10 October 2024
EMA/COMP/446111/2024
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 September 2024

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Frauke Naumann-Winter

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

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 notes 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 in-person.

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 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 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. 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 EMA Secretariat announced the names of the Committee members who delegated their vote via proxy and the Committee members who received such proxy.

The Chair welcomed the new members to the Committee.

1.2. Adoption of agenda

The agenda for 10-12 September 2024 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 16-18 July 2024 were adopted with no amendments and will be published on EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. ivosidenib - EMA/OD/0000174573

Les Laboratoires Servier; Treatment of chondrosarcoma

COMP Rapporteur: Jana Mazelova

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 requested to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition with special focus on the most up-to-date bibliographic sources given the uncertainty about some of the assumptions leading to the final proposal, such as the disease duration.

For these assumptions, the sponsor was asked to substantiate the selection criteria based on relevant sources of information.

In the written response, the sponsor recalculated the point prevalence of chondrosarcoma in the EU using the formula $P=I\times D$, where P represents prevalence, I is incidence, and D is the average disease duration.

For these calculations, the sponsor utilised incidence rates derived from recent European epidemiological data, which align with the findings of a recent review by Thorkildsen and Myklebust (2023). In the absence of specific data on disease duration for chondrosarcoma, the sponsor used median overall survival (OS) as a proxy, estimating it to be around 15 years based on studies showing a survival probability of over 70% at the end of follow-up.

The point prevalence was then estimated for different duration scenarios with a range of incidence rates from 0.02 to 0.08 per 10,000 across various studies. In the most conservative scenario using the highest reported incidence the estimated prevalence was calculated to be 1.3 per 10,000.

This approach was considered satisfactory by COMP and a positive opinion was adopted.

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

The intention to treat the condition with the medicinal product containing ivosidenib was considered justified based on preliminary clinical data which showed antitumour activity in patients with the condition.

The condition is chronically debilitating due to surgery needed including amputations, and life-threatening, in particular for patients with metastatic disease.

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

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

A positive opinion for ivosidenib, for treatment of chondrosarcoma, was adopted by consensus.

2.1.2. - EMA/OD/0000154786

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

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 COMP does not consider the proposed condition acceptable for the purpose of orphan designation. The sponsor was therefore invited to justify the proposed condition as a distinct medical entity or a valid subset or propose an alternative condition. Note that this is for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the orphan regulations and relevant guidelines (especially section A of 2022/C 440/02).

- Intention to diagnose, prevent or treat

Considering that the proposed condition from the sponsor was challenged by the COMP, the sponsor was reminded that the medical plausibility section must be aligned with the final agreed orphan condition.

Notwithstanding the issue on the condition, the sponsor was asked to clarify how relevant intimal hyperplasia and levels of MCP-1 are in clinical practice for the long-term patency of arteriovenous fistulas (AVF) in chronic kidney disease (CKD) patients.

The sponsor was invited to present any new available non-clinical efficacy data or clinical efficacy data from the ongoing phase 1 study in CKD patients undergoing surgical creation of an AVF.

- Life-threatening and debilitating nature of the condition

Considering that the proposed condition from the sponsor has been challenged by the COMP, the sponsor was reminded that the section on the "Life-threatening and debilitating nature of the condition" must be aligned with the final agreed orphan condition.

- Number of people affected

Considering that the proposed condition from the sponsor has been challenged by the COMP, the sponsor was reminded that the prevalence calculation and final estimate must be aligned with the final agreed 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

Considering that the proposed condition from the sponsor was challenged by the COMP, the sponsor was reminded that the significant benefit section of the report needs to be aligned with the final agreed orphan condition, considering possible/relevant satisfactory methods.

In the written response, and during an oral explanation before the Committee on 10 September 2024, the sponsor suggested a slight amendment to the initially proposed condition and emphasised that arteriovenous (AV) access dysfunction is not a complication of surgery but a distinct condition resulting from a biological process of `failed´ vascular wall response to altered blood flow conditions following the AV access surgery. The sponsor

described intimal hyperplasia as a key factor underlying AV access dysfunction, together with outward remodelling of the vessel. The COMP acknowledged the described underlying biological processes of AV access dysfunction but pointed out that these are nevertheless occurring secondary to the haemodynamic changes following AV fistula surgery and which is intended to facilitate a procedure (haemodialysis) for the treatment of a different underlying condition, i.e. end-stage renal disease (ESKD). The COMP considered that ESKD is the actual underlying disease entity in this population.

The COMP was also aware of the previous orphan designations but pointed out that there is a continued evolution of regulatory decision making which may prompt renewed discussions on the acceptability of an orphan condition.

The sponsor presented new clinical data from cohort 1 of their ongoing phase 1 study in chronic kidney disease patients undergoing surgical creation of an AV fistula. The COMP acknowledged the new clinical data but considered that too many uncertainties exist at present to draw general conclusions on improved efficacy from it. These uncertainties pertain mostly to the lack of information of possible confounding factors with regards to the characteristics of the patients included in the active treatment vs control arm and the limited patient numbers, particularly in the control arm. Several factors have been described as influencing the success of AV fistula maturation, such as time for surgery, waiting time until the first use of the fistula and treatment of underlying diseases (cardiovascular, metabolic) as well as the experience by the respective surgeon.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 September 2024, prior to final opinion.

2.1.3. - EMA/OD/0000178304

Treatment of pouchitis

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:

- Significant benefit

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

The sponsor was requested to detail the results of available data to support the significant benefit assumption in the context of the current therapeutic management of patients. A comparative discussion is expected versus the authorised treatments in the treatment of pouchitis. Such discussion should be based on available non-clinical and/or clinical data to elucidate the relevance of the clinical responses and duration of response in the context of the current therapeutic management of the 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 11 September 2024, the sponsor presented arguments to justify the significant benefit of their proposed product over authorised treatments for pouchitis.

The sponsor argued that, due to the proposed product novel mechanism of action, it could potentially benefit patients across a spectrum of pouchitis types, from acute to chronic. This broader applicability could support a claim of significant benefit for a wider patient population. However, when asked to provide data to substantiate this claim, the sponsor clarified that the available evidence is limited to the chronic pouchitis setting, which overlaps with the indication for the authorised treatment, vedolizumab.

The sponsor further elaborated on data from ongoing studies, suggesting that the proposed product directly targets dysbiosis and has demonstrated positive clinical outcomes. When comparing with the authorised treatment vedolizumab, the sponsor claimed that the response and remission rates would be comparable to those seen with vedolizumab and other biologics. While the rationale was understood, the COMP noted that the comparison between the available clinical data presented significant challenges due to differences in the number of patients treated and the duration of clinical interventions.

The sponsor also highlighted the limitations of current biologic therapies which would underscore the need for new treatment options. While this argument was acknowledged, the COMP found it difficult to establish claims of superior safety for a product with limited clinical exposure. Furthermore, when questioned about patients in their clinical trial who were previously unresponsive to vedolizumab, the sponsor could not identify such cases. Such data would have been valuable in strengthening the argument for significant benefit based on superior efficacy.

Overall, while several arguments put forward by the sponsor were considered relevant concerning the limitations of existing treatments, the evidence provided was deemed premature to support the claims of significant benefit at this stage. The sponsor was encouraged to resubmit the application once additional data becomes available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 September 2024, prior to final opinion.

2.1.4. - EMA/OD/0000174349

Treatment of complex regional pain syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 27 August 2024, prior to responding to the list of issues.

2.1.5. 4,9-dimethyl-6-(4-aminophenyl)-2H-furo[2,3-H]-1-benzopyran-2-one - EMA/OD/0000171663

Fondazione Per La Ricerca Sulla Fibrosi Cistica Ets; Treatment of cystic fibrosis

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 cystic fibrosis the sponsor should further elaborate on the

available non-clinical data, the interpretability of such data, and the clinical relevance of the results obtained.

- 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. Arguments should be supported by data.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development, and how the product is expected to be positioned in the treatment armamentarium.

In the written response, and during an oral explanation before the Committee on 11 September 2024, the sponsor defended their position regarding the intention to treat and the significant benefit of the proposed product for cystic fibrosis (CF) patients.

In terms of medical plausibility, the sponsor emphasised non-clinical data comparing the proposed product to other anti-inflammatory agents used to treat chronic lung inflammation in CF. The sponsor also presented data from preclinical models demonstrating the product's ability to reduce neutrophil infiltration and inflammation. New in vitro data showed that the proposed product does not interfere with CFTR modulators, reinforcing its potential as a complementary anti-inflammatory therapy.

On the question of significant benefit, the sponsor compared the proposed product to existing treatments, noting that inflammation and progressive lung damage may persist in CF patients treated with CFTR modulators despite reductions in biomarkers. Based on the available non-clinical data, the sponsor emphasised the need for complementary anti-inflammatory therapies, particularly for CF patients who are either ineligible for CFTR modulators or whose lung damage is not fully addressed by these treatments.

As the sponsor's responses were considered satisfactory, the COMP adopted a positive opinion.

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

The intention to treat the condition with the medicinal product containing 4,9-dimethyl-6-(4-aminophenyl)-2H-furo[2,3-H]-1-benzopyran-2-one was considered justified based on non-clinical data in a relevant model showing a positive effect on weight loss and inflammatory biomarkers.

The condition is chronically debilitating and life-threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

The condition was estimated to be affecting approximately 1 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 4,9-dimethyl-6-(4-aminophenyl)-2H-furo[2,3-H]-1-benzopyran-2-one will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a relevant model demonstrating anti-inflammatory activity of the proposed product. The data suggest that the proposed product may provide a benefit across a wider range of patients beyond those targeted by currently authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4,9-dimethyl-6-(4-aminophenyl)-2H-furo[2,3-H]-1-benzopyran-2-one, for treatment of cystic fibrosis, was adopted by consensus.

2.1.6. - EMA/OD/0000173551

Treatment of Wilson's 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:

- Significant benefit

The sponsor’s claim for a clinically relevant advantage should be further justified by any results from clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

The claim for major contribution to patient care based on a modified formulation offering a once-a-day dosing of the proposed medicinal product should be further justified with data.

The sponsor was invited to further elaborate and show if there are current difficulties with available formulations and how they expect their formulation to overcome these. (Commission Notice 2016).

In the written response, and during an oral explanation before the Committee on 11 September 2024, the sponsor provided a detailed bibliographical submission explaining the concerns around pill load in Wilson’s disease patients and its link to maintaining an acceptable copper ceruloplasmin level. Focus was given to sources in the literature and the SmPCs of the approved products that the use of copper chelating agents like the proposed medicinal product require several doses per day resulting in the need for a reduction in pill burden to improve adherence as reported by patients. The sponsor believed that the proposed higher dose of immediate release 300 mg taken once a day offers this possibility over the current 150 mg which is divided in 2-4 times/day administration.

Compelling testimony was given by the sponsor’s patient representative regarding adherence to treatment and the difficulties encountered, in particularly as food intake is critical for the efficacy of the products. It was noted that without some initial clinical data with the actual product for designation, showing how a reduction in pill and dosing schedule could improve patient wellbeing, it was difficult to conclude on major contribution to patient care based solely on a patient testimonial, and bridging to observations on adherence in the literature. The survey conducted by the Wilson Disease Association highlights the challenges of the current treatments but currently no evidence exists with the proposed new 300 mg dose to support significant benefit. The COMP therefore considered that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 September 2024, prior to final opinion.

2.1.7. interleukin-12, human, recombinant - EMA/OD/0000179561

Allucent (DE) GmbH; Treatment of cutaneous T-cell lymphoma (CTCL)

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:

- Significant benefit

The sponsor was invited to clarify the positioning of their product in the treatment algorithm of patients with CTCL.

The sample size of the sponsors phase 2a study is considered low, which hampers the conclusion of an added benefit of the sponsors product (in combination with LD-TSEBT) over currently authorised products. Furthermore, important information is lacking in the side-by-side comparisons of the respective efficacy data. The claim of improved efficacy should therefore be substantiated with further information on ORR/CR and should be complemented with information on the durability of the responses.

In addition, the sponsor was invited to clarify which topical treatments patients included in the sponsors study did receive and whether these included also chlormethine.

For additional clarity, the sponsor was invited to present the data from their phase 2a study as swim lane plot.

In the written response, the sponsor provided the data on the durability of the responses from the patients of Study NM-ONC-001. Many of the patients achieved a durable response up to week 40 or even week 47. The reasons for patient withdrawal included: a physician's decision, inadvertent use of a steroid for a non-CTCL condition, urgent circumstances requiring major surgery unrelated to MF/CTCL or the study treatment, a patient's decision, and loss to follow-up. The patients who demonstrated complete responses (CRs), and the patients who demonstrated partial responses (PRs) all had clinical stage IB disease. The patients who demonstrated stable disease (SD) either had clinical stage IIB or IIIB. The overall response rate (ORR) was 100% for patients with clinical stage IB and 70% for all enrolled patients. The COMP considered that response rates especially for patients with stage IB compare favourably to the ones observed with currently authorised therapies (which are also targeting patients with more advanced disease).

The sponsor further clarified that some patients with stage IB disease (one achieving PR and one CR) and one with stage IIIB (achieving SD) received previous treatment which included the authorised topical treatment chlormethine.

The COMP considered that the responses addressed the outstanding issues on significant benefit. Therefore, the oral hearing was cancelled.

The Committee agreed that the condition, cutaneous T-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing interleukin-12, human, recombinant was considered justified based on preliminary clinical data showing responses in previously treated patients with mycosis fungoides-type CTCL.

The condition is chronically debilitating due to the development of cutaneous lesions, generalised erythroderma, lymphadenopathy, pruritus and life-threatening due to disease progression or ulceration of tumours, with secondary bacterial infections.

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

A positive opinion for interleukin-12, human, recombinant, for treatment of cutaneous T-cell lymphoma (CTCL), was adopted by consensus.

2.1.8. - EMA/OD/0000160667

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

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

The pathology in anti-neutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV) with pauci-immune glomerulonephritis and no granuloma formation in MPA differs significantly from the models of choice. The sponsor was therefore asked to further justify the extrapolation of results to the applied orphan condition, also considering that the drug-target was expressed in less than 50% of the kidney biopsies from AAV patients.

Furthermore, data from relevant non-clinical models would be helpful in establishing medical plausibility. The sponsor was asked to provide an update on any experiments with the product in AAV-GN model.

- Significant benefit

Significant benefit cannot be established as long as medical plausibility is unclear.

The sponsor was therefore asked to further clarify to what extent the chosen non-clinical models are representative for the applied overarching condition including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA), which would support the claim of the broader target population than the authorised treatments.

Furthermore, the sponsor was asked to clarify to what extent the planned clinical development will support establishing a benefit for the totality of the patient population.

If the product will be developed for MPA/GPA alone, then data should be provided that the product displays a significant benefit over the treatments authorised for this condition, in particular avacopan. Assumptions made based on a different mode of action should be supported by data.

In the written response, and during an oral explanation before the Committee on 10 September 2024, the sponsor presented their justification to address the question regarding medical plausibility and significant benefit of the proposed product.

The discussion centred on the sponsor's rationale for targeting complement activation in ANCA-associated vasculitis (AAV). The sponsor provided evidence from preclinical studies and published literature to support the relevance of complement inhibition in managing AAV, suggesting that this approach could benefit a broad range of AAV patients, including those who may not exhibit direct signs of complement activation at the time of biopsy. The sponsor also presented additional data from non-clinical models of complement activation,

showing that the proposed product localises to sites of active complement activation and reduces biomarkers of kidney injury. However, the COMP expressed concerns that these models may not fully represent the pathology of AAV, particularly given their differences in inflammation profiles and underlying disease mechanisms.

The sponsor further highlighted the potential significant benefit, proposing that its mechanism of action could result in more durable responses and a reduced need for glucocorticoids compared to currently approved therapies. However, the COMP emphasised the need for these claims to be supported by direct or indirect comparative data vis a vis existing treatments, such as avacopan, and noted the lack of such comparative data at this stage.

The COMP concluded that while the proposed therapeutic approach of targeting complement activation in AAV could be valid, additional data are needed to substantiate the claims of medical plausibility and significant benefit. The sponsor was encouraged to resubmit the application when additional supportive data becomes available.

In communicating to the sponsor, the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 September 2024, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. glecirasib - EMA/OD/0000172976

PPD Bulgaria EOOD; 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 glecirasib was considered justified based on non-clinical data in a valid model of the condition which showed reduction in tumour volume and preliminary clinical data which showed responses with the proposed product in 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 glecirasib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed responses in patients pretreated with the standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for glecirasib, for treatment of pancreatic cancer, was adopted by consensus.

2.2.2. - EMA/OD/0000175107

Treatment of glioma

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 October meeting.

2.2.3. - EMA/OD/0000175157

Treatment of idiopathic pulmonary 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 October meeting.

2.2.4. navenibart - EMA/OD/0000178549

PHARA; Treatment of hereditary angioedema

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing navenibart was considered justified based on clinical data showing a reduction in angioedema attacks in patients with the condition.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

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 navenibart will be of significant benefit to those affected by the condition. The data from an indirect comparison with the sponsors preliminary clinical data suggests that the sponsors product showed better results in preventing angioedema attacks than Orladeyo, oral use. The Committee considered that this constitutes a clinically relevant advantage. In relation to Cinryze, Berinert 2000/3000 and Takhzyro, the sponsors product appears to have at least similar efficacy while having a more favourable dosing schedule and/or more convenient route of administration. The Committee considered that this constitutes a major contribution to patient care as it is expected to reduce the treatment burden for patients affected by the condition.

A positive opinion for navenibart, for treatment of hereditary angioedema, was adopted by consensus.

2.2.5. adeno-associated virus vector serotype SAN011 encoding a microRNA against DMPK mRNA - EMA/OD/0000178877

Sanofi B.V.; Treatment of myotonic dystrophies

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, myotonic dystrophies, 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 SAN011 encoding a microRNA against DMPK mRNA was considered justified based on non-clinical in vivo data in a model of the condition showing an improvement in cardiac output and improvement in myotonic activity in the gastrocnemius muscle as measured by electromyography.

The condition is chronically debilitating due to muscle weakness, pain with stiffness which can be associated with falls and serious injury, cognitive and behavioural problems. The condition is life-threatening due to cardiac and pulmonary complications.

The condition was estimated to be affecting approximately 1 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 SAN011 encoding a microRNA against DMPK mRNA, for treatment of myotonic dystrophies, was adopted by consensus.

2.2.6. sodium selenate - EMA/OD/0000179156

Monash University; Treatment of frontotemporal dementia

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing sodium selenate was considered justified based on in vivo non-clinical data showing improvement in memory function.

The condition is life-threatening and chronically debilitating due to neurological and cognitive impairment and limited life-expectancy.

The condition was estimated to be affecting approximately 3.8 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.

A positive opinion for sodium selenate, for treatment of frontotemporal dementia, was adopted by consensus.

2.2.7. genetically modified human adenovirus encoding human PH20 hyaluronidase - EMA/OD/0000179541

Theriva Biologics S.L.; Treatment of retinoblastoma

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing genetically modified human adenovirus encoding human PH20 hyaluronidase was considered justified based on in vivo non-clinical data which showed increased eye survival and limited preliminary clinical data which showed partial responses.

The condition is chronically debilitating due to partial or complete vision loss and life-threatening due to intracranial dissemination and hematogenous metastasis and the risk of development of additional malignancies.

The condition was estimated to be affecting less than 1 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 genetically modified human adenovirus encoding human PH20 hyaluronidase, for treatment of retinoblastoma, was adopted by consensus.

2.2.8. octreotide hydrochloride - EMA/OD/0000179931

Camurus AB; Treatment of autosomal dominant polycystic liver disease

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, autosomal dominant polycystic liver disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing octreotide hydrochloride was considered justified based on bibliographical data showing a reduction in total liver volume and thus hepatomegaly in patients with the condition.

The condition is life-threatening and chronically debilitating due to the severe dysfunction of organs around the liver due to the increased hepatic volume or when one or more cysts get twisted, infected or develop intra-cystic minor bleeding.

The condition was estimated to be affecting approximately 0.1 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 octreotide hydrochloride, for treatment of autosomal dominant polycystic liver disease, was adopted by consensus.

2.2.9. - EMA/OD/0000179978

Treatment of ATTR amyloidosis

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 October meeting.

2.2.10. atacicept - EMA/OD/0000180597

Boyd Consultants Limited; Treatment of primary IgA nephropathy (IgAN)

COMP Rapporteur: Fernando Mendez Hermida

The Committee agreed that the condition, primary IgA nephropathy (IgAN), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing atacicept was considered justified based on clinical data showing a reduction in proteinuria and a trend toward stabilisation of renal function over approximately 17 months.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation.

The condition was estimated to be affecting approximately 4 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 atacicept will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which has shown that atacicept can provide a benefit in IgAN patient subsets, not currently covered by the authorised treatments Filspari and Sandimmune. Furthermore, atacicept has shown a trend toward stabilisation of renal function over approximately 17 months, which has not been demonstrated for currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for atacicept, for treatment of primary IgA nephropathy (IgAN), was adopted by consensus.

2.2.11. H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt - EMA/OD/0000182415

Axoltis Pharma; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, amyotrophic lateral sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt was considered justified based on non-clinical data in a model of the condition showing improved motor function and survival.

The condition is chronically debilitating and life-threatening due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure with shortened life expectancy.

The condition was estimated to be affecting approximately 1 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 H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt will be of significant benefit to those affected by the condition. The sponsor has presented non-clinical data from a disease model demonstrating that the proposed product

attenuates motor function decline, a benefit that is not anticipated with the currently authorised medicinal product, riluzole. Furthermore, the non-clinical evidence suggests that the proposed product may be applicable to a broader patient population than tofersen, which is specifically indicated for the treatment of amyotrophic lateral sclerosis (ALS) patients with mutations in the superoxide dismutase 1 (*SOD1*) gene. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for H-L-tryphophanyl-L-seryl-glycyl-L-tryptophanyl-L-seryl-L-seryl-L-cysteinyl-L-seryl-L-arginyl-L-seryl-L-cysteinyl-glycyl-OH (disulfide bond), acetate salt, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.12. 3-(5-(2-hydroxy-2-methylpropoxy)-6-methylpyrazin-2-yl)-1H-indole-7-carbonitrile - EMA/OD/0000182648

FGK Representative Service GmbH; Treatment of X-linked spinal and bulbar muscular atrophy (Kennedy's disease)

COMP Rapporteur: Darius Matusevicius

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of X-linked spinal and bulbar muscular atrophy (Kennedy's disease)

The Committee agreed that the condition, X-linked spinal and bulbar muscular atrophy (Kennedy's disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-(5-(2-hydroxy-2-methylpropoxy)-6-methylpyrazin-2-yl)-1H-indole-7-carbonitrile was considered justified based on non-clinical data in a model of the condition showing that treatment with the proposed product resulted in improvement in muscle structure and function, as well as survival.

The condition is chronically debilitating due to progressive muscle weakness, with difficulty in walking, with some patients requiring a wheelchair 15-20 years after the onset of the disease. The condition is life-threatening since advanced cases develop dyspnoea, laryngospasm, and dysphagia that may result in aspiration and choking leading to death.

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.

A positive opinion for 3-(5-(2-hydroxy-2-methylpropoxy)-6-methylpyrazin-2-yl)-1H-indole-7-carbonitrile, for treatment of X-linked spinal and bulbar muscular atrophy (Kennedy's disease), 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 13 applications submitted and 24 upcoming 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 hereditary angioedema

The discussion was postponed.

3.1.2. -

Treatment of ovarian cancer

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

3.1.3. -

Treatment of Dravet syndrome

The COMP re-discussed the adopted proposed answers on the significant benefit issues.

3.1.4. -

Treatment of *STXBP1* developmental and epileptic encephalopathy

The COMP re-discussed the adopted 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

None

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

4.2.1. Hetronifly - serplulimab - EMEA/H/C/006170, EU/3/22/2731, EMA/OD/0000155775

Henlius Europe GmbH; Treatment of small cell lung cancer

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 October meeting.

4.2.2. - vorasidenib - EMEA/H/C/006284, EU/3/22/2737, EMA/OD/0000159477

Les Laboratoires Servier; Treatment of glioma

The status of the procedure at CHMP was noted.

4.2.3. Elahere - mirvetuximab soravtansine - EMEA/H/C/005036, EU/3/15/1458, EMA/OD/0000178274

Abbvie Deutschland GmbH & Co. KG; Treatment of ovarian cancer

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 October meeting.

4.2.4. Hympavzi - marstacimab - EMEA/H/C/006240

Pfizer Europe MA EEIG

a) Treatment of haemophilia B, EU/3/23/2866, EMA/OD/0000179102

b) Treatment of haemophilia A, EU/3/16/1752, EMA/OD/0000179103

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 October meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 7 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. Columvi - glofitamab - EMEA/H/C/005751/II/0005, EU/3/21/2497, EMA/OD/0000225358

Roche Registration GmbH; Treatment of diffuse large B-cell lymphoma

CHMP Rapporteur: Aaron Sosa Mejia; CHMP Co-Rapporteur: Jan Mueller Berghaus

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

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

The Chair welcomed Luana Mifsud Buhagiar, as the new member for Malta.

The Chair welcomed Maria Driessens, as the new member representing Patients' Organisations.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings – Hungary

The COMP noted the draft agenda for the meeting to be held face-to-face 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 6 September 2024.

7.1.5. COMP Decisions Database

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

7.1.6. Election of COMP Vice-Chairperson

The mandate of the COMP Vice-Chair, Armando Magrelli, ended on 14 June 2024.

The election of the new Vice-Chair took place in accordance with the COMP rules of procedure.

The nominations received were presented to the Committee.

The COMP elected Frauke Naumann-Winter as COMP Vice-Chair for a three-year mandate starting on 10 September 2024.

The COMP and the Agency congratulated Frauke Naumann-Winter on her election and wished her all the best in her new role as Vice-Chair of the Committee.

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)

Documents were tabled for information.

7.3.2. Innovation Task Force (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

7.7.1. Update on 2024 work plan

The COMP noted the 2024 mid-year report.

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. Large B-cell lymphoma - condition and prevalence

The COMP noted the presentation on the condition of large B-cell lymphoma (LBCL). The COMP considered the family term of LBCL similar to the 5th Edition of the World Health Organization Classification of haematolymphoid tumours, the appropriate condition for orphan designation.

This condition, as agreed to by the Oncology Working party, is intended to cover the most common subtype diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS), as well as rarer subsets often included in clinical trials during clinical development.

The COMP also discussed the impact of this approach on the estimation of prevalence and concluded that the prevalence is currently expected to be within the acceptance criteria for orphan designation.

If the actual data submitted for orphan designation focus on specific subtypes of large B-cell lymphomas, e.g. primary large B-cell lymphomas of immune-privileged sites, orphan designation may still be restricted to the rare subtype.

8.2. The European Cancer Information System (ECIS) - Incidence, Mortality, Survival and Prevalence indicators

The COMP noted the presentation on incidence, mortality, survival and prevalence indicators. The COMP considered that a follow up is needed in the near future to discuss in more details the methodology used by ECIS.

8.3. Committee meetings in Microsoft Teams and new tool for voting

The COMP was informed that from October 2024 a new virtual meeting platform will be used to run the Committee meetings. The Committee will be trained on how to work on the new platform, including a new tool for voting and interaction in the meeting.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 September 2024 COMP meeting, which was held in-person.

An asterisk (*) after the role, in the second column, signals that the member attended remotely. Additional experts participated in (part of) the meeting, either in person or 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	
Tim Leest	Member	Belgium	No interests declared	
Ioannis Kkolos	Member	Cyprus	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 (Vice-Chair)	Germany	No interests declared	
Evangelia Giannaki	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member*	Hungary	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Luana Mifsud Buhagiar	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Olimpia Neagu	Member*	Romania	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Fernando Mendez Hermida	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No interests declared	
Maria Judit Molnar	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Maria Driessens	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Tarec Christoffer El-Galaly	Expert	Denmark	No restrictions applicable to this meeting	
Andre Elferink	Expert	Netherlands	No interests declared	
Gerlienke Geurts-Voerman	Expert	Netherlands	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Caroline Auriche-Benichou	Expert	France	No interests declared	
Maria Cavaller Bellaubi	Expert	Patients' Organisation Representative	No restrictions applicable to this meeting	
Representatives 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/