EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 16-18 April 2024

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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Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

The Chair opened the meeting by welcoming all participants. The meeting was held in-person.

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members 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 thanked the departing members for their 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 16-18 April 2024 was adopted with amendments.

Topic added:

8.2. Request to NCA to start Article 8(2) procedure

1.3. Adoption of the minutes

The minutes for 12-14 March 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. quabodepistat - EMA/OD/0000133472

Otsuka Novel Products GmbH; Treatment of tuberculosis

COMP Rapporteur: Tim Leest

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 the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from Trial 323-201-00003 to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was requested to detail the results of any clinical data to support the significant benefit assumption in the context of the current recommendations of therapeutic management of drug susceptible patients. The sponsor was asked to also elaborate on the use of their product in the treatment of multidrug resistant tuberculosis with any clinical or non-clinical data they may have.

In the written response, and during an oral explanation before the Committee on 16 April 2024, the sponsor defended their position.

In the written response the sponsor considered the totality of the data to establish the basis of significant benefit in multidrug resistant tuberculosis. This included in vitro data using multidrug resistant strains of tuberculosis as well as preliminary clinical data in patients who had drug sensitive tuberculosis. The sponsor argued that Drug Sensitive-Tuberculosis (DS-TB) and Drug Resistant-Tuberculosis (DR-TB) is essentially the same disease, the only difference is that in DR-TB the patient has developed resistance to one or more of the components of the treatment, therefore the data can be extrapolated. The COMP discussed the supportive nature of the in vitro minimal inhibitory concentrations of the quabodepistat and considered that the data could be supportive of a clinically relevant advantage. The Committee was of the opinion that these preliminary results complemented those seen in the clinical setting.

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

The intention to treat the condition with the medicinal product containing quabodepistat was considered justified based on comparative minimal inhibitory concentration (MIC) results in drug-sensitive and drug-resistant mycobacterium tuberculosis strains as well as preliminary clinical data showing a reduction in bacterial load in patients with drug sensitive tuberculosis.

The condition is chronically debilitating and life-threatening due to haemoptysis, bronchiectasis, diffuse pulmonary destruction, and the possibility of extra-pulmonary infection.

The condition was estimated to be affecting approximately 4.1 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 quabodepistat will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and clinical data that demonstrate that use in combination with other antituberculosis medicines could offer an alternative in the

treatment of multidrug resistant tuberculosis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for quabodepistat, for treatment of tuberculosis, was adopted by consensus.

2.1.2. - EMA/OD/0000161033

Treatment of hypophosphatasia

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 claims a significant benefit of the proposed product versus the authorised product asfotase alfa based on three different grounds: improved efficacy, improved safety and a major contribution to patient care. The COMP did not consider that the data provided by the sponsor were sufficient to support any one of these three claims. Therefore, the sponsor was invited to further substantiate their claims of a significant benefit of the proposed product versus the authorised product asfotase alfa with data supporting the assumptions.

In the written response and during an oral explanation before the Committee on 16 April 2024, the sponsor presented the following main information in support of their significant benefit claims for improved efficacy and major contribution to patient care (MCPC).

For the improved efficacy claim, the sponsor reiterated the benefit of the proposed product of potentially targeting a broader patient population than that addressed by the asfotase alfa product label, including patients not having documented paediatric-onset and without overt bone manifestations. While the COMP agreed on this aspect, the Committee concluded that this claim is not sufficiently supported with relevant data. No new data was presented in this regard.

The MCPC claim was based on the PK/PD modelling and simulation, predicting a reduced dosing frequency and a reduced volume for subcutaneous administration. This in turn is expected to reduce patient burden, including fewer injection site reactions (ISR). While the COMP agreed that a reduced dosing frequency and a reduced volume may be associated with a reduced patient burden, no actual data with the actual intended low dose frequency and volume was presented for the proposed product. Without data, no comparison with asfotase alfa can be made and therefore the MCPC claim cannot be established. Furthermore, no relevant comparative data on ISRs was presented by the sponsor.

The COMP also noted that future extrapolations of the Phase 3 data to the paediatric population, as mentioned in the response, were beyond the remit of this initial orphan designation.

As for the burden of treatment that was briefly discussed by the sponsor, it was not clear to the COMP whether the collected "insights from healthcare professionals specialised in hypophosphatasia (HPP) management" was published somewhere or how these data were exactly collected. As of now, the data shown by the sponsor was not sufficient to support the MCPC claim. It was further not clear to the Committee in how far the proposed product could exactly be expected to alleviate the burden of treatment administration for patients with HPP.

In conclusion, the COMP did not consider the presented data sufficient to support the significant benefit of the proposed product over asfotase alfa on any of the two grounds. No additional arguments in support of an improved safety claim were presented.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2024, prior to final opinion.

2.1.3. - EMA/OD/0000156967

Treatment of familial chylomicronemia syndrome (FCS)

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 significant benefit of the proposed product vs volanesorsen is mainly based on a claim of improved safety. The sponsor was invited to present a comparison of the baseline characteristics of the patients included in the respective pivotal studies.

As the available overall safety information for the proposed product was still considered limited as compared to volanesorsen, in terms of number of patients treated and duration of treatment, the sponsor may also consider to further elaborate on their proposed claim of improved efficacy.

In the written response and during an oral explanation before the Committee on 17 April 2024, the sponsor presented the following main new information.

Demographic and baseline characteristics of patients in the respective pivotal studies were presented. Imbalances in terms of ethnicity and % in genetically confirmed FCS diagnosis were identified but not considered likely by the sponsor to impact the comparative efficacy or safety outcomes.

The sponsor further highlighted the extensive safety data for the proposed product. To date, 173 patients have been treated for a minimum of 1 year. However, no details were provided in this regard. The sponsor only concludes that the safety profile from the pooled proposed product clinical studies is in general consistent with the safety profile observed in the pivotal study.

In the response, the sponsor elaborated further on the basis of the claim for improved efficacy. Specifically, the sponsor points out that the comparative evaluation of the respective pivotal studies data suggests that the proposed product may be associated with fewer cases of acute pancreatitis and health utilisation outcomes. As regards acute pancreatitis (AP), the COMP considered this one of the most relevant efficacy endpoints for the target patient population. However, due to the limited numbers of events, specifically in the pivotal study of the comparator product and the fact that there was a significant difference in the AP events in the respective placebo groups between the respective pivotal studies, these comparative differences were difficult to interpret. Also, in the pivotal study of the comparator product, information on healthcare utilisation outcomes was not collected prospectively, hence a comparison to volanesorsen could not be made on this outcome parameter.

The COMP concluded that the claim for improved efficacy could not be established, mainly owing to the fact that over the first 6 months the efficacy in terms of comparative placebo-

adjusted triglyceride-lowering (mean percent change from baseline) suggested that volanesorsen is in fact the more potent drug. No efficacy data with the proposed product was presented from patients previously treated with volanesorsen and who could not/no longer benefit from their previous volanesorsen therapy, due to lack of tolerability/safety concerns or due to lack of efficacy.

As regards the claim for improved safety, the COMP considered the overall safety data presented for the proposed product too limited, as compared to volanesorsen . Specifically, more granularity as regards the overall safety data in the 173 patients who have been treated for a minimum of 1 year would have been expected. Nevertheless, the COMP acknowledged that the use in a potentially broader patient population could be considered a clinically relevant advantage, e.g. patients in whom volanesorsen is currently contraindicated (i.e. patients with chronic or unexplained thrombocytopenia and those with a platelet count <140 x 109/L). However, no data was presented in this regard. Of note, the sponsor attributes the potential better tolerability/safety mainly to the differences in the PK profile between the proposed product and volanesorsen (lower systemic exposure and higher biodistribution to the target organ of the liver).

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 April 2024, prior to final opinion.

2.1.4. N-(1,3-benzothiazol-2-yl)-4-[(2-hydroxy-3-methoxyphenyl)methylamino]benzenesulfonamide - EMA/OD/0000158039

FGK Representative Service GmbH; Treatment of platelet-activating anti-platelet factor 4 (PF4) disorders

COMP Rapporteur: Joao Rocha

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 is proposing heparin-induced thrombocytopenia as a valid medical entity. However, orphan diseases are usually understood to be conditions with intrinsic pathophysiological origins, and not as an adverse reaction to a medicinal product. The sponsor was therefore asked to justify the proposed condition as a valid 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).

- 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition and discuss other patient populations that can contribute to the prevalence of the proposed condition such as those in outpatient care. The sponsor was requested to discuss the completeness of the bibliographic sources.

In the written response, the sponsor defended their position.

Regarding the proposed condition heparin-induced thrombocytopenia (HIT), the sponsor argued that HIT qualifies as an orphan disease. However, during the assessment the umbrella term platelet-activating anti-platelet factor 4 (PF4) disorders was explored which includes classic HIT, autoimmune HIT, spontaneous HIT and vaccine-induced immune thrombotic thrombocytopenia (VITT). These four categories share common characteristics, including pan-cellular activation, which means not only the platelets are involved in the pathophysiology process, but also other cells, such as monocytes and polymorphonuclear leukocytes (PMNs) and the classic complement pathway. This condition was believed to be a suitable valid condition for the purpose of the orphan designation. In addition, it was clarified that the clinical development would include patients from classic, autoimmune, and spontaneous HIT.

As such, the sponsor updated the prevalence calculation to cover all the subsets within the umbrella term. It was clarified that the initially proposed indication covers the first three anti-PF4 disorders. Thus, the sponsor elaborated on how the prevalence of VITT would impact the overall prevalence calculation. However, given the ultra-rare nature of this subset the sponsor maintained the overall prevalence estimate to be 3.1 in 10,000 persons.

Overall, the responses from the sponsor were considered satisfactory by the COMP, and a positive opinion was adopted prior to the oral explanation. The sponsor was advised to request protocol assistance for the next steps in the development.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of platelet-activating anti-platelet factor 4 (PF4) disorders.

The Committee agreed that the condition, platelet-activating anti-platelet factor 4 (PF4) disorders, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing N-(1,3-benzothiazol-2-yl)-4-[(2-hydroxy-3-methoxyphenyl)methylamino]benzenesulfonamide was considered justified based on non-clinical data in a model of the condition showing the reduction of thrombosis and thrombocytopenia in both prophylactic and treatment settings.

The condition is life-threatening and chronically debilitating due to the arterial and venous thromboembolic events including organ ischemia or infarction which can lead to amputation and death.

The condition was estimated to be affecting approximately 3.1 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 N-(1,3-benzothiazol-2-yl)-4-[(2-hydroxy-3-methoxyphenyl)methylamino]benzenesulfonamide, for treatment of platelet-activating anti-platelet factor 4 (PF4) disorders, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. serdexmethylphenidate - EMA/OD/0000133251

Zevra Denmark A/S; Treatment of idiopathic hypersomnia

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing serdexmethylphenidate was considered justified based on preliminary clinical data showing improvements in the reduction of sleep inertia, brain fog and Epworth Sleepiness Scale.

The condition is chronically debilitating due to episodes of excessive daytime sleepiness.

The condition was estimated to be affecting approximately 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 serdexmethylphenidate, for treatment of idiopathic hypersomnia, was adopted by consensus.

2.2.2. - EMA/OD/0000155489

Treatment of cutaneous 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 May meeting.

2.2.3. - EMA/OD/0000159474

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 May meeting.

2.2.4. autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene - EMA/OD/0000159798

Leids Universitair Medisch Centrum (LUMC); Treatment of recombination-activating gene 1 (*RAG1*) deficiency

COMP Rapporteur: Elisabeth Johanne Rook

The Committee agreed that the condition, recombination-activating gene 1 (*RAG1*) deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene was considered justified based on non-clinical in vivo data in two models with hypomorphic RAG1 mutations, showing improvements in survival and immunoglobulin responses, as well as preliminary clinical data from two *RAG1*-severe combined immunocompromised (SCID) patients showing reconstitution of the immune function and improvement in survival after gene therapy with the proposed product.

The condition is life-threatening due to increase in mortality and chronically debilitating due to high risk of serious infections, as well as autoimmunity complications in some forms of the condition.

The condition was estimated to be affecting approximately 0.07 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene, for treatment of recombination-activating gene 1 (*RAG1*) deficiency, was adopted by consensus.

2.2.5. DNA plasmid containing the *COL7A1* gene - EMA/OD/0000161987

Branca Bunus Limited; Treatment of epidermolysis bullosa

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product containing *COL7A1* plasmid was considered justified based on non-clinical data which demonstrate restoration of type VII collagen protein expression in skin tissue/grafts derived from patients with recessive dystrophic epidermolysis bullosa.

The condition is chronically debilitating and life-threatening due to blister formation following minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

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 DNA plasmid containing the *COL7A1* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data which demonstrate the disease modifying potential of the proposed product by restoring deficient type VII collagen protein levels in the skin, possibly leading to improved wound healing. This cannot be expected from the currently authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for DNA plasmid containing the *COL7A1* gene, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.6. - EMA/OD/0000162667

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 May meeting.

2.2.7. allogeneic non-alloreactive T cells edited with mRNA to disrupt *TRAC* and *CD52* genes and transduced with lentiviral vector expressing a chimeric antigen receptor against CD22 and RQR8 depletion mechanism - EMA/OD/0000162753

Cellectis; Treatment of acute lymphoblastic leukaemia

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing allogeneic non-alloreactive T cells edited with mRNA to disrupt *TRAC* and *CD52* genes and transduced with lentiviral vector expressing a chimeric antigen receptor against CD22 and RQR8 depletion mechanism was considered justified based on clinical data in heavily pre-treated patients showing high rate of responses.

The condition is chronically debilitating and life-threatening with acute leukemic forms being fatal in a few weeks if left untreated. Symptoms include persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain. The invasion of tumour cells in the bloodstream, the bone marrow and/or the lymphatic system result in lack of normal blood cells, bone marrow failure, and organ damage.

The condition was estimated to be affecting approximately 1.9 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 non-alloreactive T cells edited with mRNA to disrupt *TRAC* and *CD52* genes and transduced with lentiviral vector expressing a chimeric antigen receptor against CD22 and RQR8 depletion mechanism will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients who were relapsed/refractory to the authorised medicinal products achieved complete responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic non-alloreactive T cells edited with mRNA to disrupt *TRAC* and *CD52* genes and transduced with lentiviral vector expressing a chimeric antigen receptor against CD22 and RQR8 depletion mechanism, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.2.8. 2,4-diamino-5-[[5-(1H-pyrazol-5-yl)-2-thienyl]methyl]-1H-pyrimidin-6-one - EMA/OD/0000164186

Pluvia AS; Treatment of hyperphenylalaninaemia

COMP Rapporteur: Enrico Costa

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

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

The intention to treat the condition with the medicinal product containing 2,4-diamino-5-[[5-(1H-pyrazol-5-yl)-2-thienyl]methyl]-1H-pyrimidin-6-one was considered justified based on non-clinical data in a model of the condition showing the reduction of elevated blood phenylalanine levels upon challenge.

The condition is chronically debilitating (if untreated) due to high blood phenylalanine levels which cause severe irreversible neurodevelopmental and 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2,4-diamino-5-[[5-(1H-pyrazol-5-yl)-2-thienyl]methyl]-1H-pyrimidin-6-one will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating the add-on effect of the proposed product when used in combination with authorised treatments for the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2,4-diamino-5-[[5-(1H-pyrazol-5-yl)-2-thienyl]methyl]-1H-pyrimidin-6-one, for treatment of hyperphenylalaninaemia, was adopted by consensus.

2.2.9. adeno-associated virus serotype 9 containing CRISPR/Cas13y and guide RNA against the human *MECP2* gene - EMA/OD/0000164451

Granzer Regulatory Consulting & Services GmbH; Treatment of *MECP2* duplication syndrome

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, *MECP2* duplication syndrome, 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 containing CRISPR/Cas13Y and guide RNA against the human *MECP2* gene was considered justified based on non-clinical data in a model of the condition showing an improvement in relevant biomarkers of the disease in combination with a partial recovery of functional and behavioural deficits.

The condition is life-threatening and chronically debilitating due to hypotonia, developmental delay, intellectual disability, epilepsy, impaired motor development, progressive spasticity in the lower extremities, recurrent infections, gastrointestinal issues, and a significant impact on the life expectancy.

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 adeno-associated virus serotype 9 containing CRISPR/Cas13Y and guide RNA against the human *MECP2* gene, for treatment of *MECP2* duplication syndrome, was adopted by consensus.

2.2.10. 7-ethyl-10-hydroxycamptothecin, irinotecan hydrochloride trihydrate - EMA/OD/0000165028

3R Pharma Consulting GmbH; Treatment of small cell lung cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing 7-ethyl-10-hydroxycamptothecin, irinotecan hydrochloride trihydrate was considered justified based on non-clinical data in models of the condition showing an inhibition of tumour growth.

The condition is chronically debilitating and life-threatening due to its rapid progression and the development of widespread metastases, with a poor 5-year overall survival.

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 7-ethyl-10-hydroxycamptothecin, irinotecan hydrochloride trihydrate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that showed a superior antitumour activity compared to authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 7-ethyl-10-hydroxycamptothecin, irinotecan hydrochloride trihydrate, for treatment of small cell lung cancer, was adopted by consensus.

2.2.11. autologous induced pluripotent stem cells-derived thymic epithelial cells transduced with a lentiviral vector encoding forkhead box protein N1 - EMA/OD/0000165289

Genewity B.V.; Treatment of DiGeorge's syndrome

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing autologous induced pluripotent stem cells-derived thymic epithelial cells transduced with a lentiviral vector encoding forkhead box protein N1 was considered justified based on non-clinical data in a model of the condition showing the restoration of functional T-cell formation as demonstrated via antigen stimulation.

The condition is chronically debilitating and life-threatening due to serious infections, chronic diarrhoea, interstitial lung disease, and failure to thrive.

The condition was estimated to be affecting less than 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 autologous induced pluripotent stem cells-derived thymic epithelial cells transduced with a lentiviral vector encoding forkhead box protein N1, for treatment of DiGeorge's syndrome, was adopted by consensus.

2.2.12. - EMA/OD/0000165562

Treatment of neonatal seizures

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 May meeting.

2.2.13. efineptakin alfa - EMA/OD/0000165806

NeoImmuneTech Inc. S.A. Oddział w Polsce; Treatment of acute radiation syndrome (ARS)

COMP Rapporteur: Tim Leest

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

The intention to treat the condition with the medicinal product containing efineptakin alfa was considered justified based on beneficial effects on survival and reconstitution of functional T cells in relevant in vivo models of the condition.

The condition is life-threatening and chronically debilitating due to haematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiple organ failure and carcinogenesis.

The condition was estimated to be affecting less than 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 efineptakin alfa, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.14. - EMA/OD/0000165835

Treatment of signet ring cell 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 May meeting.

2.2.15. afamelanotide - EMA/OD/0000165872

Clinuvel Europe Limited; Treatment of xeroderma pigmentosum (XP)

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing afamelanotide was considered justified based on clinical data in patients with the condition indicating the

reduction in photodamage provoked by ultraviolet (UV) radiation and the activation of relevant cellular repair mechanisms.

The condition is chronically debilitating due to the fact that rigorous photoprotective measures limit daytime activities and impact socio-psychological development, the need for surgical removal of hyperkeratosis, and due to the appearance of neurologic abnormalities in some patients. The severe forms can present with short stature, gonadal hypoplasia, and neurodevelopmental disability. The condition is life-threating due to the increased risk of melanomas and non-melanoma skin cancers at young age.

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 afamelanotide, for treatment of xeroderma pigmentosum, was adopted by consensus.

2.2.16. adeno-associated virus serotype rh.74 vector containing the human *PKP2* gene isoform - EMA/OD/0000166376

Rocket Pharmaceuticals B.V.; Treatment of arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene, 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 rh.74 vector containing the human *PKP2* gene isoform was considered justified based on non-clinical in vivo data showing an improvement in cardiac function, a reduction in arrythmia and improvement in survival.

The condition is chronically debilitating and life-threatening due to ventricular instability which may lead to arrhythmic sudden cardiac death, or progression of ventricular muscle disease resulting in right ventricular systolic dysfunction.

The condition was estimated to be affecting approximately 1.9 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 rh.74 vector containing the human *PKP2* gene isoform, for treatment of arrhythmogenic cardiomyopathy caused by pathogenic mutations in the *PKP2* gene, 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 22 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 24 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. –

Treatment of neurofibromatosis type 1

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 pyruvate kinase deficiency

The discussion was postponed to the May 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

4.1.1. Agilus – dantrolene sodium, hemiheptahydrate - EMEA/H/C/006009, EU/3/21/2443, EMA/OD/0000102465

Norgine B.V.; Treatment of malignant hyperthermia

A list of issues was adopted on 15 February 2024.

An oral explanation was held on 17 April 2024.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 18 April 2024, prior to final opinion.

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

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

4.3.1. Altuvoct – efanesoctocog alfa - EMEA/H/C/005968, EU/3/19/2176, EMA/OD/0000160184

Swedish Orphan Biovitrum AB (publ); Treatment of haemophilia A

COMP Rapporteur: Armando Magrelli; COMP Co-Rapporteur: Karri Penttila

A list of issues was adopted on 14 March 2024.

An opinion recommending not to remove Altuvoct, efanesoctocog alfa, EU/3/19/2176 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 April meeting.]

4.4. Appeal

None

4.5. On-going procedures

COMP co-ordinators were appointed for 1 application.

4.6. 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. 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 Moreau

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

5.3. Appeal

5.3.1. Aspaveli – pegcetacoplan - EMEA/H/C/005553/II/0011, EU/3/17/1873, EMA/OD/0000172113

Swedish Orphan Biovitrum AB (publ); Treatment of paroxysmal nocturnal haemoglobinuria

COMP Rapporteur: Elisabeth Johanne Rook; COMP Co-Rapporteur: Joao Rocha; CHMP Rapporteur: Alexandre Moreau; CHMP Co-Rapporteur: Selma Arapovic

In the grounds for appeal, and during an oral explanation before the Committee on 17 April 2024, the sponsor aimed to address the main issues which led to the negative opinion.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data, was of the opinion that all criteria for designation were now satisfied.

An opinion recommending not to remove Aspaveli, pegcetacoplan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/17/1873) from the Community Register of Orphan Medicinal Products was adopted by consensus.

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

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The Chair thanked Elisabeth Penninga for her contribution as a member for Denmark.

The Chair thanked Robert Nistico for his contribution as a member for Malta.

7.1.2. Vote by proxy

None

7.1.3. Strategic Review & Learning meetings

Preliminary feedback was noted from the COMP SRLM under the Belgian Presidency of the Council of the EU held in person on 27-28 March 2024 in Leuven, Belgium.

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met face-to-face on 16 April 2024.

7.1.5. COMP Decisions Database

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

7.1.6. Mandate of COMP Chairperson and Vice-Chairperson – call for nominations

The mandate of the COMP Chair, Violeta Stoyanova-Beninska, will expire on 5 October 2024 and that of the COMP Vice-Chair, Armando Magrelli on 14 June 2024.

The elections of a new COMP Chair will take place at the June 2024 meeting and that of the new Vice-Chair at the July 2024 meeting.

Expressions of interest should be sent to the Agency, to the COMP secretariat . Candidates are kindly asked to submit a brief CV in support of their candidature together with a cover letter highlighting their expertise.

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. Oncology Working Party (ONCWP)

Outcome of the ONCWP consultation

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

7.3.4. Committee representatives at Scientific Advice Working Party (SAWP): call for interest

Following departure of a joint COMP-SAWP alternate, a call for expression of interests was launched.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

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

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

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Collaborare project: kick off project and presentation of the tool

The COMP received an update of the project and a demonstration of the tool.

8.2. Request to NCA to start Article 8(2) procedure

The COMP was informed about a request to NCA to start an Article 8(2) procedure.

9. List of participants

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

An asterisk (*) after the role, in the second column, signals that the member attended remotely. Additional experts participated in (part of) the meeting, either in person or remotely.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
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	
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 Yannaki	Member*	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Emma Fagan	Member*	Ireland	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
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:	2.2.3. - EMA/OD/0000159474
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Judit Molnar	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Maria Cavaller Bellaubi	Expert	Patients' Organisation Representative	No restrictions applicable to this meeting	
Christiaan Keijzer	Expert	Netherlands	No restrictions applicable to this meeting	
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.

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/