16 June 2021
EMA/COMP/292909/2021
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 May 2021

Chair: Violeta Stoyanova-Beninska

Disclaimers

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

The Chairperson opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) outbreak, and the associated EMA Business Continuity Plan (BCP), 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, alternates 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 as included in the pre-meeting list of participants and restrictions.

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

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 and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 10-12 May 2021 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 13-15 April 2021 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. bomedemstat ditosilate - EMA/OD/0000052866

Imago Biosciences B.V.; Treatment of essential thrombocythaemia (ET)

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:

- Number of people affected

The sponsor had proposed a prevalence which was based on older publications and appeared to be an under-estimate. The sponsor was therefore requested to use more current publications and reconsider the life-expectancy in the condition for the complete

prevalence estimate. The sponsor was asked 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 submitted a revised prevalence estimate which was based on a the most current literature available to them. Out of ten recent publications, 5 were retained for the purpose of the requested revision.

In view of the paucity of data on survival in Europe it was noted that the SEER data and US data were used to help with estimating the life-expectancy as an improvement in patient management over the last 10 years was noted in both the US and Europe. The sponsor's proposal was the use of the weighted average of 12.7 years for the primary calculation and the mean of 14.4 years for the sensitivity analysis. The two European publications used show an increase over time of the incidence of the condition. The sponsor has generated two interpolated current incidence estimates and then proposes the mean as summarised below: (1.45 + 2.05) / 2 = 3.5 / 2 = 1.75 per 100,000. This value is used for the prevalence calculation below with the higher value of 2.05 per 100,000 being used for sensitivity analysis. The recalculated values above facilitate a new main prevalence calculation and 3 sensitivity analyses using one or both of the higher estimates for median survival and disease incidence.

The main calculation is based on the best estimates of incidence and OS (overall survival) which results in a prevalence of 2.2 per 10,000. The 3 sensitivity analyses are all in the range 2.5 to 3.0 per 10,000. Taking all the above into consideration, the sponsor's revised formal estimate of the prevalence of ET in the EU is not more than 3 per 10,000. The COMP accepted this revised prevalence estimate.

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

The intention to treat the condition with the medicinal product containing bomedemstat ditosilate was considered justified based on preliminary clinical data in patients with the condition showing a lowering of platelet counts.

The condition is life-threatening and chronically debilitating due to thrombotic and haemorrhagic episodes which can be associated with deep vein thrombosis and pulmonary embolism.

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 bomedemstat ditosilate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that in high risk patients who were intolerant to hydroxyurea and refractory to anagrelide there was a lowering of platelet counts. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bomedemstat ditosilate, for treatment of essential thrombocythaemia, was adopted by consensus.

2.1.2. - EMA/OD/0000049844

Treatment of solid organ transplantation

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

- Intention to diagnose, prevent or treat

The sponsor presented bibliographical data with different products than the one proposed for designation. To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of solid organ transplantation the sponsor was requested to further elaborate on:

a) any available data in vivo with the specific product as proposed for designation,

b) the relevance of the non-clinical models referred to in the application for the treatment of solid organ transplantation, and the interpretation of the results obtained in the experiments.

In the absence of data with the product in a relevant setting, medical plausibility cannot be assessed.

- 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 any available studies with the specific product as proposed for designation, that would support a favourable data-driven comparison versus the authorised products.

In the written response, and during an oral explanation before the Committee on 10 May 2021, the sponsor referred to regulatory guidelines and cross-species limitations in particular for ATMPs. It is argued that the non-clinical models of cardiac and skin transplantation are the only available models in the context of the proposed indication.

The sponsor pointed out that the Noylan et al data are relevant because of an ongoing collaboration with the respective laboratory and the fact that the proposed product is the first candidate that will enter the clinic as part of this collaboration. Differences between the products are acknowledged, however a comparison of key phenotypic markers on material generated in batches of cells representative of the clinical process shows that cells maintain a phenotype that is consistent with those for which the proof-of-concept data. In particular, despite the optimisations undertaken, QBEND+ cells i.e. those that have been transduced with the A2-CAR, FOXP3 and RQR8 (QBEND is a selection marker included in RQR8), express high levels of CD4, CD25 and FoxP3 (the starting population for earlier experiments). In evaluation of the submitted justification, the issue of medical plausibility has been advanced, and may be eventually considered acceptable.

Regarding the issue of significant benefit no additional observations are presented and the sponsor discusses the mechanism of action and the relevance of the mechanism, stressing

that T-cell mediated rejection is the primary driver of rejection in liver transplant. With regards to the Noylan paper it is discussed that the surrogate product prevented rejection in the absence of immunosuppressive therapy, and it is envisioned that similar results with regards to the Todo publication may be achieved. Still, only limited data (and of limited duration observation period) are available for the proposed product, while not all available products are accounted for.

During the oral explanation it was clarified that the product will only be used after patients have been stabilised after transplant, on e.g. tacrolimus. The COMP recognised that the clinical development will be challenging, and the design of the study will be important, however, to be able to grant an orphan designation the COMP wanted to see some data with the specific product in patients.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 May 2021, prior to final opinion.

2.1.3. L-ergothioneine - EMA/OD/0000037664

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of cystinuria

COMP Rapporteur: Ingeborg Barisic

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved safety and major contribution to patient care in the condition.

It is well known that extrapolation from non-clinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases. The sponsor was asked to further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

Furthermore, the applicant was requested to document any significant problems associated with the argued cumbersome management of affected patients, and provide data supporting that these may be addressed by the proposed new treatment.

In the written response, and during an oral explanation before the Committee on 10 May 2021, the sponsor discussed the safety and tolerability issues of the authorised products, with reference to the EudraVigilance database for suspected adverse drug reactions as well as for the contraindications with reference to the patient information sheets. Literature studies discussing the adverse effects for existing treatments are also discussed (Prot-Bertoye et al., 2019). In the antipode of the reported safety issues of the current products, the sponsor reports that no safety issues have yet emerged from the non-clinical studies or the one clinical study publishing results of treating healthy subjects with a maximum of 25 mg/day of L-ergothioneine (Cheah et al., 2017). The titration difficulties are also put forward as a documented difficulty for alkalizing agents, which may be obviated by the new proposed treatment. Overall, it appears that all the arguments can be summarised in an argument of improved safety, but this would be difficult to acknowledge given the non-clinical stage of development. During the OE the focus of the discussion was on the potential to treat the up to 25% of patients cannot tolerate the other treatments. The COMP accepted

that there are patients who are intolerant to the current treatments and that L-ergothioneine has to potential to treat a broader patient population.

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

The intention to treat the condition with the medicinal product containing L-ergothioneine was considered justified based on non-clinical data in a model of the condition showing inhibition of stone formation in the urinary tract.

The condition is chronically debilitating due to early onset, persistent renal stone formation which has been associated with a higher risk of developing chronic kidney disease.

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 L-ergothioneine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary non-clinical in vivo data that could support use in a patient population who is intolerant to currently authorised medicines in the proposed condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for L-ergothioneine, for treatment of cystinuria, was adopted by consensus.

2.1.4. - EMA/OD/0000051199

Treatment of Huntington's disease (HD)

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 discussed assumptions of improved safety over the authorised treatment of chorea in HD, tetrabenazine (TBZ). However, comparative efficacy of TBZ and the proposed product was not discussed based on clinical data. Moreover, no discussion vs. haloperidol was provided.

The sponsor was asked to elaborate on the arguments for significant benefit vs. TBZ and haloperidol and explain the intended clinical use of the proposed product in relation to the current standard of care.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 11 May 2021, the sponsor elaborated on selected aspects of the safety profile of tetrabenazine and the proposed product. Particularly, CNS impact was discussed in the context of the underlying predisposition of HD patients to depression and psychosis. The COMP questioned the sponsor regarding all available data with the proposed product in HD patients, which is limited. Cardiac side effects were also discussed, and the sponsor was of the opinion that hypotension was a small risk in the HD patients who are often slightly hypertensive at

baseline. Extensive experience with the use of the proposed product in cardiac patients was not considered relevant because of lack of comparability between cardiac and HD patients. Therefore, the COMP did not accept the claims of the sponsor of improved safety based on the limited HD specific data available to date. In the absence of data supporting improved efficacy or major contribution to patient care, the significant benefit claim could not be supported.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 May 2021, prior to final opinion.

2.1.5. tislelizumab - EMA/OD/0000045928

BeiGene Ireland Limited; Treatment of nasopharyngeal cancer (NPC)

COMP Rapporteur: Brigitte Schwarzer-Daum

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 potential improved efficacy in the condition based on indirect comparisons to published data of chemotherapeutic agents from 15 single-arm studies in the same treatment setting, i.e. second line and later treatment in recurrent or metastatic NPC patients. The applicant was asked to further elaborate on indirect comparisons taking the most recent publications into consideration.

The sponsor was requested to further discuss the population included in the study in terms of previous lines of treatment.

Furthermore, the sponsor was requested to provide more information on the ongoing phase 3 randomised study since the data readout was estimated in Q1 2021.

In the written response, the sponsor argued that a research of PubMed recently performed to obtain key literature in the field of recurrent or metastatic nasopharyngeal cancer in the second line and later treatment setting did not show additional publications of chemotherapy therefore the sponsor is of the opinion that the 15 single-arm studies (Prawira et al, 2017, date range from 2002 to 2012) still represent a complete picture of the published efficacy results of chemotherapeutic agents in this treatment setting taking into account that the latest ESMO guideline (published on December 21, 2020; Bossi et al, 2020) was based on this series of studies and publications.

In addition, regarding the population included in the ongoing study the sponsor clarified that all 21 patients enrolled in the NPC cohort of the study, had received at least one prior line of treatment and all had received prior radiotherapy. Most of the patients had 1 or 2 lines of prior systemic therapies that are recommended by ESMO. There are more than 50% patients who received prior treatment with cisplatin plus gemcitabine, recently considered as standard of care for first line treatment in NPC. No patients have received any prior immunotherapy. Details of the prior anti-cancer systemic therapy in the study were provided. In these heavily treated patients, the median overall survival (mOS) is 25.0 months. The overall response rate (ORR) is 47.6% with duration of response (DOR) of 8.8 months. A response was observed in all patients treated with 0-3 lines of prior therapy. In addition, for the 11 patients who received gemcitabine and cisplatin as frontline therapy as

recommended by NCCN and ESMO guidelines, treatment with tislelizumab achieved an ORR of 27.3% and a disease control rate (DCR) of 90.9%.

The COMP considered that the information provided confirmed the responses observed and that the preliminary clinical data demonstrated that patients with advanced relapsed or refractory nasopharyngeal cancer who had received prior lines of therapy responded to treatment, therefore the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing tislelizumab was considered justified based on the responses observed in preliminary clinical data.

The condition is chronically debilitating due to epistaxis, obstruction of the nasopharynx, hearing impairment and tinnitus, headache, diplopia, facial pain and numbness or paresthesia and life-threatening due to reduced survival.

The condition was estimated to be affecting approximately 0.8 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 tislelizumab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate responses in subjects with advanced relapsed or refractory nasopharyngeal cancer who had received prior lines of therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tislelizumab, for treatment of nasopharyngeal cancer, was adopted by consensus.

2.1.6. imatinib - EMA/OD/0000051869

MDC RegAffairs GmbH; Treatment of pulmonary arterial hypertension

COMP Rapporteur: Eva Malikova

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 whether there exists a scientific rationale for the development of the proposed product for treatment of pulmonary arterial hypertension the sponsor was asked to elaborate on the extrapolation from the reference products in the cited literature studies to the inhalation formulation as proposed for designation. Any available data with the inhalation formulation as proposed for designation should be presented for assessment.

- Significant benefit

The sponsor was requested to elaborate on the results from literature studies to justify the assumption of significant benefit of the specific product as proposed for designation over authorised medicinal products for the proposed orphan condition. Data with the specific inhalation formulation as proposed for designation was asked to be presented for assessment.

In the written response, and during an oral explanation before the Committee on 11 May 2021, the sponsor made reference to a non-clinical model, where inhaled imatinib reduced the right ventricular (RV) systolic pressure and Lumen/Media ratio (Medarametla Pulm Circ. 2014; 4(1): 82-102). Data from the sponsor's phase 1 study was also discussed. This was a phase 1 trial in healthy volunteers (N=74) with single ascending doses (SAD) ranging from 1 mg – 90 mg. Multiple doses at 10 mg, 30 mg, and 90 mg were administered twice daily for seven days in the multiple ascending doses part of the trial. A cohort of subjects (N=8) in the SAD part of the study was administered a single dose of oral imatinib (400 mg) to allow for a comparison between the systemic exposure of inhaled and oral imatinib. It is reported that the steady state plasma concentrations of inhaled imatinib (90 mg) over time are well within the imatinib plasma concentrations after 400 mg of oral imatinib. Based on these observations, an extrapolation from the effects reported above for the oral imatinib formulations, may be considered justified.

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

The intention to treat the condition with the medicinal product containing imatinib was considered justified based on non-clinical data in a relevant model of the condition showing a decrease in right ventricular systolic pressure and hypertrophy. In addition, literature data was provided demonstrating improved exercise capacity in pulmonary arterial hypertension patients using imatinib.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to premature death.

The condition was estimated to be affecting approximately 1.4 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 imatinib will be of significant benefit to those affected by the condition. The sponsor has provided bibliographical data, showing an improvement in the 6-minute walking distance on top of standard treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for imatinib, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. humanised IgG2 monoclonal antibody against TNFSF13 - EMA/OD/0000024142

Otsuka Pharmaceutical Netherlands B.V.; Treatment of primary IgA nephropathy

COMP Rapporteur: Martin Mozina

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

The intention to treat the condition with the medicinal product containing humanised IgG2 monoclonal antibody against TNFSF13 was considered justified based on non-clinical in vivo data in a model of the condition showing a reduction in IgA, proteinuria and glomerulosclerosis.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation.

The condition was estimated to be affecting approximately 3.7 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 humanised IgG2 monoclonal antibody against TNFSF13 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate a reduction in proteinuria and glomerulosclerosis through an alternative mode of action which could be used in a broader patient population to the authorised medicine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG2 monoclonal antibody against TNFSF13, for treatment of primary IgA nephropathy, was adopted by consensus.

2.2.2. - EMA/OD/0000045468

Treatment of glioma

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

2.2.3. adeno-associated virus serotype 9 expressing human CLN5 - EMA/OD/0000047485

Real Regulatory Limited; Treatment of neuronal ceroid lipofuscinosis

COMP Rapporteur: Giuseppe Capovilla

The Committee agreed that the condition, neuronal ceroid lipofuscinosis, 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 expressing human CLN5 was considered justified based on neurological functional and visual improvements with a surrogate product in an in vivo model of the condition.

The condition is life-threatening and chronically debilitating due to visual, cognitive, and motor skills decline, speech impediment, behavioural alterations, seizures, cerebral atrophy which lead to early death.

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 expressing human CLN5 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a model of type 5 neuronal ceroid lipofuscinosis, for which no authorised products are indicated. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 9 expressing human CLN5, for treatment of neuronal ceroid lipofuscinosis, was adopted by consensus.

2.2.4. allogenic placenta-derived mesenchymal stromal cells secretome - EMA/OD/0000049662

Corion Biotech S.r.l.; Treatment of pre-eclampsia

COMP Rapporteur: Olimpia Neagu

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

The intention to treat the condition with the medicinal product allogenic placenta-derived mesenchymal stromal cells secretome was considered justified based on improved foetal survival, placental weight, reduced maternal hypertension and proteinuria.

The condition is life-threatening due to seizures and risk of maternal and foetal death and chronically debilitating due to complications associated with hypertension and reduced renal function.

The condition was estimated to be affecting approximately 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 allogenic placenta-derived mesenchymal stromal cells secretome will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the use of the product leads to a marked reduction in hypertension and proteinuria, reduced systemic inflammation, increased placental weight and improved foetal survival. This compares favourably to currently used medicines which address individual symptoms of the disease only. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogenic placenta-derived mesenchymal stromal cells secretome, for treatment of pre-eclampsia, was adopted by consensus.

2.2.5. (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide - EMA/OD/0000052133

Eli Lilly Nederland B.V.; Treatment of mantle cell lymphoma

COMP Rapporteur: Maria Elisabeth Kalland

The Committee agreed that the condition, mantle 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 (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide was considered justified based on durable and high overall response rates in late line treatment of mantle cell lymphoma patients, who were treated with the product as monotherapy.

The condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that show responses in a heavily pre-treated relapsed/refractory population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide, for treatment of mantle cell lymphoma, was adopted by consensus.

2.2.6. - EMA/OD/0000053160

Treatment of primary biliary cholangitis

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 June meeting

2.2.7. hydrocortisone hydrogen succinate - EMA/OD/0000053493

Laboratoire Aguettant; Prevention of bronchopulmonary dysplasia

COMP Rapporteur: Lenka Gaidadzi

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

The intention to prevent the condition with the medicinal product containing hydrocortisone hydrogen succinate was considered justified based on publications reporting data in patients at risk of developing the condition showing a reduction in the development of bronchopulmonary dysplasia and improved survival following treatment.

The condition is life-threatening and chronically debilitating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The population of patients eligible for prevention of the condition was estimated to be less than 2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for hydrocortisone hydrogen succinate, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.2.8. melatonin - EMA/OD/0000053556

Worphmed S.r.l.; Prevention of retinopathy of prematurity

COMP Rapporteur: Darius Matusevicius

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

The intention to prevent the condition with the medicinal product containing melatonin was considered justified based on non-clinical data in a model of the condition which showed prevention of pathologic neovascularization, protection of the neuroglial cells and anti-inflammatory effects.

The condition is chronically debilitating due to visual loss that may progress to blindness in the most severe cases.

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

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

A positive opinion for melatonin, for prevention of retinopathy of prematurity, was adopted by consensus.

2.2.9. - EMA/OD/0000053899

Treatment of follicular lymphoma

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

2.2.10. - EMA/OD/0000054015

Treatment of hereditary angioedema

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

2.2.11. - EMA/OD/0000054743

Treatment of diffuse large B-cell lymphoma

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

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 19 May 2021.]

2.2.12. humanised monoclonal antibody derivative against fibroblast growth factor receptor 3 - EMA/OD/0000055239

Genzyme Europe B.V.; Treatment of achondroplasia

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing humanised monoclonal antibody derivative against fibroblast growth factor receptor 3 was considered justified based on non-clinical data showing improved long bone growth and bone density.

The condition is chronically debilitating due to manifestations such as otolaryngeal system dysfunction, and rhizomelic short stature, thoracolumbar kyphosis, spinal stenosis, and foramen magnum stenosis and life-threatening with approximately 10 years shorter life expectancy compared to the general population.

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

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

A positive opinion for humanised monoclonal antibody derivative against fibroblast growth factor receptor 3, for treatment of achondroplasia, was adopted by consensus.

2.2.13. - EMA/OD/0000055257

Treatment of growth hormone deficiency

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 June meeting

2.2.14. H-D-valyl1-D-alanyl-D-glutamyl-D-alanyl-D-arginyl5-D-glutamyl-D-glutamyl-D-leucyl-D-glutamyl-D-arginyl10-D-leucyl-D-glutamyl-D-alanyl-D-arginyl-D-leucyl15-glycyl-D-glutaminyl-D-alanyl-D-arginyl-glycyl20-D-glutamyl-D-leucyl-D-lysyl-D-lysyl-D-tryptophyl25-D-lysyl-D-methionyl-D-arginyl-D-arginyl-D-asparaginyl30-D-glutaminyl-D-phenylalanyl-D-tryptophyl-D-leucyl-D-lysyl35-D-leucyl-D-glutaminyl-D-arginine - EMA/OD/0000055289

Sapience Therapeutics Limited; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

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 H-D-valyl1-D-alanyl-D-glutamyl-D-alanyl-D-arginyl5-D-glutamyl-D-glutamyl-D-leucyl-D-glutamyl-D-arginyl10-D-leucyl-D-glutamyl-D-alanyl-D-arginyl-D-leucyl15-glycyl-D-glutaminyl-D-alanyl-D-arginyl-glycyl20-D-glutamyl-D-leucyl-D-lysyl-D-lysyl-D-tryptophyl25-D-lysyl-D-methionyl-D-arginyl-D-arginyl-D-asparaginyl30-D-glutaminyl-D-phenylalanyl-D-tryptophyl-D-leucyl-D-lysyl35-D-leucyl-D-glutaminyl-D-arginine was considered justified based on the tumour growth delay in non-clinical models of the condition.

The condition is debilitating due to symptoms caused the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive impairment. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

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 H-D-valyl1-D-alanyl-D-glutamyl-D-alanyl-D-arginyl5-D-glutamyl-D-glutamyl-D-leucyl-D-glutamyl-D-arginyl10-D-leucyl-D-glutamyl-D-alanyl-D-arginyl-D-leucyl15-glycyl-D-glutaminyl-D-alanyl-D-arginyl-glycyl20-D-glutamyl-D-leucyl-D-lysyl-D-lysyl-D-tryptophyl25-D-lysyl-D-methionyl-D-arginyl-D-arginyl-D-asparaginyl30-D-glutaminyl-D-phenylalanyl-D-tryptophyl-D-leucyl-D-lysyl35-D-leucyl-D-glutaminyl-D-arginine will be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate in vivo evidence in models of the condition reporting effects in monotherapy and even better effects in combination with temozolomide compared to temozolomide alone.

A positive opinion for H-D-valyl1-D-alanyl-D-glutamyl-D-alanyl-D-arginyl5-D-glutamyl-D-glutamyl-D-leucyl-D-glutamyl-D-arginyl10-D-leucyl-D-glutamyl-D-alanyl-D-arginyl-D-leucyl15-glycyl-D-glutaminyl-D-alanyl-D-arginyl-glycyl20-D-glutamyl-D-leucyl-D-lysyl-D-lysyl-D-tryptophyl25-D-lysyl-D-methionyl-D-arginyl-D-arginyl-D-asparaginyl30-D-glutaminyl-D-phenylalanyl-D-tryptophyl-D-leucyl-D-lysyl35-D-leucyl-D-glutaminyl-D-arginine, for treatment of glioma, was adopted by consensus.

2.2.15. - EMA/OD/0000055340

Treatment of medulloblastoma

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

2.2.16. adeno-associated virus serotype 9 containing the human FXN gene isoform 1 - EMA/OD/0000055345

Novartis Gene Therapies EU Limited; Treatment of Friedreich`s ataxia

COMP Rapporteur: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing adeno-associated virus serotype 9 containing the human FXN gene isoform 1 was considered justified based on non-clinical in vivo data in two models of the condition showing an improvement in sensory and motor function as well as cardiac function and survival.

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

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

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

A positive opinion for adeno-associated virus serotype 9 containing the human FXN gene isoform 1, for treatment of Friedreich`s ataxia, was adopted by consensus.

2.2.17. - EMA/OD/0000055663

Treatment of soft-tissue sarcoma

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

2.2.18. - EMA/OD/0000055883

Treatment of nontraumatic spontaneous intracerebral hemorrhage

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

2.2.19. adeno-associated viral vector LK03 encoding human methylmalonyl-CoA mutase - EMA/OD/0000056297

Parexel International (Irl) Limited; Treatment of methylmalonic acidaemia

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, methylmalonic acidaemia, 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 viral vector LK03 encoding human methylmalonyl-CoA mutase was considered justified based on non-clinical data in models of the condition demonstrating reduction of plasma methylmalonic acid and improved survival.

The condition is chronically debilitating and life-threatening due to neurological, gastroenterological and haematological complications.

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.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector LK03 encoding human methylmalonyl-CoA mutase will be of significant benefit to those affected by the condition. The administration of the proposed product in non-clinical models resulted in production of methylmalonyl-CoA mutase, the protein defective in the condition. The sponsor has provided non-clinical data in models of the condition, showing that the proposed product not only improves hyperammonaemia but also improves survival, on which the medicinal product currently authorised has no effects. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing adeno-associated viral vector LK03 encoding human methylmalonyl-CoA mutase, for treatment of methylmalonic acidaemia, was adopted by consensus.

2.2.20. - EMA/OD/0000056592

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 June meeting.

2.2.21. - EMA/OD/0000056712

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 June 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 coordinators were appointed for 3 applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of transthyretin-mediated amyloidosis in patients with cardiomyopathy

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 mucopolysaccharidosis type I

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

3.1.3. -

Treatment of glioma

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

3.2. Finalised letters

3.2.1. -

Diagnosis of AL amyloidosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of Gaucher disease

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of pancreatic cancer

The new request was noted.

3.3.2. -

Treatment in haematopoietic stem cell transplantation

The new request was noted.

3.3.3. -

Treatment of myelodysplastic syndromes

The new request was noted.

3.3.4. -

Treatment of acute myeloid leukemia

The new request was noted.

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. Skysona – elivaldogene autotemcel - EMEA/H/C/003690/0000, EMA/OD/009/12, EU/3/12/1003, EMA/OD/0000044429

Accelerated Assessment

bluebird bio (Netherlands) B.V; Treatment of adrenoleukodystrophy

COMP Rapporteur: Darius Matusevicius; Expert: Armando Magrelli

An opinion recommending not to remove Skysona, elivaldogene autotemcel, EU/3/12/1003 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting.]

4.2.2. Bylvay – odevixibat - EMEA/H/C/004691/0000, EMA/OD/022/12, EU/3/12/1028, EMA/OD/0000048989

Accelerated Assessment

Albireo; Treatment of progressive familial intrahepatic cholestasis

COMP Rapporteurs: Elisabeth Johanne Rook; Olimpia Neagu

An opinion recommending not to remove Bylvay, odevixibat, EU/3/12/1028 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting.]

4.2.3. Darzalex - daratumumab - EMEA/H/C/004077/II/0043 EMA/OD/207/17, EU/3/18/2020, EMA/OD/0000049819

Janssen-Cilag International NV; Treatment of AL amyloidosis

COMP Rapporteur: Karri Penttilä; Expert: Armando Magrelli; CHMP Rapporteur: Sinan B. Sarac; CHMP Co-Rapporteur: Blanca Garcia Ochoa

An opinion recommending not to remove Darzalex, daratumumab, EU/3/18/2020 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting.]

4.2.4. Imcivree – setmelanotide - EMEA/H/C/005089/0000

Accelerated assessment

TMC Pharma (EU) Limited

COMP Rapporteurs: Dinah Duarte; Vallo Tillman

a) Treatment of leptin receptor deficiency, EU/3/18/2101, EMA/OD/0000040440

An opinion recommending not to remove Imcivree, setmelanotide, EU/3/18/2101 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting.]

b) Treatment of pro-opiomelanocortin deficiency, EMA/OD/063/16, EU/3/16/1703, EMA/OD/0000040443

An opinion recommending not to remove Imcivree, setmelanotide, EU/3/16/1703 from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

[Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting.]

4.2.5. – avalglucosidase alfa - EMEA/H/C/005501, EU/3/14/1251, EMA/OD/0000048959

Genzyme Europe BV; Treatment of Pompe's disease

The status of the procedure at CHMP was noted.

4.2.6. – eflornithine / sulindac - EMEA/H/C/005043/0000, EMA/OD/130/12, EU/3/12/1086, EMA/OD/0000061571

Cancer Prevention Pharma (Ireland) Limited; Treatment of familial adenomatous polyposis

The status of the procedure at CHMP was noted.

4.3. Appeal

None

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

None

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 7 May 2021.

7.1.3. Election of COMP Vice-Chairperson

No nominations were received. The election was postponed to take place next month.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.2.2. CAT-COMP Working Group

The CAT-COMP Working Group met remotely on 7 May 2021.

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)

None

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

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

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2021 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. Update from the Research and Innovation (RNI) workstream

The COMP noted the presentation about the collaboration between RSI Task Force (includes ITF, Horizon scanning and business pipeline) and COMP, which is in the centre of innovation.

The Task Force will look at the technologies which will affect EMA in the future, with COMP playing a key role, including in reach out activities to rare diseases community. The importance of understanding new areas of innovation and what expertise are needed were highlighted. To this end, Regulatory Science and Innovation Task Force (TRS) is reporting to COMP on innovation topics in order to increase awareness and obtain feedback from COMP experts, who are involved in analysing innovation topics and identifying their impact. It should be further discussed the needs for future preparedness (e.g. training, expertise, topic discussions) and generate regulatory science research questions

8.2. Marketing Authorisation Applications 3-year forecast report

The document was tabled for information.

9. List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 May 2021 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova - Beninska	Chair	Netherlands	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Gaidadzi	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No restrictions applicable to this meeting	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert*	Expert via WebEx	Patients' Organisation Representative	No restrictions applicable to this meeting	
Armando Magrelli*	Expert via WebEx	Italy	No interests declared	
Meeting run with support from relevant EMA staff				

* Experts were only 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/