20 June 2024
EMA/COMP/259816/2024
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 21-23 May 2024

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

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members and experts for concerned agenda topics.

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 Chair welcomed the new member and thanked the departing member for his contributions to the Committee.

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

1.2. Adoption of agenda

The agenda for 21-23 May 2024 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 16-18 April 2024 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/0000155489

Treatment of cutaneous T-cell lymphoma

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 6 May 2024, prior to responding to the list of issues.

2.1.2. - EMA/OD/0000165835

Treatment of gastric carcinoma

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

Signet ring cell carcinoma is not considered as a distinct medical entity or a valid subset. 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).

The sponsor was asked to further justify the validity of the proposed orphan condition in view of the relevance of the underlying adenocarcinoma for prognosis and treatment decisions and the lack of an accepted cut-off level for the signet ring morphology across different adenocarcinomas.

The sponsor was requested to further justify the acceptability of extrapolating in silico data predicting T-cell response against a viral infection to efficacy of an anti-cancer vaccine.

Furthermore, the rationale of selecting the epitopes of tumour antigens differs from the planned process of the proposed product. The sponsor was also asked to discuss the applicability of the chosen antigens (gastric cancer) specific for the treatment of the applied condition (signet ring cell carcinoma).

The anti-tumour activity observed cannot be disentangled from the concomitant chemoimmunotherapy. The sponsor was asked to comment on this on potential bias.

In the absence of data reflecting the entire concept of the proposed product in a valid orphan condition, the medical plausibility cannot be established.

- Number of people affected

The prevalence is subject to the acceptance of the proposed condition.

- Significant benefit

The significant benefit is subject to the acceptance of the proposed condition and the medical plausibility.

In the written response, and during an oral explanation before the Committee on 21 May 2024, the sponsor expanded the scope of the orphan condition to include a broader patient population and proposed ''gastric carcinoma'' as an orphan condition. The sponsor argued regarding the medical plausibility and the use of in silico data from COVID-19 to predict T-cell responses in gastric cancer is justified by the fact that both infectious diseases and cancer involve the presentation of antigens via HLA molecules and the subsequent activation of T-cell responses. The predictive model used in COVID-19 has been adapted to account for the unique complexities of tumour antigen presentation, an approach supported by literature. In addition, the selection of the therapeutic targets (tumour-specific antigens)

was guided by data derived from peer-reviewed literature due to the unavailability of tumour samples .

The COMP considered that the issues regarding the medical plausibility were not resolved regarding the validity of the system, and the limited data and the unavailability of tumour samples .

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

The sponsor did not recalculate the prevalence for the new applied condition of "gastric carcinoma".

Regarding the significant benefit the sponsor argued that the personalised vaccine represents a significant therapeutic advancement in the treatment of gastric cancer by addressing the limitations of current therapies through a novel, targeted, and personalised approach. However, no additional data was presented to support this except of the mechanism of action.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 May 2024, prior to final opinion.

2.1.3. topiramate - EMA/OD/0000165562

Granzer Regulatory Consulting & Services GmbH; Treatment of neonatal encephalopathy

COMP Rapporteur: Darius Matusevicius

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 neonatal seizures as a distinct medical entity but rather a symptom within a specific age group. Therefore, the sponsor was asked to propose a condition that would be more suitable to meet the criteria for an orphan condition. The COMP has previously accepted "neonatal encephalopathy" as distinct medical entity.

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).

- Medical plausibility

The sponsor was asked to discuss the data on medical plausibility in light of the amended orphan condition.

- Number of people affected

The sponsor was invited to revise the prevalence calculation in line with the amended 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

The sponsor was invited to revise the significant benefit discussion, in line with the amended orphan condition, taking into account the standard of care in the condition.

In the written response, the sponsor agreed to the COMP proposal and changed the orphan condition, i.e. neonatal encephalopathy (instead of neonatal seizures). Neonatal encephalopathy (NE) is a neurologic syndrome in term and near-term neonates. NE describes disturbed neurological function in a neonate with abnormal level of consciousness and any combination of seizures, difficulty initiating and maintaining respiration, abnormal tone or reflexes, or disturbances of suck or swallowing. One of the most frequent etiological pathways to NE includes a period of peripartum or intrapartum hypoxia-ischemia (McIntyre et al., 2021). Reduced blood flow and/or oxygenation around the time of birth can cause NE. This subset of NE, with accompanying low Apgar scores and acidaemia, is termed hypoxic-ischemic encephalopathy (HIE) and is the most frequent subtype of NE.

The sponsor provided the same publications supporting the medical plausibility which were submitted in the original application essentially focusing on the treatment of HIE as a most common subset of NE.

The number of affected people was recalculated taking to account the changed condition of NE. The COMP accepted a prevalence estimate of approximately 0.2 per 10,000 persons, in line with an up-rounded value of the sponsors proposal.

The significant benefit discussion is not applicable, since no products are currently authorised for treatment of the condition.

Overall, the responses from the sponsor were considered satisfactory by the COMP, and a positive opinion was adopted prior to the oral explanation.

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

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

The intention to treat the condition with the medicinal product containing topiramate was considered justified based on bibliographic clinical data which describe a reduction or suppression of seizures in neonates with neonatal encephalopathy.

The condition is life-threatening due to the occurrence of treatment refractory severe seizures and chronically debilitating due to brain damage and the risk of development of later-life epilepsy.

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

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

A positive opinion for topiramate, for treatment of neonatal encephalopathy, was adopted by consensus.

2.1.4. - EMA/OD/0000159474

Treatment of Duchenne muscular dystrophy

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 are based on an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor provided limited statements that vamorolone does not address the underlying cause of the Duchenne muscular dystrophy (DMD) in contrast to the proposed product and that ataluren is not appropriate treatment option for patients with exon 51 skip amenable mutation.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any non-clinical in vivo data or preliminary clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 22 May 2024, the sponsor defended their position.

A side-by-side comparison of therapeutic and safety characteristics associated with vamorolone use versus the sponsor's product was provided but no data to support this either in the non-clinical or clinical setting. It was also highlighted that a Cochrane review indicated that corticosteroid use only added 2 years of life when compared to patients who received no corticosteroids. However, in the absence of any survival data in patients with the sponsor's product the claim of better survival cannot be supported.

Statements about a potentially disease modifying mode of action were given, however the sponsor did not provide any additional data which would support making an assumption that the different mode of action would result in a significant benefit versus vamorolone. PK/PD modelling was presented based on non-clinical data and the sponsor claimed that their treatment resulted in an increase of dystrophin at or above 10% of the normal level. This claim was linked to reported findings in the literature that indicate that a higher level of dystrophin measured in patients is related to a milder clinical phenotype. In Neri et al., 2007 it was reported that residual dystrophin protein levels above 30% might be needed to protect from symptoms of muscular dystrophy. Authors of this publication also stated that these levels correspond rather well with measurable improvements following the introduction of dystrophin in non-clinical in vivo models published elsewhere. The COMP noted that the increase in dystrophin levels above 10% of normal values was not supported by any real data with the product so these arguments, while of interest, could not be considered.

The sponsor discussed a clinical study in which the intention is to include patients on a stable dose of vamorolone or other glucorticoids. An add-on effect of the sponsor's product could be considered supportive of significant benefit and preliminary data, when available, describing clinical endpoints from such patients could help establish a clinically relevant advantage. In the absence of such data the COMP 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 23 May 2024, prior to final opinion.

2.1.5. - EMA/OD/0000162667

Treatment of hepatocellular carcinoma

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

Significant benefit over immunotherapy combination therapy has not been established. The sponsor was therefore invited to further support significant benefit with relevant scientific data.

The sponsor was also asked to clarify whether the few patients which showed a partial response (following single agent treatment) would in principle have been eligible for the currently authorised combination therapies of atezolizumab with bevacizumab and/or durvalumab with/or without tremelimumab (e.g. non-eligibility due to autoimmune diseases).

The sponsor was also asked to clarify whether the proposed product is envisaged as a monotherapy or a combination therapy with a checkpoint inhibitor.

In the written response, and during an oral explanation before the Committee on 22 May 2024, the sponsor clarified that the few patients that experienced a partial response did not receive the current recommended first-line therapies of atezolizumab with bevacizumab or durvalumab with or without tremelimumab because those therapies had not yet been approved or provided by payers in the regions of those patients at that time.

The sponsor emphasised the strong biological rational which supports the combination of the sponsors product with immunotherapy such as anti-PD-(L)1 therapies like atezolizumab. Preclinical and mechanistic data point towards immune reactivation through the sponsors product with a potential for genomic instability and neoepitope formation leading to an immunogenic cell death, and, in addition, to an induction of "cyclic GMP–AMP synthase" (cGAS)–"stimulator of interferon genes" (STING) pathway activation. The cGAS–STING pathway is an evolutionarily conserved defence mechanism against viral infections and its role in activating immune surveillance has also led to its putative role as a tumour suppressor. In non-clinical models of hepatocellular carcinoma (HCC) the administration of the sponsors product with atezolizumab induces greater antitumor effects than the administration of each compound as a single agent. However, how these compare to currently authorised first line (combination) immunotherapy options could not be further clarified. The future clinical development foresees a combination of the sponsors product with atezolizumab.

During the oral hearing the sponsor presented new clinical data in a few patients.

While the COMP noted that only a few patients were (amongst other products also) pre-treated with atezolizumab plus bevacizumab or carbozantinib, only stable disease was achieved . No data on patients pretreated with durvalumab was presented.

The COMP considered that these data were not sufficient to support the significant benefit over currently authorised first line (combination) immunotherapy options in advanced stage HCC.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 May 2024, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000139776

Prevention of T-cell engaging immunotherapy induced cytokine release syndrome (CRS)

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 June meeting.

2.2.2. sargramostim - EMA/OD/0000160866

CATS Consultants GmbH; Treatment of pulmonary alveolar proteinosis

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing sargramostim was considered justified based on clinical data showing improvements in lung function parameters.

The condition is chronically debilitating due to progressive decrease in lung function leading to the need of oxygen supplementation, recurrent pulmonary infections and life-threatening due to respiratory failure.

The condition was estimated to be affecting less than 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 sargramostim, for treatment of pulmonary alveolar proteinosis, was adopted by consensus.

2.2.3. afatinib - EMA/OD/0000162432

Akigai AS; Treatment of complex regional pain syndrome

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing afatinib was considered justified based on non-clinical in vivo data and preliminary clinical observational reports showing pain relief in complex regional pain syndrome patients.

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

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

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 afatinib, for treatment of complex regional pain syndrome, was adopted by consensus.

2.2.4. - EMA/OD/0000162927

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 June meeting.

2.2.5. - EMA/OD/0000163852

Treatment of hepatocellular carcinoma

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 June meeting.

2.2.6. - EMA/OD/0000164215

Treatment of myasthenia gravis

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 June meeting.

2.2.7. (R)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)piperidine-1-carboxamide - EMA/OD/0000164848

FGK Representative Service GmbH; Treatment of hyperphenylalaninemia

COMP Rapporteur: Cécile Dop

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

The intention to treat the condition with the medicinal product containing (R)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)piperidine-1-carboxamide was considered justified based on preliminary clinical data showing a reduction of elevated blood phenylalanine levels in patients with the condition.

The condition is chronically debilitating due to high blood phenylalanine levels which cause cognitive impairment.

The condition was estimated to be affecting less than 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)piperidine-1-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product can reduce elevated blood phenylalanine levels in a broader patient population than indicated for authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (R)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)piperidine-1-carboxamide, for treatment of hyperphenylalaninemia, was adopted by consensus.

2.2.8. - EMA/OD/0000164923

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 June meeting.

2.2.9. - EMA/OD/0000164949

Treatment of retinitis pigmentosa

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 June meeting.

2.2.10. nerandomilast - EMA/OD/0000165100

Boehringer Ingelheim International GmbH; Treatment of idiopathic pulmonary fibrosis (IPF)

COMP Rapporteur: Joao Rocha

The Committee agreed that the condition, idiopathic pulmonary fibrosis (IPF), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nerandomilast was considered justified based on clinical data in patients with the condition demonstrating a reduction in the rate of decline of forced vital capacity and an increase in the diffusing capacity for carbon monoxide compared to control groups.

The condition is chronically debilitating due to progressive dyspnoea and loss of respiratory function, with limited exercise capability and decreased quality of life, and life-threatening due to respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nerandomilast will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition that demonstrate improvement in forced vital capacity when the proposed product was used as add-on therapy to authorised products nintedanib or pirfenidone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for nerandomilast, for treatment of idiopathic pulmonary fibrosis (IPF), was adopted by consensus.

2.2.11. - EMA/OD/0000167882

Treatment of variegate porphyria

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 June meeting.

2.2.12. human IgG1 monoclonal antibody against hepatitis B virus, surface antigen - EMA/OD/0000167926

Yes Pharmaceutical Development Services GmbH; Treatment of hepatitis D virus infection

COMP Rapporteur: Ioannis Kkolos

The Committee agreed that the condition, hepatitis D virus infection, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human IgG1 monoclonal antibody against hepatitis B virus, surface antigen was considered justified based on preliminary clinical data showing a significant reduction in hepatitis D virus markers as well as improvements in hepatic biomarkers.

The condition is chronically debilitating and life-threatening due to the development of cirrhosis, portal hypertension and liver insufficiency.

The condition was estimated to be affecting approximately 2.5 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 human IgG1 monoclonal antibody against hepatitis B virus, surface antigen will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in hepatitis D biomarkers in patients who are not indicated for treatment with the currently authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human IgG1 monoclonal antibody against hepatitis B virus, surface antigen, for treatment of hepatitis D virus infection, was adopted by consensus.

2.2.13. L-methionine - EMA/OD/0000168828

Imagine Institut Des Maladies Genetiques Necker Enfants Malades; Treatment of pulmonary alveolar proteinosis (PAP)

COMP Rapporteur: Joao Rocha

The Committee agreed that the condition, pulmonary alveolar proteinosis (PAP), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing L-methionine was considered justified based on clinical data showing improvements in functional and respiratory parameters.

The condition is chronically debilitating due to progressive decrease in lung function leading to the need of oxygen supplementation, recurrent pulmonary infections and life-threatening due to respiratory failure.

The condition was estimated to be affecting less than 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 L-methionine, for treatment of pulmonary alveolar proteinosis (PAP), was adopted by consensus.

2.2.14. (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl) pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone - EMA/OD/0000168887

Granzer Regulatory Consulting & Services GmbH; Treatment of pachyonychia congenita

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing (R)-(3-(2'-cyclopropyl-3-(hydroxymethyl)-[1,1'-biphenyl]-4-yl) pyrrolidin-1-yl)(5-fluoropyridin-2-yl)methanone was considered justified based on preliminary clinical data showing that treatment with the proposed product resulted in improvement in plantar keratoderma and a reduction on self-perceived pain in patients affected by the condition.

The condition is chronically debilitating due to impaired ambulation associated with plantar keratoderma, blistering and pain.

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

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

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

2.2.15. complement factor H, human, recombinant - EMA/OD/0000168931

Greenovation Biotech GmbH; Treatment of C3 glomerulopathy

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, C3 glomerulopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing complement factor H, human, recombinant was considered justified based on non-clinical data on a model of the condition showing elevation of serum C3 levels and a reduction in glomerular C3 deposits.

The condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure.

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

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 complement factor H, human, recombinant, for treatment of C3 glomerulopathy, was adopted by consensus.

2.2.16. 4-[[[4-[5-chloro-2-[[trans-4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]cyclohexyl]amino]-4-pyridinyl]-2-thiazolyl]amino]methyl]tetrahydro-2H-pyran-4-carbonitrile - EMA/OD/0000168982

Sellas Life Sciences Limited; Treatment of acute myeloid leukaemia

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing 4-[[[4-[5-chloro-2-[[trans-4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]cyclohexyl]amino]-4-pyridinyl]-2-thiazolyl]amino]methyl]tetrahydro-2H-pyran-4-carbonitrile was considered justified based on in vivo non-clinical data which showed reduction in tumour growth and increased survival and preliminary clinical data which showed responses in patients with relapsed/refractory acute myeloid leukaemia who have been treated with the proposed product in combination with venetoclax and azacitidine.

The condition is life-threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-[[[4-[5-chloro-2-[[trans-4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]cyclohexyl]amino]-4-pyridinyl]-2-thiazolyl]amino]methyl]tetrahydro-2H-pyran-4-carbonitrile will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed improved responses in patients with relapsed/refractory acute myeloid leukaemia compared to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-[[[4-[5-chloro-2-[[trans-4-[[(1R)-2-methoxy-1-methyl-ethyl]amino]cyclohexyl]amino]-4-pyridinyl]-2-thiazolyl]amino]methyl]tetrahydro-2H-pyran-4-carbonitrile, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.17. - EMA/OD/0000169022

Treatment of symptomatic obstructive hypertrophic cardiomyopathy

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 June meeting.

2.2.18. uridine triacetate - EMA/OD/0000169049

Serb; Treatment of hereditary orotic aciduria

COMP Rapporteur: Cécile Dop

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

The intention to treat the condition with the medicinal product containing uridine triacetate was considered justified based on clinical data in patients with the condition indicating the stabilisation of the haematologic parameters in previously treated patients.

The condition is life-threatening and chronically debilitating due to haematologic abnormalities such as severe anaemia, and developmental delays, failure to thrive, and if untreated, early mortality.

The condition was estimated to be affecting less than 0.001 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 uridine triacetate, for treatment of hereditary orotic aciduria, was adopted by consensus.

2.2.19. - EMA/OD/0000169065

Treatment of eosinophilic esophagitis

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 June meeting.

2.2.20. - EMA/OD/0000169553

Treatment of peripheral T-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 June meeting.

2.2.21. - EMA/OD/0000169732

Treatment of hepatocellular carcinoma

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 June meeting.

2.2.22. 2-(((2E)-3-(3-methoxy-4-(2-propyn-1-yloxy)phenyl)-1-oxo-2-propen-1-yl)amino)benzoic acid - EMA/OD/0000169763

AdRes EU B.V.; Treatment of systemic sclerosis

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing 2-(((2E)-3-(3-methoxy-4-(2-propyn-1-yloxy)phenyl)-1-oxo-2-propen-1-yl)amino)benzoic acid was considered justified based on clinical data in patients with the condition indicating a positive effect on fibrosis using multiple validated scoring systems of the condition when compared to placebo.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin leading to skin ulcers and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, which may lead to severe complications such as pulmonary arterial hypertension, interstitial lung disease, progressive dysphagia, renal crisis and cardiac failure.

The condition was estimated to be affecting approximately 3.4 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 2-(((2E)-3-(3-methoxy-4-(2-propyn-1-yloxy)phenyl)-1-oxo-2-propen-1-yl)amino)benzoic acid will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in patients with the condition demonstrating disease modifying potential and efficacy on several domains currently not addressed by approved treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(((2E)-3-(3-methoxy-4-(2-propyn-1-yloxy)phenyl)-1-oxo-2-propen-1-yl)amino)benzoic acid, for treatment of systemic sclerosis, was adopted by consensus.

2.2.23. nizubaglustat - EMA/OD/0000169912

Azafaros B.V.; Treatment of GM1 gangliosidosis

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, GM1 gangliosidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nizubaglustat was considered justified based on non-clinical in vivo data which showed improvements in survival.

The condition is life-threatening due to a reduced life expectancy and chronically debilitating due to neurodegeneration causing cognitive decline, seizures, muscle weakness, spasticity, dystonia and ataxia, as well as skeletal abnormalities, visual impairment and hepatosplenomegaly.

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 nizubaglustat, for treatment of GM1 gangliosidosis, was adopted by consensus.

2.2.24. ethyl(2E,4S)-4-({(2S)-2-[3-{[(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2H)-yl]pent-4-ynoyl}amino)-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-enoate, pocapavir - EMA/OD/0000169976

Virodefense IRE Limited; Treatment of poliovirus infection

COMP Rapporteur: Evangelia Giannaki

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

The intention to treat the condition with the medicinal product containing ethyl(2E,4S)-4-({(2S)-2-[3-{[(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2H)-yl]pent-4-ynoyl}amino)-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-enoate, pocapavir was considered justified based on in vitro data showing a synergistic and additive antiviral activity of ethyl(2E,4S)-4-({(2S)-2-[3-{[(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2H)-yl]pent-4-ynoyl}amino)-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-enoate, pocapavir combination against drug selected resistant variants of poliovirus.

The condition is life-threatening due to paralysis with bulbar involvement, fatal respiratory and cardiovascular collapse and chronically debilitating due to myalgias, respiratory distress, joint pain, atrophy, dysphagia, and generalised fatigue.

The condition was estimated to be affecting approximately 0.008 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 ethyl(2E,4S)-4-({(2S)-2-[3-{[(5-methyl-1,2-oxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2H)-yl]pent-4-ynoyl}amino)-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-enoate, pocapavir, for treatment of poliovirus infection, was adopted by consensus.

2.2.25. apilimod - EMA/OD/0000170993

Maxia Strategies-Europe Limited; 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 apilimod was considered justified based on non-clinical in vivo data in a model of the condition showing improved motor function.

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 apilimod will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data in a model of the condition that demonstrate that the product can attenuate motor function decline which cannot be expected from the currently authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for apilimod, for treatment of amyotrophic lateral sclerosis, 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 6 applications.
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2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 19 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of pyruvate kinase deficiency

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

3.1.2. -

Treatment of Prader-Willi syndrome

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 acute myeloid leukaemia

The discussion was postponed to the June meeting.

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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. Nezglyal – leriglitazone - EMEA/H/C/005757, EU/3/16/1770, EMA/OD/0000144315

Minoryx Therapeutics S.L.; Treatment of adrenoleukodystrophy

The status of the procedure at CHMP was noted.

[Post-meeting note: The applicant formally withdrew the marketing authorisation application for Nezglyal at the CHMP May meeting.]

4.2.2. Livmarli - maralixibat - EMEA/H/C/005857/II/0003/G, EU/3/13/1216, EMA/OD/0000136132

Mirum Pharmaceuticals International B.V.; Treatment of progressive familial intrahepatic cholestasis

COMP Rapporteur: Armando Magrelli; COMP Co-Rapporteur: Elisabeth Rook; CHMP Rapporteur: Martina WeiseAn opinion recommending not to remove Livmarli, maralixibat, EU/3/13/1216 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 May meeting.]

4.2.3. Adzynma - apadamtase alfa - EMEA/H/C/006198, EU/3/08/588, EMA/OD/0000150694

Takeda Manufacturing Austria AG; Treatment of thrombotic thrombocytopenic purpura

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 June meeting.

4.2.4. Akantior - polihexanide - EMEA/H/C/005858, EU/3/07/498, EMA/OD/0000152081

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

COMP Rapporteur: Armando Magrelli; COMP Co-Rapporteur: Tim LeestAn opinion recommending not to remove Akantior, polihexanide, EU/3/07/498 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 May meeting.]

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 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. Kinpeygo - budesonide - EMEA/H/C/005653/II/0008, EU/3/16/1778, EMA/OD/0000157484

STADA Arzneimittel AG; Treatment of primary IgA nephropathy

COMP Rapporteur: Elisabeth Johanne Rook; COMP Co-Rapporteur: Armando Magrelli; CHMP Rapporteur: Christian GartnerAn opinion recommending not to remove Kinpeygo, budesonide, EU/3/16/1778 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 May meeting.]

5.2.2. Blincyto – blinatumomab - EMEA/H/C/003731/II/0056, EU/3/09/650, EMA/OD/0000162410

Amgen Europe B.V.; Treatment of acute lymphoblastic leukaemia

; CHMP Rapporteur: Alexandre MoreauThe status of the procedure at CHMP was noted.

5.2.3. Adcetris – brentuximab vedotin - EMEA/H/C/002455/II/0111, EU/3/08/596

Takeda Pharma A/S; Treatment of Hodgkin lymphoma

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

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The Chair welcomed Boje Kvorning Pires, as the new member for Denmark.

The Chair thanked Armando Magrelli for his contribution as a member appointed by the EC on EMA's recommendation.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 21 May 2024.

7.1.5. COMP Decisions Database

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

7.1.6. Scientific Committee Meetings – alternating face-to-face and virtual meetings schedule for 2025

The COMP 2025 meeting dates were noted and agreed.

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. Innovation Task Force (ITF) meetings

The COMP noted the upcoming ITF meetings.

7.3.3. Scientific Advice Working Party (SAWP): nomination of COMP member to SAWP

The call for expression of interests was extended, following departure of a joint COMP-SAWP alternate.

7.3.4. Oncology Working Party (ONCWP)

Outcome of the ONCWP consultation.

The COMP noted the additional clarifications from the ONCWP to COMP questions on diffuse large B-cell lymphoma (DLBCL) indications and orphan drugs.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

7.8.3. Marketing Authorisation Applications (MAAs) 3-year forecast report (March 2024 to December 2026)

The Committee was informed about the availability of the 3-year forecast report and was presented with a brief overview of the MAAs pipeline expected in the next three years.

8. Any other business

8.1. Spinal muscular atrophy (SMA) registry report

The COMP discussed a registry-based cohort study of spinal muscular atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).

8.2. Update on Real-World Evidence, including DARWIN EU®

EMA presented the results of a study conducted via DARWIN EU to compare direct and indirect methods to estimate prevalence of chronic diseases using real-world data. Comments provided during the plenary discussion, as well as prior to the discussion by the Real-World Evidence (RWE) liaison group, were duly noted. Finally, an update was provided on recent and upcoming events, including the DARWIN EU summer school on 5 and 6 June 2024, the next Real-World Academy event on data quality on 3 July 2024, as well as joint HMA-EMA multistakeholder workshop on RWE methods on 14 June 2024. The COMP members welcomed the update.

9. List of participants

List of participants including any restrictions with respect to involvement of members/experts following evaluation of declared interests for the 21-23 May 2024 COMP meeting, which was held remotely.

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

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Ruta Mameniskiene	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Baginska	Member	Poland	No restrictions applicable to this meeting	
Joao Rocha	Member	Portugal	No restrictions applicable to this meeting	
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	
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 participation in discussion, final deliberations and voting on:	2.1.4. - EMA/OD/0000159474

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Maria Judit Molnar	Member	Expert recommended by EMA	No participation in discussion, final deliberations and voting on:	2.1.4. - EMA/OD/0000159474 2.2.8. - EMA/OD/0000164923 2.2.6. - EMA/OD/0000164215
A representative from the European Commission attended the meeting.				
Observer from FDA (USA) 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.

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/