7 September 2023
EMA/COMP/353726/2023
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 11-13 July 2023

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

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 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 in-person with some members connected 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 in upcoming discussions 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

1.2. Adoption of agenda

The agenda for 11-13 July 2023 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 13-15 June 2023 were adopted with no 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/0000134159

Treatment of tuberculosis

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 20 June 2023, prior to responding to the list of issues.

2.1.2. - EMA/OD/0000077804

Treatment of non-traumatic spontaneous intracerebral haemorrhage (ICH)

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 sponsor was invited to further substantiate how the reduction in neuronal death in the model translates to functional outcomes in the condition.

In the written response, and during an oral explanation before the Committee on 11 July 2023 the sponsor further emphasised the following. Neuronal cell death resulting from ICH or from (subsequent) ischemic stroke plays a crucial role in the development of neurological deficits following the injury. Inflammation is triggered through a common pathway shared by both acute ischaemic stroke and intracerebral haemorrhage and plays a crucial part in the development of brain oedema.

The translation of functional effects from pre-clinical models to humans is difficult; reasons include differences in recovery potential and expected variability due to differences in injured brain location which result in different functional impairment.

Studies correlated plasma biomarkers, such as neurofilament light (NfL) and phosphorylated axonal neurofilament subunit (pNH-H), with neurological, functional, and cognitive status in ICH patients (Gendron et al., 2020; Cai et al., 2013).

While the sponsors arguments were duly acknowledged by the COMP, they did not help the Committee to understand if or how exactly the proposed product induced decrease in neuronal death in the model translates to functional outcomes in the condition. The COMP also pointed out that no positive effects on reducing oedema formation were observed which might have been expected when reducing neuroinflammation. Furthermore, no data on the NfL and pNH-H plasma biomarkers were available.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 July 2023, prior to final opinion.

2.1.3. - EMA/OD/0000135389

Treatment of amyotrophic lateral sclerosis

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 22 June 2023, prior to responding to the list of issues.

2.1.4. allogeneic faecal microbiota, pooled - EMA/OD/0000126381

Maat Pharma; Treatment in allogeneic haematopoietic stem cell transplantation

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:

- Targeted condition

The sponsor was asked to justify the appropriateness of the proposed condition, in view of the absence of outcome data with the product in the proposed condition.

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment in haematopoietic stem cell transplantation, the sponsor should further elaborate on the relevance of the presented results obtained in different conditions with similar products using different routes of administration.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action. However, no data (e.g. transplant-related mortality) neither in non-clinical models nor in patients treated with the proposed product were submitted to support a claim of improving outcomes after haematopoietic stem cell transplantation. The sponsor was requested to further justify the assumptions.

In the written response, and during an oral explanation before the Committee on 12 July 2023, the sponsor did not elaborate on the possibility to change the proposed condition. Instead, they presented new follow-up data from an ongoing clinical study, in which acute myeloid leukaemia/myelodysplastic syndromes (AML/MDS) patients were treated with the proposed product. Of the 21 AML patients, 9 underwent allogeneic haematopoietic stem cell transplantation (allo-HSCT) in the months after administration of the proposed product. 2 patients out of 9 developed a graft-versus-host disease (GvHD) and 1 patient out of 9 died. The sponsor argued that the expected aGvHD incidence after alloHSCT would be 40-60%, and attributes the observed low GvHD rate to the treatment with the proposed product, even though several months passed between treatment and alloHSCT.

Additional data were presented on the microbiota richness of the included patients. The last study-visit at Day 44 (+/- 10) showed a persisting effect on microbiota diversity and a successful "engraftment" of microbiota. Based on this data, the COMP concluded that the medical plausibility was considered justified based on published clinical data which showed improved outcomes after haematopoietic stem cell transplantation associated with improved gut microbiome diversity. This data was considered sufficient to support the applied proposed condition and the significant benefit when the proposed product was used prior to HSCT.

The Committee agreed that the condition, treatment in haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic faecal microbiota, pooled was considered justified based on published clinical data which showed improved outcomes after haematopoietic stem cell transplantation associated with improved gut microbiome diversity.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

The condition was estimated to be affecting approximately 0.6 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 allogeneic faecal microbiota, pooled will be of significant benefit to those affected by the condition. The sponsor has provided published clinical data which showed improved outcomes when the proposed product was used prior to

haematopoietic stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic faecal microbiota, pooled, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.5. - EMA/OD/0000131231

Treatment of malaria

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 previous timeframes to 2020, since this year would not be representative given the travel restrictions due to the COVID-19 pandemic.

- Significant benefit

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

The sponsor was invited to provide results of any non-clinical or clinical studies to support the significant benefit assumption in the context of the authorised medicinal products for which claims were made (i.e., treatment posology, effect on resistances to currently approved anti-malarial agents, recrudescence).

In the written response, and during an oral explanation before the Committee on 12 July 2023, the sponsor relied on the ECDC Surveillance Report from 2019, where 8,641 malaria cases were reported in the EU/EEA. As per this data, the overall notification rate in 2019 was 1.3 cases per 100,000 population. Hence, as per this data, in 2019, the incidence of malaria in Europe is 0.13 cases per 10,000 population. The sponsor considered that malaria infections are normally either cured or lethal within days (i.e., less than one year), hence the annual incidence rate is used to describe the prevalence of malaria. The proposed recalculation was accepted by the COMP.

Addressing the significant benefit comparison with available treatments, the sponsor emphasised the claims on a better compliance and less resistance potential. To support this claim, the attention was drawn to the available clinical data in patients with the condition. On the course of the oral explanation, enquires were also posed on the treatment regime, and the potential advantage over the recurrence phenomenon. However, the response produced by the sponsor did not dispel the existing doubts. Overall, it was the opinion of the COMP that the arguments brought by the sponsor did not sufficiently address the comparison question with other available treatments for the applied orphan condition. The sponsor withdrew the application prior to adoption of an opinion by the COMP.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2023, prior to final opinion.

2.1.6. - EMA/OD/0000134554

Treatment of neurofibromatosis type 1 (NF1)

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 23 June 2023, prior to responding to the list of issues.

2.1.7. - EMA/OD/0000135309

Treatment of glioma

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 asked to specify the exact claim(s) for the significant benefit of the proposed product over all currently authorised treatment options and support the claim(s) with relevant data.

In the written response, and during an oral explanation before the Committee on 12 July 2023, the sponsor emphasised the following. The proposed product can cross the blood-brain barrier (BBB). The mechanism of action of the product is new and promising in glioblastoma multiforme (GBM). In newly diagnosed GBM patient-derived xenograft models the proposed product added to the standard of care (temozolomide + radiotherapy) showed a trend in prolonging survival, as compared to standard of care (SoC) alone in 3 out of 8 models (GBM79, GBM102 and GBM59). However, in all three cases the prolonged survival with the triple combination was not statistically significant as compared to the standard of care (temozolomide + radiotherapy) alone. In 2 additional models (GBM28 and GBM43), the product combined with SoC (temozolomide + radiotherapy) performed better than radiotherapy only and temozolomide alone.

When considering the treatment of patients with recurrent glioma (including GBM), carmustine and lomustine are nitrosoureas that provide limited clinical benefit. They have not yet been tested in non-clinical studies together with the proposed product.

The COMP concluded that no new relevant data has been presented by the sponsor to support a positive conclusion on the significant benefit of the proposed product vis a vis current standard of care therapies. At least a conclusive improvement in survival vis a vis the first-line standard of care temozolomide + radiotherapy would have been expected by the COMP. Furthermore, the Committee would have required more clarifications on the non-clinical data presented as regards the specific number of animals per treatment group, the censoring in the survival curves and the calculation determining the significance of the survival data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 July 2023, prior to final opinion.

2.1.8. - EMA/OD/0000131435

Treatment of gastro-entero-pancreatic neuroendocrine tumours

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 were based on a modified release formulation which may offer a clinically relevant advantage.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the preliminary findings from the on-going open label Phase III study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Products authorised for carcinoid syndrome should also be considered.

In the written response, and during an oral explanation before the Committee on 13 July 2023, the sponsor clarified several points regarding the clinical trial data. The patients who were enrolled in the study were on authorised treatments for GEP-NETS before they were enrolled and started on the sponsor's product. The proportion of patients who were Grade 1, 2 or 3 were different from the study which had a higher proportion of Grade 1 patients.

It was argued that because there was a high proportion of patients with Grade 2 that there is a trend towards clinical superiority for the sponsor's product and this could be the basis of significant benefit. The limitations being that the study is still on-going and single blind, so the results are not yet known to the sponsor.

The merits of the Phase II study where patients with GEP-NETS had been recruited was also discussed in an effort to understand if the data could support the clinically relevant advantage. The sponsor claimed that the symptoms were stabilised or improved when patients were switched to the proposed product. However, the preliminary nature of the observations and the limited number of patients were not conclusive enough to support the significant benefit.

The COMP concluded that there was only equivalent clinical efficacy and no basis for a clinically relevant advantage.

The major contribution to patient care was further discussed. The sponsor explained the problems with the somatostatin injections such as storage (fridge or not), limitation to travel, concerns with finding nurses to administer the product while travelling, injection pain and post injection pain. Current available products are for intramuscular or subcutaneous injections once a month which have to be done by a health care professional. The proposed product will be for self-administration. These points were not however supported with any preliminary findings from studies with the proposed product. The sponsor informed the COMP that they were measuring patient reported outcomes in their on-going Phase III study (results still blinded) and that there was no such data from the Phase II study.

The COMP concluded 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 13 July 2023, prior to final opinion.

2.1.9. - EMA/OD/0000134260

Treatment of amyotrophic lateral sclerosis (ALS)

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 22 June 2023, prior to responding to the list of issues.

2.1.10. alprostadil - EMA/OD/0000101423

Oresund Pharma ApS; Treatment in solid organ transplantation

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:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment in solid organ transplantation the sponsor should further justify the positioning of the proposed product in the current clinical practice based on more recent publications.

- Significant benefit

The significant benefit is subject to acceptability of the arguments/data that support the medical plausibility. The sponsor was requested to provide additional arguments in support of the significant benefit.

In the written response, the sponsor provided additional data based on more recent applications. Most specifically for the heart, a PGE1-derivate, the EP4 Receptor-specific agonist (2E)-17,18,19,20-tetranor-16-(3-biphenyl)-2,3,13,14-tetradehydro-PGE1, has shown in a dose dependent manner, to prevent post-ischemic infiltration of monocytes/macrophages (evidenced by ED-1, and MCP-1), T-cells (evidenced by CD4 and CD8), MMP-2 and MMP-9. Animal and clinical studies regarding the role of inflammatory cytokines (Hide et al., 1995; Lemay et al., 2000; Zhu et al., 2017a and b), have shown that PGE1 can improve ischemia reperfusion injury in several biological systems (Ma et al., 2004; Sako et al., 2006; Blogowski et al., 2012; Erer et al., 2016; Gezginci-Oktayoglu et al., 2016), and Zhu et al. reviewed these effects in humans in a Meta-analysis (Zhu et al., 2017a).

Based on the more recent evidence, the COMP considered that the medical plausibility and the significant benefit have been justified and the oral explanation was cancelled.

The Committee agreed that the condition, treatment in solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing alprostadil was considered justified based on non-clinical data showing improved condition of the graft supported by positive effect on inflammatory infiltration and ischemia-reperfusion injury and published preliminary clinical data showing a preventive effect in early graft rejection in heart transplant patients and lower incidence of delayed graft function in kidney transplant patients.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation, graft loss and only approximately 50% of patients retaining a functional organ after 10 years.

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.

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 alprostadil will be of significant benefit to those affected by the condition. The sponsor has provided published non-clinical data showing improved condition of the graft and published preliminary clinical data that demonstrate decreased early graft rejection when the product is used as an add-on to authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for alprostadil, for treatment in solid organ transplantation, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000122901

Treatment of thalassaemia intermedia and major

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. - EMA/OD/0000124476

Treatment of Duchenne muscular dystrophy

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.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 4 August 2023.]

2.2.3. virus-like particle containing Cas9/gRNA ribonucleoprotein targeting the human *HTT* gene - EMA/OD/0000128591

Laura Nae; Treatment of Huntington's disease

COMP Rapporteur: Enrico Costa

The Committee agreed that the condition, Huntington'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 virus-like particle containing Cas9/gRNA ribonucleoprotein targeting the human *HTT* gene was considered justified based on non-clinical in vivo data in a model of the condition which showed an improvement in motor function tests.

The condition is life-threatening and chronically debilitating due to severe behavioural and cognitive disturbances and progressive motor dysfunction.

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 virus-like particle containing Cas9/gRNA ribonucleoprotein targeting the human *HTT* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the product can target the production of the mutant protein and disease progression, therefore treating aspects not fully addressed by authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for virus-like particle containing Cas9/gRNA ribonucleoprotein targeting the human *HTT* gene, for treatment of Huntington's disease, was adopted by consensus.

2.2.4. - EMA/OD/0000128649

Treatment of transthyretin-mediated 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 September meeting.

2.2.5. herpes simplex virus-1, derived from strain F, with deletions on genes gamma (1) 34.5 and UL39 - EMA/OD/0000131298

Regenold GmbH; Treatment of glioma

COMP Rapporteur: Jana Mazelova

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

The intention to treat the condition with the medicinal product containing herpes simplex virus-1, derived from strain F, with deletions on genes gamma (1) 34.5 and UL39 was considered justified based on non-clinical data in a model of the condition showing a positive effect on survival, as well as preliminary clinical data which showed an effect on tumour volume in pre-treated paediatric patients with high-grade glioma.

The condition is chronically debilitating due to symptoms caused by the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with a limited median overall survival.

The condition was estimated to be affecting approximately 2.6 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 herpes simplex virus-1, derived from strain F, with deletions on genes gamma (1) 34.5 and UL39 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that indicate increased survival with the proposed product in high-grade glioma patients pre-treated with standard of care treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for herpes simplex virus-1, derived from strain F, with deletions on genes gamma (1) 34.5 and UL39, for treatment of glioma, was adopted by consensus.

2.2.6. - EMA/OD/0000133480

Treatment of Stargardt'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.

2.2.7. mitazalimab - EMA/OD/0000133609

Alligator Bioscience AB; 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 mitazalimab was considered justified based on synergistic antitumour activity on a non-clinical model of the condition as well as preliminary clinical data which showed increased response rate in patients with metastatic pancreatic ductal adenocarcinoma when used in combination to modified FOLFIRINOX.

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 2.3 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 mitazalimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary data that showed antitumour activity in combination with FOLFIRINOX in the non-clinical and clinical setting, when compared to standard of care treatment in patients with metastatic pancreatic ductal adenocarcinoma. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.8. lithium carbonate - EMA/OD/0000134075

Laboratoires Delbert; Treatment of Kleine-Levin syndrome

COMP Rapporteur: Tim Leest

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

The intention to treat the condition with the medicinal product containing lithium carbonate was considered justified based on published clinical data which indicated reduction on the frequency of episodes per year.

The condition is chronically debilitating due to severe hypersomnia associated with cognitive and behavioural disturbances such as confusion, derealisation, apathy, compulsive eating, and hypersexuality.

The condition was estimated to be affecting approximately 0.04 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 lithium carbonate, for treatment of Kleine-Levin syndrome, was adopted by consensus.

2.2.9. - EMA/OD/0000135016

Treatment of diffuse large B-cell lymphoma

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.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 26 July 2023.]

2.2.10. 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting PLP1 pre-mRNA - EMA/OD/0000135549

Ionis Development (Ireland) Limited; Treatment of Pelizaeus-Merzbacher disease

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, Pelizaeus-Merzbacher disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting PLP1 pre-mRNA was considered justified based on non-clinical data in valid models of the condition which showed restoration of oligodendrocyte survival and myelination, improved survival and motor function.

The condition is chronically debilitating due to progressive loss of motor function with loss of ambulation, spasticity, dysphagia, seizures, cognitive impairment, impaired or absent verbal communication and life-threatening due to the progressive neurologic deterioration including respiratory complications.

The condition was estimated to be affecting approximately 0.02 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 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting PLP1 pre-mRNA, for treatment of Pelizaeus-Merzbacher disease, was adopted by consensus.

2.2.11. adeno-associated virus vector serotype 9 containing the *PKP2* gene - EMA/OD/0000136490

Qdossier B.V.; Treatment of arrhythmogenic right ventricular cardiomyopathy (ARVC) due to plakophilin-2 gene (*PKP2*) mutations

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, arrhythmogenic right ventricular cardiomyopathy due to plakophilin-2 gene mutations, 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 *PKP2* gene was considered justified based on non-clinical in vivo data in a valid model of the condition, showing potential to attenuate disease progression with improved survival and heart function and a reduction in arrhythmia scores.

The condition is chronically debilitating due to palpitations, syncope, and ventricular tachycardia and life-threatening due to ventricular fibrillation resulting in sudden death and heart failure.

The condition was estimated to be affecting approximately 1.4 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 adeno-associated virus vector serotype 9 containing the *PKP2* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid model of the condition which showed that the product could modify the underlying disease mechanism resulting in improved heart function, reduced cardiac fibrosis and improved survival, which cannot be expected from currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus vector serotype 9 containing the *PKP2* gene, for treatment of arrhythmogenic right ventricular cardiomyopathy due to plakophilin-2 gene mutations, was adopted by consensus.

2.2.12. - EMA/OD/0000137651

Treatment of Smith-Magenis 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.

2.2.13. - EMA/OD/0000138272

Treatment of hypothalamic obesity

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/0000138974

Treatment of pancreatic 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 September meeting.

2.2.15. - EMA/OD/0000139967

Treatment of Guillain-Barre 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.

2.2.16. cedazuridine, decitabine - EMA/OD/0000140431

Otsuka Pharmaceutical Netherlands B.V.; Treatment of patients with myelodysplastic syndromes and chronic myelomonocytic leukaemia

COMP Rapporteur: Karri Penttila

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

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

The intention to treat the condition with the medicinal product containing cedazuridine, decitabine was considered justified based on clinical data showing complete responses and a reduction in the number of required red blood cell or platelet transfusions in patients with intermediate and high-risk myelodysplastic syndromes.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as severe infections, internal bleeding, fatigue and need for repeated red blood cell or platelet transfusions and a risk of transformation into acute myeloid leukaemia.

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 cedazuridine, decitabine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which demonstrate similar efficacy with currently approved therapies for patients with intermediate and high-risk myelodysplastic syndromes who are ineligible for receiving allogeneic stem cell transplantation. The oral fixed-dose combination might reduce the burden of parenteral therapies. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for cedazuridine, decitabine, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.2.17. - EMA/OD/0000140620

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 September meeting.

2.2.18. - EMA/OD/0000140879

Treatment of limb-girdle muscular dystrophy (LGMD)

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.

2.2.19. - EMA/OD/0000140986

Treatment of Duchenne muscular dystrophy

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.

2.2.20. - EMA/OD/0000141035

Treatment of amyotrophic lateral sclerosis (ALS)

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. adeno-associated virus serotype 9 vector containing the human *LAMP2* isoform B transgene - EMA/OD/0000141142

Rocket Pharmaceuticals B.V.; Treatment of Danon disease

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, Danon disease, 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 serotype 9 vector containing the human *LAMP2* isoform B transgene was considered justified based on non-clinical in vivo data showing a significant improvement in cardiac function and preliminary clinical data showing an improvement in NYHA class heart failure grading.

The condition is life-threatening and chronically debilitating due to cognitive disabilities, hypertrophic cardiomyopathy, and muscle weakness. Men have a high morbidity and are unlikely to reach the age of 25 years without a cardiac transplantation.

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 adeno-associated virus serotype 9 vector containing the human *LAMP2* isoform B transgene, for treatment of Danon disease, was adopted by consensus.

2.2.22. - EMA/OD/0000142116

Treatment of amyotrophic lateral sclerosis

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.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 21 July 2023.]

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 14 applications.

[Post-meeting note: The COMP appointed additionally 16 rapporteurs by written procedure following its July meeting.]

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 2 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of achondroplasia

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

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

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. Tevimbra - tislelizumab - EMEA/H/C/005919/0000, EU/3/20/2357, EMA/OD/0000129253

Novartis Europharm Limited; Treatment of oesophageal cancer

COMP Rapporteur: Frauke Naumann-Winter; COMP Co-Rapporteur: Bozenna Dembowska-Baginska

An opinion recommending not to remove Tevimbra, tislelizumab, EU/3/20/2357 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. - quizartinib - EMEA/H/C/005910/0000, EU/3/09/622, EMA/OD/0000134652

Daiichi Sankyo Europe GmbH; Treatment of acute myeloid leukaemia

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.

4.2.3. - cedazuridine, decitabine - EMEA/H/C/005823/0000, EU/3/21/2548, EMA/OD/0000141337

Otsuka Pharmaceutical Netherlands B.V.; Treatment of acute myeloid leukaemia

The discussion was cancelled as the Marketing Authorisation Application had been withdrawn after the CHMP June meeting.

4.2.4. Bylvay - odevixibat - EMEA/H/C/004691/II/0011, EU/3/12/1040, EMA/OD/0000123138

Albireo AB; Treatment of Alagille syndrome

COMP Rapporteur: Zsofia Gyulai; COMP Co-Rapporteur: Joao Rocha; CHMP Rapporteur: Johann Lodewijk Hillege; A list of issues was adopted on 15 June 2023.

An oral explanation was held on 11 July 2023.

An opinion recommending the removal of Bylvay, odevixibat, EU/3/12/1040 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.]

4.2.5. Tepkinly - epcoritamab - EMEA/H/C/005985/0000, EU/3/22/2581, EMA/OD/0000104478

Abbvie Deutschland GmbH & Co. KG; Treatment of diffuse large B-cell lymphoma

COMP Rapporteur: Maria Elisabeth Kalland; COMP Co-Rapporteur: Frauke Naumann-WinterA list of issues was adopted on 15 June 2023.

An oral explanation to be held on 12 July 2023, was cancelled.

An opinion recommending not to remove Tepkinly, epcoritamab, EU/3/22/2581 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.]

4.2.6. Talvey - talquetamab - EMEA/H/C/005864/0000, EU/3/21/2486, EMA/OD/0000126657

Accelerated assessment

Janssen - Cilag International; Treatment of multiple myeloma

COMP Rapporteur: Frauke Naumann-Winter; COMP Co-Rapporteur: Karri PenttilaA list of issues was adopted on 15 June 2023.

An oral explanation was held on 12 July 2023.

An opinion recommending not to remove Talvey, talquetamab, EU/3/21/2486 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 2 applications.

4.5. Orphan Maintenance Reports

None

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. Carvykti - ciltacabtagene autoleucel - EMEA/H/C/005095/II/0021, EU/3/20/2252, EMA/OD/0000141581

Janssen - Cilag International; Treatment of multiple myeloma

CHMP Rapporteur: Jan Mueller-Berghaus

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

5.2.2. Adcetris - brentuximab vedotin - EMEA/H/C/002455/II/0107, EU/3/08/596, EMA/OD/0000136638

Takeda Pharma A/S; Treatment of Hodgkin lymphoma

CHMP Rapporteur: Johann Lodewijk Hillege; CHMP Co-Rapporteur: Jan Mueller-Berghaus

The status of the procedure at CHMP was noted.

5.2.3. Onivyde pegylated liposomal - irinotecan- EMEA/H/C/004125/II/0034, EU/3/11/933, EMA/OD/0000144740

Les Laboratoires Servier; Treatment of pancreatic cancer

CHMP Rapporteur: Filip Josephson

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 2 applications.

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

New membership:

The Chair welcomed Maria Judit Molnar, as the new member nominated by the European Commission on the EMA's recommendation.

7.1.2. Vote by proxy

Cécile Dop gave a proxy to Jana Mazelova to vote on behalf of Cécile Dop during the entire duration of meeting.

Lyubina Todorova Racheva gave a proxy to Eva Malikova to vote on behalf of Lyubina Todorova Racheva during the entire duration of meeting.

Maria Judit Molnar gave a proxy to Zsofia Gyulai to vote on behalf of Maria Judit Molnar during the entire duration of meeting.

7.1.3. Strategic Review & Learning meetings

COMP noted the upcoming SRLM meeting in Madrid under the Spanish Presidency of the Council of the EU, which will be held on 17-18th October 2023. There will be joint session held with PDCO.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met face-to-face on 11 July 2023.

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 2023

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2023 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. Update Presentation: Results on historical review of indirect comparisons

COMP was updated on the project reviewing indirect comparisons used in significant benefit assessment at maintenance. The data and presentation were shared with the Committee. The outcome of the project will be published in a scientific paper.

8.2. COMP members nominated on EMA's recommendation by the European Commission

COMP noted the re-nomination of Ingeborg Barisic and nomination of Maria Judit Molnar, as the new member nominated by the European Commission on the EMA's recommendation.

8.3. CXMP 2024 meetings format and F-2-F meeting dates for COMP

COMP noted the presented plan on the F-2-F meeting dates.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 11-13 July 2023 meeting.

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	
Armando Magrelli	Vice-Chair	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttila	Member	Finland	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Evangelia Yannaki	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	
Ruta Mameniskiene	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	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	
Eva Malikova	Member	Slovak Republic	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Judit Molnar	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Maria Cavaller Bellaubi	Expert – via WebEx*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Outi Mäki-Ikola	CHMP Member – via WebEx*	Finland	No restrictions applicable to this meeting	
Johann Lodewijk Hillege	CHMP Member – via WebEx*	Netherlands	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts 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.

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