20 February 2025
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Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 03-05 December 2024

Chair: Tim Leest – Vice-Chair: Frauke Naumann-Winter

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 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 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).

[1] Removal of internal reference in section 3 - Adopted by the Committee on 23 January 2025

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
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Table of contents

1. Introduction 5

1.1. Welcome and declarations of interest of members and experts 5

1.2. Adoption of agenda 5

1.3. Adoption of the minutes 5

2. Applications for orphan medicinal product designation 5

2.1. For opinion 5

2.1.1. camostat mesilate - EMA/OD/0000226832 5

2.1.2. - EMA/OD/0000227928 7

2.1.3. volixibat potassium - EMA/OD/0000223853 8

2.1.4. adeno-associated virus serotype 9 containing the human *RPE65* gene - EMA/OD/0000226506 9

2.1.5. alvelestat - EMA/OD/0000224798 10

2.1.6. - EMA/OD/0000223155 12

2.1.7. allogenic umbilical cord-derived osteoblast cells - EMA/OD/0000227422 12

2.2. For discussion / preparation for an opinion 13

2.2.1. elraglusib - EMA/OD/0000178930 13

2.2.2. elraglusib - EMA/OD/0000179381 14

2.2.3. rilzabrutinib - EMA/OD/0000225145 14

2.2.4. - EMA/OD/0000225792 15

2.2.5. - EMA/OD/0000228469 15

2.2.6. - EMA/OD/0000228739 15

2.2.7. - EMA/OD/0000230149 15

2.2.8. - EMA/OD/0000230201 15

2.2.9. N-(2-methoxyethyl)-6-methyl-N-[(3-methyl-2-thienyl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide - EMA/OD/0000230429 16

2.2.10. clofutriben - EMA/OD/0000230573 16

2.2.11. [4-(methyl-1H-pyrazol-4-yl)-benzyl]-(6[7-(3-pyrrolidin-1-yl-propoxy)-imidazo[1,2-a]pyridin-3-yl]-pyrimidin-4-yl]-amine - EMA/OD/0000230712 17

2.2.12. - EMA/OD/0000231115 17

2.3. Revision of the COMP opinions 17

2.4. Amendment of existing orphan designations 18

2.5. Appeal 18

2.6. Nominations 18

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs 18

2.7. Evaluation on-going 18

3. Requests for protocol assistance with significant benefit question 18

3.1. Ongoing procedures 18

3.1.1. -..... 18

3.1.2. -..... 18

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation 18

4.1. Orphan designated products for which CHMP opinions have been adopted 18

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion 19

4.2.1. - beremagene geperpavec - EMEA/H/C/006330, EU/3/18/2012, EMA/OD/0000233504 19

4.2.2. Andembry - garadacimab - EMEA/H/C/006116, EU/3/21/2532, EMA/OD/0000133460..... 19

4.2.3. Seladelpar Gilead - seladelpar - EMEA/H/C/004692, EU/3/17/1930, EMA/OD/0000170646 19

4.2.4. Beyonttra - acoramidis - EMEA/H/C/006333, EU/3/18/2081, EMA/OD/0000224696 19

4.2.5. Pemazyre - pemigatinib - EMEA/H/C/005266/II/0015, EU/3/19/2216, EMA/OD/0000167021 20

4.2.6. Emcitate - tiratricol - EMEA/H/C/005220, EU/3/17/1945, EMA/OD/0000168628 20

4.3. Appeal 20

4.3.1 Hetronifly - serplulimab - EMEA/H/C/006170, EU/3/22/2731, EMA/OD/0000237657 20

4.4. On-going procedures 21

4.5. Orphan Maintenance Reports..... 21

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension 21

5.1. After adoption of CHMP opinion 21

5.2. Prior to adoption of CHMP opinion 21

5.2.1. Blincyto - blinatumomab - EMEA/H/C/003731/II/0056, EU/3/09/650, EMA/OD/0000162410 21

5.2.2. Amvuttra - vutrisiran - EMEA/H/C/005852/II/0015, EU/3/18/2026, EMA/OD/019/18 21

5.2.3. Darzalex - daratumumab - EMEA/H/C/004077/II/0077, EU/3/13/1153, EMA/OD/038/13.. 22

5.2.4. Darzalex - daratumumab - EMEA/H/C/004077/II/0076, EU/3/13/1153, EMA/OD/038/13.. 22

5.3. Appeal 22

5.4. On-going procedures 22

6. Application of Article 8(2) of the Orphan Regulation 22

7. Organisational, regulatory and methodological matters 22

7.1. Mandate and organisation of the COMP 22

7.1.1. COMP membership..... 22

7.1.2. Vote by proxy 22

7.1.3. Strategic Review & Learning meetings..... 23

7.1.4. Protocol Assistance Working Group (PAWG) 23

7.1.5. COMP Decisions Database..... 23

7.2. Coordination with EMA Scientific Committees or CMDh-v 23
7.2.1. Recommendation on eligibility to PRIME – report 23
7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups 23
7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP) 23
7.3.2. Innovation Task Force (ITF) meetings 23
7.4. Cooperation within the EU regulatory network 23
7.4.1. European Commission 23
7.5. Cooperation with International Regulators 23
7.5.1. Food and Drug Administration (FDA) 23
7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA) 23
7.5.3. Therapeutic Goods Administration (TGA), Australia 24
7.5.4. Health Canada 24
7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee 24
7.7. COMP work plan 24
7.7.1. Draft COMP Work Plan for 2025 24
7.8. Planning and reporting 24
7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2024 24
7.8.2. Overview of orphan marketing authorisations/applications 24
8. Any other business 24
8.1. Implementation of new fee regulation (EU) 2024/568 from 1 January 2025 24
8.2. Feedback from HTA/EMA workshop on uncertainties 24
9. List of participants 25
10. Explanatory notes 27

1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

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

Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional interests or restrictions were declared.

Restrictions applicable to this meeting are captured in the List of participants included in the minutes.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

The Chair welcomed the new member and thanked the departing member for his contribution 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 03-05 December 2024 was adopted with amendments:

5.2.4. Darzalex - daratumumab - EMEA/H/C/004077/II/0076, EU/3/13/1153, EMA/OD/038/13

1.3. Adoption of the minutes

The minutes for 05-07 November 2024 were adopted with no amendments and will be published on EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. camostat mesilate - EMA/OD/0000226832

Pangenix Pharma Limited; Treatment of chronic pancreatitis

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:

- Number of people affected

The COMP questioned the validity of meta-analysis in view of the highly diverse estimates for prevalence reported across different databases and settings.

Furthermore, the sponsor seemed to have applied the positive predictive value (PPV) even to physician-verified diagnosis.

The sponsor was asked to discuss the validity of the submitted publications for the estimation of the contemporaneous prevalence in view of the improved diagnostics and the rise in risk factors of the disease in an ageing population. The sponsor was asked to discuss these issues and was asked to provide a more conservative estimate of the current prevalence of chronic pancreatitis (CP) in the overall population in the 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".

In the written response, and during an oral explanation before the Committee on 04 December 2024, the sponsor further discussed their chosen approach in estimating the prevalence of CP in the EU. Main points made/discussed were as follows.

The results from an additional sensitivity analysis of the meta-analysis were presented. This analysis was considered very conservative by the sponsor as it used a higher positive predictive value (PPV) as reported in Kierkegaard, 2020 (up to 83%) for both registry studies by Olesen et al., 2021, and Chonchubhair et al., 2017, and, in addition, including acute pancreatitis (AP) cases of Levy et al., 2006 (a fundamentally flawed approach as CP and AP are distinct diseases). While this analysis resulted in a higher prevalence estimate then before, i.e. increasing from 4 to 4.34 per 10,000 persons, it still remained below the critical threshold of <5 in 10,000 persons.

While this new sensitivity analysis was acknowledged by the COMP, it was not considered to address the main issue of employing a meta-analytical approach here in the first place, i.e. the large heterogeneity (100%) of the data sources likely due to the different methodologies of case ascertainment and possible selection bias from the different settings. Of note, the heterogeneity measure of a meta-analysis quantifies the relationship between within- and between-study variability in the data. A focus on prioritising data sources considered most robust would be preferred by the Committee. It was acknowledged by both the sponsor and the COMP that the available epidemiologic data is scarce for CP and the one which is available (and discussed here) is of limited quality each with their own set of limitations (incl. uncertainty over the robustness of coding of pancreatitis in health databases, distinguishing recurrent acute from chronic pancreatitis, incomplete data sources as regards those patient counted from primary care/ outpatient visits vs hospital admission data, double entries for recurring patients, etc.). This causes uncertainty over the true prevalence value of CP throughout the EU.

Nevertheless, the COMP acknowledged that most of the published epidemiologic studies suggest that the prevalence of CP in the EU is still below the threshold of 5 per 10,000 persons and could therefore still be considered a rare disease. Strong evidence of an

increasing trend of CP throughout the EU over the past years could not be found. However, the Committee pointed out that it is difficult to define a specific prevalence estimate for CP with certainty, due to the general data scarcity and the limited data quality. Also, the reason as to why the most recent epidemiologic data from Denmark (Olesen et al., 2021) reported a prevalence of CP, which is three times the value of the accepted threshold to meet the orphan designation criteria, has not been sufficiently clarified. This dataset, however, clearly stands out compared to all other reported prevalence data in CP and adds to the general uncertainty over true CP prevalence in the EU. Since the COMP agreed to the importance of physician-confirmed diagnosis in view of the high possibility of misclassification, the registry-based data was considered an outlier, and the COMP accepted a prevalence estimate of approximately 4.9 in 10,000 persons.

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

The intention to treat the condition with the medicinal product containing camostat mesilate was considered justified based on bibliographic clinical data showing reduction in pain, inflammation, and fibrosis, and preventing disease progression, particularly of patients with early and intermediate stages of the condition.

The condition is life-threatening due to possible severe complications including pancreatic cancer, kidney or multi-organ failure if left untreated and chronically debilitating due to persistent pain and digestive problems which can significantly impact quality of life.

The condition was estimated to be affecting approximately 4.9 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 camostat mesilate, for treatment of chronic pancreatitis, was adopted by consensus.

2.1.2. - EMA/OD/0000227928

Treatment of glioma

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

- 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 glioma the sponsor was requested to further elaborate on the results obtained in vitro with the proposed product only, the results from the in vivo experiments which are mentioned but not presented, and the clinical data presented.

- 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 figure presented by the sponsor is an underestimate. The sponsor was requested to describe and justify the methodology used for the prevalence calculation. The sponsor was

asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registries for the proposed orphan condition.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit based on relevant data in order to justify the assumptions of significant benefit over authorised medicinal products for the proposed orphan condition.

In addition, the arguments presented by the sponsor cannot justify the significant benefit in the absence of acceptance of the medical plausibility.

In the written response, and during an oral explanation before the Committee on 03 December 2024, the sponsor did not present any new data and did not address the questions which were raised. The sponsor highlighted the mechanism of action, however, in the absence of data the COMP considered that the medical plausibility, the prevalence and the significant benefit were not justified by the sponsor.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 04 December 2024, prior to final opinion.

2.1.3. volixibat potassium - EMA/OD/0000223853

Mirum Pharmaceuticals International B.V.; Treatment of primary biliary cholangitis

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

- Significant benefit

The sponsor was asked to provide a discussion on the significant benefit of volixibat over elafibranor (Iqirvo) and support any claims made with relevant data.

In the written response, the sponsor justified the significant benefit of volixibat over elafibranor in the treatment of primary biliary cholangitis (PBC) as follows.

Interim results from the sponsors clinical study with volixibat in combination with ursodeoxycholic acid (UDCA) showed statistically and clinically significant improvements in pruritus as compared to patients only receiving placebo in combination with UDCA. In this study, the primary outcome of interest was the comparison of baseline pruritus to the average pruritus scores from weeks 13-24, measured using the 10-point Adult Itch Reported Outcome (ItchRO).

In contrast, the efficacy data of elafibranor on pruritus was assessed by the CHMP as "neither statistically significant nor clinically relevant" (reference was made to the CHMP Assessment Report on Iqirvo, EMA/372188/2024). Cholestatic pruritus was included as secondary endpoint in the pivotal study with elafibranor.

The COMP considered that this preliminary clinical data suggested that volixibat reduces cholestatic pruritus in patients with the condition. This has not been demonstrated with currently authorised medicinal products. Cholestatic pruritus is one of the most burdensome symptoms for PBC patients.

As a general note, the marketing authorisation of obeticholic acid (Ocaliva) has now been revoked officially by the European Commission (EC) and removed from the Union Register

of active medicinal products for human use (see Union Register of medicinal products - Public health - European Commission).

This makes UDCA and elafibranor (Iqirvo) the only relevant satisfactory methods for the purpose of this procedure.

Based on the sponsors written responses, the COMP adopted a positive opinion and the oral hearing was cancelled.

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

The intention to treat the condition with the medicinal product containing volixibat potassium was considered justified based on preliminary clinical data which showed a reduction in cholestatic pruritus in patients with the condition.

The condition is chronically debilitating due to pruritus, fatigue, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopenia and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular carcinoma.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing volixibat potassium will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data with volixibat when used in combination with ursodeoxycholic acid, which showed a reduction in cholestatic pruritus in patients with the condition, which has not been demonstrated with currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for volixibat potassium, for treatment of primary biliary cholangitis, was adopted by consensus.

2.1.4. adeno-associated virus serotype 9 containing the human *RPE65* gene - EMA/OD/0000226506

Granzer Regulatory Consulting & Services GmbH; Treatment of inherited retinal dystrophy due to defects in the *RPE65* gene

COMP Rapporteur: Ruta Mameniskiene

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

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over the authorised medicinal product voretigene neparvovec (Luxturna) for the proposed orphan condition. The difference in the efficacy in adeno-associated virus serotypes should be further elaborated in the clinical setting of inherited retinal dystrophies.

In the written response, and during an oral explanation before the Committee on 04 December 2024, the sponsor provided preliminary clinical data showing improved efficacy to Luxturna regard best-corrected visual acuity (BCVA), kinetic visual field (KVF) and full-field stimulus (FST). All dose cohorts demonstrated visual and retinal function improvements. BCVA, KVF, and FST values in a few patients treated with a high dose of the proposed medicinal product demonstrated better efficacy results than published results for Luxturna (Russell et al., 2017). Although the mechanistic reason for the difference was not understood the difference in efficacy was large enough to support the significant benefit at time of orphan designation.

The sponsor also claimed that their product did not cause chorioretinal atrophy which has been reported in the SmPC for Luxturna and also in the 15 year follow-up safety study from where 5 year data has been reported for 106 patients. The sponsor provided limited data in treated patients which the COMP considered insufficient at time of designation to establish a clinically relevant advantage versus Luxturna based on safety.

The COMP concluded that the preliminary clinical data supported improved efficacy to Luxturna and that this represented a clinically relevant advantage to support significant benefit. It was therefore agreed that the Committee could recommend granting the orphan designation.

The Committee agreed that the condition, inherited retinal dystrophy due to defects in the *RPE65* 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 9 containing the human *RPE65* gene was considered justified based on preliminary clinical data showing an improvement in visual acuity as measured by full-field stimulus threshold change and best-corrected visual acuity.

The condition is chronically debilitating due to loss of vision.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

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 9 containing the human *RPE65* gene will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improved visual acuity as measured by full-field stimulus threshold change when indirectly compared to the only authorised medicinal product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 9 containing the human *RPE65* gene, for treatment of inherited retinal dystrophy due to defects in the *RPE65* gene, was adopted by consensus.

2.1.5. alvelestat - EMA/OD/0000224798

Mereo Biopharma Ireland Limited; Treatment of congenital alpha-1 antitrypsin deficiency

COMP Rapporteur: Vallo Tillmann

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

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the Phase 2 studies with alvelestat (ASTRAEUS and ATALANTa), to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition, particularly in patients with forced expiratory volume per second (FEV1) predicted above 65%.

In the written response, the sponsor provided additional arguments to support the significant benefit of alvelestat over authorised augmentation therapies.

The sponsor maintained their view that available data do not support the benefit of augmentation therapy for patients with congenital alpha-1 antitrypsin deficiency–lung disease (AATD-LD) and lung function >65% forced expiratory volume in one second (FEV1) > 65%, i.e. reference is made to the three studies included in the meta-analysis by Chapman et al., 2009 and, two additional studies (Tonelli et al., 2009, Fraughen et al., 2023). Of note, all of these studies were registry-based with no randomised control group. Furthermore, the sponsor pointed out that the study by Wencker et al., 2001, which is included in the meta-analysis by Chapman et al., 2009, only included very few patients and had several methodological limitations, as also noted in a recent publication (Pierce, 2024).

A recent systematic review of all adequate well-controlled trials and observational studies reported there may be benefit of augmentation within the FEV1 bands 30-49%, with some evidence including up to 65% (Pierce, 2024). For those with better preserved FEV1, augmentation therapy may be considered only if there is evidence of rapid respiratory progression or other features of severe functional respiratory compromise. These conclusions are also largely reflected in organisational and national treatment recommendations for congenital alpha-1 antitrypsin deficiency (AATD) throughout the EU.

In contrast, alvelestat has demonstrated evidence of efficacy in two randomised, placebo-controlled trials in AATD-LD, including in patients with near normal lung function values (baseline FEV1>80%). In this regard the sponsor presented new pooled efficacy analyses from their two clinical trials in a subgroup of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) status 1 airflow limitation (i.e. baseline FEV1>80%) at week 12 (and week 16). These analyses are suggestive of a possible benefit of alvelestat in this particular patient subset when compared to the placebo-treated patients (positive trends in the total score and the activity domain of patient reported outcome tool of the "St George's Respiratory Questionnaire condensed form (SGRQ-C)" and a positive trend in showing fewer acute exacerbations of COPD).

In conclusion, the COMP considered that the data presented by the sponsor is sufficient to support the significant benefit of alvelestat over authorised augmentation therapies, for the purpose of initial orphan designation. Available data suggests that alvelestat has protective effects against inflammation and structural lung damage and has demonstrated positive effects on health-related quality of life measures, including in patients with near normal lung function values (baseline FEV1>80%). This has not been demonstrated for currently authorised augmentation therapies.

The Committee adopted a positive opinion and cancelled the oral hearing.

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 alvelestat was considered justified based on preliminary clinical data showing improvement in biomarkers indicative of lung damage which correlated with improvements in health-related quality of life.

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.

The condition was estimated to be affecting approximately 2.8 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 alvelestat will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement in biomarkers indicative of structural lung damage which correlated with improvements in health-related quality of life in a broader target patient population as compared to currently authorised augmentation therapy, including those with less severely impacted lung function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for alvelestat, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

2.1.6. - EMA/OD/0000223155

Treatment of pancreatic 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 19 November 2024, prior to responding to the list of issues.

2.1.7. allogenic umbilical cord-derived osteoblast cells - EMA/OD/0000227422

Opis S.r.l.; Treatment of non-traumatic osteonecrosis

COMP Rapporteur: Ines Alves

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

- Number of people affected

It was noted that an average for the incidence was provided from the literature search. Recent publications indicated that there has been a progressive increase in the incidence of the proposed condition (Dima et al., 2018). The proposed incidence appears to be an under-estimate of what could be the current incidence. The sponsor was invited to recalculate the prevalence using an incidence which is more current than the proposed average.

The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

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, the sponsor provided a revised literature search regarding the question on prevalence.

From these publications the sponsor proposed a prevalence estimate of 3 in 10,000 which was accepted by the COMP.

The COMP concluded that they could recommend granting the orphan designation.

The Committee agreed that the condition, non-traumatic osteonecrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogenic umbilical cord-derived osteoblast cells was considered justified based on preliminary clinical data showing after one-year follow up significant improvements were observed in both radiological and clinical outcomes.

The condition is chronically debilitating due to pain and reduced range of motion.

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 allogenic umbilical cord-derived osteoblast cells, for treatment of non-traumatic osteonecrosis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. elraglusib - EMA/OD/0000178930

Actuate Therapeutics Limited; Treatment of pancreatic cancer

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing elraglusib was considered justified based on non-clinical data in a model of the condition showing a positive effect on survival and tumour volume, in combination with clinical data in patients with the condition showing improved survival when used in combination to standard of care.

The condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing elraglusib will be of significant benefit to those affected by the

condition. The sponsor has provided non-clinical data and preliminary clinical data in patients with the condition which showed superior responses when the product was used as add-on to standard of care treatment compared to standard of care alone. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.2. elraglusib - EMA/OD/0000179381

Actuate Therapeutics Limited; Treatment of soft tissue sarcoma

COMP Rapporteur: Jana MazelovaThe Committee agreed that the condition, soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing elraglusib was considered justified based on in vivo non-clinical data which showed antitumour effect of the proposed product in monotherapy and in combination with doxorubicin in a liposarcoma tumour model and the preliminary clinical data which showed responses in heavily pretreated patients with soft tissue sarcoma.

The condition is chronically debilitating due to the possible need for amputation of limbs and life-threatening with a high recurrence and metastasis rate with reduced life expectancy.

The condition was estimated to be affecting approximately 4.7 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 elraglusib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed responses in heavily pretreated patients with soft tissue sarcoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for elraglusib, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.3. rilzabrutinib - EMA/OD/0000225145

Sanofi B.V.; Treatment of autoimmune haemolytic anaemia

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing rilzabrutinib was considered justified based on preliminary clinical data in patients with the condition showing increased haemoglobin levels.

The condition is life-threatening and chronically debilitating due to venous or arterial thrombotic events, infections, requirement of red blood cell transfusion and decreased quality of life.

The condition was estimated to be affecting approximately 2.4 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 rilzabrutinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that rilzabrutinib confers a clinical benefit by increasing haemoglobin levels in patients whose disease cannot be sufficiently controlled despite treatment with approved therapies for this condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rilzabrutinib, for treatment of autoimmune haemolytic anaemia, was adopted by consensus.

2.2.4. - EMA/OD/0000225792

Treatment of mucosal melanoma

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 January meeting.

2.2.5. - EMA/OD/0000228469

Treatment of amyotrophic lateral sclerosis

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

2.2.6. - EMA/OD/0000228739

Treatment of primary sclerosing cholangitis

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 January meeting.

2.2.7. - EMA/OD/0000230149

Treatment of functional cobalamin deficiency in genetic defects of intracellular cobalamin processing

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 January meeting.

2.2.8. - EMA/OD/0000230201

Treatment of limb-girdle muscular dystrophy

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the January meeting.

2.2.9. N-(2-methoxyethyl)-6-methyl-N-[(3-methyl-2-thienyl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide - EMA/OD/0000230429

AdRes EU B.V.; Treatment of adult polyglucosan body disease

COMP Rapporteur: Maria Judit Molnar

The Committee agreed that the condition, adult polyglucosan body 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-(2-methoxyethyl)-6-methyl-N-[(3-methyl-2-thienyl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide was considered justified based on non-clinical in vivo data showing improvement in survival and muscle function and preliminary clinical data showing an improvement in muscle function.

The condition is chronically debilitating due to neuromuscular involvement in infancy which appears as global muscle weakness, hypotonia, arthrogryposis, and respiratory distress, and in children as gross motor delay, hyperlordosis, and proximal weakness. In adults it manifests as spastic gait, neurogenic bladder, and peripheral neuropathy. Hepatomegaly as well as primary myocardial disease or cardiomyopathy can be present. It is life-threatening in infancy or early childhood as it is reported to be lethal.

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

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

A positive opinion for N-(2-methoxyethyl)-6-methyl-N-[(3-methyl-2-thienyl)methyl]-2-oxo-1,2-dihydropyridine-4-carboxamide, for treatment of adult polyglucosan body disease, was adopted by consensus.

2.2.10. clofutriben - EMA/OD/0000230573

Scendea (NL) B.V.; Treatment of Cushing's syndrome

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, Cushing'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 clofutriben was considered justified based on clinical data in patients with the condition showing an effect in relevant biomarkers of the disease and a reduction in cortisol-driven morbidities.

The condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric conditions.

The condition was estimated to be affecting approximately 0.7 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 clofutriben will be of significant benefit to those affected by the

condition. The sponsor has provided clinical data in patients with the condition indicating that treatment with the proposed product led to response rates in pretreated patients across several disease morbidities. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for clofutriben, for treatment of Cushing's syndrome, was adopted by consensus.

2.2.11. [4-(methyl-1H-pyrazol-4-yl)-benzyl]-(6[7-(3-pyrrolidin-1-yl-propoxy)-imidazo[1,2-a]pyridin-3-yl]-pyrimidin-4-yl]-amine - EMA/OD/0000230712

Voisin Consulting Life Sciences; Treatment of gastrointestinal stromal tumours

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing [4-(methyl-1H-pyrazol-4-yl)-benzyl]-(6[7-(3-pyrrolidin-1-yl-propoxy)-imidazo[1,2-a] pyridin-3-yl]-pyrimidin-4-yl]-amine was considered justified based on in vivo non clinical data which showed tumour regression and preliminary clinical data which showed durable responses in patients with metastatic and/or surgically unresectable gastrointestinal stromal tumours.

The condition is chronically debilitating and life-threatening in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival.

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.

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-(methyl-1H-pyrazol-4-yl)-benzyl]-(6[7-(3-pyrrolidin-1-yl-propoxy)-imidazo[1,2-a]pyridin-3-yl]-pyrimidin-4-yl]-amine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed responses in patients with gastrointestinal stromal tumours who were pretreated with the authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for [4-(methyl-1H-pyrazol-4-yl)-benzyl]-(6[7-(3-pyrrolidin-1-yl-propoxy)-imidazo[1,2-a]pyridin-3-yl]-pyrimidin-4-yl]-amine, for treatment of gastrointestinal stromal tumours, was adopted by consensus.

2.2.12. - EMA/OD/0000231115

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 January 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 10 applications submitted and upcoming applications.

2.7. Evaluation on-going

2 applications for orphan designation will not be discussed as evaluation is ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of hereditary angioedema

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.

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

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

None

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

4.2.1. - beremagene geperpavec - EMEA/H/C/006330, EU/3/18/2012, EMA/OD/0000233504

Krystal Biotech Netherlands B.V.; Treatment of epidermolysis bullosa

The status of the procedure at CHMP was noted.

4.2.2. Andembry - garadacimab - EMEA/H/C/006116, EU/3/21/2532, EMA/OD/0000133460

CSL Behring GmbH; Treatment of hereditary angioedema

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 19 November 2024, prior to responding to the list of issues. The sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 19 November 2024.

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

4.2.3. Seladelpar Gilead - seladelpar - EMEA/H/C/004692, EU/3/17/1930, EMA/OD/0000170646

Cymabay Ireland Limited; Treatment of primary biliary cholangitis

COMP Rapporteur: Zsofia Gyulai; COMP Co-Rapporteur: Irena RogovskaAn opinion recommending not to remove Seladelpar Gilead, seladelpar, EU/3/17/1930 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 December meeting.]

4.2.4. Beyonttra - acoramidis - EMEA/H/C/006333, EU/3/18/2081, EMA/OD/0000224696

BridgeBio Europe B.V.; Treatment of ATTR amyloidosis

A list of issues was adopted on 07 November 2024.

An oral explanation was held on 03 December 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 05 December 2024, prior to final opinion.

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

4.2.5. Pemazyre - pemigatinib - EMEA/H/C/005266/II/0015, EU/3/19/2216, EMA/OD/0000167021

Incyte Biosciences Distribution B.V.; Treatment of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2

CHMP Rapporteur: Alexandre Moreau; CHMP Co-Rapporteur: Janet KoenigThe status of the procedure at CHMP was noted.

4.2.6. Emcitate - tiratricol - EMEA/H/C/005220, EU/3/17/1945, EMA/OD/0000168628

Rare Thyroid Therapeutics; Treatment of monocarboxylate transporter 8 (MCT8) deficiency

COMP Rapporteur: Vallo Tillmann; COMP Co-rapporteur: Darius MatuseviciusAn opinion recommending not to remove Emcitate, tiratricol, EU/3/17/1945 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 December meeting.]

4.3. Appeal

4.3.1 Hetronifly - serplulimab - EMEA/H/C/006170, EU/3/22/2731, EMA/OD/0000237657

Henlius Europe GmbH; Treatment of small cell lung cancer

Appeal COMP Rapporteur: Jana Mazelova; Appeal COMP Co-Rapporteur: Bozenna Dembowska-Baginska

In its grounds for appeal, and during an oral explanation before the Committee 03 December 2024, the sponsor aimed to address the main issues which led to the negative opinion.

The COMP concluded that the proposed therapeutic indication, serplulimab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of small cell lung cancer.

The prevalence of small cell lung cancer is estimated to remain below 5 in 10,000 and was concluded to be 1.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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.

Although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Hetronifly may be of potential significant benefit to those affected by the orphan condition still holds. Hetronifly showed a better overall survival outcome compared to atezolizumab and durvalumab. These results suggest that Hetronifly may offer a significant benefit in terms of efficacy, as demonstrated through indirect comparisons.

An opinion recommending not to remove Hetronifly, serplulimab, EU/3/22/2731 from the EC Register of Orphan Medicinal Products was adopted by majority (by 26 out of 28 votes). The Norwegian COMP member agreed with the above-mentioned recommendation of the COMP. The COMP member of Liechtenstein was absent. The Icelandic mandate is vacant.

The divergent positions (Brigitte Schwarzer-Daum, Elisabeth Johanne Rook) were appended to this opinion.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

4.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

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

COMP Rapporteur: Frauke Naumann-Winter; COMP Co-Rapporteur: Karri PenttilaAn opinion recommending not to remove Blincyto, blinatumomab, EU/3/09/650 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 December meeting.]

5.2.2. Amvuttra - vutrisiran - EMEA/H/C/005852/II/0015, EU/3/18/2026, EMA/OD/019/18

Alnylam Netherlands B.V; Treatment of transthyretin-mediated amyloidosis

CHMP Rapporteur: Janet Koenig; CHMP Co-Rapporteur: Fatima VenturaThe COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.2.3. Darzalex - daratumumab - EMEA/H/C/004077/II/0077, EU/3/13/1153, EMA/OD/038/13

Janssen Cilag International N.V.; Treatment of plasma cell myeloma

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

5.2.4. Darzalex - daratumumab - EMEA/H/C/004077/II/0076, EU/3/13/1153, EMA/OD/038/13

Janssen Cilag International N.V.; Treatment of plasma cell myeloma

CHMP Rapporteur: Boje Kvorning Pires EhmsenThe 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 2 applications.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

The Chair welcomed Sine Buhl Næss-Schmidt, as the new member for Denmark.

The Chair thanked Boje Kvorning Pires Ehmsen for his contribution as the member for Denmark.

7.1.2. Vote by proxy

Dinko Vitezic gave a proxy to Ingeborg Barisic to vote on behalf of Dinko Vitezic during the entire meeting.

Evangelia Giannaki gave a proxy to Liesbeth Rook to vote on behalf of Evangelia Giannaki during part of the meeting.

Maria Driessens gave a proxy to Julian Isla to vote on behalf of Maria Driessens during part of the meeting.

Ioannis Kkolos gave a proxy to Evangelia Giannaki to vote on behalf of Evangelia Giannaki during part of the meeting.

Enrico Costa gave a proxy to Joao Rocha to vote on behalf of Enrico Costa during part of the meeting.

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 02 December 2024.

7.1.5. COMP Decisions Database

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

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

None

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

Documents were tabled for information.

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

7.7.1. Draft COMP Work Plan for 2025

COMP Chair: Tim Leest

Documents were circulated.

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. Implementation of new fee regulation (EU) 2024/568 from 1 January 2025

The COMP noted the update on the implementation of the new fee regulation.

8.2. Feedback from HTA/EMA workshop on uncertainties

COMP member: Frauke Naumann-Winter

A summary of the discussion points on a case study between the regulatory agencies and the HTA agencies was presented.

Both parties agreed on the usefulness of earlier dialogue for better preparation of post-approval evidence generation.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 03-05 December 2024 COMP meeting, which was held remotely.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Tim Leest	Chair	Belgium	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Sine Buhl Naess-Schmidt	Member	Denmark	No restrictions applicable to this meeting	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttila	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member (Vice-Chair)	Germany	No interests declared	
Evangelia Giannaki	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Ruta Mameniskiene	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Luana Mifsud Buhagiar	Member	Malta	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Jana Schweigertova	Member	Slovak Republic	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ines Alves	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Mariette Driessens	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Fernando Mendez Hermida	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No interests declared	
Maria Judit Molnar	Member	Expert recommended by EMA	No participation in discussion, final deliberations and voting on:	2.2.12. - EMA/OD/0000231115
Maria Cavaller Bellaubi	Expert	Patients' Organisation Representative	No restrictions applicable to this meeting	
Clemens Mittmann	Expert	Germany	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

Experts' declared interests were evaluated against the agenda topics or activities they participated in.

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate

the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

For a list of acronyms and abbreviations, see:

Abbreviations used in EMA scientific committees & CMD documents and in relation to EMA's regulatory activities

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