12 September 2024
EMA/COMP/350725/2024
Human Medicines Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes for the meeting on 16-18 July 2024

Chair: Violeta Stoyanova-Beninska

**Disclaimers**

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

**Note on access to documents**

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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# 1. Introduction

## 1.1. Welcome and declarations of interest of members and experts

The Chair opened the meeting by welcoming all participants. The meeting was held remotely.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants for agenda topics was identified.

Participants were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair announced the start of the Hungarian presidency of the Council of the European Union (EU).

## 1.2. Adoption of agenda

The agenda for 16-18 July 2024 was adopted with no amendments.

## 1.3. Adoption of the minutes

The minutes for 13-15 June 2024 were adopted with amendments and will be published on the EMA website.

# 2. Applications for orphan medicinal product designation

## 2.1. For opinion

### 2.1.1. - EMA/OD/0000159992

Treatment of acute lymphoblastic leukaemia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Condition

The proposed medicinal product was intended for lymphodepletion prior to CAR-T cell therapy with the sponsors investigational allogenic anti-CD22 CAR-T cell product. The

proposed medicinal product was expected to improve the outcome of allogenic anti-CD22 CAR-T cell product treatment. Therefore, the sponsor was asked to further justify the proposed condition of treatment of acute lymphoblastic leukaemia (ALL) or propose a more suitable orphan condition.

The sponsor's attention was drawn to the orphan regulations and relevant guidelines (especially section A of 2022/C 440/02).

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product in the treatment of acute lymphoblastic leukaemia the sponsor was requested to further elaborate on the results obtained from their clinical dose-escalation study and to justify that the addition of the proposed medicinal product in the lymphodepletion step prior to allogenic anti-CD22 CAR-T cell treatment does lead to improved efficacy of allogenic anti-CD22 CAR-T cell, as compared to lymphodepletion which does not contain the proposed medicinal product .

In addition, the sponsor was invited to provide evidence for improved lymphodepletion due to the proposed medicinal product, as compared to fludarabine and cyclophosphamide alone. The sponsor was also invited to submit any new data from their ongoing clinical study that might have become available meanwhile.

- Life-threatening and debilitating nature of the condition

As the condition wording was still under discussion by the COMP, the sponsor was reminded that this section may have to be revised according to the final orphan condition.

- Number of people affected

As the condition wording was still under discussion by the COMP, the sponsor was reminded that this section may have to be revised according to the final orphan condition.

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

As the condition wording was still under discussion by the COMP, the sponsor was reminded that this section may have to be revised according to the final orphan condition.

In the written response, and during an oral explanation before the Committee on 16 July 2024, the sponsor maintained their view that treatment of ALL is the most adequate orphan condition. The proposed medicinal product contributes to the improved lymphodepletion, the delayed host lymphocyte recovery and the overall treatment effect in patients with relapsed/refractory B-cell ALL. The COMP did not agree with this position. While the Committee acknowledged the contribution of the proposed medicinal product, this product is intended to work as an auxiliary agent for the investigational allogenic CD22 directed CAR-T product, from the same sponsor and which has already received an orphan designation. While allogenic CD22 directed CAR-T is the product which is actually intended to treat ALL by targeting CD22, the proposed medicinal product is intended for use in the preparatory lymphodepletion step which precedes the infusion of allogenic CD22 directed CAR-T. The COMP therefore considered that treatment of ALL is not a suitable orphan condition for the proposed medicinal product.

The sponsor also provided additional data which showed that the proposed medicinal product containing lymphodepletion results in increased allogenic CD22 directed CAR-T expansion and that there may be a correlation between allogenic CD22 directed CAR-T expansion and clinical response in B-cell ALL patients.

In communicating to the sponsor, the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 July 2024, prior to final opinion.

### 2.1.2. humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R - EMA/OD/0000173345

Raremoon Consulting Esp S.L.; Treatment of AL amyloidosis

COMP Rapporteur: Enrico Costa

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of AL amyloidosis the sponsor was requested to further elaborate on the clinical relevance of the non-clinical data in the non-clinical AA amyloidosis model for the proposed condition (AL amyloidosis), considering the different types of involved amyloid proteins (Light Chains and Serum Amyloid A) and the general difference of the two conditions in terms of pathophysiology, etiology, clinical presentation and management.

In addition, the sponsor was invited to present any available new PD/efficacy data in patients with AL amyloidosis from the currently ongoing clinical trial.

- Significant benefit

The sponsor was asked to clarify whether they envisage the use of their product in the newly diagnosed (first line) or the second line (previously treated, relapsed/refractory) setting or both. The sponsor was also asked to further discuss the significant benefit of their product, to demonstrate an improved efficacy over current standard of care (including daratumumab) in AL amyloidosis.

In the written response, the sponsor provided additional data.

The COMP considered that the additional data was sufficient to support the medical plausibility and the significant benefit in patients with AL amyloidosis. The therapeutic goal of the sponsors product is a reversal of cardiac dysfunction due to product-mediated clearance of tissue amyloid (antibody-mediated phagocytosis). It is expected that the sponsors product will be administered to AL patients with a stable hematologic response to plasma cell directed (PCD) therapy, who have ongoing organ dysfunction from amyloid that has been deposited in tissues, particularly the heart. The product may be used in combination with maintenance daratumumab treatment. The sponsor provided non-clinical data showing a reduction in amyloid load in various tissues and preliminary clinical data showing positive trends in amyloid deposition markers and cardiac response in patients with a good haematologic response (CR/VGPR) to previous plasma-cell directed therapy but with persistent organ amyloid deposits and organ dysfunction. Therefore, an orphan designation was supported by the COMP and the oral explanation was cancelled.

Protocol assistance was recommended to the sponsor to discuss the data requirements which could support the significant benefit of the sponsors product over current standard of care therapy at time of marketing authorisation.

The Committee agreed that the condition, AL amyloidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R was considered justified based on non-clinical data showing a reduction in amyloid load in various tissues and preliminary clinical data showing positive trends in amyloid deposition markers and cardiac response.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupt normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

The condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing positive trends in amyloid deposition markers and cardiac response in patients successfully treated with previous plasma-cell directed therapy but with persistent organ amyloid deposits and organ dysfunction. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R, for treatment of AL amyloidosis, was adopted by consensus.

### 2.1.3. humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R - EMA/OD/0000173347

Raremoon Consulting Esp S.L.; Treatment of ATTR amyloidosis

COMP Rapporteur: Enrico Costa

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ATTR amyloidosis the sponsor was requested to further elaborate on the clinical relevance of the non-clinical data in the non-clinical AA amyloidosis model, to provide a scientific rationale for the sponsors product as a potential treatment in ATTR amyloidosis.

In addition, the sponsor was asked to provide information on the concomitant use of medicines by the patient included in the report (i.e., background medications which may

confound the effects on the cardiac markers as presented by the sponsor), as well as the availability of updated clinical data from other ATTR patients enrolled in the study.

- Significant benefit

The sponsor was invited to further substantiate their claim for improved efficacy of their product over currently authorised treatments of ATTR amyloidosis.

In the written response, the sponsor provided additional data.

The COMP considered that the additional data provided by the sponsor was sufficient to support the medical plausibility and the significant benefit in patients with ATTR amyloidosis. The therapeutic goal of the sponsors product is a reversal of cardiac dysfunction due to product-mediated clearance of tissue amyloid (antibody-mediated phagocytosis). Case reports in a few Transthyretin Amyloid Cardiomyopathy (ATTR-CM) patients with heart failure described reversion to near-normal cardiac structure and function. These patients had spontaneously developed autoantibodies that bound to ATTR amyloid (Fontana, 2023). The sponsors product may be administered to ATTR amyloidosis patients who have ongoing organ dysfunction and amyloid deposits, particularly in the heart, despite current or previous treatment with standard of care therapy tafamidis. The data in additional patients with ATTR-CM amyloidosis on the endpoints of cardiac extracellular volume (ECV) and on the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) at week 24 for the lower and the higher dose of the sponsors product, suggest a positive dose-response effect. Of note, more participants were receiving the current standard of care therapy tafamidis in the lower dose cohort compared with the higher dose cohort, suggesting that the observed positive effects are not attributable to tafamidis. Therefore, an orphan designation was supported by the COMP and the oral explanation was cancelled.

Protocol assistance was recommended to the sponsor to discuss the data requirements which could support the significant benefit of the sponsors product over current standard of care therapy at time of marketing authorisation.

The Committee agreed that the condition, ATTR amyloidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R was considered justified based on non-clinical data showing a reduction in amyloid load in various tissues and preliminary clinical data showing positive effect on an amyloid deposition marker.

The condition is life-threatening and chronically debilitating in particular due to the development of neuropathy and cardiomyopathy.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting a decrease in amyloid deposition with the proposed product in combination with

standard of care therapy, indicating a disease modifying potential. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG1 monoclonal antibody against misfolded immunoglobulin G, fused with pan-amyloid-reactive peptide p5R, for treatment of ATTR amyloidosis, was adopted by consensus.

### 2.1.4. - EMA/OD/0000169543

Treatment of chronic pancreatitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of chronic pancreatitis the sponsor should further elaborate on all available clinical data. In particular, the sponsor was invited to rely on contemporaneous studies and discuss the inconclusive outcomes observed in some of the studies.

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The analyses presented by the sponsor lead to several methodological concerns that need addressing. The balance between false positives and false negatives in national registries remained unclear, and the consistency of physician-verified diagnoses across studies was not guaranteed. The use of outdated data and the inclusion of non-EU studies further complicate the prevalence estimation.

For a more accurate and relevant assessment, the sponsor was requested to use actual sample sizes from each study in the meta-analysis, restrict the meta-analysis to studies based on EU population, and exclude outdated studies to ensure contemporary relevance.

In the written response, and during an oral explanation before the Committee on 18 July 2024, the sponsor defended their position.

The Committee's request for further elaboration on the clinical data supporting the use of the proposed product for chronic pancreatitis (CP) was addressed thoroughly. Limitations of the inconclusive studies were highlighted, noting that the patient population, which included end-stage CP patients, is not representative of the intended treatment population. The sponsor argued that the proposed product would be more effective in early and intermediate stages of CP, where inflammation and fibrosis are active targets. A discussion was also held on the pain assessment methods used, emphasising the need to capture the multifaceted nature of CP pain. The COMP found the response satisfactory, recognising the relevance of the clinical findings for the intended patient population.

To address the Committee's concerns about the prevalence estimate of CP, a comprehensive response was provided, focusing on accuracy and relevance. Outdated and non-EU studies were excluded, emphasising the importance of verified diagnoses using standardised diagnostic criteria to avoid false positives. A meta-analysis on EU studies was

presented yielding a weighted prevalence of 31 per 100,000 population for CP within the EU. This estimate was supported by Eurostat data, distinguishing between acute pancreatitis (AP) and CP. However, the COMP identified limitations in the sponsor's approach. The exclusion and inclusion criteria for relevant sources were unclear, and there was uncertainty regarding variations in diagnostic criteria and reporting practices across studies and national registries, which introduced inconsistencies in the prevalence estimate. The potential for false positives and negatives further complicated the reliability of the estimate. Additionally, data representative of different EU regions was scarce, which could have provided a more comprehensive and accurate assessment.

The COMP concluded that the sponsor's prevalence estimate did not provide a sufficiently robust basis for orphan disease designation. Consequently, the COMP maintained a negative trend. The sponsor was encouraged to address these limitations and provide more comprehensive data in future submissions.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2024, prior to final opinion.

### 2.1.5. interleukin 4 - interleukin 10 fusion protein - EMA/OD/0000164952

Synerkine Pharma B.V.; Treatment of complex regional pain syndrome

COMP Rapporteur: Michel Hoffmann

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of complex regional pain syndrome (CRPS) the sponsor was requested to further elaborate on the results obtained in vivo in the spared nerve injury (SNI) model and most importantly in the chronic post-ischemia pain (CPIP) model which is specifically designed to mimic the symptoms and pathology of CRPS type I which is the targeted indication.

In the written response, the sponsor argued that the inflammatory models represent an important feature of CRPS type 1, which is the neuroinflammation driven central sensitisation. Furthermore, the sponsor further explained that endpoints (allodynia) and assessment used (von Frey filaments or heat test) were representative for the clinical assessments to diagnose and further characterise the CRPS pain patients.

Finally, the sponsor argued that within the limits of the models, the non-clinical data presented showed unprecedented reversal of central sensitisation. In addition, there is literature evidence for the indication that the cytokines comprised in the proposed product were under-expressed in CRPS patients making it plausible that this patient population could benefit from the proposed product.

The COMP acknowledged the limitations with the non-clinical models and agreed that the medical plausibility was considered justified. Therefore, the oral explanation was cancelled.

The Committee agreed that the condition, complex regional pain syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing interleukin 4 - interleukin 10 fusion protein was considered justified based on non-clinical data which showed long-term reversal of mechanical and thermal hypersensitivity after repeat dosing in a valid inflammatory model of the condition.

The condition is chronically debilitating due to symptoms such as pain, hyperesthesia or allodynia, local oedema, weakness, tremor, dystonia, as well as skin trophic changes.

The condition was estimated to be affecting approximately 3.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing interleukin 4 - interleukin 10 fusion protein will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data which support the assumption that the product has the potential to cover a broader population compared to the authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for interleukin 4 - interleukin 10 fusion protein, for treatment of complex regional pain syndrome, was adopted by consensus.

### 2.1.6. (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone - EMA/OD/0000172086

Granzer Regulatory Consulting & Services GmbH; Treatment of punctate palmoplantar keratoderma

COMP Rapporteur: Frauke Naumann-Winter

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

With reference to the EC Guideline ENTR/6283/00, the rationale for the use of the medicinal product in the orphan condition should be provided. However, this rationale was not clear in particular regarding the expression analysis, and therefore further argumentation was needed. As such, to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of punctate palmoplantar keratoderma the sponsor was requested to further elaborate on the preliminary clinical data provided. This included elaborating on the observed improvements in the severity score, particularly given that effects on itch or pain were not documented. Clarification of these aspects will help determine the potential clinical relevance and therapeutic benefit of the product for patients with the condition.

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical data to justify the assumption of significant benefit over authorised medicinal products for hyperkeratosis which is present in the proposed orphan condition.

In the written response, the sponsor defended their position.

Addressing the medical plausibility question, particularly the absence of baseline pain scores reported in the clinical results, the sponsor elaborated on disease progression and clinical data. Clinically, the sponsor indicated that punctate palmoplantar keratoderma 1 (PPPK1) manifests as multiple hyperkeratotic papules that evolve over time, typically asymptomatic but sometimes causing pain due to pressure on the lesions.

The sponsor discussed the available data from a phase I study involving a few PPPK1 patients with confirmed AAGAB mutations treated with the proposed topical product. Around 80% of the patients showed reduced disease severity, as measured by Clinician Global Impression of Severity (CGI-S) and Patient Global Impression of Severity (PGI-S) scores, with no changes in pain or itch. Improvements included a reduction in the number, size, and dimpling of papules, flattening of the papules, and prolonged physical activity duration.

The sponsor also addressed the significant benefit uncertainties of the proposed product for treating PPPK1. The specific mechanism of action was put forward which is distinct from current treatments like retinoids. Non-clinical studies showed a favourable safety profile, with no adverse systemic effects. Clinical studies reported no drug-related serious adverse events and mostly mild, local treatment-emergent adverse events that resolved without sequelae, with negligible plasma exposure indicating good tolerability.

Overall, while preliminary, the available clinical data and proposed administration route suggest that the proposed product could serve as an alternative for patients unsuitable for systemic retinoid therapy.

Given that the provided written responses were considered satisfactory, the COMP cancelled the oral explanation and adopted a positive opinion.

The Committee agreed that the condition, punctate palmoplantar keratoderma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone was considered justified based on preliminary clinical data in patients with the condition indicating the improvement in the severity score and hyperkeratotic papules, and the prolongation in physical activity duration.

The condition is chronically debilitation due to severe pain in some patients, social impairment, and progressive lesions that significantly impact quality of life, hinder walking, and interfere with manual activities.

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with the condition indicating that the proposed topical formulation of the product serves as a treatment alternative for patients that cannot be treated with the available therapy (i.e., systemic retinoids). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone, for treatment of punctate palmoplantar keratoderma, was adopted by consensus.

## 2.1.7. - EMA/OD/0000166750

Treatment of epidermolysis bullosa

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Medical plausibility

The sponsor was asked to elaborate on the results of all endpoints from their clinical phase 3 study with respect to effect size and clinical relevance to justify the medical plausibility.

- Significant benefit

The sponsor was also requested to further discuss the arguments provided for significant benefit. Outcomes of patients with epidermolysis bullosa simplex should be reported to substantiate the claim of targeting a broader patient population compared to the authorised product.

Furthermore, the sponsor was asked to present the background standard of care products used in the clinical trial, including the use of antiseptics.

In the written response, the sponsor underlined the broad range of potentially beneficial mechanisms of action of the proposed product to be administered in high concentration (6%) regularly to the entire body surface.

The sponsor reported that adulterated placebo was used in the clinical study. This impacted the result of a portion of the clinical study. The current sponsor acquired the proposed product program and reassessed the clinical study data.

The COMP noted that neither the publication by the investigators of the ESSENCE study, nor the accompanying natural history information as derived from the vehicle control group from the phase III trial were referenced by the sponsor. The principal investigator of the study had noted that higher-than-expected responses are often observed in epidermolysis bullosa trials in the vehicle group, possibly due to improved wound care in the controlled setting of a trial or potential benefits from daily application of vehicle containing also other ingredients (such as lanolin oil or cod liver oil). There was no mentioning of adulterated placebo in the public domain.

The COMP noted that there were major differences in the outcomes as reported by the sponsor compared to the figures in the publication (one month difference in wound complete closure vs no difference).

The results that were considered most impressive in the original application (difference in infection), had not been collected in a standardised manner, but where part of the safety assessment and therefore differences in reporting between the two arms cannot be ruled out, thereby questioning the validity of concluding on a statistically significant difference.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2024, prior to final opinion.

## 2.1.8. - EMA/OD/0000165577

Treatment of Fabry disease

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was invited to expand the bibliographic search in order to identify suitable contemporaneous sources for the estimation of the prevalence of the condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 18 July 2024, the sponsor defended their position.

Regarding the prevalence question, the sponsor expanded their bibliographical search and included additional references, resulting in a proposed birth prevalence figure of 1.15 per 10,000. However, the COMP recommended adjustments for gender-specific data and more reliable calculation methods. Excluding gender-specific data and using a worst-case scenario, the adjusted prevalence figure was 2.6 per 10,000, which could be acceptable.

Regarding the significant benefit question, the sponsor elaborated on the available non-clinical data, presenting the proposed product as a therapy for continuous endogenous production of the GLA enzyme. Unlike enzyme replacement therapies (ERTs) that require bi-weekly infusions and show moderate efficacy, this product aims to provide stable, long-term enzyme expression with a single administration. Preclinical studies showed durable GLA activity, correction of substrate accumulation, and phenotype improvement. The sponsor also claimed that the product could prevent disease progression, reduce immunogenicity, and improve patient quality of life by avoiding frequent infusions and the production of anti-drug antibodies.

Overall, while the rationale put forward on the advantages over ERTs is acknowledged, limitations remain. The lack of comparative data with authorised ERTs and the absence of patient perspectives on infusion burden and quality of life impact limit the interpretability of results. Consequently, the COMP maintained a negative trend.

The sponsor was advised to resubmit the application once preliminary clinical data becomes available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2024, prior to final opinion.

## 2.2. For discussion / preparation for an opinion

### 2.2.1. - EMA/OD/0000154786

Prevention of arteriovenous access dysfunction in patients undergoing surgical creation of an arteriovenous fistula for haemodialysis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

### 2.2.2. gallium ($^{68}$Ga) boclatixafortide - EMA/OD/0000155550

Pentixapharm AG; Diagnosis of marginal zone lymphoma

COMP Rapporteur: Boje Kvorning Pires Ehmsen

The Committee agreed that the condition, marginal zone lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to diagnose the condition with the medicinal product containing gallium ($^{68}$Ga) boclatixafortide was considered justified based on literature data which showed sensitivity and specificity of the proposed product for the diagnose and staging of the marginal zone lymphoma.

The condition is chronically debilitating and life-threatening due to lymphadenopathy, splenomegaly, mucosa and bone-marrow involvement with development of pancytopenia and increased risk of opportunistic infections. Five-year survival ranges from 30% to up to 90%.

The population of patients eligible for diagnosis of the condition was estimated to be approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gallium ($^{68}$Ga) boclatixafortide will be of significant benefit to those affected by the condition. The sponsor has provided literature data that showed higher sensitivity and specificity of imaging with the proposed product for the diagnosis and staging of marginal zone lymphoma compared to the authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gallium ($^{68}$Ga) boclatixafortide, for treatment of marginal zone lymphoma, was adopted by consensus.

### 2.2.3. - EMA/OD/0000160667

Treatment of anti-neutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

### 2.2.4. - EMA/OD/0000167672

Treatment of small cell lung cancer

The sponsor withdrew the application for orphan designation on 17 July 2024 prior to the COMP adoption of a list of issues.

### 2.2.5. IgG-like T-cell engager binding to DLL3 and CD3 - EMA/OD/0000168913

Boehringer Ingelheim International GmbH; Treatment of pulmonary neuroendocrine carcinoma

COMP Rapporteur: Bozenna Dembowska-Baginska

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of pulmonary neuroendocrine carcinoma.

The Committee agreed that the condition, pulmonary neuroendocrine carcinoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing IgG-like T-cell engager binding to DLL3 and CD3 was considered justified based on preliminary clinical data which showed responses in patients with large-cell neuroendocrine carcinoma of the lung and small cell lung carcinoma.

The condition is chronically debilitating due to persistent cough, chest pain, shortness of breath, unexplained weight loss and fatigue and life-threatening with poor prognosis.

The condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing IgG-like T-cell engager binding to DLL3 and CD3 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed responses in patients pretreated with the currently approved products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for IgG-like T-cell engager binding to DLL3 and CD3, for treatment of pulmonary neuroendocrine carcinoma, was adopted by consensus.

### 2.2.6. IgG-like T-cell engager binding to DLL3 and CD3 - EMA/OD/0000168919

Boehringer Ingelheim International GmbH; Treatment of extrapulmonary neuroendocrine carcinoma

COMP Rapporteur: Bozenna Dembowska-Baginska

The Committee agreed that the condition, extrapulmonary neuroendocrine carcinoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing IgG-like T-cell engager binding to DLL3 and CD3 was considered justified based on preliminary clinical data which showed responses in heavily pretreated patients with extrapulmonary neuroendocrine carcinoma.

The condition is life-threatening and chronically debilitating due to its propensity for distant metastases, rapid progression and poor prognosis.

The condition was estimated to be affecting approximately 0.8 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition/for the population at risk of developing the condition.

A positive opinion for IgG-like T-cell engager binding to DLL3 and CD3, for treatment of extrapulmonary neuroendocrine carcinoma, was adopted by consensus.

### 2.2.7. polihexanide - EMA/OD/0000168961

SIFI S.p.A.; Treatment of fungal keratitis

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, fungal keratitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing polihexanide was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in mycotic load.

The condition is chronically debilitating due to a spectrum of potential complications that can irreversibly affect the eye. Many patients develop corneal ulcers. In severe cases, the infection may extend to the inner coats of the eye, causing endophthalmitis, or even worse, the infection may encompass the entirety of the structures of the eyeball, causing panophthalmitis. The worst-case scenario includes profound vision impairment and blindness.

The condition was estimated to be affecting approximately 0.15 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for polihexanide, for treatment of fungal keratitis, was adopted by consensus.

### 2.2.8. autologous CD34+ cells edited with a CRISPR/Cas9 system and transduced with an adeno-associated vector containing a codon-optimised version of *WAS* gene - EMA/OD/0000169888

Danaus Pharmaceuticals S.L.; Treatment of Wiskott Aldrich syndrome (WAS)

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, Wiskott Aldrich syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ cells edited with a CRISPR/Cas9 system and transduced with an adeno-associated vector containing a codon-optimised version of *WAS* gene was considered justified based on non-

clinical data showing successful engraftment and restoration of the function of cell types affected in the condition.

The condition is life-threatening and chronically debilitating due to thrombocytopenia leading to prolonged bleeding episodes, immunodeficiency leading to recurrent infections that may result in sepsis, autoimmunity resulting in cytopenias, as well as due to the development of haematological malignancies.

The condition was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for autologous CD34+ cells edited with a CRISPR/Cas9 system and transduced with an adeno-associated vector containing a codon-optimised version of *WAS* gene, for treatment of Wiskott Aldrich syndrome, was adopted by consensus.

### 2.2.9. 4-(1H-pyrrolo[2,3-b]pyridin-2-yl)phenol hydrochloride - EMA/OD/0000170073

SeaBeLife; Prevention of acute liver failure

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, acute liver failure, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing 4-(1H-pyrrolo[2,3-b]pyridin-2-yl)phenol hydrochloride was considered justified based on non-clinical data in a model of acute liver failure showing reduced hepatotoxicity and improved survival.

The condition is life-threatening, with acute and rapid deterioration of liver function leading to encephalopathy with intracranial hypertension, and to the development of multi-organ failure and sepsis. Acute liver failure is associated with high mortality.

The population of patients eligible for prevention of the condition was estimated to be approximately 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-(1H-pyrrolo[2,3-b]pyridin-2-yl)phenol hydrochloride will be of significant benefit to the population at risk of developing the condition. The sponsor has provided non-clinical data in a model of acute liver failure showing reduced hepatotoxicity and improved survival when their product was used in combination with the currently authorised product in the applied for condition, as compared to the authorised product alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-(1H-pyrrolo[2,3-b]pyridin-2-yl)phenol hydrochloride, for prevention of acute liver failure, was adopted by consensus.

### 2.2.10. - EMA/OD/0000171663

Treatment of cystic fibrosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

### 2.2.11. adeno-associated virus vector serotype 9 containing the human *GCDH* gene - EMA/OD/0000171786

Consorcio Centro De Investigacion Biomedica En Red; Treatment of glutaric aciduria

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, glutaric aciduria, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype 9 containing the human *GCDH* gene was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement in biomarkers specific to the condition in the liver and striatum as well as improvement in histological and anatomical characteristics of the central nervous system. Improved survival was noted when compared to the untreated group.

The condition is life-threatening and chronically debilitating due to irreversible neurological injury during an encephalopathic crisis in childhood. Patients can also present clinically with hepatomegaly, non-ketotic hypoglycaemia, metabolic acidosis, hypotonia, and neonatal onset cardiomyopathy. Severe neonatal forms, typically present with hypo- or non-ketotic hypoglycaemia and metabolic acidosis during the first days of life and this is typically fatal.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for adeno-associated virus vector serotype 9 containing the human *GCDH* gene, for treatment of glutaric aciduria, was adopted by consensus.

### 2.2.12. - EMA/OD/0000173551

Treatment of Wilson's disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

### 2.2.13. - EMA/OD/0000174349

Treatment of complex regional pain syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

### 2.2.14. - EMA/OD/0000174573

Treatment of chondrosarcoma

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the September meeting.

## 2.2.15. - EMA/OD/0000178304

Treatment of pouchitis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

## 2.2.16. adeno-associated viral vector serotype 3B encoding human *CYP27A1* - EMA/OD/0000178496

Vivet Therapeutics S.A.S.; Treatment of inborn errors of primary bile acid synthesis

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, inborn errors of primary bile acid synthesis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 3B encoding human *CYP27A1* was considered justified based on non-clinical in vivo data in a model of the condition showing decreased hepatomegaly, metabolic correction and normalisation of upregulated compensatory enzymes.

The condition is chronically debilitating due to progressive neurological decline, fat malabsorption and fat-soluble vitamin deficiencies and life-threatening in particular due to the development of liver cirrhosis and liver failures.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 3B encoding human *CYP27A1* will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrated a reduction of hepatomegaly, normalisation of upregulated compensatory enzymes and of primary and secondary bile acids when compared to authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 3B encoding human *CYP27A1*, for treatment of inborn errors of primary bile acid synthesis, was adopted by consensus.

## 2.2.17. sodium valproate - EMA/OD/0000178582

Raremoon Consulting Esp S.L.; Treatment of pulmonary arterial hypertension

COMP Rapporteur: Joao Rocha

The Committee agreed that the condition, pulmonary arterial hypertension, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium valproate was considered justified based on preliminary clinical data in patients with the condition indicating that the product is effective in addressing key pathological aspects of the disease such as the increased pulmonary arterial hypertension and the decreased cardiac output.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to premature death.

The condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium valproate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with the condition that demonstrate that treatment with the proposed product on top of existing pulmonary arterial hypertension medication results in further amelioration of key hallmarks of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sodium valproate, for treatment of pulmonary arterial hypertension, was adopted by consensus.

### 2.2.18. olezarsen sodium - EMA/OD/0000179126

Ionis Ireland Limited; Treatment of familial chylomicronemia syndrome (FCS)

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, familial chylomicronemia syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing olezarsen sodium was considered justified based on preliminary clinical data showing an improvement in triglyceride levels and a reduction in acute pancreatitis attacks.

The condition is life-threatening and chronically debilitating due to recurrent episodes of pancreatitis which may lead to pancreatic insufficiency resulting in malabsorption, failure to thrive and diabetes mellitus.

The condition was estimated to be affecting approximately 0.13 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing olezarsen sodium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product can be used in patients who cannot be treated with the only authorised medicine due to low platelet counts. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for olezarsen sodium, for treatment of familial chylomicronemia syndrome, was adopted by consensus.

### 2.2.19. 4-benzoyl-D-phenylalanyl-D-seryl-D-tryptophyl-D-seryl-2,3,4,5,6-pentafluoro-D-phenylalanyl-3-cyclohexyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-glutaminyl-D-arginyl-D-arginine acetate - EMA/OD/0000179366

Syneos Health Netherlands B.V.; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

The Committee agreed that the condition, pancreatic cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-benzoyl-D-phenylalanyl-D-seryl-D-tryptophyl-D-seryl-2,3,4,5,6-pentafluoro-D-phenylalanyl-3-cyclohexyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-glutaminyl-D-arginyl-D-arginine acetate was considered justified based on non-clinical data in a valid model of the condition which showed reduction in tumour volume with the proposed product administered as monotherapy and as combination with cisplatin and preliminary clinical data which showed responses with the proposed product in combination with cisplatin and nivolumab in heavily pretreated patients with pancreatic cancer.

The condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-benzoyl-D-phenylalanyl-D-seryl-D-tryptophyl-D-seryl-2,3,4,5,6-pentafluoro-D-phenylalanyl-3-cyclohexyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-glutaminyl-D-arginyl-D-arginine acetate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed responses in heavily pretreated patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-benzoyl-D-phenylalanyl-D-seryl-D-tryptophyl-D-seryl-2,3,4,5,6-pentafluoro-D-phenylalanyl-3-cyclohexyl-D-alanyl-D-arginyl-D-arginyl-D-arginyl-D-glutaminyl-D-arginyl-D-arginine acetate, for treatment of pancreatic cancer, was adopted by consensus.

## 2.2.20. - EMA/OD/0000179561

Treatment of cutaneous T-cell lymphoma (CTCL)

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the September meeting.

## 2.2.21. (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride - EMA/OD/0000183012

Kiora Pharmaceuticals GmbH; Treatment of syndromic inherited retinal dystrophies of the rod-dominant phenotype

COMP Rapporteur: Tim Leest

The Committee agreed that the condition, syndromic inherited retinal dystrophies of the rod-dominant phenotype, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride was considered justified based on clinical data showing improvement in the visual acuity.

The condition is chronically debilitating due to visual impairment progressing to blindness.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride, for treatment of syndromic inherited retinal dystrophies of the rod-dominant phenotype, was adopted by consensus.

### 2.2.22. bemarituzumab - EMA/OD/0000171163

Amgen Europe B.V.; Treatment of gastric cancer

COMP Rapporteur: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of gastric cancer.

The Committee agreed that the condition, gastric cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing bemarituzumab was considered justified based on clinical data which shows improved tumour responses, progression-free survival and overall survival as compared to current standard of care regimen.

The condition is life-threatening and chronically debilitating due to dysphagia, weight loss and gastric bleeding.

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bemarituzumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which show that bemarituzumab in combination with a fluoropyrimidine- and platinum-containing regimen leads to improved tumour responses, progression-free survival and overall survival as compared to this chemotherapy regimen alone, in patients with HER2-negative locally advanced unresectable or metastatic gastric or gastro-oesophageal-junction adenocarcinoma who are FGFR2b biomarker positive and would not be eligible for authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bemarituzumab, for treatment of gastric cancer, was adopted by consensus.

## 2.3. Revision of the COMP opinions

None

## 2.4. Amendment of existing orphan designations

None

## 2.5. Appeal

None

## 2.6. Nominations

### 2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP rapporteurs were appointed for 15 applications.

## 2.7. Evaluation on-going

None

# 3. Requests for protocol assistance with significant benefit question

## 3.1. Ongoing procedures

### 3.1.1. -

Treatment of *STXBP1* developmental and epileptic encephalopathy

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

### 3.1.2. -

Treatment of hereditary angioedema

The discussion was postponed.

### 3.1.3. -

Treatment of primary sclerosing cholangitis

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

### 3.1.4. -

Treatment of glioma

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

### 3.1.5. -

Treatment of Dravet syndrome

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

# 4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

## 4.1. Orphan designated products for which CHMP opinions have been adopted

### 4.1.1. Ordspono - odronextamab - EMEA/H/C/006215

Regeneron Ireland Designated Activity Company

COMP Rapporteur: Maria Elisabeth Kalland; COMP Co-Rapporteur: Bozenna Dembowska-Baginska

a) Treatment of follicular lymphoma, EU/3/22/2649, EMA/OD/0000168564

b) Treatment of diffuse large B-cell lymphoma, EU/3/22/2656, EMA/OD/0000168574

A list of issues was adopted on 20 June 2024.

An oral explanation was held on 17 July 2024.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 17 July 2024, prior to final opinion.

The orphan designation withdrawal assessment report will be publicly available on the EMA website.

### 4.1.2. Tepkinly - epcoritamab - EMEA/H/C/005985/II/0001, EU/3/22/2634, EMA/OD/0000157895

Abbvie Deutschland GmbH & Co. KG; Treatment of follicular lymphoma

COMP Rapporteur: Maria Elisabeth Kalland; COMP Co-Rapporteur: Frauke Naumann-Winter; CHMP Rapporteur: Peter Mol; CHMP Co-Rapporteur: Ingrid Wang

A list of issues was adopted on 20 June 2024.

An oral explanation was held on 17 July 2024.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 17 July 2024, prior to final opinion.

The orphan designation withdrawal assessment report will be publicly available on the EMA website.

## 4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

### 4.2.1. Iqirvo - elafibranor - EMEA/H/C/006231/0000, EU/3/19/2182, EMA/OD/0000173044

Ipsen Pharma; Treatment of primary biliary cholangitis

COMP Rapporteur: Elisabeth Johanne Rook; COMP Co-Rapporteur: Joao Rocha; CHMP Rapporteur: Patrick Vrijlandt; CHMP Co-Rapporteur: Paolo Gasparini

An opinion recommending not to remove Iqirvo, elafibranor, EU/3/19/2182 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

*[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting.]*

### 4.2.2. Vyloy - chimeric monoclonal antibody against claudin-18 splice variant 2 - EMEA/H/C/005868, EU/3/10/803, EMA/OD/0000166702

Astellas Pharma Europe B.V.; Treatment of gastric cancer

COMP Rapporteur: Brigitte Schwarzer-Daum; COMP Co-Rapporteur: Frauke Naumann-Winter; CHMP Rapporteur: Jan Mueller-Berghaus; CHMP Co-Rapporteur: Carolina Prieto Fernandez

An opinion recommending not to remove Vyloy, chimeric monoclonal antibody against claudin-18 splice variant 2, EU/3/10/803 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

*[Post-meeting note: The COMP adopted the opinion by written procedure following its July meeting.]*

## 4.3. Appeal

None

## 4.4. On-going procedures

COMP co-ordinators were appointed for 4 applications.

## 4.5. Orphan Maintenance Reports

Documents were tabled for information.

# 5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

## 5.1. After adoption of CHMP opinion

None

## 5.2. Prior to adoption of CHMP opinion

### 5.2.1. Lutathera - lutetium ($^{177}$Lu) oxodotreotide - EMEA/H/C/004123/II/0052, EU/3/07/523

Advanced Accelerator; Treatment of gastro-entero-pancreatic neuroendocrine tumours

CHMP Rapporteur: Janet Koenig

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

### 5.2.2. Ngenla - somatrogon - EMEA/H/C/005633/II/0016, EU/3/12/1087

Pfizer Europe MA EEIG; Treatment of growth hormone deficiency

CHMP Rapporteur: Finbarr Leacy

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

## 5.3. Appeal

None

## 5.4. On-going procedures

None

# 6. Application of Article 8(2) of the Orphan Regulation

None

# 7. Organisational, regulatory and methodological matters

## 7.1. Mandate and organisation of the COMP

### 7.1.1. COMP membership

None

### 7.1.2. Vote by proxy

None

### 7.1.3. Strategic Review & Learning meetings - Hungary

The Committee was updated about the next strategic review and learning meeting to be held in person on 29-30 October 2024 in Budapest, Hungary.

### 7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 17 July 2024.

### 7.1.5. COMP Decisions Database

The COMP acknowledged the importance of adding further topics to the database.

## 7.2. Coordination with EMA Scientific Committees or CMDh-v

### 7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

## 7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

### 7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

None

### 7.3.2. Upcoming ITF meetings

The COMP noted the upcoming ITF meetings.

## 7.4. Cooperation within the EU regulatory network

### 7.4.1. European Commission

None

## 7.5. Cooperation with International Regulators

### 7.5.1. Food and Drug Administration (FDA)

None

### 7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

### 7.5.3. Therapeutic Goods Administration (TGA), Australia

None

### 7.5.4. Health Canada

None

## 7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

## 7.7. COMP work plan

None

## 7.8. Planning and reporting

### 7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2024

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2024 were circulated.

### 7.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

# 8. Any other business

## 8.1. EMA business Pipeline activity

The business pipeline report for Q2/2024 was presented for information.

# 9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 16-18 July 2024 COMP meeting, which was held remotely.

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Violeta Stoyanova-Beninska | Chair | Netherlands | No interests declared | |

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Tim Leest | Member | Belgium | No interests declared | |
| Jana Mazelova | Member | Czechia | No interests declared | |
| Boje Kvorning Pires Ehmsen | Member | Denmark | No interests declared | |
| Vallo Tillmann | Member | Estonia | No interests declared | |
| Karri Penttila | Member | Finland | No interests declared | |
| Cecile Dop | Member | France | No interests declared | |
| Frauke Naumann-Winter | Member | Germany | No interests declared | |
| Evangelia Giannaki | Member | Greece | No restrictions applicable to this meeting | |
| Zsofia Gyulai | Member | Hungary | No interests declared | |
| Emma Fagan | Member | Ireland | No interests declared | |
| Enrico Costa | Member | Italy | No interests declared | |
| Irena Rogovska | Member | Latvia | No restrictions applicable to this meeting | |
| Ruta Mameniskiene | Member | Lithuania | No interests declared | |
| Michel Hoffmann | Member | Luxembourg | No interests declared | |
| Elisabeth Johanne Rook | Member | Netherlands | No interests declared | |
| Maria Elisabeth Kalland | Member | Norway | No interests declared | |
| Bożenna Dembowska-Baginska | Member | Poland | No restrictions applicable to this meeting | |
| Joao Rocha | Member | Portugal | No restrictions applicable to this meeting | |
| Gloria Maria Palomo Carrasco | Member | Spain | No interests declared | |

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Darius Matusevicius | Member | Sweden | No restrictions applicable to this meeting | |
| Fernando Mendez Hermida | Member | Expert recommended by EMA | No interests declared | |
| Maria Judit Molnar | Member | Expert recommended by EMA | No restrictions applicable to this meeting | |
| Julian Isla | Expert | Spain | No interests declared | |
| Ines Alves | Expert | Portugal | No restrictions applicable to this meeting | |
| Maria Driessens | Expert | Netherlands | No restrictions applicable to this meeting | |
| Johanna de Groot | Expert | Netherlands | No interests declared | |
| A representative from the European Commission attended the meeting | | | | |
| Meeting run with support from relevant EMA staff | | | | |

Experts' declared interests were evaluated against the agenda topics or activities they participated in.

## 10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

**Abbreviations / Acronyms**

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

**Orphan Designation** *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

**Protocol Assistance** *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

**Maintenance of Orphan Designation** *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

For a list of acronyms and abbreviations, see:

Abbreviations used in EMA scientific committees & CMD documents and in relation to EMA's regulatory activities

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/