18 July 2024
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Human Medicines Division

# Committee for Orphan Medicinal Products (COMP)

## Minutes for the meeting on 18-20 June 2024

Chair: Violeta Stoyanova-Beninska

**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 agenda 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 agenda 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 agenda 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).

[1] *4.1.1. Adzynma - rADAMTS13 - EMEA/H/C/006198, EU/3/08/588, EMA/OD/0000150694 - correction of active substance*.

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# Table of contents


**1. Introduction 6**

**1.1. Welcome and declarations of interest of members and experts ..... 6**

**1.2. Adoption of agenda ..... 6**

**1.3. Adoption of the minutes ..... 6**

**2. Applications for orphan medicinal product designation 6**

**2.1. For opinion ..... 6**

2.1.1. - EMA/OD/0000164215 ..... 6

2.1.2. - EMA/OD/0000139776 ..... 7

2.1.3. - EMA/OD/0000164923 ..... 9

2.1.4. - EMA/OD/0000169022 ..... 9

2.1.5. (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride - EMA/OD/0000164949 ..... 9

2.1.6. camrelizumab - EMA/OD/0000163852 ..... 11

2.1.7. rivoceranib mesilate - EMA/OD/0000169732 ..... 12

2.1.8. afamelanotide - EMA/OD/0000167882 ..... 14

2.1.9. - EMA/OD/0000169065 ..... 15

2.1.10. - EMA/OD/0000162927 ..... 15

2.1.11. 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/0000169553 ..... 16

**2.2. For discussion / preparation for an opinion ..... 17**

2.2.1. - EMA/OD/0000159992 ..... 17

2.2.2. - EMA/OD/0000164952 ..... 17

2.2.3. - EMA/OD/0000165577 ..... 17

2.2.4. emavusertib - EMA/OD/0000166679 ..... 17

2.2.5. - EMA/OD/0000166750 ..... 18

2.2.6. urokinase, catalytic domain, fused with a single-chain antibody against von Willebrand factor - EMA/OD/0000167609 ..... 18

2.2.7. adeno-associated virus vector serotype 8 containing the human *TYMP* gene (CpG-depleted) - EMA/OD/0000168590 ..... 18

2.2.8. - EMA/OD/0000169543 ..... 19

2.2.9. befiradol fumarate - EMA/OD/0000169884 ..... 19

2.2.10. N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide - EMA/OD/0000171666 ..... 20

2.2.11. cannabidiol acid methyl ester - EMA/OD/0000171870 ..... 20

2.2.12. - EMA/OD/0000172086 ..... 21

2.2.13. sodium phenylbutyrate, ursodoxicoltaurine - EMA/OD/0000172230 ..... 21

2.2.14. heterologous swine glyco-humanised polyclonal antibody against T lymphocytes - EMA/OD/0000172445 ..... 21

2.2.15. adeno-associated virus serotype A101 containing the codon-optimised human *CFTRdeltaR* - EMA/OD/0000172743 ..... 22
2.2.16. adeno-associated virus vector serotype rh.10 containing the human *FXN* gene - EMA/OD/0000172857 ..... 23
2.2.17. N,N'-([cyclohexylmethylene]di-4,1-phenylene)bis(2-[1-pyrrolidinyl]acetamide) - EMA/OD/0000173341 ..... 23
2.2.18. - EMA/OD/0000173345 ..... 24
2.2.19. - EMA/OD/0000173347 ..... 24
**2.3. Revision of the COMP opinions ..... 24**
**2.4. Amendment of existing orphan designations ..... 24**
**2.5. Appeal ..... 24**
**2.6. Nominations ..... 24**
2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs ..... 24
**2.7. Evaluation on-going ..... 24**
**3. Requests for protocol assistance with significant benefit question 25**
**3.1. Ongoing procedures ..... 25**
3.1.1. - ..... 25
3.1.2. - ..... 25
3.1.3. - ..... 25
**4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation 25**
**4.1. Orphan designated products for which CHMP opinions have been adopted ..... 25**
4.1.1. Adzynma - rADAMTS13 - EMEA/H/C/006198, EU/3/08/588, EMA/OD/0000150694 ..... 25
**4.2. Orphan designated products for discussion prior to adoption of CHMP opinion .... 26**
4.2.1. Masitinib AB Science- masitinib - EMEA/H/C/005897, EMA/OD/081/16, EMA/OD/0000125972 ..... 26
4.2.2. Tepkinly - epcoritamab - EMEA/H/C/005985/II/0001, EU/3/22/2634, EMA/OD/0000157895 ..... 26
4.2.3. Winrevair - sotatercept - EMEA/H/C/005647, EU/3/20/2369, EMA/OD/0000157014 ..... 26
4.2.4. Vyloy - zolbetuximab - EMEA/H/C/005868, EU/3/10/803, EMA/OD/0000166702 ..... 26
4.2.5. Ordspono - odronextamab - EMEA/H/C/006215 ..... 26
4.2.6. Iqirvo - elafibranor - EMEA/H/C/006231, EU/3/19/2182, EMA/OD/0000173044 ..... 27
**4.3. Appeal ..... 27**
**4.4. On-going procedures ..... 27**
**4.5. Orphan Maintenance Reports ..... 27**
**5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension 27**
**5.1. After adoption of CHMP opinion ..... 27**

**5.2. Prior to adoption of CHMP opinion ..... 27**
5.2.1. Darzalex – daratumumab – EMEA/H/C/004077/II/0072, EU/3/13/1153, EMA/OD/0000171125 ..... 27
**5.3. Appeal ..... 27**
**5.4. On-going procedures ..... 27**
**6. Application of Article 8(2) of the Orphan Regulation 27**
**7. Organisational, regulatory and methodological matters 28**
**7.1. Mandate and organisation of the COMP ..... 28**
7.1.1. COMP membership ..... 28
7.1.2. Vote by proxy ..... 28
7.1.3. Strategic Review & Learning meetings ..... 28
7.1.4. Protocol Assistance Working Group (PAWG) ..... 28
7.1.5. COMP Decisions Database ..... 28
7.1.6. Election of COMP Chairperson ..... 28
**7.2. Coordination with EMA Scientific Committees or CMDh-v ..... 28**
7.2.1. Recommendation on eligibility to PRIME – report ..... 28
7.2.2. Joint resolution on the principles of conduct within EMA Scientific Committees, WPs and CMDx ..... 28
**7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups ..... 29**
7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP) ..... 29
7.3.2. Innovation Task Force (ITF) meetings ..... 29
7.3.3. Scientific Advice Working Party (SAWP): nomination of COMP member to SAWP ..... 29
**7.4. Cooperation within the EU regulatory network ..... 29**
7.4.1. European Commission ..... 29
**7.5. Cooperation with International Regulators ..... 29**
7.5.1. Food and Drug Administration (FDA) ..... 29
7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA) ..... 29
7.5.3. Therapeutic Goods Administration (TGA), Australia ..... 29
7.5.4. Health Canada ..... 29
**7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee ..... 29**
**7.7. COMP work plan ..... 30**
**7.8. Planning and reporting ..... 30**
7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2024 ..... 30
7.8.2. Overview of orphan marketing authorisations/applications ..... 30
**8. Any other business 30**
**8.1. Spinal muscular atrophy (SMA) registry report ..... 30**

9. List of participants 30
10. Explanatory notes 33

# 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 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 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 18-20 June 2024 was adopted with no amendments.

## 1.3. Adoption of the minutes

The minutes for 21-23 May 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/0000164215

Treatment of myasthenia gravis

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 05 June 2024 prior to responding to the list of issues.

### 2.1.2. - EMA/OD/0000139776

Prevention of T-cell engaging immunotherapy-induced cytokine release syndrome

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

Prevention of T-cell engaging immunotherapy induced cytokine release syndrome (CRS) should be further justified as a distinct medical entity or a valid subset.

In case of a claim as a distinct medical entity, the sponsor was invited to provide further justification on the proposed condition not being an iatrogenic condition.

In case of a claim of a valid subset, the sponsor was invited to discuss whether the proposed medicinal product is expected/will also work in preventing CRS induced by other triggers, apart from T-cell engaging immunotherapies and substantiate their views with any relevant scientific data.

Note that this is for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the orphan regulations and relevant guidelines (especially section A of 2022/C 440/02).

- Intention to diagnose, prevent or treat

Notwithstanding the discussion on the condition, to establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of T-cell engaging immunotherapy induced cytokine release syndrome (CRS), the sponsor was requested to further elaborate on the relevance of using an LPS-challenge clinical model for the prevention of T-cell engaging immunotherapy-induced cytokine release syndrome (CRS) instead of any authorised T-cell engaging immunotherapy. This is important since the condition of interest is claimed by the sponsor as a distinct entity inherently linked to T-cell engaging immunotherapy that varies from all other types of CRS. The sponsor was also requested to further elaborate on the interpretation of the results obtained in the study, especially the lack of significant difference over placebo on highly-relevant clinical symptoms for CRS, including fever and blood pressure.

- Number of people affected

In line with the above comment on the condition, the sponsor was reminded that the prevalence calculation and estimate have to be in line with the final agreed orphan condition. In case the condition changes, the prevalence information will have to be revised accordingly.

The sponsor was reminded to use data sources which are representative for the entire EU.

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 discuss the significant benefit in line with any potential changes in the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 18 June 2024, the sponsor maintained their view that the proposed condition is a 'treatment modality' or 'treatment method' and not an iatrogenic condition.

The COMP stated that a "treatment method" in relation to defining a distinct condition is linked to a use in "medicinal procedures". The COMP considers that "medicinal procedures" relate to clinical procedures such as transplantation and surgery but not medicinal products.

In addition, the sponsor referenced the WHO definition of iatrogenesis, i.e. 'any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.' (WHO, 1972). According to the sponsor, one of these three criteria was not met for their proposed orphan condition, i.e. criterion 2: 'unintended'. The occurrence of T-cell engaging immunotherapy induced CRS is a natural and unavoidable consequence of the engagement of T-cells, as it is fundamentally and intrinsically linked to the binding of the T-cells by BsAbs and CAR-T therapies. The COMP did not agree with this view. CRS is a serious, possibly fatal, adverse drug reaction without a clear correlation with the extent of the intended pharmacological anti-tumour effect of T-cell engaging immunotherapies. The intended effect of authorised T-cell engaging immunotherapies is to treat the patient for their underlying condition and not to cause harm to the patient.

As regards the distinction of CRS caused by T-cell engaging immunotherapies from CRS caused by other triggers, the sponsor pointed out that there are fundamental differences in disease aetiology which make T-cell engaging immunotherapy CRS a distinct condition/medical entity. During the oral hearing, the sponsor clarified that the timepoint of the initiation of the release of cytokines in the overall CRS process is earlier (more upstream) in the dysregulation process of CRS caused by T-cell engaging immunotherapies and directly triggered by T-cell activation. For CRS caused by other triggers, such as viral or bacterial infections, the initiation of the release of cytokines in the overall CRS process is later (more downstream) and rather a secondary consequence of the inflammation process.

From the current literature it appears that qualitative and quantitative differences in CRS mediators (incl. cytokine composition) and clinical presentations exist between CRS caused by different initial insults. However, a general scientific consensus of the definition of CRS or of CRS caused by different initial insults for the purpose of disease classification is lacking.

In addition, the COMP noted that there was little data to support the specific efficacy of the proposed product in the proposed subset of T-cell engaging immunotherapy-induced cytokine release syndrome, as compared to CRS caused by other triggers. The data presented by the sponsor in support of medical plausibility was not specific for T-cell engaging immunotherapy-induced cytokine release syndrome.

The COMP did not consider the additional information as sufficient to support the proposed orphan condition or condition subset of 'prevention of T-cell engaging immunotherapy-induced cytokine release syndrome'.

While the sponsor claimed that the non-clinical lipopolysaccharide (LPS) challenge study is relevant, it does not claim it has unique relevance to CD3 engaging immunotherapy induced CRS.

The COMP agreed that the information in the Horizonscan from the Dutch National Health Care Institute ('ZorgInstituut Nederland, ZIN') could be accepted as a more conservative prevalence estimate of the sponsors proposed condition.

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

### 2.1.3. - EMA/OD/0000164923

Treatment of Duchenne muscular dystrophy

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 03 June 2024 prior to responding to the list of issues.

### 2.1.4. - EMA/OD/0000169022

Treatment of symptomatic obstructive hypertrophic cardiomyopathy

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 05 June 2024 prior to responding to the list of issues.

### 2.1.5. (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride - EMA/OD/0000164949

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

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:

- Intention to diagnose, prevent or treat

Retinitis pigmentosa should be justified 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 also drawn to the position paper published by the COMP in 2023 and the recommendation regarding nomenclature for inherited retinal dystrophies. In this case the Committee considers a more comprehensive name of the condition would be treatment of non-syndromic inherited retinal dystrophies of the rod-dominant phenotype.

- Number of people affected

The sponsor has provided a prevalence estimate for retinitis pigmentosa. The COMP believed that the condition should be broadened to non-syndromic inherited retinal dystrophies of the rod-dominant phenotype as per the guidance given in 2023. The sponsor was therefore invited to provide a revised prevalence estimate for the proposed revised condition by the COMP.

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".

In the written response, and during an oral explanation before the Committee on 18 June 2024, the sponsor acknowledged the new ontology and was principally not opposed to moving towards the suggested indication, but pointed out that their product would likely be useful not only in rod-dominant but also in cone-dominant phenotypes, and this in both non-syndromic and syndromic inherited retinal dystrophies (IRDs).

The sponsor first suggested to leave the cone-dominant phenotype IRDs out of the current submission based on the fact that they have no non-clinical/clinical data to support this. However, the sponsor did note that both syndromic and non-syndromic retinitis pigmentosa exists and hence the sponsor suggested amending the indication to treatment of syndromic and non-syndromic inherited retinal dystrophies of the rod-dominant phenotype.

Given the broadly applicable nature of the treatment, the available supportive non-clinical and clinical data and the scientific rationale the COMP discussed the acceptability of treatment of syndromic and non-syndromic inherited retinal dystrophies of the rod-dominant phenotype. The COMP was of the opinion that it was better to separate the two forms and hence accepted the treatment of non-syndromic inherited retinal dystrophies of the rod-dominant phenotype.

The sponsor also prepared a new prevalence calculation based on the indication the COMP accepted and used several sources suggesting a prevalence of 3.1/10,000. This final estimate was accepted by the Committee and concluded that they could recommend granting the orphan designation.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of non-syndromic inherited retinal dystrophies of the rod-dominant phenotype.

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

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

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

The condition was estimated to be affecting approximately 3.1 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 (E)-2-((4-((4-benzyl(ethyl)amino)phenyl)diazinyl)phenyl)amino-N,N,N-triethyl-2-oxoethan-1-aminium chloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in visual acuity in a broader patient population than the indication for the only authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

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

## 2.1.6. camrelizumab - EMA/OD/0000163852

CATS Consultants GmbH; Treatment of hepatocellular carcinoma

COMP Rapporteur: Frauke Naumann-Winter

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

- Prevalence

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 estimate provided for the prevalence of hepatocellular carcinoma (HCC) seems to be an underestimate. The indirect estimation of prevalence should be based on more recent survival experience of patients with HCC in the EU.

- Significant benefit

The arguments on significant benefit are based on the potential improved efficacy in the condition.

The sponsor was requested to provide the pre-treatment history of patients included in the phase 3 study investigating the combination of camrelizumab and rivoceranib in patients with incurable, locally advanced or metastatic HCC who had failed prior systemic treatment.

In addition, the significant benefit over all authorised treatments in patients who had not previously received systemic treatment is not considered established. The sponsor was asked to further elaborate on the significant benefit over immunotherapy combination treatments.

In the written response, the sponsor provided additional data in their presentation which was submitted to the COMP before the oral explanation.

For the prevalence the sponsor provided most recent EU data with 87,000 European patients diagnosed with HCC and 78,000 who died from it (LA et al., Journal of Hepatology 2024). Based on this the survival used for the calculation of the prevalence was 1.2 years and the final proposed prevalence 1.45 in 10,000 persons. The COMP considered that the proposed prevalence is close to the figure agreed recently and concluded that a prevalence of approximately 2 should be retained for this procedure.

Regarding the significant benefit, the sponsor provided updated efficacy data from the phase 3 study (data cut-off 14th June 2023) and two network meta-analysis: Ciliberto D. et al., 2023 and Fulgenzi C. et al., 2023. The updated efficacy results confirmed the improvement in overall survival (OS) observed with camrelizumab + rivoceranib over sorafenib in the intent to treat (ITT) population (hazard ratio (HR): 0.64), representing a 36% reduction in the risk of death in the camrelizumab + rivoceranib arm compared with the sorafenib arm. The confirmed objective response rate (ORR) were 26.8% in the camrelizumab + rivoceranib arm and 5.9% in the sorafenib arm.

In the meta-analysis data, camrelizumab + rivoceranib combination was compared versus the combinations atezolizumab + bevacizumab and durvalumab + tremelimumab. The SUCRA score was used to evaluate which treatment is likely to be the most efficacious. SUCRA values showed that the ORR and the OS observed with the combination

camrelizumab + rivoceranib was higher versus the combinations atezolizumab + bevacizumab and durvalumab + tremelimumab.

The COMP considered that these data can justify the significant benefit of the proposed product versus the authorised medicinal products at the stage of the initial orphan designation without pre-empting the outcome at the maintenance of the orphan designation. Therefore, the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing camrelizumab was considered justified based on clinical data which showed responses with camrelizumab as monotherapy in patients with hepatocellular carcinoma who received ≥1 prior line of systemic treatment and with the combination of camrelizumab and rivoceranib in patients with incurable, locally advanced or metastatic hepatocellular carcinoma who had not received prior systemic treatment.

The condition is chronically debilitating and life-threatening due to increased mortality and liver dysfunction.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing camrelizumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data and published network meta-analysis that indicated higher responses and longer survival with the proposed product versus the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage that fulfils the criterion of the significant benefit at the time of the initial orphan designation.

A positive opinion for camrelizumab, for treatment of hepatocellular carcinoma, was adopted by consensus.

### 2.1.7. rivoceranib mesilate - EMA/OD/0000169732

CATS Consultants GmbH; Treatment of hepatocellular carcinoma

COMP Rapporteur: Frauke Naumann-Winter

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

- Prevalence

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 estimate provided for the prevalence of hepatocellular carcinoma (HCC) seems to be an underestimate. The indirect estimation of prevalence should be based on more recent survival experience of patients with HCC in the EU.

- Significant benefit

The arguments on significant benefit are based on the potential improved efficacy in the condition.

The sponsor was requested to provide the pre-treatment history of patients included in the phase 3 study investigating the combination of camrelizumab and rivoceranib in patients with incurable, locally advanced or metastatic HCC who had failed prior systemic treatment.

In addition, the significant benefit over all authorised treatments in patients who had not previously received systemic treatment is not considered established. The sponsor was asked to further elaborate on the significant benefit over immunotherapy combination treatments.

In the written response, the sponsor provided additional data in their presentation which was submitted to the COMP before the oral explanation.

For the prevalence the sponsor provided most recent EU data with 87,000 European patients diagnosed with HCC and 78,000 who died from it (LA et al., Journal of Hepatology 2024). Based on this the survival used for the calculation of the prevalence was 1.2 years and the final proposed prevalence 1.45 in 10,000 persons. The COMP considered that the proposed prevalence is close to the figure agreed recently and concluded that a prevalence of approximately 2 should be retained for this procedure.

Regarding the significant benefit, the sponsor provided updated efficacy data from the phase 3 study (data cut-off 14th June 2023) and two network meta-analysis: Ciliberto D. et al., 2023 and Fulgenzi C. et al., 2023. The updated efficacy results confirmed the improvement in overall survival (OS) observed with camrelizumab + rivoceranib over sorafenib in the intent to treat (ITT) population (hazard ratio (HR): 0.64), representing a 36% reduction in the risk of death in the camrelizumab + rivoceranib arm compared with the sorafenib arm. The confirmed objective response rate (ORR) were 26.8% in the camrelizumab + rivoceranib arm and 5.9% in the sorafenib arm.

In the meta-analysis data, camrelizumab + rivoceranib combination was compared versus the combinations atezolizumab + bevacizumab and durvalumab + tremelimumab. The SUCRA score was used to evaluate which treatment is likely to be the most efficacious. SUCRA values showed that the ORR and the OS observed with the combination camrelizumab + rivoceranib was higher versus the combinations atezolizumab + bevacizumab and durvalumab + tremelimumab.

The COMP considered that these data can justify the significant benefit of the proposed product versus the authorised medicinal products at the stage of the initial orphan designation without pre-empting the outcome at the maintenance of the orphan designation. Therefore, the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing rivoceranib mesilate was considered justified based on responses with rivoceranib as monotherapy in patients with hepatocellular carcinoma who received ≥1 prior line of systemic treatment and with the combination of rivoceranib and camrelizumab in patients with incurable, locally advanced or metastatic hepatocellular carcinoma who had not received prior systemic treatment.

The condition is chronically debilitating and life-threatening due to increased mortality and liver dysfunction.

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 rivoceranib mesilate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data and published network meta-analysis that indicated higher responses and longer survival with the proposed product versus the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage that fulfils the criterion of the significant benefit at the time of the initial orphan designation.

A positive opinion for rivoceranib mesilate, for treatment of hepatocellular carcinoma, was adopted by consensus.

### 2.1.8. afamelanotide - EMA/OD/0000167882

Clinuvel Europe Limited; Treatment of variegate porphyria

COMP Rapporteur: Enrico Costa

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of variegate porphyria the sponsor should further elaborate on the preliminary clinical data namely on the trial design and clinical relevance, the validity of the endpoints measured, and the lack of baseline data and the way potential confounders have been managed including the known placebo effect in this condition.

In the written response, the sponsor provided a response to questions raised by the COMP. The primary aim of their study CUV040 was to establish a proof-of-concept for the use of afamelanotide in the treatment of chronic manifestations of variegate porphyria (VP). As VP is an orphan disease with a low prevalence, the sponsor considered it appropriate to conduct an open-label, non-controlled study, with a sample size of six patients. It was highlighted that it is not possible to establish a baseline for this condition as cutaneous disease activity in VP is a direct function of solar irradiation, which varies with each season. The concern with potential confounders was addressed and it was noted that the use of a placebo implant makes little practical sense, since participants would be unblinded based on the pharmacodynamic effect of afamelanotide, which causes visible melanogenesis (tanning). A participant with a suboptimal treatment response disproves a universal placebo effect. The fact that new skin lesions generally decreased during the pre-treatment period while direct sun exposure increased, at a time of peak yearly solar irradiance, is incompatible with the placebo effect, and instead suggests a mechanistic effect of afamelanotide.

A range of endpoints was chosen to capture as much information as possible in CUV040 on the potential clinical effectiveness of afamelanotide. Key endpoints included are a count of new lesions, time spent in direct sunlight, skin fragility and skin condition scores, as well as

the effect of VP on regular daily activities. The clinical relevance of these endpoints has been discussed in the response. All study endpoints showed median improvements following treatment with afamelanotide.

In conclusion, the sponsor stated that the melanogenic mechanism of afamelanotide prevents new cutaneous lesions from occurring in VP patients as they expose themselves to direct sunlight. The results are supported by feedback from physicians and study participants.

The COMP accepted the responses submitted and agreed to recommend granting the orphan designation. The oral explanation was cancelled.

The Committee agreed that the condition, variegate porphyria, 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 preliminary clinical data showing an improvement in Clinical Global Impression of Change (CGIC) and a reduction in skin lesions and fragility.

The condition is life-threatening and chronically debilitating due to cutaneous manifestations which are associated with chronic blistering photosensitivity, typically on the backs of the hands. Neurovisceral symptoms can occur at any age after puberty as acute attacks but may become chronic. The most common symptoms are abdominal pain; nausea and vomiting; constipation; pain in the back, chest, and extremities; and a predominantly motor peripheral neuropathy resulting in muscle weakness that may progress to quadriparesis and respiratory paralysis, anxiety and seizures. An acute attack can be fatal in the presence of severe manifestations including neuropathy, seizures, and respiratory compromise.

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 afamelanotide, for treatment of variegate porphyria, was adopted by consensus.

### 2.1.9. - EMA/OD/0000169065

Treatment of eosinophilic esophagitis

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 03 June 2024 prior to responding to the list of issues.

### 2.1.10. - EMA/OD/0000162927

Treatment of small cell lung cancer

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 29 May 2024 prior to responding to the list of issues.

## 2.1.11. 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/0000169553

Sellas Life Sciences Limited; Treatment of peripheral T-cell lymphoma

COMP Rapporteur: Evangelia Giannaki

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

- Significant benefit

The arguments on significant benefit of the proposed product versus the authorised treatments are based on the potential improved efficacy in the condition versus brentuximab vedotin.

The sponsor was asked to provide updated clinical data if available. In addition, the sponsor was requested to further discuss the arguments provided for significant benefit and justify the assumption of significant benefit over brentuximab vedotin for the proposed orphan condition based on the CD-30 expression status.

In the written response, the sponsor provided updated results from the study GFH009X2101 (cut-off date 26 February 2024). Furthermore, the sponsor, submitted results from a phase 1b/2 study in patients with relapsed/refractory peripheral T-cell lymphomas (r/r PTCL).

Based on the response observed in a limited number of patients who were heavily pre-treated the COMP considered that the significant benefit can be justified, and the oral explanation was cancelled.

However, the COMP recommended that protocol assistance is sought from the Agency prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit.

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

The intention to treat the condition with the medicinal product containing 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 preliminary clinical data which showed responses in few patients with relapsed/refractory peripheral T-cell lymphoma.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive subtypes.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-[[[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 responses in a few heavily pretreated patients. 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 peripheral T-cell lymphoma, was adopted by consensus.

## 2.2. For discussion / preparation for an opinion

### 2.2.1. - EMA/OD/0000159992

Treatment of acute lymphoblastic leukaemia

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

### 2.2.2. - EMA/OD/0000164952

Treatment of complex regional pain syndrome

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

### 2.2.3. - EMA/OD/0000165577

Treatment of Fabry disease

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

### 2.2.4. emavusertib - EMA/OD/0000166679

Orphix Consulting GmbH; Treatment of primary large B-cell lymphoma of immune-privileged sites

COMP Rapporteur: Evangelia Giannaki

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of primary large B-cell lymphoma of immune-privileged sites.

The Committee agreed that the condition, primary large B-cell lymphoma of immune-privileged sites, is a distinct medical entity and meets the criteria for orphan designation.

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

The condition is life-threatening and chronically debilitating due to various symptoms, including visual impairment, severe neuropsychiatric symptoms, seizures, cognitive changes, cranial neuropathy and focal neurological deficits.

The condition was estimated to be affecting approximately 0.4 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 emavusertib, for treatment of primary large B-cell lymphoma of immune-privileged sites, was adopted by consensus.

### 2.2.5. - EMA/OD/0000166750

Treatment of epidermolysis bullosa

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 July meeting.

### 2.2.6. urokinase, catalytic domain, fused with a single-chain antibody against von Willebrand factor - EMA/OD/0000167609

TargED Biopharmaceuticals B.V.; Treatment of thrombotic thrombocytopenic purpura

COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing urokinase, catalytic domain, fused with a single-chain antibody against von Willebrand factor was considered justified based on non-clinical in vivo data showing a normalisation of platelet counts as well as lactate dehydrogenase, haemoglobin and haematocrit.

The condition is life-threatening and chronically debilitating due to the risk of severe neurological impairment, as well as cardiac and renal manifestations which are related to thrombotic events.

The condition was estimated to be affecting approximately 0.3 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 urokinase, catalytic domain, fused with a single-chain antibody against von Willebrand factor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a normalisation of lactate dehydrogenase, a marker for cell injury of the condition, an effect not observed with the only currently available medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for urokinase, catalytic domain, fused with a single-chain antibody against von Willebrand factor, for treatment of thrombotic thrombocytopenic purpura, was adopted by consensus.

### 2.2.7. adeno-associated virus vector serotype 8 containing the human *TYMP* gene (CpG-depleted) - EMA/OD/0000168590

Fundacio Hospital Universitari Vall D Hebron Institut De Recerca; Treatment of mitochondrial neurogastrointestinal encephalomyopathy

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype 8 containing the human *TYMP* gene (CpG-depleted) was considered justified based on studies in a preclinical model of the condition, where treatment with the product resulted in restoration of thymidine phosphorylase activity in the liver and normalisation of systemic levels of thymidine and deoxyuridine.

The condition is chronically debilitating and life-threatening, in particular due to gastrointestinal dysmotility, peripheral neuropathy, leukoencephalopathy and reduced life expectancy, with most patients not surviving beyond the 4th decade of life.

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 adeno-associated virus vector serotype 8 containing the human *TYMP* gene (CpG-depleted), for treatment of mitochondrial neurogastrointestinal encephalomyopathy, was adopted by consensus.

### 2.2.8. - EMA/OD/0000169543

Treatment of chronic pancreatitis

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 July meeting.

### 2.2.9. befiradol fumarate - EMA/OD/0000169884

Neurolixis; Treatment of spinocerebellar ataxia

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing befiradol fumarate was considered justified based on non-clinical in vivo data in a model of the condition showing improvement in motor function and increases in dopamine neuron density.

The condition is chronically debilitating due to a slow progressive loss of gait coordination which is often associated with poor coordination of hands, speech as well as eye movements.

The condition was estimated to be affecting approximately 0.3 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 befiradol fumarate, for treatment of spinocerebellar ataxia, was adopted by consensus.

## 2.2.10. N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide - EMA/OD/0000171666

Biomarin International Limited; Treatment of congenital alpha-1 antitrypsin deficiency

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, congenital alpha-1 antitrypsin deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide was considered justified based on non-clinical in vivo data showing improvement in liver function and a reduction of polymers associated with the condition.

The condition is life-threatening and chronically debilitating due to the early development of lung emphysema in adults and liver disease in children and adults. In liver disease, intracellular accumulation of mutant alpha-1 antitrypsin polymers in hepatocytes causes liver inflammation leading to hepatitis with cholestasis, cirrhosis or liver scarring. Liver cancer may occur later in life. Liver transplant may be required in cases of liver failure; death may occur where transplant is unavailable.

The condition was estimated to be affecting approximately 2.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in liver function which is not treated with authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

## 2.2.11. cannabidiol acid methyl ester - EMA/OD/0000171870

Scendea (NL) B.V.; Treatment of Prader-Willi syndrome

COMP Rapporteur: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing cannabidiol acid methyl ester was considered justified based on non-clinical data showing an effect on weight loss and an improvement in hyperphagia.

The condition is life-threatening and chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour, hyperphagia and morbid obesity leading to increased cardiovascular morbidity and mortality.

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 cannabidiol acid methyl ester will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data indicating a reduction in hyperphagia. The product could be added to the currently used growth hormone treatment to address the clinically relevant aspect of the condition which is not treated by growth hormone alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol acid methyl ester, for treatment of Prader-Willi syndrome, was adopted by consensus.

### 2.2.12. - EMA/OD/0000172086

Treatment of punctate palmoplantar keratoderma

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 July meeting.

### 2.2.13. sodium phenylbutyrate, ursodoxicoltaurine - EMA/OD/0000172230

Amylyx Pharmaceuticals EMEA B.V.; Treatment of Wolfram syndrome

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing sodium phenylbutyrate, ursodoxicoltaurine was considered justified based on in vivo non-clinical data in valid animal model showing an improvement of glucose tolerance, as well as preliminary clinical data showing an improvement in C-peptide levels.

The condition is life-threatening with a life-expectancy of 30 years and chronically debilitating due to the development of diabetes mellitus and optic nerve atrophy.

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 sodium phenylbutyrate, ursodoxicoltaurine, for treatment of Wolfram syndrome, was adopted by consensus.

### 2.2.14. heterologous swine glyco-humanised polyclonal antibody against T lymphocytes - EMA/OD/0000172445

Xenothera; Treatment of peripheral T-cell lymphoma

COMP Rapporteur: Jana Mazelova

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

The intention to treat the condition with the medicinal product containing heterologous swine glyco-humanised polyclonal antibody against T lymphocytes was considered justified based on in vivo non-clinical data which showed tumour growth inhibition in valid models of the condition.

The condition is life-threatening and chronically debilitating due to poor response to therapy and high rate of relapses. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive subtypes.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

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 heterologous swine glyco-humanised polyclonal antibody against T lymphocytes will be of significant benefit to those affected by the condition. The sponsor has provided in vivo non-clinical data that demonstrate higher tumour growth inhibition compared to first line standard of care chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for heterologous swine glyco-humanised polyclonal antibody against T lymphocytes, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

### 2.2.15. adeno-associated virus serotype A101 containing the codon-optimised human *CFTRdeltaR* - EMA/OD/0000172743

Pharma Gateway AB; Treatment of cystic fibrosis

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype A101 containing the codon-optimised human *CFTRdeltaR* was considered justified based on non-clinical in vivo data showing restoration of CFTR function and preliminary clinical data which showed improvements in percent predicted forced expiratory volume in 1 second (ppFEV1) and improvements in respiratory symptoms, following treatment with the product.

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

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype A101 containing the codon-optimised human *CFTRdeltaR* will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that indicate efficacy in a patient

population who is intolerant or not covered by current CFTR modulators. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype A101 containing the codon-optimised human *CFTRdeltaR*, for treatment of cystic fibrosis, was adopted by consensus.

### 2.2.16. adeno-associated virus vector serotype rh.10 containing the human *FXN* gene - EMA/OD/0000172857

Scendea (NL) B.V.; Treatment of Friedreich ataxia

COMP Rapporteur: Maria Judit Molnar

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

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype rh.10 containing the human *FXN* gene was considered justified based on non-clinical in vivo data in a model of the condition showing improvement in cardiac function and survival.

The condition is chronically debilitating and life-threatening due to ataxia, progressive disability that requires the use of a wheelchair, and cardiac involvement in the form of hypertrophic cardiomyopathy.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus vector serotype rh.10 containing the human *FXN* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate an improvement in cardiac function which is not currently addressed by the only authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus vector serotype rh.10 containing the human *FXN* gene, for treatment of Friedreich ataxia, was adopted by consensus.

### 2.2.17. N,N'-([cyclohexylmethylene]di-4,1-phenylene)bis(2-[1-pyrrolidinyl]acetamide) - EMA/OD/0000173341

RegSmart Life Science AB; Treatment of Creutzfeldt-Jakob disease

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing N,N'-([cyclohexylmethylene]di-4,1-phenylene)bis(2-[1-pyrrolidinyl]acetamide) was considered justified based on models of the condition demonstrating reduced prion protein aggregation, delay in the progression of neurological and psychological symptoms, and improved survival.

The condition is life-threatening due to rapid disease progression with a marked reduction in the median survival and chronically debilitating due to rapid neurological degeneration that produces muscle spasms and progressive loss of mental function, reduced muscular coordination, personality changes, impaired memory and impaired vision.

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 N,N'-([cyclohexylmethylene]di-4,1-phenylene)bis(2-[1-pyrrolidinyl]acetamide), for treatment of Creutzfeldt-Jakob disease, was adopted by consensus.

### 2.2.18. - EMA/OD/0000173345

Treatment of AL amyloidosis

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

### 2.2.19. - EMA/OD/0000173347

Treatment of ATTR amyloidosis

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

## 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 20 applications.

## 2.7. Evaluation on-going

None

# 3. Requests for protocol assistance with significant benefit question

## 3.1. Ongoing procedures

### 3.1.1. -

Treatment of narcolepsy

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 glioma

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

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

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

### 4.1.1. Adzynma - rADAMTS13 - EMEA/H/C/006198, EU/3/08/588, EMA/OD/0000150694

Takeda Manufacturing Austria AG; Treatment of thrombotic thrombocytopenic purpura

COMP Rapporteur: Elisabeth Johanne Rook; COMP Co-Rapporteur: Karri Penttila;

A list of issues was adopted on 23 May 2024.

The oral explanation scheduled on 19 June 2024, was cancelled.

An opinion recommending not to remove Adzynma, rADAMTS13, EU/3/08/588 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.

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

### 4.2.1. Masitinib AB Science- masitinib - EMEA/H/C/005897, EMA/OD/081/16, EMA/OD/0000125972

AB Science.; In combination with riluzole for the treatment of adult patients with amyotrophic lateral sclerosis

The status of the procedure at CHMP was noted.

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

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

CHMP Rapporteur: Peter Mol; CHMP Co-Rapporteur: Ingrid WangThe 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 July meeting.

### 4.2.3. Winrevair - sotatercept - EMEA/H/C/005647, EU/3/20/2369, EMA/OD/0000157014

Merck Sharp & Dohme B.V.; Treatment of pulmonary arterial hypertension

COMP Rapporteur: Joao Rocha; COMP Co-Rapporteur: Elisabeth Johanne RookAn opinion recommending not to remove Winrevair, sotatercept, EU/3/20/2369 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 June meeting.]*

### 4.2.4. Vyloy - zolbetuximab - EMEA/H/C/005868, EU/3/10/803, EMA/OD/0000166702

Astellas Pharma Europe B.V.; Treatment of gastric 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 July meeting.

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

Regeneron Ireland Designated Activity Company

a) Treatment of follicular lymphoma, EU/3/22/2649, EMA/OD/0000168564The 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 July meeting.

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

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 July meeting.

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

Ipsen Pharma; Treatment of primary biliary cholangitis

The status of the procedure at CHMP was noted.

## 4.3. Appeal

None

## 4.4. On-going procedures

COMP co-ordinators were appointed for 2 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. Darzalex – daratumumab – EMEA/H/C/004077/II/0072, EU/3/13/1153, EMA/OD/0000171125

Janssen Cilag International; Treatment of plasma cell myeloma

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

COMP co-ordinators were appointed for 1 application.

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

None

# 7. Organisational, regulatory and methodological matters

## 7.1. Mandate and organisation of the COMP

### 7.1.1. COMP membership

The Chair welcomed Fernando Mendez Hermida, as the new member nominated by the European Commission on the 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 face-to-face on 18 June 2024.

### 7.1.5. COMP Decisions Database

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

### 7.1.6. Election of COMP Chairperson

The mandate of the COMP Chair, Violeta Stoyanova-Beninska, will expire on 15 September 2024. The election of the new Chair took place in accordance with the COMP rules of procedure.

The nominations received were presented to the Committee.

The COMP elected Tim Leest as COMP Chair for a three-year mandate starting on 16 September 2024 .

The COMP and the Agency congratulated Tim Leest on his election and wished him all the best in his new role as Chair of the Committee.

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

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

Documents were tabled for information.

### 7.2.2. Joint resolution on the principles of conduct within EMA Scientific Committees, WPs and CMDx

The COMP members noted the presentation on the principles of conduct within EMA Scientific Committees, WPs and CMDx.

## 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 following member was appointed:

- COMP SAWP member: Elisabeth Johanne Rook

## 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. Spinal muscular atrophy (SMA) registry report

Scope: Outcome of the SMA registry study

COMP received detailed feedback on the outcome of the spinal muscular atrophy (SMA) registry study. COMP was informed that the final report can be found in the HMA-EMA catalogue and a manuscript is under preparation.

# 9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 18-20 June 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 | |
| Brigitte Schwarzer-Daum | Member | Austria | No restrictions applicable to this meeting | |
| Tim Leest | Member | Belgium | No interests declared | |
| Dinko Vitezic | Member | Croatia | No interests declared | |
| Ioannis Kkolos | Member | Cyprus | No interests declared | |

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

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| Darius Matusevicius | Member | Sweden | No restrictions applicable to this meeting | |
| 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: | 2.2.10. N-[(1R)-1-[(S)-(2-chloro-3-fluorophenyl)hydroxymethyl]butyl]-7-fluoro-2,3-dihydro-2-oxo-1H-indole-4-carboxamide - EMA/OD/0000171666 |
| Fernando Mendez Hermida | Member* | Expert recommended by EMA | No interests declared | |
| Ingeborg Barisic | Member | Expert recommended by EMA | No interests declared | |
| Maria Judit Molnar | Member | Expert recommended by EMA | No participation in discussion, final deliberations and voting on: | 2.1.3. EMA/OD/0000164923<br>2.2.7. adeno-associated virus vector serotype 8 containing the human *TYMP* gene (CpG-depleted) - EMA/OD/0000168590<br>2.1.1. - EMA/OD/0000164215 |
| Maria Driessens | Expert | Netherlands | No restrictions applicable to this meeting | |
| Sabine Scherer | Expert | Germany | No interests declared | |
| Sylvie Benchetrit | Expert | France | No interests declared | |
| Dana Marin | Expert | Romania | No interests declared | |
| A representative from the European Commission attended the meeting | | | | |

| Name | Role | Member State or affiliation | Outcome restriction following evaluation of e-DoI | Topics on agenda for which restrictions apply |
|---|---|---|---|---|
| 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/