Committee for Orphan Medicinal Products (COMP)
Minutes for the meeting on 07-09 November 2023

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

Disclaimers

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

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

Note on access to documents

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

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

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

In accordance with the Agency’s policy on handling of declarations of interests of scientific Committees’ members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified.

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

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

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

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 07-09 November 2023 was adopted with amendments.

Topic added:

5.2.1. Kinpeygo – budesonide - EMEA/H/C/5653/II/0008, EU/1/22/1657, EMA/OD/0000157484

1.3. **Adoption of the minutes**

The minutes for 03-05 October 2023 were adopted with amendments and will be published on the EMA website.

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

2.1. **For opinion**

2.1.1. brogidirsen - EMA/OD/0000142974

Medpace Finland Oy; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Julian Isla
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 Duchenne muscular dystrophy the sponsor should further elaborate on:

- immunohistochemical data in the muscle biopsy regarding ratio of the dystrophin positive fibres and the individual amount of the dystrophin levels based on the Western blot after the treatment with their product,
- the correlation between dystrophin levels and clinical improvements,
- the results obtained in the preliminary clinical data particularly regarding the improvements in muscle function.

In the written response, and during an oral explanation before the Committee on 7 November 2023, the sponsor provided additional data up to 63 weeks from their Phase 1/2, open label Investigator Initiated Trial (NCNP/DMT02).

The sponsor claimed that the data show that the increase in dystrophin levels over 26 weeks was associated with a stabilisation of motor function. The COMP still considered that no clear correlation was shown, at 26 weeks, between dystrophin levels and the motor function tests presented. Additional data at 63 weeks showed interesting trends in the North Star Ambulatory Assessment (NSAA) test both when looking at individual trends and by cohort. Although the numbers were very small the COMP considered that there may be some improvement in stabilisation of muscle function in Cohort 2 in which the 80 mg/kg dose was used. This preliminary evidence in patients of an add-on effect using the sponsor’s product in combination with corticosteroids was considered supportive of the intention to treat.

The COMP concluded that the sponsor had provided sufficient preliminary clinical data to support the medical plausibility for the purpose of an initial orphan designation and recommended to granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing brogidirsen was considered justified based on preliminary clinical data showing an improvement in dystrophin levels and stable motor function after 63 weeks of treatment.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles; this is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing brogidirsen will be of significant benefit to those affected by
the condition. The sponsor has provided preliminary clinical data that demonstrate an effect in patients with exon 44-45 deletion which are not covered by the only authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for brogidirsen, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

### 2.1.2. - EMA/OD/0000146696

**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 October 2023, prior to responding to the list of issues.

### 2.1.3. golcadomide hydrochloride - EMA/OD/0000143407

**Bristol-Myers Squibb Pharma EEIG; Treatment of follicular lymphoma**

**COMP Rapporteur: Karri Penttila**

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical and clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Regarding the clinical data, the sponsor was invited to detail the specific prior lines of therapy and the response observed in patients with follicular lymphoma (FL).

In addition, the sponsor was invited to clarify where in the treatment armamentarium the proposed product is intended to be positioned.

In the written response, and during an oral explanation before the Committee on 7 November 2023, the sponsor defended their position.

As part of the initial assessment, the Committee concluded that no significant benefit had been demonstrated versus authorised medicinal products, and that the positioning of the proposed product in the treatment armamentarium was unclear.

As part of the answer, the sponsor provided additional information on the ongoing Phase 1 Study from Parts A and B. Part A is to evaluate the safety and tolerability of escalating doses of the proposed product in patients ≥ 18 years of age with relapse or refractory (R/R) FL who have had progression of disease after at least 2 lines of therapy (or who have received at least one prior line of standard therapy and are not eligible for autologous stem cell transplant), while Part B is to evaluate the safety and efficacy of golcadomide in combination with rituximab in subjects with R/R FL. Overall, responses were observed in patients heavily pretreated for FL with an overall response rate of 72.7%, including 4 complete responses and 4 partial responses.
A summary of available data (baseline characteristics including prior therapies and best overall response) for the proposed product as monotherapy was provided. The positioning of the product with regards to the intended target population was also clarified which would entail 2 lines + R/R FL and potentially 1 line FL as a chemo-free alternative. However, the positioning as 1 line has not been actively demonstrated.

During the oral explanation, the sponsor introduced cases of R/R patients to treatments such as CAR-T treatments and bispecific antibodies who then responded to the treatment with the proposed product as monotherapy. While the magnitude of effect and duration of response were limited due to the reduced number of patients and the ongoing nature of the study, the Committee believed that this could be sufficient for supporting an initial orphan designation.

Overall, although preliminary, the clinical data can be supportive of a positive opinion. The COMP adopted a positive opinion after the oral explanation. The COMP advised the sponsor to request EMA protocol assistance for further development.

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

The intention to treat the condition with the medicinal product containing golcadomide hydrochloride was considered justified based on non-clinical data in a valid model of the condition showing a reduction in tumour volume, in combination with preliminary clinical data which showed responses in patients with relapsed or refractory follicular lymphoma.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma.

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.

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 golcadomide hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed responses in pretreated patients with relapsed or refractory follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for golcadomide hydrochloride, for treatment of follicular lymphoma, was adopted by consensus.

2.1.4. marstacimab - EMA/OD/0000145792

Pfizer Europe MA EEIG; Treatment of haemophilia B

COMP Rapporteur: Armando Magrelli

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
In order to demonstrate the significant benefit of the proposed product the sponsor was invited to further elaborate on the potential advantages of the proposed product and provide a valid comparison against authorised products in haemophilia B patients with or without inhibitors.

In particular, the sponsor was invited to:

- provide adequate justification for the assumption that subcutaneous administration of the proposed product will be a major contribution to patient care instead of intravenous administration (as relevant for the currently used products);
- to further justify the claim of a clinically relevant advantage over long-acting FIX products in patients without inhibitors and over FEIBA and NovoSeven in patients with inhibitors to FIX.

In the written response, and during an oral explanation before the Committee on 8 November 2023, the sponsor provided additional data on the use of their product in both haemophilia A and haemophilia B patients. The sponsor reiterated that marstacimab is a novel anti-tissue factor pathway inhibitor (TFPI) and a potential first-in-class, non-factor treatment, utilising the extrinsic coagulation pathway of coagulation for bleeding control that directly addresses an unmet medical and patient need for adolescent and adult patients with haemophilia B. The sponsor had done a subgroup analysis of the patients without inhibitors and claimed better clinical effect and efficacy.

Pre-clinical in-vitro marstacimab spike-in experiments utilising plasma samples from patients with haemophilia A and B with inhibitors was provided in support of the effect in haemophilia B patients. A dose-dependent increase in thrombin generation was observed for marstacimab in plasma, while no effect was seen in the control group.

As it is recognised that haemophilia B is a very rare condition and patients with inhibitors is an even smaller group, the COMP could at the time of orphan designation accept the assumption that marstacimab could be efficacious also in patients with inhibitors. This is based on an extrapolation from the haemophilia A patients with inhibitors, in which marstacimab has been shown to work, supported by the above in-vitro data.

Concerning use in adolescent patients the sponsor clarified that only four of the twenty recruited patients had haemophilia B but that they all showed trends to improvements.

No additional compelling data was submitted regarding major contribution to patient care.

After deliberation the COMP accepted the argumentation that the product could be used in severe haemophilia B (Srivastava, 2020; Bolton-Maggs, 2003; Male, 2020), with previously untreated patients and minimally treated patients (MTPs) at highest risk. Data from Study B7841007, an open-label extension study to assess the long-term safety, tolerability, and efficacy of prophylaxis treatment with marstacimab in participants who successfully completed the Phase 3 Study B7841005, was considered supportive. Approximately 145 adolescent and adult participants 12 to <75 years of age with severe haemophilia A or moderately severe to severe haemophilia B (defined as FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitors were planned to be enrolled in this study during which they received prophylactic treatment with marstacimab once weekly prophylaxis (defined as scheduled treatment by SC injection of marstacimab) at the dose established during participation in Study B7841005. All 25 haemophilia B non-inhibitor
participants completed Study B7841005. As of cut-off date of 10 March 2023, 20 participants rolled over to Study B7841007.

In the non-inhibitor prophylaxis group, of the 20 haemophilia B participants, 14 had 0 new treated bleeding events. Bleed events were reported in 6/20 haemophilia B participants (3 participants with 1 [over 43 to 379 days], 1 with 2 [over 99 days], 1 with 3 [over 323 days] and 1 with 5 new bleeding events [over 162 days]).

Based on this last data set the COMP considered it could accept the preliminary clinical results for severe haemophilia B patients but considered that at the time of review for the maintenance of the orphan designation the sponsor will need more compelling data. The COMP recommended granting the initial orphan designation.

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

The intention to treat the condition with the medicinal product containing marstacimab was considered justified based on preliminary clinical data showing a significant reduction in annual bleeding rate.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury. Bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening.

The condition was estimated to be affecting approximately 0.17 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 marstacimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a significant reduction in annual bleeding rate in patients with severe haemophilia B who no longer respond to treatment adequately. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for marstacimab, for treatment of haemophilia B, was adopted by consensus.

2.1.5. - EMA/OD/0000142982

Treatment of moderate to severe traumatic brain injury

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 12 October 2023, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. allogeneic amniotic fluid-derived mesenchymal stem cells with lung specificity - EMA/OD/0000137167

Amniotics AB (publ); Prevention of primary graft dysfunction following lung transplantation
COMP Rapporteur: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of primary graft dysfunction following lung transplantation.

The Committee agreed that the condition, primary graft dysfunction following lung transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic amniotic fluid-derived mesenchymal stem cells with lung specificity was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in severity in graft dysfunction.

The condition is life-threatening and chronically debilitating due to developing bronchiolitis obliterans syndrome and an increased risk of acute graft rejection.

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 allogeneic amniotic fluid-derived mesenchymal stem cells with lung specificity, for treatment of primary graft dysfunction following lung transplantation, was adopted by consensus.

2.2.2. (S)-N-(1-(3-fluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)-2-oxopiperidin-3-yl)-5-(pyridin-2-yl)thiophene-2-sulfonamide - EMA/OD/0000140599

Selabtec Sciences S.L.; Treatment of soft tissue sarcoma

COMP Rapporteur: Bozenna Dembowska-Baginska

The 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 (S)-N-(1-(3-fluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)-2-oxopiperidin-3-yl)-5-(pyridin-2-yl)thiophene-2-sulfonamide was considered justified based on non-clinical in vivo data showing reduction in tumour size.

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 (S)-N-(1-(3-fluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)-2-oxopiperidin-3-yl)-5-(pyridin-2-yl)thiophene-2-sulfonamide will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing growth inhibition in xenografts from patient-derived resistant tumour cells. The Committee considered that this constitutes a clinically relevant advantage.
A positive opinion for (S)-N-(1-(3-fluoro-2'-methoxy-[1,1'-biphenyl]-4-yl)-2-oxopiperidin-3-yl)-5-(pyridin-2-yl)thiophene-2-sulfonamide, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.3. **allogeneic umbilical cord-derived mesenchymal stromal cells, pooled**

ESPL Regulatory Consulting Limited; Treatment of perinatal asphyxia

COMP Rapporteur: Zsofia Gyulai

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

The intention to treat the condition with the medicinal product containing allogeneic umbilical cord-derived mesenchymal stromal cells, pooled was considered justified based on bibliographical data in non-clinical in vivo models of the condition showing improvements in neurological function.

The condition is chronically debilitating due to the long lasting neurological and developmental sequelae. The condition is also life threatening due to the high mortality associated with the most severe cases.

The condition was estimated to be affecting approximately 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 allogeneic umbilical cord-derived mesenchymal stromal cells, pooled, for treatment of perinatal asphyxia, was adopted by consensus.

2.2.4. **selumetinib**

AstraZeneca AB; Treatment of glioma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing selumetinib was considered justified based on preliminary clinical data on paediatric low-grade glioma patients who showed objective responses following selumetinib monotherapy.

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

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 selumetinib will be of significant benefit to those affected by
the condition. The sponsor has provided preliminary clinical data that demonstrated that patients with recurrent, refractory or progressive paediatric low-grade gliomas responded to treatment with the proposed product as monotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for selumetinib, for treatment of glioma, was adopted by consensus.

2.2.5. methyl 4-(2-acetamidoethylsulfanyl)-4-oxobutanoate - EMA/OD/0000147097

Abliva AB; Treatment of Leigh syndrome
COMP Rapporteur: Joao Rocha

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

The intention to treat the condition with the medicinal product containing methyl 4-(2-acetamidoethylsulfanyl)-4-oxobutanoate was considered justified based on non-clinical data in a valid model of the condition showing the delay in the motor decline and an improvement in the body weight gain.

The condition is chronically debilitating due to neurological deficits, psychomotor delay, dysmorphic features, cardiac, renal and metabolic dysfunction, and life-threatening with most patients dying in early childhood.

The condition was estimated to be affecting approximately 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 methyl 4-(2-acetamidoethylsulfanyl)-4-oxobutanoate, for treatment of Leigh syndrome, was adopted by consensus.

2.2.6. autologous T lymphocytes containing a T-cell receptor against Epstein–Barr virus - EMA/OD/0000147441

Carthagenetics Iberica S.L.; Treatment of peripheral T-cell lymphoma
COMP Rapporteur: Frauke Naumann-Winter

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 autologous T lymphocytes containing a T-cell receptor against Epstein–Barr virus was considered justified based on bibliographical clinical data in patients with extranodal peripheral T-cell lymphomas (nasal type) showing improved progression free survival and overall survival after long-term follow-up.

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 autologous T lymphocytes containing a T-cell receptor against Epstein–Barr virus will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that when the product is given as post-remission therapy there is an improvement in progression free survival and overall survival after long-term follow-up. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T lymphocytes containing a T-cell receptor against Epstein–Barr virus, for treatment of peripheral T-cell lymphoma, was adopted by consensus.

2.2.7. 2'-O, 4'-C-methylene-P-thio-adenylyl-(3'->5')-2'-O, 4'-C-methylene-P-thio-
guanylyl-(3'->5')-2'-O, 4'-C-methylene-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-
adenylyl-(3'->5')-2'-deoxy-P-thio-thymidylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-
(3'->5')-2'-deoxy-P-thio-guanylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-
deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-
adenylyl-(3'->5')-2'-deoxy-P-thio-thymidylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->
5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-
cytidylyl-(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-
C-methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-C-methyleneguanosine -
EMA/OD/0000148726

Ultragenyx Germany GmbH; Treatment of Angelman syndrome

COMP Rapporteur: Gloria Maria Palomo Carrasco

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

The intention to treat the condition with the medicinal product containing 2'-O, 4'-C-
methylene-P-thio-adenylyl-(3'->5')-2'-O, 4'-C-methylene-P-thio-guanylyl-(3'->5')-2'-O, 4'-
C-methylene-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-
thio-thymidylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-
(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-
deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-
thymidylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-
(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-C-
methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-C-methyleneguanosine was considered
justified based on non-clinical data showing a dose-dependent effect on UBE3A gene
expression, in combination with clinical data in patients with the condition that could
indicate an improvement in cognition and receptive communication.

The condition is chronically debilitating due to developmental delay, motor and cognitive
impairment, hyperactivity and epileptic seizures that are often treatment-resistant.

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.

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

A positive opinion for 2'-O, 4'-C-methylene-P-thio-adenylyl-(3'->5')-2'-O, 4'-C-methylene-
P-thio-guanylyl-(3'->5')-2'-O, 4'-C-methylene-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-
adenylyl-(3'->5')-2'-deoxy-P-thio-thymidylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-(3'->5')-2'-deoxy-P-thio-guanylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-thymidylyl-(3'->5')-2'-deoxy-P-thio-cytidylyl-(3'->5')-2'-deoxy-P-thio-adenylyl-(3'->5')-2'-deoxy-P-thio-thymidylyl-(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-cytidylyl-(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-C-methylene-5-methyl-P-thio-uridylyl-(3'->5')-2'-O, 4'-C-methyleneguanosine, for treatment of Angelman syndrome, was adopted by consensus.

2.2.8. - EMA/OD/0000148755

Treatment of amyotrophic lateral sclerosis

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 December 2023 meeting.

2.2.9. cutamesine - EMA/OD/0000149115

3R Pharma Consulting GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Michel Hoffmann

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

The intention to treat the condition with the medicinal product containing cutamesine was considered justified based on in vivo non-clinical data in a valid disease model showing improved motor function and prolonged survival.

The condition is chronically debilitating and life-threatening due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure with shortened life expectancy.

The condition was estimated to be affecting approximately 1.1 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 cutamesine will be of significant benefit to those affected by the condition. The sponsor has provided in vivo non-clinical data which showed improved motor function and survival compared to the authorised treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cutamesine, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.10. - EMA/OD/0000149222

Treatment of diffuse large B-cell lymphoma

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 December 2023 meeting.
2.2.11. - EMA/OD/0000149464

Treatment of hyperinsulinism

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 December 2023 meeting.

2.2.12. bersiporocin - EMA/OD/0000149586

Propharma Group The Netherlands B.V.; Treatment of idiopathic pulmonary fibrosis

COMP Rapporteur: Eva Malikova

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

The intention to treat the condition with the medicinal product containing bersiporocin was considered justified based on non-clinical data in models of the condition showing a reduction in disease biomarkers and fibrosis score.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing bersiporocin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate improvement in disease biomarkers and fibrosis score when the proposed product was used as add-on therapy to existing standard of care products nintedanib or pirfenidone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bersiporocin, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.13. - EMA/OD/0000149631

Treatment of amyotrophic lateral sclerosis

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 December 2023 meeting.

2.2.14. ovine polyclonal fragment antigen-binding against ricin - EMA/OD/0000150150

Serb; Treatment of ricin poisoning

COMP Rapporteur: Cécile Dop

The Committee agreed that the condition, ricin poisoning, is a distinct medical entity and meets the criteria for orphan designation.
The intention to treat the condition with the medicinal product containing ovine polyclonal fragment antigen-binding against ricin was considered justified based on non-clinical data showing a dose dependent positive effect on clinical symptoms of intoxication, change in body weight, and survival.

The condition is life-threatening and chronically debilitating due to rapid development of multi-organ failure and shock, usually leading to death in a few days.

The condition was estimated to be affecting approximately less than 0.001 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention in the European Union for the population at risk of developing the condition.

A positive opinion for ovine polyclonal fragment antigen-binding against ricin, for treatment of ricin poisoning, was adopted by consensus.

2.2.15. - EMA/OD/0000150249

Treatment of autosomal dominant polycystic kidney disease

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 December 2023 meeting.

2.2.16. - EMA/OD/0000150398

Treatment of eosinophilic granulomatosis with polyangiitis (EGPA)

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 December 2023 meeting.

2.2.17. - EMA/OD/0000150558

Treatment of eosinophilic esophagitis

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 December 2023 meeting.

2.2.18. 3,3-dimethyl-N-(6-methyl-5-([2-(1-methyl-1H-pyrazol-4-yl)pyridine-4-yl]oxy)pyridine-2-yl)-2-oxopyrrolidine-1-carboxamide hydrochloride hydrate - EMA/OD/0000150801

Amador Bioscience; Treatment of tenosynovial giant-cell tumour, local and diffuse type

COMP Rapporteur: Jana Mazelova

The Committee agreed that the condition, tenosynovial giant-cell tumour, local and diffuse type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3,3-dimethyl-N-(6-methyl-5-([2-(1-methyl-1H-pyrazol-4-yl)pyridine-4-yl]oxy)pyridine-2-yl)-2-oxopyrrolidine-1-carboxamide hydrochloride hydrate was considered justified based on preliminary clinical data showing complete and partial responses, reduction in tumour volume and improvement in range of motion, pain and stiffness.
The condition is chronically debilitating due to loss of function of the affected joints, the development of secondary arthritis, pain and the highly recurrent nature of the condition.

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 3,3-dimethyl-N-(6-methyl-5-{[2-(1-methyl-1H-pyrazol-4-yl)pyridine-4-yl]oxy}pyridine-2-yl)-2-oxopyrrolidine-1-carboxamide hydrochloride hydrate, for treatment of tenosynovial giant-cell tumour, local and diffuse type, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for 19 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 17 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of ovarian cancer

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. Rezzayo – rezafungin - EMEA/H/C/005900, EU/3/20/2385, EMA/OD/0000140230

Mundipharma GmbH; Treatment of invasive candidiasis

COMP Rapporteur: Olimpia Neagu; COMP Co-Rapporteur: Zsofia Gyulai

A list of issues was adopted on 10 October 2023.

The oral explanation scheduled on 8 November 2023, was cancelled.

An opinion recommending not to remove Rezzayo, rezafungin, EU/3/20/2385 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.

4.1.2. Elrexfio - humanised IgG2k Fc-modified bispecific monoclonal antibody against CD3 and BCMA - EMEA/H/C/005908, EU/3/21/2471, EMA/OD/0000147440

Pfizer Europe MA EEIG; Treatment of multiple myeloma

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 25 October 2023, prior to responding to the list of issues. The sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 27 October 2023.

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

4.1.3. Albrioza – sodium phenylbutyrate / ursodoxicoltaurine - EMEA/H/C/005901, EU/3/20/2284, EMA/OD/0000096503

Amylyx Pharmaceuticals EMEA; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Darius Matusevicius; COMP Co-Rapporteur: Gloria Palomo Carrasco

CHMP negative opinion was noted.

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

4.2.1. - sparsentan - EMEA/H/C/005783/0000, EU/3/20/2345, EMA/OD/0000110380

Vifor France; Treatment of primary IgA nephropathy

The status of the procedure at CHMP was noted.
4.2.2.  **leniolisib** - EMEA/H/C/005927/0000, EU/3/20/2339, EMA/OD/0000117371

Pharming Technologies B.V.; Treatment of activated phosphoinositide 3-kinase delta syndrome

The status of the procedure at CHMP was noted.

4.2.3.  **Rystiggo - rozanolixizumab** - EMEA/H/C/005824/0000, EU/3/20/2272, EMA/OD/0000129455

UCB Pharma; Treatment of myasthenia gravis

COMP Rapporteur: Armando Magrelli; COMP Co-Rapporteur: Elisabeth Penninga

An opinion recommending not to remove Rystiggo, rozanolixizumab, EU/3/20/2272 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.

4.2.4.  **Spexotras - trametinib dimethyl sulfoxide** - EMEA/H/C/005886/0000, EU/3/20/2374, EMA/OD/0000134200

Novartis Europharm Limited; Treatment of glioma

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

An opinion recommending not to remove Spexotras, trametinib dimethyl sulfoxide, EU/3/20/2374 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.

4.2.5.  **momelotinib dihydrochloride** - EMEA/H/C/005768/0000, EU/3/11/886, EMA/OD/0000129901

GlaxoSmithKline Trading Services Limited; Treatment of post-polycythaemia vera myelofibrosis

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 December 2023 meeting.

4.2.6.  **momelotinib dihydrochloride** - EMEA/H/C/005768/0000, EU/3/11/887, EMA/OD/0000130955

GlaxoSmithKline Trading Services Limited; Treatment of post-essential thrombocythaemia myelofibrosis

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 December 2023 meeting.

4.2.7.  **momelotinib dihydrochloride** - EMEA/H/C/005768/0000, EU/3/11/888, EMA/OD/0000130957

GlaxoSmithKline Trading Services Limited; Treatment of primary myelofibrosis
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 December 2023 meeting.

4.2.8.  **Ayvakyt - avapritinib - EMEA/H/C/005208/II/0023, EU/3/18/2074, EMA/OD/0000127063**

Blueprint Medicines; Treatment of mastocytosis

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

An opinion recommending not to remove Ayvakyt, avapritinib, EU/3/18/2074 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.

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

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

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 December 2023 meeting.

4.3. **Appeal**

None

4.4. **On-going procedures**

COMP co-ordinators were appointed for 5 applications.

4.5. **Orphan Maintenance Reports**

Documents were tabled for information.

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

5.1. **After adoption of CHMP opinion**

None

5.2. **Prior to adoption of CHMP opinion**

5.2.1. **Kinpeygo – budesonide - EMEA/H/C/5653/II/0008, EU/1/22/1657, EMA/OD/0000157484**

STADA Arzneimittel AG; Treatment of primary IgA nephropathy

CHMP Rapporteur: Christian Gartner; CHMP Co-Rapporteur: Martina Weise
The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.3. **Appeal**

None

5.4. **On-going procedures**

COMP co-ordinators were appointed for 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**

None

7.1.2. **Vote by proxy**

None

7.1.3. **Strategic Review & Learning meetings**

Feedback was noted from the COMP SRLM under the Spanish Presidency of the Council of the EU held in person on 17-18 October 2023 in Madrid, Spain.

7.1.4. **Protocol Assistance Working Group (PAWG)**

The working group on Protocol Assistance met remotely on 6 November 2023.

7.1.5. **COMP Decisions Database**

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

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

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

Documents were tabled for information.
7.3. **Coordination with EMA Working Parties/Working Groups/Drafting Groups**

7.3.1. **Working Party with Patients’ and Consumers’ Organisations (PCWP) and Working Party with Healthcare Professionals’ Organisations (HCPWP)**

Documents were tabled for information.

7.3.2. **Upcoming ITF meetings**

The COMP noted the upcoming ITF meetings.

7.4. **Cooperation within the EU regulatory network**

7.4.1. **European Commission**

None

7.4.2. **C4C multistakeholder meeting on perinatal asphyxia**

The COMP was informed about the C4C (conect4children) multistakeholder meeting on perinatal asphyxia held on 18 and 19 September 2023.

7.5. **Cooperation with International Regulators**

7.5.1. **Food and Drug Administration (FDA)**

None

7.5.2. **Japanese Pharmaceuticals and Medical Devices Agency (PMDA)**

None

7.5.3. **Therapeutic Goods Administration (TGA), Australia**

None

7.5.4. **Health Canada**

None

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

None

7.7. **COMP work plan**

None
7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2023

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2023 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1. Presentation of Reflection Paper on the use of real-world data to generate real-world evidence in non-interventional studies

The COMP noted the summary of the scope and content of the Methodology Working Party (MWP) agreed draft Reflection Paper on behalf of the drafting group. At the end of the presentation, the COMP members were invited to review the draft and provide comments in the next 2 weeks, until 23 November 2023.

8.2. Nomination of COMP representative for ENCePP Steering Group 2024-2026

The COMP agreed that Frauke Naumann-Winter will continue to represent COMP in ENCePP Steering Group 2024-2026.

8.3. Pilot on new maintenance procedure

The process agreed by the COMP to be piloted in April 2023 has been reviewed and only minor changes were considered needed. The experience showed that the process gained efficiency and improved quality of the orphan maintenance assessment report (OMAR). The internal guidance document and templates have been amended accordingly.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 07-09 November 2023 COMP meeting, which was held remotely.

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<tr>
<th>Name</th>
<th>Role</th>
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<td>Armando Magrelli</td>
<td>Vice-Chair</td>
<td>Expert recommended by EMA</td>
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<td>Tim Leest</td>
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<td>Member State or affiliation</td>
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<td>Judit Molnar</td>
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<td>Maria Cavaller Bellaubi</td>
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<tr>
<td>Stine Hasling Mogensen</td>
<td>Expert</td>
<td>Denmark</td>
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Meeting run with support from relevant EMA staff

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

10. Explanatory notes

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

**Abbreviations / Acronyms**

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission
OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

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

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

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

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

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

**Sponsor**

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

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

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

More detailed information on the above terms can be found on the EMA website: [www.ema.europa.eu/](http://www.ema.europa.eu/)