amyloidosis is a rare, multi-systemic and complex condition with limited UK prescribers

It is important to provide additional medical context on transthyretin amyloidosis ("**ATTR Amyloidosis**"). ATTR Amyloidosis is a rare, complex and underdiagnosed condition. There are two types of ATTR Amyloidosis: wild-type transthyretin amyloidosis ("**wildtype ATTR**") and hereditary transthyretin amyloidosis ("**hereditary ATTR**").

The most common form of ATTR Amyloidosis is wildtype ATTR and the majority of these patients present with cardiac manifestations. Whilst autonomic neuropathy is commonly seen in wildtype ATTR, **peripheral** neuropathy has not been well established in wildtype patients.

Hereditary ATTR Amyloidosis is considered a rarer and more complicated form of ATTR Amyloidosis. It is a more heterogeneous disease (presenting very differently in different people and with different variants) involving multiple body systems like the nerves (both peripheral and autonomic) and heart due to misfolded transthyretin protein deposits, leading to varied presentations including both neuropathy and cardiomyopathy. Due to the complex and unpredictable mix of presentations, patients with hereditary ATTR Amyloidosis are likely to be misdiagnosed, be sent from specialist to specialist and, once diagnosed, their symptoms are still not fully managed.

Hereditary ATTR Amyloidosis can present with misfolded TTR deposition in various tissues, such as in the Central Nervous System (CNS), kidneys or eyes. However, for current purposes we will focus on polyneuropathy and cardiomyopathy because these presentations are key with respect to the licensing of available treatments.

As the Panel noted in their decision, "*the multisystem presentation of amyloidosis was not in dispute between the parties*".

Diagnosis and management of ATTR Amyloidosis is limited in the UK to very few prescribers, however ongoing monitoring of patients is a shared responsibility between the expert centre and a patient's local cardiology and neurology teams

The [named specialist centre] was the only centre in the UK specialising in amyloidosis and at the time of the Alnylam meetings in 2024, was the sole NHS commissioned management and treatment prescribing centre in England for ATTR Amyloidosis. However, cardiologists and neurologists played important roles in the identification and ongoing monitoring of patients with ATTR Amyloidosis.

At the time of the Alnylam meetings, there were four treatment options, with differing indications, licensed and available in the UK for the management of ATTR Amyloidosis; specifically, tafamidis 61mg was licensed for the treatment of ATTR-CM, whilst inotersen, patisiran and vutrisiran were all licensed for the treatment of hereditary ATTR Amyloidosis with stages 1 or 2 polyneuropathy (hereditary ATTR-PN) which, as explained above, may also include cardiac manifestations.

Allegation 3 - Promotion of a medicine not in accordance with the terms of its marketing authorisation - ESC Alnylam sponsored Tutorial 2

Pfizer accepted that the authorised indication was clear

Pfizer agreed with Alnylam that hereditary ATTR Amyloidosis is a multisystem disease and patients with hereditary ATTR Amyloidosis with polyneuropathy may present with cardiac manifestations. This topic was the focus of the tutorial. Pfizer acknowledged that Alnylam have made the licensed indication for vutrisiran clear, stating "*The second tutorial session mentioned vutrisiran for the treatment of patients with hATTR-PN with mixed phenotype and cardiac manifestations.* ***Pfizer accepts that Alnylam made the licensed indication in hereditary ATTR polyneuropathy clear in the tutorial****…*".

Despite this clarity, Pfizer alleged, that they *"…remain concerned that ATTR-CM was discussed in this promotional tutorial, which is an off-label indication, given that cardiac manifestations were covered.*". Pfizer has not provided any substantive evidence on how and where vutrisiran was presented as an option for patients with ATTR-CM, despite attending the tutorial. In fact, Pfizer accepts that vutrisiran's indication was clearly communicated.

There was no off-label promotion

Alnylam did not promote to UK healthcare professionals ("**HCPs**") an unauthorised indication. Alnylam had no intention to give, and did not give, the impression that vutrisiran was a suitable treatment for ATTR-CM patients. The content of the presentation and discussion focused specifically on patients with hereditary ATTR-PN.

The material presented was carefully structured and designed to avoid any risk of promotion that was not in accordance with the terms of its marketing authorisation. In particular:

- The licensed indication for vutrisiran was displayed prominently and for a prolonged period at the start of the session and repeated multiple (4) times.

including on slides discussing cardiac biomarkers and clinical assessments in a cardiology clinic. The licensed indication was therefore made clear, as expressly agreed by Pfizer (see section above, “Pfizer accepted that the authorised indication was clear”).

- The development status of vutrisiran for ATTR-CM was explicitly stated, with clear references that it was still in development for this indication.

- Only two of the 54 slides presented included cardiac outcomes (LV thickness, global longitudinal strain, cardiac output and LV end-diastolic volume), observed in hereditary ATTR-PN patients during the HELIOS-A study and consistent with the SmPC. Cardiologists involved in the care of patients with hereditary ATTR-PN will need to understand the ways in which patients can be monitored, especially with regards to any cardiac manifestations, given the high propensity for cardiac manifestations in such patients as described earlier. The SmPC for vutrisiran at the time provided information on NT-proBNP and LV wall thickness. These are relevant endpoints for the cardiologist to consider in such hereditary ATTR-PN patients in the context of the licensed indication for vutrisiran. Any cardiac biomarker data shown for vutrisiran in the tutorial was secondary to the primary neurological outcomes seen in HELIOS-A. Importantly, the slides included statements that “Despite the observed values for NT-proBNP and LV wall thickness, a clinical benefit in regard to cardiomyopathy is yet to be confirmed.”

As mentioned below (see section “Medical education on cardiac manifestations in hereditary ATTR-PN is essential”), a third of hereditary ATTR-PN patients had cardiac involvement. Section 5.1 of the vutrisiran SmPC, describes the registration study population: “According to the New York Heart Association (NYHA) classification of heart failure, 9% of patients had class I and 35% had class II. Thirty-three percent (33%) of patients met pre-defined criteria for cardiac involvement (baseline LV wall thickness $\geq$ 13mm with no history of hypertension or aortic valve disease).” Thus a third of patients in the registration study that supported Alnylam’s hereditary ATTR-PN authorisation had cardiac disease, and as such cardiac involvement is a key part of the picture in hereditary ATTR-PN diagnosis. The description of Tutorial 2 provided in the speaker briefing makes clear that the objective of Tutorial 2 was to explore only those clinical manifestations of hATTR-PN patients that are relevant to a cardiologist assessing such patients, and how the cardiologist audience could consider treating those patients as part of the multidisciplinary team that reviews hereditary ATTR-PN patients. It is not promoting an unlicensed indication to talk to cardiologists about how to diagnose, assess and manage cardiac signs and symptoms in hereditary ATTR-PN. Rather, it is essential to ensure that cardiologists are cognisant of current thinking and best practice in managing this very rare condition. The ECG data, bone scans, cine-CMR images and other cardiac scans displayed within the case studies shared in Tutorial 2 were relevant and necessary to achieve this goal as these assessments would be carried out by cardiologists managing a hereditary ATTR-PN patient as part of a multidisciplinary team.

- The subjects of the case studies were both patients with hereditary ATTR-PN who had cardiac manifestations. These are real-world case studies of hereditary ATTR-PN patients who were assessed using the assessments discussed during the tutorial and this eventually led to key changes to optimise the management of their disease. There were no case studies of patients with ATTR-CM.

- Attendees were directed to prescribing information made available at the Alnylam Tutorials Registration Desk.

- The speaker briefing expressly instructed that “vutrisiran is not approved for the treatment of ATTR-cardiomyopathy (ATTR-CM), and therefore vutrisiran in the context of treating ATTR-CM, including information around the HELIOS-B trial results, should not be discussed at this meeting” and all responses to questions “should remain strictly on label” This instruction was strictly adhered to throughout.

- There were no independent complaints from any other attendees or third parties regarding the content or conduct of the tutorial.

- It is important to note that the Panel’s own finding of no breach under Clause 5.6 in this case for ‘Allegation 1’ confirms that the material was appropriately directed to a relevant audience - namely, HCPs, including cardiologists, whose clinical practice involves the management of hereditary ATTR-PN and its cardiac manifestations. This aligns with the context set out above, which demonstrates that the content of Tutorial 2 was both clinically appropriate and necessary for this audience, given the multisystem nature of hereditary ATTR and the recognised need for multidisciplinary care.

Based on the above, Alnylam is surprised by Pfizer’s concern that ATTR-CM was discussed in the promotional tutorial. Their staff members attended the tutorial and saw first-hand that the presentation and discussion was focused on hereditary ATTR Amyloidosis patients with hereditary ATTR-PN (the licensed indication) and additional cardiac manifestations, rather than ATTR-CM specifically. The heterogeneity of symptom presentation in hereditary ATTR-PN is well understood by Pfizer. To suggest that discussing cardiac manifestations equates to promotion in relation to ATTR-CM is disingenuous. As described in the medical background section, wildtype ATTR and hereditary ATTR present differently and patients with ATTR-CM are predominantly wildtype ATTR. Cardiologists with an interest in hereditary ATTR Amyloidosis patients with polyneuropathy, an ultra-rare condition, are likely to understand the distinction between ATTR-CM and hereditary ATTR-PN and understand that all of the discussion was specifically in the context of the hereditary ATTR-PN with cardiac manifestations.

So not only was the authorised indication clear, but the tutorial focused solely on patients with hereditary ATTR-PN (the authorised indication) with additional cardiac manifestations (as detailed in the SmPC).

For the reasons given above, Alnylam strongly disagrees with the Panel’s reasoning that repeated emphasis on cardiac manifestations, cardiac subpopulation analyses and

treatment-related cardiac endpoints created the impression that vutrisiran was being positioned as a treatment option primarily for patients with cardiac manifestations, regardless of whether the presented with a mixed phenotype or not. It is important that content is bespoke and relevant to the audience (a requirement of the ABPI Code). It is relevant for a tutorial on monitoring hATTR-PN patients in a cardiology clinic to have references to cardiac manifestations as such manifestations would be the focus of this specialist audience when reviewing hATTR-PN patients as part of the multi-disciplinary team.

The Panel took account of the 'broader context that Alnylam was due to make a regulatory submission for an indication related to ATTR-CM in the near future for vutrisiran'. At the time of the tutorial (and notwithstanding the fact that the tutorial makes no reference to the use of vutrisiran in ATTR-CM), Alnylam had not made any regulatory submission anywhere in the world and no decision had been made on when a regulatory submission would be made. The subject matter of this tutorial is one which is important for hereditary ATTR-PN patients and is a topic of medical education by Alnylam and other companies for a number of years prior to ESC 2024.

Medical education on cardiac manifestations in hereditary ATTR-PN is essential

At the time of the meeting, vutrisiran was indicated for hereditary ATTR-PN, which, as understood by the Panel in their decision, often presents as a mixed picture, including cardiac manifestations.

A significant proportion of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy as a result of the disease. This possibility is noted on Pfizer's website: "because amyloid fibrils can deposit in different parts of the body, including in the heart and nerves, some patients may present with mixed phenotype, namely, symptoms of both cardiomyopathy and polyneuropathy", alongside which Adams et al (2020) is cited. The presentation of cardiac manifestations in hereditary ATTR Amyloidosis patients with polyneuropathy (hereditary ATTR-PN) may present at different times and in different ways.

The diagram below shows the complexity of hereditary ATTR-PN. Depending on the type of gene mutation, certain hereditary ATTR-PN patients (those falling under the blue section in the diagram below) may have a more dominant presentation of cardiac manifestations. Management of such symptoms may be required by local cardiologists or specialist amyloidosis centres depending on the severity of symptoms. This highlights the importance of education on the various assessments available to correctly and promptly identify and manage the cardiac manifestations of hereditary ATTR-PN patients across the entire spectrum but particularly those hereditary ATTR-PN patients who may progress to severe cardiac features with time.

[Graphic showing genotype-phenotype correlation in ATTR amyloidosis]

A publication by Transthyretin Amyloidosis Outcomes Survey (THAOS - a Pfizer-supported registry): "noted that a significant portion of over 3,500 patients involved in the study on patients with ATTR Amyloidosis were classified as mixed phenotype ("approximately one-third of symptomatic patients… were classified at enrolment or follow-up as mixed phenotype").

Pfizer's own NICE submission for its NICE appraisal of tafamidis for treating ATTR amyloidosis with cardiomyopathy in 2024, provides information on the incidence of ATTR Amyloidosis and the ultra rare nature of hereditary ATTR Amyloidosis vs. wildtype ATTR Amyloidosis]:

[Graphic showing overview of ATTR population for wild-type ATTR vs hereditary ATTR]

The Panel noted that it did not have before it any evidence regarding the extent or prevalence of cardiologist involvement or prescribing in hereditary ATTR-PN with cardiac manifestations. To provide context, there is one single expert centre in England (the [named specialist centre]) who guided all prescribing decisions for ATTR Amyloidosis in the UK, including for hereditary ATTR-PN. However, cardiologists outside of this centre will review patients with hereditary ATTR-PN in their clinics and will monitor and manage with (non-disease modifying) therapies if cardiac manifestations present. It is therefore highly relevant and important to provide education for cardiologists on recognizing and managing hereditary ATTR-PN with cardiac manifestations. The assessments discussed in the tutorial are fully relevant for specialist cardiologists reviewing and monitoring a patient with hereditary ATTR-PN. Without these assessments being carried out by cardiologists, patients may not be optimally managed and their disease may progress.

Patients with hereditary ATTR Amyloidosis often move between different parts of the NHS without a clear route to diagnosis and disease management. Individuals can present for years with unexplained symptoms, seeing multiple specialists before the underlying condition is identified. Patients with genetic conditions, such as hereditary ATTR Amyloidosis, may undergo repeated investigations that rule out common causes without triggering referral to specialist genetic diagnostic centres. As a result, patients with this condition typically wait years to be diagnosed, by which time the condition has further developed and is then usually fatal within 4.7 years. As stated on Pfizer's website, "it is important to get an accurate diagnosis as soon as possible, because treatments may be more successful if started early."

No single doctor is responsible for coordination of these patients. Therefore, to improve patient outcomes, a co-ordinated multidisciplinary approach is needed, with each specialist managing the hereditary ATTR-PN patient within their expertise area. One of the biggest needs for patients with hereditary ATTR-PN is for it to be higher on the index of suspicion of cardiologists and for their cardiac manifestations to be managed promptly and correctly, which may include referral to specialist centres. Medical education of healthcare professionals on cardiac manifestations in hereditary ATTR-PN is therefore essential for patients.

Summary

In summary, the presentation at Tutorial 2 was made to guide cardiologists on what assessments to do if they see a hereditary ATTR-PN patient. Given the multi-systemic nature of the disease, it is vital for cardiologists to conduct these assessments to provide holistic management to this patient population otherwise patients may not be managed appropriately. The inclusion of the cardiac data in the case studies and

tutorial was therefore clinically appropriate and necessary. Not providing this education in this poorly understood disease area would be detrimental to patients.

Alnylam was very careful to frame the medical discussion of cardiac biomarkers, assessments and manifestations within the marketing authorisation of hereditary ATTR-PN, and that was entirely consistent with the SmPC for vutrisiran. Moreover, Pfizer accepted that the authorised indication was made clear.

For these reasons, it cannot be correct to conclude that the "overall impression created by the presentation" was misleading or that vutrisiran was being promoted outside its licensed indication. Alnylam took great care to ensure that its activities were fully in compliance with the Code to promote the authorised use of vutrisiran in patients with hereditary ATTR-PN with cardiac manifestations. Absent any actual evidence of off-label promotion there is no basis for a finding of breach of Clause 11.2 on the balance of probabilities."

Allegation 5: Potential promotional meeting where off-label information was presented

Provision of information on the unauthorised use of a medicine is not always promotional

The Panel in their ruling state "*the proactive provision of information by a pharmaceutical company about the unauthorised use of a medicine was very likely to be seen as promotion*." However, there are many instances where proactive provision of information by a pharmaceutical company about the unauthorised use of a medicine is not seen as promotion. For example, press releases routinely share results from clinical trials of unauthorised products or indications and similarly, stock market analysts and investors may attend presentations about financial results that include mention of pipeline developments, and health professionals may be involved in legitimate exchange during the development of a medicine.

The (now archived) 2016 PMCPA Guidance on LEMS, stated "*if a company is producing information on an as yet unlicensed indication for a product that has a marketing authorization, for example at a company symposium at a learned society's meeting, this must be a genuine legitimate exchange of medical and scientific information during the development of that medicine, involving debate which would enhance the current state of scientific knowledge*".

Therefore, the PMCPA guidance archived at the time of the meeting was clear that proactive provision of information about an unauthorised use of a medicine is allowed.

Moreover, in AUTH/3469/2/21 (Complainant v Takeda) "*the Panel noted the broad definition of promotion in the Code and that although the promotion of a medicine prior to the grant of its marketing authorisation was prohibited, the Code permitted companies to undertake certain activities with regard to unlicensed medicines and/or indications. The legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that this did not constitute promotion*."

The meeting was a legitimate exchange of medical and scientific information (LEMS)

The meeting was carefully designed and delivered as a non-promotional exchange of evidence-based highly scientific, medical and clinical information between expert HCPs specializing in the field of ATTR Amyloidosis. Alnylam disagrees that this meeting promoted vutrisiran for an unlicensed indication. In fact, Alnylam took great care not to breach Clause 11.2.

The purpose of this meeting was to engage experts in this disease area to learn and challenge one another on the current evidence base and models of care. The discussions were designed to:

- enhance the scientific and medical community's understanding of ATTR Amyloidosis; and
- provide Alnylam with insights to feed into its strategy and development programme.

Given the underserved patient population for this rare, complex disease, there is considerable need for and value in medical debate in this disease area, such as discussion on practical challenges and models of care. In rare and complex diseases such as ATTR amyloidosis, practical challenges and models of care are precisely the areas where the exchange of new and pivotal data can enhance current medical and scientific knowledge. This meeting served as an important forum to exchange both scientific information (led predominantly by debate between global experts (including the Chief Innovation Officer, R&D at Alnylam) in the plenary session) and information on the medical side (particularly during the model of care discussions during the breakout sessions).

Faculty and Attendee perception of the meeting was scientific and medical, not promotional

Alnylam reached out to two UK clinical experts that participated in the meeting, a member of the faculty and an attendee (noting that none of the UK HCPs attending were prescribers in ATTR Amyloidosis at the time of the meeting, but were critical in development and implementation of the referral, diagnosis and monitoring pathways). It is clear from their statements that this meeting was not promotional:

Faculty member statement

"Dear [Alnylam],

Thank you for reaching out. I was a faculty participant at the ESC meeting on [date] August and can comment only in relation to my involvement.

From my perspective, the session functioned as a scientific exchange. The discussion focused on the evolving evidence base in ATTR-CM, recent data from different studies, and practical considerations in patient management within a rare disease setting.

The faculty selected and shaped the content relevant to this scientific discussion, including referencing HELIOS-B because it was newly available and provided important context for the broader topic being addressed. The aim was to support an informed and balanced conversation for attendees, who may not have been familiar with newer data. Please let me know if any further clarification about my role is helpful. Kind regards,

[Healthcare Professional]

Attendee statement

RE: International Deep Dive into ATTR Amyloidosis - Alnylam Event, ESC London [date] August 2024.

I was an invited attendee at the above ESC meeting on [date] August 2024 and provided [sic] comment only in relation to my own involvement at that event.

I found the meeting a very useful opportunity to meet and network with other like-minded clinicians to discuss the evolving care pathways for patients with amyloidosis, identifying commonality amongst challenges and needs.

The main focus of that meeting were the more informal round table discussions that took place in the breakout group discussions. In particular, I found the round table discussions on the existing care pathways and unmet needs helpful, especially in light of our imminent plans to submit an application for [CONFIDENTIAL - ATTENDEE'S HOSPITAL] to be a formally commissioned centre through NHS Highly Specialised Commissioning; the formal tendering process was initiated by NHS England on 24th September 2024 for "Provision of Amyloidosis Networked Model of Care". The discussions on the evolving evidence base also helped me to identify the research needs and gaps that I have since been able to take forward in our own research.

It is notable that at the time of this meeting, the [CONFIDENTIAL - ATTENDEE'S AMYLOIDOSIS SERVICE] was not formally commissioned as a network centre and we did not, therefore, have any prescribing rights; indeed, only the [named specialist centre], [named hospital] had the ability to prescribe disease modifying treatments for ATTR in England on the NHS at the time of this event. [CONFIDENTIAL INFORMATION REMOVED]

In conclusion, in my opinion, this meeting was primarily aimed at scientific exchange, and it is contradictory to assert that the event was for designed for promotional purposes.

Yours sincerely, [Healthcare Professional]

Alnylam acted diligently in accordance with the available guidance at the time of the event

At the time of the ESC congress ([date]August 2024), the previous guidance on Clause 3 had been archived (the 2016 PMCPA Guidance on Clause 3), there was little in terms of supplementary information in the 2021 version of the Code, and there were only a handful of published Code cases relating to LEMS activity. Alnylam carefully

considered the applicable rules, archived guidance and cases, and used its best efforts to comply with them through its compliance processes.

Since the congress, a new version of the Code (2024) and 2025 PMCPA guidance on Clauses 3.1 and 11 have been published, which further define risks and identify additional factors to take into consideration. However, that did not exist or apply at the relevant time of the Alnylam meeting. Furthermore, Alnylam is not a member of the ABPI and was not involved in the planning or development of the updated Code or new guidance, so it had no way of knowing what would be in it. Accordingly, Alnylam's activities should not be judged against the current rules and guidance, but against the rules and guidance that applied as of August 2024.

The Panel commented that *"it would be more difficult for a company to establish that a medicine with a marketing authorisation is 'in development' in relation to an unlicensed indication being discussed, particularly if the licensed medicine was available in a dosage form that could be used for the unlicensed indication"*, however guidance to this effect was only introduced into the 2025 updated PMCPA guidance on Clauses 3.1 and 11, released in September 2025 and not included in the archived Clause 3 guidance, nor available for consideration at the time of the Alnylam meeting. A relevant case at the time was AUTH/2782/7/15 (AbbVie v Bristol-Myers Squibb) the product was already in use for another indication while Phase III studies for PsA were ongoing. In that case the medicine was considered to be 'in development'.

Vutrisiran was still in development at the time; no regulatory submissions had been made anywhere in the world. A second Alnylam investigational product was in development for ATTR Amyloidosis at the time

From Alnylam's perspective, the information obtained from the meeting was intended to inform Alnylam's continuing development of vutrisiran and another Alnylam investigational product in the same therapy area, nucresiran, by increasing Alnylam's understanding of the needs of clinicians across multiple jurisdictions in relation to diagnosis, management and treatment of patients with ATTR Amyloidosis, so as to inform and shape: (a) research, project plans, clinical study design, and further analysis of data from prior clinical trials; (b) models of care, unmet needs and future directions for ATTR Amyloidosis management and research; and (c) future reimbursement/approval discussions.

From the attendees' perspective, the meeting provided a unique opportunity for meaningful scientific debate and the sharing of clinical experience in a rare disease area where such opportunities are extremely limited.

There are several precedents which ought to inform this appeal, recognizing that each is individual and assessed on its own merits.

As expressed by the Panel in AUTH/3250/10/19 (Lilly/Director v Janssen), a case involving a Company sponsored session at a learned Society meeting, including discussion on unlicensed data for an existing licensed product, "*the Panel considered that it was not necessarily unacceptable for such products to be the subject of legitimate exchange of scientific and medical information in relation to its unlicensed use but companies should be especially cautious when so doing and would have to*

establish that the medicine was in development in relation to the subject matter of the legitimate exchange". This was also the case in AUTH/2781/7/15 (AbbVie v Bristol-Myers Squibb), where no breach of Clause 3.2 was ruled.

In AUTH/2651/11/13 (Health Professional v Merck Sharp & Dohme), an exhibition stand that contained information relating to pipeline products, including one which had been submitted to the Regulators for authorisation, was found not in breach of pre-licence promotion. Vintafolide had been submitted to the European Medicines Agency (EMA) for conditional approval for the treatment of platinum-resistant ovarian cancer and regulatory approval, if granted, was estimated to be six to nine months away. Notably, even though the Panel did not consider the stand in that case constituted legitimate exchange, they did not believe it constituted pre-licence promotion and ruled no breach.

The timing of regulatory submission has also been considered in other cases where a breach of the Code was found but in each of those the regulatory submission was further progressed than in Alnylam's case: in AUTH/2868/8/16 (Janssen v Sanofi Genzyme) there was no MA but a licence had been applied for in the US, and an EU licence application was about to be made; in AUTH/2978/9/17 (Anonymous consultant dermatologist v Janssen) the product was unlicensed but applications had been made for MA. In contrast to these cases, Alnylam had not made any regulatory submission anywhere in the world.

In light of these precedents there are several relevant factors which Alnylam wish to highlight in assessment of this case:

- Regulatory submission has historically been taken as a critical timepoint when determining if something is pre-licence promotion or not. The Alnylam meeting was planned before the HELIOS-B trial results for vutrisiran were known, and it took place before Alnylam had decided any timeline to make regulatory submissions anywhere in the world, in advance of the relevant submissions even being compiled. It was almost another year (July 2025) before the licence was granted by the MHRA. Thus, this meeting was not in the 'pre-licence' period as would be commonly understood by HCPs.

- Moreover, Alnylam has a pipeline of products in development. At the time of the meeting, nucresiran was not even in late-stage clinical trials (protocols for the Phase III clinical trials for ATTR Amyloidosis with Cardiomyopathy and hereditary ATTR Amyloidosis with Polyneuropathy were developed in late 2025). There was sufficient time for Alnylam to take away relevant insights from the meeting for the trial designs for this investigational product.

- Alnylam did take learnings from the meeting and these were incorporated into the development of both nucresiran and vutrisiran. These insights from the meeting are commercially sensitive but, by way of example, included trial patient population, dosing and administration, and comparator therapies.

- Importantly, in the context of a new indication for a product in a rare therapy area and a disparate model of care globally, it is not only trial design and

regulatory submission that are relevant during development. It is also paramount that the model of care is considered, to understand how a new therapy could be integrated into the clinical pathway and to ensure that patient access and outcomes are optimised. The learnings from the meeting were relevant to future development activities with respect to vutrisiran.

- There was no compassionate use or named patient programme for the treatment of ATTR Amyloidosis with Cardiomyopathy with vutrisiran.

- Any risk of off-label promotion was countered and mitigated by the procedures and safeguards put in place by Alnylam at the meeting. Alnylam took particular care to ensure that the meeting was not promotional in nature or intent and involved meaningful two-way exchange of scientific and medical information. As discussed further below, the time was used to have valid and cogent discussion on numerous aspects of ATTR-CM, with the aim of improving patient experience and outcomes - vital in furthering understanding of the condition and how best to help this underserved population. All materials made very clear, repeatedly, that vutrisiran was "*an investigational RNAi therapeutic in development for the treatment of ATTR Amyloidosis with cardiomyopathy (ATTR-CM)*", so that its licensing status was obvious to the audience. There is no evidence that any delegates felt they had been promoted to or misled, and Pfizer provided no such evidence in its complaint.

Alnylam's senior leaders in R&D and clinical development were in attendance at the meeting to take away learnings to incorporate into Alnylam's research and development activities.

There was meaningful exchange of information

The meeting entitled "International Deep Dive into ATTR Amyloidosis" was specifically designed to facilitate highly scientific, meaningful two-way debate amongst an international audience of expert HCPs and with Alnylam personnel.

Attendees – expertise and active discussion

In the context of rare diseases, it is particularly important to ensure that expertise from around the world can be shared, challenged, and discussed. The meeting provided a valuable opportunity to examine how ATTR Amyloidosis is approached in different countries, to debate, and to identify unmet needs, as well as to consider the evolving treatment landscape.

Attendees were specifically selected for their expertise in ATTR Amyloidosis diagnosis and management. Attendees were divided into small, focused country groups to maximise meaningful participation and exchange. This targeted approach ensured that discussions were informed by those with direct experience in diagnosing and managing ATTR Amyloidosis in their own country.

It was made clear to all attendees that their active contribution was expected. The "save the date" calendar invites stated: "*Join us for an evening of sharing insights,*

engaging in scientific debate, and fostering discussion with peers, with the aim of advancing our understanding of the field and shaping the future of ATTR amyloidosis." The "save the date" PDF further emphasised that the faculty would initiate conversation with a fireside chat on key topics, with active participation of attendees in an interactive debate and Q&A session, followed by deeper discussions in country groups.

The meeting's structure was deliberately designed to maximise meaningful, two-way scientific exchange

The event was carefully structured to ensure dedicated, meaningful and interactive discussion and debate by all delegates throughout, including faculty panel discussion, audience polling, Q&A sessions and interactive country-level workshops, with the intention that Alnylam could use the insights from these discussions to inform its development programme and regulatory submissions. Alnylam staff and faculty in attendance at the meeting were briefed that discussion and exchange of information was essential.

The structure and content of the meeting prioritised genuine exchange and participation. A 65-minute faculty- led debate, 10-minute Q&A and 45 minutes of breakout workshops meant that nearly 50% of the total meeting time was specifically dedicated to hearing the concerns, questions, and challenges of the delegates.

Faculty-led debate: The 65-minute faculty-led session included active debate on stage, with key opinion leaders and faculty members discussing scientific and medical topics relevant to ATTR Amyloidosis. This was not a one-way presentation but involved genuine discussion and challenge among experts. Speakers were instructed to lead the conversation by asking each other and the attendees topic-related questions (with some pre-prepared questions written in advance to keep the discussion flowing had that been required).

Polling and Q&A: Throughout the presentations, all delegates were able to electronically answer polling questions and submit questions to be answered in a dedicated Q&A segment, allowing attendees to interact and contribute to the debate. This facilitated two-way communication and ensured that the session was not simply a dissemination of information. As recognised by the Panel in Case AUTH/2781/3/15 (AbbVie v Bristol-Myers Squibb), such interactive elements support the legitimate exchange of scientific information. There was also the opportunity for attendees to raise questions via an open mic during the plenary session.

Breakout Sessions

- As well as for collecting insights, the breakout sessions were designed to stimulate exchange between attendees, particularly relevant in the context of a rare disease where sharing clinical experience and perspectives is vital.
- Attendees were divided into small country-level groups of 8 to 10 HCPs to encourage meaningful participation and exchange of views.
- Medical team members in the breakout sessions were given clear instructions: their role was to guide, monitor and manage the discussion, ensuring all topics were covered. They were also present to collate feedback from the discussions (including in order to incorporate into Alnylam's strategy). The primary reason for collating feedback was to share back to the wider group in

the 15-minute feedback session, highlighting country similarities and differences in needs and challenges. The notes also allowed Alnylam to review and reflect on the discussions internally, but the immediate purpose was to facilitate group learning and exchange.

- It should be noted that the roundtable discussions were not carried out over a three-course meal (see page 17 of the Panel's ruling). Cold starters were already on the table when attendees were seated and were eaten during the plenary session. The roundtable discussions themselves took place over the main course, and the faculty presented back country-level findings during dessert.

This structure directly addressed the concern raised in the Panel Ruling about lack of engagement and insufficient opportunity for meaningful debate due to the scale of the event. The size of the meeting (70 delegates) was not prohibitive to meaningful exchange. This is comparable to popular oral presentations during Learned Society meetings, where legitimate scientific exchange routinely occurs. In addition, the structure and tools adopted allowed delegates to contribute both digitally (during Q&A) and in person (in small group workshop discussions).

We refer the Panel to the AUTH/2781/7/15 (AbbVie v Bristol-Myers Squibb) where no breach was ruled despite 158 attendees being present (over double the attendees of the LEMS meeting). In that case, the in-person symposium at the 2015 BSR comprised three presentations (total 60 minutes) and a Q&A session (30 minutes). Throughout the presentations, delegates could use mobile devices to send comments or questions directly to the faculty and speakers. This demonstrates that a meeting of significant size, when structured to facilitate interactive participation and genuine scientific exchange, can be compliant with the Code.

In contrast, in AUTH/2978/9/17 (Anonymous consultant dermatologist v Janssen), the meeting format was found to be less conducive to meaningful exchange. Although there were approximately 70 attendees, the symposium included a part pre-recorded presentation, and the speaker for that segment was unavailable to answer questions at the meeting. Questions could only be handed in to the speaker or chairman by card, or asked directly from the floor, which the Appeal Board considered contributed to a low level of questions and limited engagement. The Panel concluded that the company should have done more to engage the audience and stimulate debate to enable two-way discussion and an exchange of medical and scientific information (in contrast to Alnylam's meeting). The lack of practical mechanisms to facilitate interactive participation was a key factor in the finding of a breach.

Alnylam's LEMS meeting exceeded the standards and duration of engagement seen in the BMS case, thereby enabling a more comprehensive and meaningful debate, distinct from the less interactive Janssen case.

Contingency arrangements

The meeting included robust contingency arrangements. For the faculty-led session, some pre-prepared questions were available for use in case there were few or no questions from the audience; in practice, these were not needed as there was active engagement and sufficient questions from attendees. Additionally, break-out session

discussion topics were carefully designed to assist and stimulate exchange, and these sessions were led by country-level Medical Directors who facilitated the discussions and ensured that all participants had the opportunity to contribute. This approach stands in contrast to the Janssen case (AUTH/2978/9/17), where the meeting format included two presentations (total 30 minutes, with the first being pre-recorded) and a Q&A session of only 10 minutes. The Appeal Board in that case noted that more should have been done to engage the audience and stimulate debate.

The meeting was scientific and medical in nature

As mentioned above, given the underserved patient population, there is considerable need for and value in medical debate in this disease area, such as discussion on practical challenges and models of care. This meeting served as an important forum to exchange both scientific information and information on the medical side. Both are equally important: whilst the development and regulatory submission of a drug needs to be optimised to generate relevant and sound outcomes, the model of care needs to be established and optimised for a rare condition such as ATTR Amyloidosis. This is critical for improving the diagnosis and management of the condition and to ensure the appropriate utilisation of any new therapy. In the UK there are currently around 250 patients diagnosed with ATTR-CM. For the UK country table, the ability to discuss ways in which care is evolving and to identify the challenges and needs was relevant and timely, particularly in light of the ongoing NHS England consultation to build a network for amyloidosis care.

The meeting provided a platform for scientific debate and exchange, consistent with the requirements for a legitimate exchange under the Code. The faculty panel session was designed by a faculty comprising three leading experts from the [named specialist centre], one expert from France and one expert from Spain along with a senior member of the Alnylam R&D team. They addressed topics which are key to scientific understanding and as a result development of therapies for ATTR amyloidosis. For example, session one addressed the evolution of knowledge and understanding of ATTR Amyloidosis and included an overview of the history of innovations in the field of ATTR Amyloidosis that have facilitated better understanding of the disease, advancements in diagnosis, development of therapies (not limited to Alnylam therapies) and improvements in patient care.

The HELIOS-B data presented at the meeting was newsworthy and constituted new and pivotal information its selection for the ESC congress hotline session and publication in The New England Journal of Medicine should not be used as a reason to find the meeting in breach but taken as an indication of the scientific importance and medical relevance of the findings. It was the faculty themselves who requested its inclusion as a separate slide. Presenting such data at the meeting provided attendees with access to the latest evidence. Importantly, the presentation of HELIOS-B data at the meeting was not disproportionately emphasised – see section below ("*There was no promotion of vutrisiran with HELIOS-B data"*) – and other clinical trials (APOLLO-B, ATTR-ACT, ATTRibute-CM, CARDIO-TTRansform) and treatment options (both available and in development, including non-disease modifying therapies) were also discussed.

This approach aligns with AUTH/2781/7/15 (AbbVie v Bristol-Myers Squibb) where a meeting agenda included presentations defining the “at-risk” individual, as well as on disease biomarkers and clinical trials in an area with no approved products. In that case, the Panel concluded that the meeting encouraged new ways of thinking and did not promote a licensed product for an unauthorised indication; accordingly, the company was found not in breach. The structure and content of the Alnylam meeting similarly prioritised scientific exchange and education, rather than product promotion, and should be viewed in this context.

The Panel’s ruling does not acknowledge that clinical debate is also relevant in the satisfaction of the LEMS criteria. Clinical debate was conducted both during the faculty panel sessions (e.g. “Navigating the diagnostic challenges and multisystemic nature of ATTR amyloidosis”) and in the breakout sessions (e.g. “Does the model of care in your region/country work well for patients with ATTR amyloidosis? Would this model of care work in the future? What changes would help improve patient care?”).

In rare and complex diseases such as ATTR, practical challenges and models of care are precisely the areas where the exchange of new and pivotal data can enhance current medical and scientific knowledge. This is a new therapy area, where the model of care differs between countries and there is no clear patient pathway.

It is important to clarify that the LEMS meeting was a disease-led session, rather than medicine-led, discussion. The meeting’s broader remit was intentional: it provided a forum to understand the unmet patient needs in ATTR Amyloidosis, a rare and complex condition, and to enhance the overall scientific and medical understanding of the disease. This approach ensured that ongoing and future development efforts would be informed by real-world clinical challenges and would target the most relevant endpoints for patients. While part of the meeting addressed the evolving treatment landscape - including investigational and approved therapies - this was delivered in a way that enabled meaningful participation by all delegates, with the aim of advancing scientific discussion and improving patient care across the entire patient journey. The meeting did not focus on Alnylam’s medicine in development for ATTR-CM, nor did it promote vutrisiran in a manner inconsistent with its licensed indication. Instead, the content was balanced, fair, and centred on understanding the management of ATTR Amyloidosis as a whole.

The Panel commented that “*the focus was primarily on practical challenges, models of care and future optimisation of ATTR management. In this regard, the Panel questioned Alnylam’s submission that the meeting sought to inform future research, and queried whether the sessions, in context, constituted scientific debate about the development of a medicine.*” However, such discussion and debate is not precluded by ABPI guidance and understanding the challenges and needs of the real world is paramount in ensuring clinical trials are designed to collectively achieve the true needs of patients and the clinicians treating them. The learnings from this session were able to guide Alnylam’s development in ATTR Amyloidosis as previously stated, e.g. in identifying the right patient populations, practicalities in dosing and administration and the right comparator treatments.

There was no promotion of vutrisiran with HELIOS-B data

As the Panel noted, LEMS during the development of a medicine is not prohibited, provided that such information or activity does not constitute promotion.

In this regard, and contrary to the Panel's ruling, this meeting was not product-focused but disease-focused (see above), and the discussions were designed to enhance the scientific and medical community's understanding of ATTR Amyloidosis and provide Alnylam with insights to feed into its strategy and development programme.

It is important to recognise that all HCPs invited were experts in amyloidosis and would have been knowledgeable in the existing data sets. Three of the faculty members at the relevant meeting were from the [named specialist centre], none of the UK HCPs invited or attending were prescribers in ATTR Amyloidosis. The meeting was structured to provide a balanced discussion of the evolving treatment landscape, including other clinical trials and therapies, and not to focus disproportionately on HELIOS-B. The slide which solely presented HELIOS-B was included at the specific request of the faculty, because the HELIOS-B study had only just reported the day before. It was therefore important to dedicate time to ensure HCPs were brought up-to-speed with the latest data as part of the scientific exchange so that they were able to have a meaningful debate in the context of the broader treatment landscape. In addition, the content was simply a scientific presentation of the HELIOS-B data, in the same form as presented at ESC itself. There was no commercial branding. The slide was designed solely to inform attendees of the new data, not to persuade or influence. Given this context, the inclusion of a single slide on HELIOS-B does not represent a disproportionate focus, but is necessary to ensure a balanced and informed discussion.

Furthermore, the presentation of HELIOS-B data was contextualised alongside other clinical trials (APOLLO-B (published 2023), ATTR-ACT (published 2019), ATTRibute-CM (published 2024), CARDIO-TTRansform (ongoing)) in the "evolving treatment landscape and patient management strategies" segment of the panel segment of the session. As these studies were either published some time ago (and so audience members would be familiar with them) or are still ongoing, they did not require a dedicated slide.

In summary, only a small proportion of the faculty session was devoted to HELIOS-B and vutrisiran. Only 4 slides in the 40-slide, one-hour long, discussion slide-deck addressed HELIOS-B. It was made clear on a slide included early in the plenary (slide 5), prior to any discussion, that HELIOS-B had only just been published with a clear and prominent statement that "*Vutrisiran is an investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis with cardiomyopathy (ATTR-CM*)", so it was clear to attendees that vutrisiran was in development for ATTR-CM and not a treatment option.

The Panel suggested there was proactive provision of information by Alnylam about the unauthorised use of a medicine. However:

- The discussion was only focused on legitimate scientific and medical exchange during the development of a medicine, not promotion of unauthorised use.
- The advertising of the meeting was not displayed at any promotional stand nor provided to congress attendees; all aspects of the meeting's advertising were

non-promotional. Invitations, such as the “save the date” calendar invites and PDFs, were shared with attendees in advance of the ESC Congress (and prior to the results being publicly available for the HELIOS-B study) by members of the Alnylam Medical Affairs team and explicitly stated the meeting’s purpose as scientific debate and discussion with the aim of advancing understanding of the field and shaping the future of ATTR amyloidosis, and emphasised interactive participation and exchange among experts. This approach ensured that the meeting was clearly distinguished from any promotional activity and that attendees understood the non-promotional nature of the event.

- The meeting materials and presentations made it absolutely clear that vutrisiran was not authorised for ATTR-CM and included the following disclaimers:

- The opening slide of the meeting included the following text:

  “Note: Patisiran does not have marketing authorization for the treatment of ATTR-CM. Vutrisiran is in development for treating ATTR-CM. Patisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hereditary ATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. Vutrisiran is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hereditary ATTR amyloidosis*) in adult patients with stage 1 or stage 2 polyneuropathy.*”

- The slide referenced in the complaint, which showed the HELIOS-B publication, also included a bold boxed statement:

  “*Vutrisiran is an investigational RNAi therapeutic in development for the treatment of ATTR Amyloidosis with cardiomyopathy (ATTR-CM).*”

  This approach is comparable to the AbbVie v Bristol-Myers Squibb case (AUTH/2781/7/15), where, although one slide was headed ‘Why should we try abatacept?’, the Panel noted that it was possible the audience might interpret this as a prompt to try abatacept for disease prevention. However, it was also clearly stated on another slide that the APIPPRA study was now recruiting across the UK and the Netherlands, making the context and status of the medicine clear to the audience.

- The materials presented had a scientific non-promotional appearance.

- Clear briefings were given to all Alnylam attendees regarding their roles and conduct, including the absolute need to avoid promotion.

- Senior Medical and Compliance personnel were involved in all discussions relating to the content and arrangements for the meeting.

The Board will notice that Pfizer provided very little in the way of evidence to support its allegation that attendees were promoted to at the meeting. As outlined in the Introduction to the PMCPA Constitution and Procedure, the complainant bears the burden of proving their complaint on the balance of probabilities. However, Pfizer has provided nothing substantive - only supposition and postulative argument. For

example, Pfizer stated it was “questionable” whether vutrisiran could be considered an investigational molecule, “questioned” whether each delegate had a meaningful opportunity to contribute, but did not provide any evidence that they had not, and had “the impression” that the workshops negated the validity of the scientific discussion. Pfizer was “unable to comment” on the fairness or balance of the presentations as they had not seen them and merely speculated that it was “highly likely” there would be heavy weighting towards Alnylam’s product. As the Panel itself noted, Pfizer “had a number of concerns” and proceeded to list these unfounded questions. Only one (non-promotional HELIOS-B) slide from the presentation was provided by Pfizer. None of this amounts to evidence of promotion prior to licence; rather, it reflects a speculative complaint from a competitor without substantiation.

Summary

In summary, this meeting was a LEMS which served as an important forum for the discussion of ATTR amyloidosis, a rare and complex disease with an underserved patient population, helping Alnylam in the development of its medicines. It was carefully designed and delivered as a non-promotional legitimate exchange of evidence-based scientific, medical and clinical information between Alnylam and expert HCPs specialising in the field of ATTR Amyloidosis. Witness statements from the faculty and an attending HCP confirm that it was also perceived as a LEMS and highly valued as such. There was limited PMCPA guidance at the time (the 2016 PMCPA Guidance on Clause 3 had been archived), Alnylam carefully considered the available and applicable rules, guidance and cases, and used its best efforts to comply with them through its compliance processes. The structure and content of the meeting achieved meaningful two-way scientific and medical exchange, with faculty-led debate (including the Chief Innovation Officer in Research and Development at Alnylam), interactive polling, Q&A and breakout sessions (along with contingency arrangements to ensure debate), with the intention that Alnylam could use the insights from these discussions to inform its development programme and regulatory submissions, while enhancing the scientific and medical community’s understanding of ATTR Amyloidosis. The limited mention of HELIOS-B data included by the faculty was necessary because it had been released only the day before and it was important to ensure HCPs were brought up-to-speed with the latest data as part of the scientific exchange so that they were able to have a meaningful, balanced and informed debate in the context of the broader treatment landscape. No regulatory submission for vutrisiran had been filed anywhere in the world for ATTR-CM, while nucresiran was not even in late-stage trials. Alnylam was careful to display prominent statements that vutrisiran was still in development for the treatment of ATTR-CM and through briefings and content Alnylam ensured there was no promotion at this meeting. Pfizer has provided no proof to the contrary but instead has made nothing but unsubstantiated allegations when it was not even in attendance. Accordingly, we do not see any basis for a finding of breach of Clause 11.2.

Allegations 7-8: High standards and confidence in the industry

Alnylam notes that the Panel determined that it would solely rule on Clauses 5.1 and 2 in relation to the overall circumstances of the meeting, although in practice it also took into account its ruling on Tutorial 2. It follows that if the Board rules that there was no

breach of Clause 11.2 at the LEMS meeting or Tutorial 2, there was no breach of Clauses 5.1 or 2.

We wish to emphasise that the LEMS meeting was held in the context of a rare, complex, underdiagnosed, and underserved disease area, with significant unmet patient need and a lack of comprehensive guidelines. The focus was on advancing scientific and medical understanding to improve patient outcomes, not on promoting a particular product.

Alnylam's intent was clear throughout, as demonstrated by the detailed briefings and guidance provided to all staff, faculty and facilitators. The LEMS meeting instructions emphasised the non-promotional, disease-led nature of the meeting, the need for balanced and fair scientific exchange, and the importance of compliance with the Code.

Alnylam assures the Board that it is committed to compliance and followed its robust policies, procedures, and internal standards to ensure that all activities are conducted in accordance with the ABPI Code and relevant guidance. This includes comprehensive training for all staff, regular review of materials and meetings by compliance and medical teams, and a culture of transparency and accountability. Alnylam undertook a thorough review of all available cases, the Code and guidance in force at the time. For the reasons given in this response, Alnylam remains of the view that its activities were fully in compliance.

If, notwithstanding the above, a breach is found, Alnylam submits that a ruling under Clause 2 or Clause 5.1 would not be appropriate. The company's intention was to ensure discussion of this rare and underserved disease to ultimately help patient care and outcomes. Both the meetings were designed to support best practice: the promotional meeting (Tutorial 2) provided clear medical education for specialists managing hereditary ATTR-PN patients, whilst the non-promotional LEMS meeting provided a forum for discussion and debate by experts who have limited opportunity to focus on this rare condition.

Alnylam has not brought discredit upon or reduced confidence in the pharmaceutical industry. Alnylam demonstrated that the education on this complex disease provided during the tutorial was beneficial for clinicians and the legitimate exchange advanced scientific and medical understanding, each with the ultimate aim of improving patient outcomes. In developing and delivering these activities, Alnylam further demonstrated they did fully consider and apply the guidance in place at the time, ABPI Code and relevant case precedent."

RESPONSE FROM PFIZER

Pfizer's written basis for appealing is reproduced below, with some typographical errors corrected:

> "Further to our letter dated 18 December 2024, Pfizer thanks the Panel for their careful consideration of the case and agrees with the rulings given, which were breaches of Clauses 2, 5.1 and 11.2 (x 2). Given the overwhelming evidence contained in the Alnylam enclosures pack and a social media post included in our initial complaint, Pfizer believes strongly that the Panel rulings should be upheld by the Appeal Board.

To reiterate the context of the allegations, the top line results of the Alnylam sponsored HELIOS-B phase 3 study were communicated as part of the main ESC scientific programme at a late breaker Hot Line session as well as at an Alnylam a press conference. The HELIOS-B study evaluated the efficacy and safety of vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM). Vutrisiran was at the time not indicated for the treatment of ATTR-CM but did have an indication for 'the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy. Alnylam confirmed that the regulatory submissions to FDA and EMA to gain an indication for patients with ATTR-CM were made approximately 6 weeks after ESC congress 2024.

Please find below Pfizer responses to Alnylam's Appeal letter, dated 6 February 2026, focussing only on the aspects of our original complaint which were ruled in breach by the Panel.

Allegation 3, Tutorial 2: Expert Exchange: Treating hATTR Polyneuropathy Patients with a Mixed Phenotype (Polyneuropathy and Cardiomyopathy)

Panel ruling: Vutrisiran had been promoted in a manner that was inconsistent with the terms of its marketing authorisation, a breach of Clause 11.2

Alnylam held a promotional tutorial at ESC congress 2024 where vutrisiran for the treatment of patients with hATTR-PN with mixed phenotype was discussed. Pfizer maintains that the overall perception of vutrisiran during this tutorial was misleading and was designed to promote the use of vutrisiran in ATTR-CM, which was inconsistent with the terms of its marketing authorisation.

Alnylam enclosures document, 'Redacted Tutorial 2 slides.pdf', depicts 3 patient case studies which were presented by the facilitators during the promotional tutorial. All 3 cases overwhelmingly focussed on the cardiac aspects of the disease, rather than providing a balanced view of both the cardiac and neurological manifestations. For example, in the first patient case study, Slide 15 and 16 are entitled 'Evaluation of a patient with hATTR-PN mixed phenotype (with cardiac manifestations ' and on slide 15 there is a mention of a polyneuropathy assessment but the rest of the case study discussion is then dedicated entirely to the cardiac investigations (slide 17 – ECG tracings, slide 19 – bone scan with cardiac uptake, slide 21, 23, 25 and 26 discuss cardiac MRI findings). The other 2 case studies were also presented in a similar manner.

Additionally, Slide 34 was entitled 'Vutrisiran showed benefits in exploratory measures of cardiac stress vs external placebo at Month 18 in patients with hATTR-PN'. Thereby making a claim about the cardiac benefits of vutrisiran based on an exploratory analysis in the HELIOS-A trial and promoting an off-label indication.

Pfizer acknowledges that hereditary ATTR may present with mixed polyneuropathy and cardiomyopathy requiring multidisciplinary care; however, this does not justify promotion beyond the licensed indication. Whilst Pfizer noted that the licenced indication of vutrisiran was included on some of the tutorial slides, it appeared in small print and only in the footnotes. The repeated emphasis on cardiac manifestations, subgroup analyses and cardiac endpoints throughout the presentation was not merely contextual but

created a misleading impression that vutrisiran was suitable for patients with ATTR-CM, which was inconsistent with the licenced indication at the time. Additionally, with the proximity of planned regulatory submissions for an ATTR-CM indication, just six weeks after the ESC conference, there was a heightened risk that the promotional tutorial would be perceived as pre-positioning vutrisiran for ATTR-CM, prior to being granted a marketing authorisation for this indication.

Through this activity at ESC 2024, vutrisiran was promoted for an indication which was not covered by its marketing authorisation at the time. Given the clear evidence presented above, Pfizer believe strongly that the Panel ruling of a breach of Clause 11.2 should be upheld by the Appeal Board.

Allegation 5: Potential promotional meeting where off-label information was presented

Panel ruling: Vutrisiran had been promoted for an unlicenced indication at the time of the complaint, a breach of Clause 11.2

Context

During the ESC congress 2024, Pfizer was made aware of an Alnylam organised meeting on the [date] August 2024, via a social media post which showed the HELIOS-B data being presented on a screen at the meeting. The post provides direct contemporaneous evidence that HELIOS-B featured at the event.

During intercompany dialogue, Alnylam maintained that the event was a legitimate exchange of medical and scientific information (LEMS) meeting.

Pfizer maintains its allegation that the arrangements of this meeting did not meet the criteria of a LEMS but instead, it was a pre-licence/off-label promotional activity in relation to vutrisiran for ATTR-CM, and the associated dissemination of the HELIOS-B trial results.

Code definitions

The definition of ‘promotion ’is broad, and the proactive provision of information about an unlicensed medicine or indication is likely to be seen as promotion and in breach of the Code, unless a company can clearly demonstrate otherwise. In relation to LEMS, the exchange of information is not prohibited, but only if it does not constitute promotion, and additionally the context and audience are important factors when determining acceptability.

Proximate timing of regulatory submission

Pfizer maintains this meeting does not satisfy the ‘during development ’test that must be met for a LEMS. Critically, for the meeting to be regarded as a legitimate exchange of scientific data the relevance of how close the company was to a regulatory filing must be considered, as there needs to be sufficient time between the meeting and expected licence application date for the company to act upon insights in a way that could shape the medicine’s development.

Alnylam confirmed during the intercompany dialogue that regulatory submissions to the FDA and EMA for ATTR-CM were made approximately 6 weeks after the meeting in question, therefore the filing window was extremely proximate. At 6 weeks prior to FDA/EMA submission, the regulatory dossier would have been near finalised and therefore Pfizer considers it difficult for Alnylam to credibly establish that this meeting was held to inform the development of vutrisiran, as opposed to disseminating pivotal results and shaping the treatment landscape ahead of marketing authorisation.

Promotion prior to licence

Even if the timing of this meeting had been appropriate to allow for a LEMS discussion, the content of the meeting was not aligned with a non-promotional, balanced scientific meeting. On review of Alnylam enclosures document, 'Redacted slides presented at ATTR Meeting.pdf', the opening slide depicts an image of a young women, which has a promotional feel and in fact is the exact imagery that is used for the opening slide of Alnylam's promotional tutorial (Alnylam enclosures document, 'Redacted Tutorial 2 slides.pdf').

It is an established principle under the Code that promotional and non-promotional activities must be clearly separated, to avoid disguised promotion. In reference to the Panel comments in Alnylam enclosure document, 'AUTH/26/22/13 Health Professional v MSD', 'The Panel noted that the PMCPA Guidance about Clause 3 included advice about the legitimate exchange of medical and scientific information during the development of a medicine. Companies must ensure that such activities constituted a genuine exchange of information and were not promotional. Documents must not have the appearance of promotional material'.' Contrary to this established guidance the material utilised at the Alnylam meeting had a promotional look and feel from the outset.

Additionally, in the Alnylam enclosures document, 'Redacted slides presented at ATTR Meeting.pdf', slide 4 is entitled 'RNAi therapeutics: Mechanism of action', where only the mechanism of action of Alnylam's medicines was discussed and there was no mention of the mechanism of action of any other disease modifying drugs either on the slide or in the facilitator notes, therefore not giving a balanced view of the treatment landscape. Slide 5 presented the 'Primary Analysis of HELIOS-B Published Today in The New England Journal of Medicine'. No other trial results were displayed in this manner throughout the presentation deck.

Further in the same presentation deck, slide 32 entitled 'ATTR-CM clinical trial endpoints depicts HELIOS-B as one of 4 trials. For the APOLLO-B trial, there is a disclaimer 'Patisiran is not licenced for the treatment of ATTR-CM but for the HELIOS-B trial it is not made clear anywhere on the slide that Vutrisiran is not licenced for ATTR-CM.

The following slide (Slide 33) is dedicated to only the HELIOS-B trial results with an overview of the results from the HELIOS-B study and a promotional claim in the title of the slide, which reads 'Vutrisiran met all 10 primary and secondary endpoints, in both overall and monotherapy populations'. A further claim at the bottom of the slide reads 'Vutrisiran showed acceptable safety and tolerability profiles as previously established'. Again, nowhere on either slide 32, slide 33 or in the briefing document for the faculty, is it made clear that Alnylam viewed vutrisiran as investigational or in development and not

licenced for use in ATTR-CM. None of the other clinical trials mentioned were presented in the detail that the HELIOS-B study was presented. It is therefore clear that the presentation was not fair and balanced, was misleading as to the licenced indication for vutrisiran and that undue emphasis was given to the HELIOS-B trial results at this meeting. This confirms Pfizer's view that it was not a bona fide scientific exchange and was instead a pre-licence/off-label promotional activity for vutrisiran in ATTR-CM, designed to disseminate the HELIOS-B trial results.

Pfizer notes that in their Appeal Letter, Alnylam included personal statements from 1 Faculty Member and 1 attendee at the meeting, stating that in their view the meeting was non-promotional. However, responsibility for Code compliance rests with the company, not the attendees. PMCPA guidance makes it clear that acceptability depends on context, audience and content, not the subjective views of participants who may not be experts in the Code.

Insufficient exchange of scientific data

During intercompany dialogue, Alnylam stated it was not relevant whether insights from the meeting would influence its clinical development programme. Pfizer considers that statement inconsistent with the PMCPA concept that LEMS during development should be capable of enhancing scientific knowledge and supporting genuine debate in a way that can inform development decisions.

The logistics of the session appears to have consisted of faculty-led presentations, panel discussions, polling and workshops. Pfizer acknowledges that interaction is relevant but notes the PMCPA guidance that a LEMS requires more than just the presence of discussion segments - delegates must be able to participate meaningfully, and the activity must facilitate genuine challenge and exchange of views. The event was attended by 100 attendees of which approximately 70 were external delegates, seated in a banquet style layout. Faculty and Alnylam presentations lasted 1 hour, followed by Q&A (10mins), a workshop (60mins) and faculty group reflections (20mins), raising serious doubts as to whether each delegate had an opportunity to meaningfully contribute to an in-depth 2-way debate or exchange.

Alnylam enclosures document, 'Redacted ATTR Meeting briefing document for faculty.pdf ' slide 7, states 'A facilitator can encourage KOLs to share their experiences and insights using multiple choice polling questions, creation of word clouds and ranking/prioritisation of different topics', this suggests the workshop was an insights gathering/consensus exercise and raises further doubts as to whether there was any deep and meaningful scientific debate which involved all 70 HCPs, that could shape the development of vutrisiran.

In addition, Pfizer notes that the workshop content explored 'local needs and challenges and models of care both now and in the future', which gives the impression of implementation and pathway planning rather than a scientific exchange designed to shape the development of a medicine. The PMCPA guidance stresses that the audience and context of a LEMS are important; when workshop discussions are framed around 'optimising management now and in the future 'in an unlicensed indication setting, Pfizer considers the risk of preparatory promotion is heightened.

Conclusion of potential promotional meeting

Taking all circumstances together, Pfizer concludes that the event cannot be described as a bona fide LEMS meeting, due to the:

1. Proximate regulatory timing: filing for FDA and EMA marketing authorisation occurred just ~6 weeks after the ESC congress 2024.

2. Promotion prior to licence: undue prominence was given to HELIOS-B, the slides presented had a promotional look and feel and there was a lack of clarity on key slides to evidence that Alnylam considered vutrisiran investigational or in development.

3. Lack of meaningful debate/in depth 2-way exchange: with approximately 70 delegates, banquet style seating and multiple-choice polling, it is doubtful that each attendee could contribute meaningfully to a 2-way genuine debate.

4. Purpose drift toward implementation: the described country workshops and 'optimising management now and in the future' give an overall impression of pathway planning/market shaping rather than development-stage scientific exchange.

Accordingly, Pfizer maintains that the meeting constituted promotion not in accordance with the terms of vutrisiran's marketing authorisation at the time, a breach of Clause 11.2, and that the overall circumstances failed to maintain high standards, a breach of Clause 5.1 and resulted in reduced confidence in the industry, a breach of Clause 2.

Overall Case Conclusion

The described activities took place at a large international cardiology congress with a high presence of prominent and influential healthcare professionals and Alnylam should have taken more care to ensure their activities were compliant and aligned with the UK ABPI Industry Standards.

Pfizer would again like to express our gratitude to the Panel for their thorough review of the case and we strongly agree with the determinations made, namely the breaches of Clauses 2, 5.1 and 11.2 (x2). In light of the substantial evidence within the Alnylam enclosures pack, together with the social media post referenced in our original complaint, Pfizer firmly maintains that the Panel's decisions should be upheld by the Appeal Board, as described below:

1. Alnylam's promotional tutorial at ESC congress 2024, misleadingly implied vutrisiran was licensed for ATTR-CM, thereby promoting an unapproved indication and breaching Clause 11.2 of the ABPI Code.

2. The Alnylam organised event, which took place on the [date] August 2024, did not fulfil the criteria of a LEMS meeting and instead it constituted promotion of vutrisiran for use in ATTR-CM. This was not

in accordance with the terms of its marketing authorisation at the time and therefore caused a breach of Clause 11.2.

3. Alnylam's overall ESC congress 2024 activities were a deliberate attempt to promote a potential new indication for vutrisiran ahead of licensure. We believe that Alnylam have not upheld the high standards expected of the pharmaceutical industry, a breach of Clause 5.1 and through these actions they have reduced confidence in the industry, a breach of Clause 2.'

APPEAL BOARD RULING

The Appeal Board noted this was a respondent appeal following the Panel's ruling of breaches in relation to Tutorial 2 and the ATTR meeting.

Tutorial 2

The Appeal Board accepted that ATTR amyloidosis was a complex, multisystem, rare disease and that patients with ATTR-PN might also present with cardiac manifestations.

The Appeal Board observed from the slides that the subjects of each of the case studies were patients with hereditary ATTR-PN mixed phenotype with cardiac manifestations. It further noted that the licensed indication for vutrisiran was repeatedly mentioned.

In the Appeal Board's view, ATTR-PN and ATTR-CM were not entirely discrete conditions but represented different aspects of a continuum, reflecting the multisystem nature of the disease. In that context, and noting the tutorial was delivered at a cardiology congress, the Appeal Board concluded that the case studies, which placed emphasis on cardiac manifestations in ATTR-PN mixed phenotype patients, did not appear to fall outside of the licensed indication of vutrisiran.

The Appeal Board considered there was no evidence that vutrisiran had been promoted outside the terms of its marketing authorisation and that Pfizer had not established its case in this regard. The Appeal Board therefore ruled **no breach of Clause 11.2** in relation to Tutorial 2. The appeal was successful on this point.

ATTR meeting

The second matter for the Appeal Board to consider was whether the ATTR meeting constituted a legitimate exchange of medical and scientific information, or whether it amounted to the promotion of a medicine outside the terms of its marketing authorisation.

The Appeal Board observed that the Alnylam-organised meeting included the proactive provision of data from the HELIOS-B trial which related to the use of vutrisiran for ATTR-CM, an unlicensed indication at the time of the meeting. The

Appeal Board noted that, in such circumstances, when the medicine was already available for use for another indication, the proactive provision of such information was likely to be considered promotional unless the company could clearly demonstrate otherwise.

In considering whether the meeting constituted a legitimate exchange of medical and scientific information, the Appeal Board considered the arrangements of the meeting.

The Appeal Board took into account the meeting took place in August 2024 and that regulatory submissions for the ATTR-CM indication were made approximately six weeks later. The Appeal Board queried, whether, in those circumstances, the meeting could be regarded as taking place during the development of the medicine and whether there was sufficient time for any insights gained to meaningfully inform its development.

The Appeal Board considered the content and format of the evening meeting, including that the slides used at the ATTR meeting were similar to those used in the promotional tutorial referred to above. The Appeal Board further noted, from the agenda, that there was limited opportunity for meaningful two-way exchange, particularly given that discussion took place over dinner.

The Appeal Board took note of the two letters provided by attendees of the meeting which had not been available to the original Panel which provided the attendees perspectives on the level of scientific discussion held at the meeting.

However, whilst the Appeal Board noted Alnylam's submission that the purpose of the meeting was to discuss models of care, pathway design and administration, it did not consider, particularly in the context of the timing, format, and content of the ATTR meeting, that the activity constituted a legitimate exchange of medical and scientific information.

Taking all the circumstances into account, the Appeal Board concluded that the proactive provision of information relating to vutrisiran for ATTR-CM, meant that vutrisiran had been promoted outside the terms of its marketing authorisation. The Appeal Board upheld the Panel's ruling of a **breach of Clause 11.2.** The appeal on this point was unsuccessful.

High standards and discredit on the industry

The Appeal Board observed that the Panel's rulings of a breach of Clause 5.1 and Clause 2 were in relation to the overall circumstances of both Tutorial 2 and the evening ATTR meeting. Noting it's determination of no breach for Tutorial 2, the Appeal Board confined its assessment of these clauses to the ATTR meeting alone.

The Appeal Board considered that vutrisiran had been promoted for an unlicensed indication and that Alnylam had failed to maintain high standards in this regard. The Appeal Board therefore upheld the Panel's ruling of a **breach of Clause 5.1.** The appeal on this point was unsuccessful.

The Appeal Board considered with care whether there had also been a breach of Clause 2 in light of the finding that there had been the promotion of a medicine prior to the grant of a marketing authorisation, and that high standards had not been maintained. The Appeal Board considered whether the company had brought discredit upon or reduced confidence in the pharmaceutical industry.

The Appeal Board noted that Clause 2 was a sign of particular censure and reserved for such use.

The Appeal Board determined, on balance, that a finding under Clause 2 would, in the particular circumstances of this case, be disproportionate. The Appeal Board determined that the breach of Clause 5.1 adequately and appropriately covered the matter. The Appeal Board therefore ruled **no breach of Clause 2**. The appeal on this point was successful.

Complaint received **19 December 2024**

Case completed **21 April 2026**