20 May 2020
EMA/COMP/238684/2020
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 21-23 April 2020

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

21 April 2020, 09:00-18:55, Remote virtual meeting

22 April 2020, 08:30-19:40, Remote virtual meeting

23 April 2020, 08:30-13:35, Remote virtual meeting

Disclaimers

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

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

Further information with relevant explanatory notes can be found at the end of this document.

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

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 the restricted involvement of some meeting participants in upcoming discussions 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 21-23 April 2020 was adopted with the following topic under A.O.B:

- Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP).

1.3. Adoption of the minutes

The minutes for 17-19 March 2020 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. autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains - EMA/OD/0000020940

FGK Representative Service GmbH; Treatment of multiple myeloma

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 persons affected by the condition

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to provide an updated prevalence estimate by taking into account:

a) a more comprehensive overview of all epidemiological sources and databases and

b) ECIS data.

Furthermore, sensitivity analyses with respect to the rise in incidence and improvement of survival was also requested.

In the written response, the sponsor provided an extended calculation of the prevalence, including a sensitivity analysis, which allowed for varied incidence and duration of the condition. The most conservative estimate calculated was 4.8 in 10,000 persons in the EU. The COMP considered, however, that the true prevalence is more likely to fall around 4 in 10,000 as previously seen in other applications for the same condition. Therefore, this less conservative value was accepted based on all information provided.

The Committee agreed that the condition, multiple myeloma, 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 lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains was considered justified based on clinical data demonstrating improvement in overall response rates in patients with relapsed refractory multiple myeloma.

The condition is chronically debilitating due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with a reduced life expectancy;

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 autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the product can be used in heavily pre-treated, relapsed refractory patients to achieve a high rate of responses, including complete and durable responses. This compares favourably to other therapies used in this setting in an indirect comparison analysis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T lymphocyte-enriched population of cells transduced with a lentiviral vector encoding a chimeric antigen receptor targeting human B cell maturation antigen with 4-1BB and CD3-zeta intracellular signalling domains, for treatment of multiple myeloma, was adopted by consensus.

2.1.2. lutetium (^{177}Lu) lilotomab satetraxetan - EMA/OD/0000023090

Nordic Nanovector ASA; Treatment of marginal zone lymphoma

COMP Rapporteur: Bozenna Dembowska-Baginska

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 provided a 5 years partial prevalence calculation yet survival at 5 years is quite high. The sponsor was requested to provide 10 year partial prevalence and a point prevalence calculation to clearly establish what the current prevalence is.

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

In the written response, the sponsor provided several assumptions regarding the revised prevalence estimate. marginal zone lymphoma (MZL) accounts for approximately eight percent of all non-Hodgkin lymphoma (NHL) cases. Based on the 2018 incidence rates for non-Hodgkin lymphoma obtained from the European Cancer Observatory (EUCAN) database, the incidence of MZL in the Community in 2018 could be estimated as 7884 cases (i.e. 8% of 98550 NHL cases). The 2018 incidence rates were the most current values. This was equivalent to an incidence of 1.5 cases per 100,000 based on the Community population of 518,061,400 at January 1, 2018. The 10-year overall survival rate of roughly 53% for all MZL translates into a disease duration of MZL of approximately 11 years.

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

The intention to treat the condition with the medicinal product containing lutetium (^{177}Lu) lilotomab satetraxetan was considered justified based on preliminary clinical data in relapse and refractory patients with a high overall response rate.

The condition is chronically debilitating and life-threatening due to lymphadenopathy, splenomegaly, mucosa and bone-marrow involvement with development of pancytopenia and increased risk of opportunistic infections. Five-year survival ranges from 30% to up to 90%.

The condition was estimated to be affecting approximately 1.7 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 lutetium (^{177}Lu) lilotomab satetraxetan will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that in relapsed and refractory patients who received several lines of therapy there was a high overall response rate. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lutetium (^{177}Lu) lilotomab satetraxetan, for treatment of marginal zone lymphoma, was adopted by consensus.

2.1.3. - EMA/OD/0000023993

Treatment of insulinoma

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 did not provide any comparative data to support the improved efficacy of the proposed product over the standard of care in patients with insulinoma.

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 studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition. Additional data to compare relative efficacies of all authorised products (including diazoxide and octreotide) were also required.

Furthermore, the committee considered useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 21 April 2020, the sponsor provided an additional discussion highlighting the shortcoming of the existing forms of treatment (octreotide, diazoxide and glucagon). The sponsor also identified a group of refractory patients who would benefit from the proposed new treatment. To support the efficacy of the product in this group of patients the sponsor highlighted the mechanism of action and the improved pharmacokinetics of the product compared to glucagon. The COMP considered, however, that in absence of comparative data in a model of insulinoma or in patients, an assumption of significant benefit could not be made. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 April 2020, prior to final opinion.

2.1.4. methotrexate - EMA/OD/0000009482

Helio Vision Germany GmbH; Treatment of retinal detachment

COMP Rapporteur: Martin Mozina

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:

- Proposed condition

The COMP noted the different types of retinal detachment and invited the sponsor to justify the appropriateness of the proposed condition as a distinct medical entity valid for the purpose of orphan designation.

- 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 retinal detachment the sponsor was requested to further elaborate on the available clinical data in light of the uncontrolled nature of the observations. The sponsor was asked to discuss in detail the studied population.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

It seemed that the sponsor excluded part of the population which may not be eligible for treatment. The sponsor was requested to consider the entirety of the population covered by the orphan condition and provide a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 21 April 2020, it was proposed that the indication was amended to "treatment of rhegmatogenous retinal detachment" in order to reduce heterogeneity in the scope of the application. The COMP considered that while most of detachment cases are rhegmatogenous, with established risk factors, there are similarities between types that would argue in favour of encompassing all under the same orphan condition "retinal detachment"; one important element towards this end was that proliferative vitreoretinopathy (PVR) itself may render a rhegmatogenous to a tractional detachment.

As regards the available clinical observations, the sponsor further elaborated on the treated patients and noted that an additional 16 patients had been treated of label. A consistent reduction of the number of detachment episodes after treatment was noted. The COMP considered that despite the uncontrolled nature of the observations and the potential selection bias, a trend in favour of the proposal could be acknowledged.

With regards to the number of affected individuals, annualized incidence rates were proposed by the sponsor as a relevant epidemiological index. This was based on the assumption that most clinically relevant cases (approximately 85%) are cured after surgery, and as such the duration of the condition could be considered to be less than a year. The COMP accepted the justification of the selected epidemiological index and adopted the estimate of 2.2 per 10,000 people in line with the initial considerations of the sponsor.

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

The intention to treat the condition with the medicinal product containing methotrexate was considered justified based on the reduction of recurrence in patients affected by rhegmatogenous retinal detachment.

The condition is chronically debilitating due to associated visual impairment.

The condition was estimated to be affecting approximately 2.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for methotrexate, for treatment of retinal detachment, was adopted by consensus.

2.1.5. - EMA/OD/0000023410

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 2 April 2020, prior to responding to the list of issues.

2.1.6. - EMA/OD/0000019446

Treatment of Cushing's Disease

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:

- Proposed Indication

The sponsor was invited to broaden the proposed indication e.g. to "adrenocorticotropin-dependent Cushing's syndrome" or even "treatment of Cushing's syndrome", thereby including all endogenous and exogenous causes of the condition.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation". The sponsor was invited to recalculate the estimate for the new amended indication.

- 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 in vivo studies and their relevance for the clinical endpoints, in order to justify the assumption of significant benefit over all authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 21 April 2020, the sponsor addressed the raised issued. The sponsor defended the restriction to the proposed indication (and the related prevalence calculation) on the grounds of the mechanism of action of the proposed product. Extension to any other Cushing syndrome, including ACTH-dependent Cushing's syndrome was refuted. A prevalence recalculation was not performed because of that.

As for the significant benefit issue, the sponsor focused on the originally proposed indication and stressed that the product restrains tumoral ACTH secretion, thus comparing favourably to existing compounds acting down-stream to the pituitary tumour. However, no new data in either in vivo models or patients were discussed. Several limitations and safety issues with the authorized counterparts were listed, but no data supporting an assumption of significant benefit were put forward.

In the absence of data to justify significant benefit, the committee considered that the criteria could not be considered met, and the sponsor withdrew the application prior to final opinion of the COMP.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 April 2020, prior to final opinion.

2.1.7. - EMA/OD/0000023461

Treatment of primary sclerosing cholangitis

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 3 April 2020, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000022335

Treatment of pericarditis

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 proposed condition seemed to concern a manifestation of other underlying distinct conditions. The sponsor was requested to further justify the proposed condition as distinct entity for orphan designation. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of pericarditis the sponsor was asked to further elaborate on the presented preliminary clinical data and the background therapy of enrolled patients. The sponsor was requested to discuss how efficacy can be established when taking into account the single arm trial design in patients with recurrent pericarditis.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was invited to justify the current prevalence estimate as it seems to exclude patients that were not hospitalised. The COMP expected a prevalence estimate that includes all patients affected by the condition reflecting all aetiologies and independent of severity or site of treatment.

The sponsor was requested to provide a sensitivity analysis on all of the underlying assumptions on incidence and recurrence rates.

- Significant benefit

The sponsor was invited to search the national formularies and provide an overview of all authorised therapies for pericarditis including all therapeutic indications of NSAIDs and colchicine.

The sponsor was asked to provide significant benefit over each authorised active substance (including national authorisations, if available).

In the written response, and during an oral explanation before the Committee on 22 April 2020 the sponsor elaborated on the raised issues.

As regards the eligibility of the condition for orphan designation, the sponsor discussed the existence of idiopathic cases without clear underlying conditions, referred to treatment guidelines and WHO ICD codes for acute pericarditis and drew parallels to other orphan designations. The COMP was of the view that such arguments are to be considered with caution, inter alia because with regards to treatment a search for underlying conditions is advised, pericarditis can be a part of other systemic disorders, and there is no specific classification codes for the broader condition as proposed for designation. Therefore the proposal would not be eligible as a distinct medical entity valid for the purpose of orphan designation.

As for the intention to treat, the sponsor further elaborated on the clinical study design, population and, in particular, the results based on a supplementary analysis of patients depending on their use of other prior therapies. A reduction in the annualised number of pericarditis episodes was reported. A trend of improvement in quality of life as measures by PROMIS scale was also discussed.

With regards to the prevalence issue, it was clarified that the references used in the calculation include hospitalized and non-hospitalized patients. The assumptions used in the calculation are also discussed and it is assumed that under highest-case assumptions, 30% of patients with an initial episode of pericarditis will recur within one year (actual data say that 15-30% recur within 1.5 years), 50% for the next recurrence and 40% from the third onwards. A worst-case scenario of 4.45/10,000 was included in the sponsor's position, taking into consideration the highest reported incidence from a study in Torino. The COMP considered that this issue would be conditional to the acceptability of the proposed condition, which remains in need of justification.

Importantly, no further arguments were provided for the purpose of establishing significant benefit as the sponsor asserts that no specifically authorized products have been identified, and that the studied patients have received the standard of care. The COMP noted that in several Member States products are authorised for the proposed condition, e.g. in France colchicine in combination with NSDAIDs or corticosteroids. The COMP members expressed concerns that a list of authorized products in the EU for the sought indication was missing, and a justification of significant benefit had not been provided.

Therefore, the condition proposed had not been justified as eligible for the orphan framework, and the criteria as discussed above could not be considered met. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 April 2020, prior to final opinion.

2.1.9. - EMA/OD/0000023994

Treatment of oesophageal squamous cell carcinoma

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

Justify oesophageal squamous cell carcinoma as a distinct medical entity or a valid subset. The sponsor was requested to broaden the condition to oesophageal cancer.

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of oesophageal cancer the sponsor was requested to further elaborate on:

- The relevance of the non-clinical in vivo data regarding the proposed target condition.
- The patient characteristics and efficacy outcome measures used in the preliminary clinical data from the on-going trial discussed in the submission as well as any other clinical data they may have.
- The mechanism of action of this product in the context of other PD-1 inhibitors investigated in this condition.

- Number of people affected

The sponsor has provided a prevalence estimate for oesophageal squamous cell cancer which is a subset of oesophageal cancer, the condition the COMP has previously designated. The sponsor was requested to re-evaluate the prevalence for the whole condition of oesophageal cancer.

For the estimate and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimate and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The arguments on significant benefit were based on the alternative 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 in vivo non-clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was requested to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients including chemotherapy.

In the written response, and during an oral explanation before the Committee on 22 April 2020, the sponsor failed to provide an update of the non-clinical in vivo data as requested in the list of questions. The sponsor however provided more data from two ongoing clinical studies that were conducting in oesophageal squamous cell carcinoma (ESCC).

The first trial was randomizing patients undergoing second-line treatment for squamous cell carcinoma of the oesophagus to the product used as monotherapy or the Investigator's choice of either paclitaxel or irinotecan.

The median overall survival (OS) was 7.2 (95%CI: 5.8-9.7) months for sponsor's product and 6.2 (95%CI: 5.4-7.9) months for investigator's choice chemotherapy. The sponsor stated that, the primary analysis results demonstrated that their product was superior to chemotherapy in patients receiving second-line treatment for ESCC, with a significant prolongation in OS (HR 0.701, p=0.03226), and median OS improvement of 1.02-month.

The second on-going trial was a multi-centre, double-blind, 1:1 randomized phase III clinical trial evaluating the efficacy and safety of sponsor's product vs. placebo, in combination with chemotherapy, for first-line treatment of unresectable locally advanced,

recurrent, or metastatic oesophageal squamous cell carcinoma. Only preliminary data was available, and the sponsor stated that by a specific cut-off date, a total of 166 subjects have enrolled in the trial, among whom 69 (41.6%) subjects have TPS≥10%. Among 133 subjects who had at least once tumour imaging evaluation, blinded interim analysis showed ORR and DCR was 66.4% and 92.9%, respectively.

The later study offered some more compelling data for medical plausibility.

Regarding significant benefit the applicant sponsor provided an indirect comparison to KEYNOTE-181, in a randomized, open-label, phase III study comparing pembrolizumab and chemotherapy as second-line therapy for patients with advanced/ metastatic squamous cell carcinoma (SCC) and adenocarcinoma (ACC) of the oesophagus (NCT02564263). In patients with SCC, median OS was 8.2 months vs 7.1 months (HR, 0.78; 95% CI, 0.63-0.96; P ¼ 0.0095), however in the ITT (intention to treat group), median OS was 7.1 months for both treatment groups. The COMP considered that the study was not relevant for the justification of significant benefit as the sponsor did not adequately answer the question on significant benefit as the indirect comparison was to pembrolizumab, which is not authorised in Europe for the condition.

The sponsor did not discuss other previous therapies the patients had received. As the data appears to have been generated in third countries where the treatment algorithms maybe different from Europe, the COMP required this information to be verified and that the results could be extrapolated to the European population. Without this explanation, the COMP could not contextualise the clinically relevant advantage of using the product in last line therapy. The COMP concluded that the clinical data provided by the sponsor was not enough to support significant benefit.

The COMP considered they could not recommend granting an orphan designation as the sponsor had not adequately justified the proposed condition, the prevalence and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 22 April 2020, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000009060

Treatment of myelodysplastic syndrome (MDS)

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

2.2.2. (E/Z)-(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1h-pyrazolo(3,4-d)pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile - EMA/OD/0000021615

Clinical Network Services (NL) B.V.; Treatment of immune thrombocytopenia

COMP Rapporteur: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing (E/Z)-(R)-2-(3-(4-amino-3-(2-fluoro-4-phenoxyphenyl)-1h-pyrazolo(3,4-d)pyrimidin-1-yl)piperidine-1-carbonyl)-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile (rilzabrutinib) was considered justified based on preliminary clinical observations showing increase in platelet counts in patients with relapsed chronic immune thrombocytopenia.

The condition is life-threatening and chronically debilitating due to bleeding, which may occur without an obvious precipitating event and can involve the skin, oral cavity and gastrointestinal tract, as well as manifest with intracranial haemorrhage.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing rilzabrutinib will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients who did not respond to previous existing treatments responded to treatment with the proposed product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rilzabrutinib, for treatment of immune thrombocytopenia, was adopted by consensus.

2.2.3. lumacaftor - EMA/OD/0000021857

Qanatpharma GmbH; Treatment of aneurysmal subarachnoid haemorrhage

COMP Rapporteur: Michel Hoffmann

Following review of the application by the Committee, it was agreed to rename the indication to treatment of non-traumatic subarachnoid haemorrhage.

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

The intention to treat the condition with the medicinal product containing lumacaftor was considered justified based on non-clinical in vivo data in a model of the condition showing improvement in the neurological outcomes because it reduces the importance of the delayed cerebral ischemia associated with the haemorrhage.

The condition is life-threatening and chronically debilitating due to cerebral ischemia, hydrocephalus, intracerebral haemorrhage, interventricular haemorrhage, subdural hematoma, seizures, increased intracranial pressure, left ventricular systolic dysfunction or myocardial infarction. The condition over a 5-year period has a high mortality rate which is between 65-70%.

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lumacaftor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate improved neurological outcomes when compared to nimodipine. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lumacaftor, for treatment of non-traumatic subarachnoid haemorrhage, was adopted by consensus.

2.2.4. - EMA/OD/0000022027

Treatment of chromosome 15q duplication syndrome

The sponsor formally withdrew the application for orphan designation, on 8 April 2020. issues.

2.2.5. (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1h-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) - EMA/OD/0000023613

Novartis Europharm Limited; Treatment of paroxysmal nocturnal haemoglobinuria (PNH)

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) was considered justified based on clinical data showing a normalisation of haemoglobin levels.

The condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications in the central nervous system are the most common cause of death.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)) will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate that the product on top of eculizumab prevents both intra- and extravascular complement-driven haemolysis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (4-{(2S,4S)-4-ethoxy-1-[(5-methoxy-7-methyl-1H-indol-4-yl)methyl]piperidin-2-yl}benzoic acid-hydrogen chloride(1/1)), for treatment of paroxysmal nocturnal haemoglobinuria, was adopted by consensus.

2.2.6. - EMA/OD/0000025548

Treatment of blastic plasmacytoid dendritic cell neoplasm

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

2.2.7. viltolarsen - EMA/OD/0000025790

Medpace Finland Oy; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Elisabeth Penninga

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 viltolarsen was considered justified based on preliminary clinical observations supporting improvements in muscle function in treated patients compared to matched historical controls.

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 often by late adolescence; patients rarely live beyond the age of 30.

The condition was estimated to be affecting less than 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 viltolarsen will be of significant benefit to those affected by the condition. The sponsor has provided clinical observations supporting improvement in muscle function, in patients with multiple deletions in the dystrophin gene. In comparison, the authorised treatment is only indicated in patients with non-sense mutations. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.8. - EMA/OD/0000025945

Treatment of idiopathic pulmonary fibrosis

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

2.2.9. Ile-Ala-Leu-Ile-Leu-Glu-Pro-Ile-Cys-Cys-Gln-Glu-Arg-Ala-Ala-(discrete-polyethylene glycol)24 - EMA/OD/0000026429

Clinipace GmbH; Treatment of neonatal encephalopathy

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing Ile-Ala-Leu-Ile-Leu-Glu-Pro-Ile-Cys-Cys-Gln-Glu-Arg-Ala-Ala-(discrete-polyethylene glycol)24 was considered justified based on non-clinical in vivo data showing a reduction in neuropathological damage and improved behavioural and cognitive functioning.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing Ile-Ala-Leu-Ile-Leu-Glu-Pro-Ile-Cys-Cys-Gln-Glu-Arg-Ala-Ala-(discrete-polyethylene glycol)24 will be of significant benefit to those affected by the condition. The sponsor provided non-clinical in vivo data that demonstrate added benefit when the sponsor's product is used in combination with hypothermia. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Ile-Ala-Leu-Ile-Leu-Glu-Pro-Ile-Cys-Cys-Gln-Glu-Arg-Ala-Ala-(discrete-polyethylene glycol)24, for treatment of neonatal encephalopathy, was adopted by consensus.

2.2.10. sodium phenylbutyrate, tauroursodeoxycholic acid - EMA/OD/0000026509

Drug Development and Regulation S.L.; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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 sodium phenylbutyrate, tauroursodeoxycholic acid was considered justified based on clinical data showing improvement of the ALS Functional Rating scale (ALSFRS-R), as well as upper extremities strengths and lung function in patients treated with the proposed product.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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 provided sufficient justification for the assumption that the medicinal product containing sodium phenylbutyrate, tauroursodeoxycholic acid will be of significant benefit to those affected by the condition. The sponsor provided clinical data showing improvement of ALSFRS-R, as well as upper extremities strengths and lung function in patients treated with the proposed product, who were on background treatment with riluzole, the only treatment currently authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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

2.2.11. 1-((2S,4S)-2-((((S)-(4-bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride - EMA/OD/0000027842

Medivir AB; Treatment of hepatocellular carcinoma

COMP Rapporteur: Brigitte Schwarzer-Daum

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

The intention to treat the condition with the medicinal product containing 1-((2S,4S)-2-((((S)-(4-bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride was considered justified based on non-clinical in vivo data showing a relevant reduction in tumour size.

The condition is life-threatening and chronically debilitating due to increased mortality and liver dysfunction. Median survival without therapy can be greater than 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

The condition was estimated to be affecting approximately 2.9 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 1-((2S,4S)-2-((((S)-(4-bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride will be of significant benefit to those affected by the condition. The sponsor provided non-clinical in vivo data that demonstrate a relevant efficacy compared to lenvatinib and sorafenib and when the product is used in combination with sorafenib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-((2S,4S)-2-((((S)-(4-bromophenoxy)(((S)-1-oxo-1-(((S)-pentan-2-yl)oxy)propan-2-yl)amino)phosphoryl)oxy)methyl)-1,3-dioxolan-4-yl)-2-oxo-1,2-dihydropyrimidin-4-aminium chloride, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2.12. - EMA/OD/0000027959

Treatment of Becker muscular dystrophy

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

2.2.13. - EMA/OD/0000028068

Diagnosis of gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs)

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

2.2.14. autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding an affinity enhanced T cell receptor specific to MAGE-A4 - EMA/OD/0000028117

Adaptimmune Limited; 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 autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding an affinity enhanced T cell receptor specific to MAGE-A4 was considered justified based on clinical data in synovial sarcoma patients who showed objective responses to treatment with the product.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 4.56 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding an affinity enhanced T cell receptor specific to MAGE-A4 will be of significant benefit to those affected by the condition. The sponsor provided clinical data showing responses in heavily pre-treated patients who had failed existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous CD4+ and CD8+ T cells transduced with a lentiviral vector encoding an affinity enhanced T cell receptor specific to MAGE-A4*,* for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.15. adeno-associated virus serotype 9 containing the human *ASPA* gene - EMA/OD/0000028197

Raremoon Consulting Limited; Treatment of Canavan disease

COMP Rapporteur: Dinah Duarte

The Committee agreed that the condition, Canavan disease, 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 ASPA gene was considered justified based on non-clinical data in a model of the condition showing improved survival and motor function.

The condition is life-threatening with life expectancy less than 10 years for the infantile variant of the condition and chronically debilitating due to developmental delay, hypotonia developing into muscle stiffness and rigidity, optic atrophy, seizures, swallowing difficulties, sleep disturbances and inability to move voluntarily.

The condition was estimated to be affecting approximately 0.04 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 *ASPA* gene, for treatment of Canavan disease, 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 twenty-two applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of Niemann-Pick disease type C

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 II (Hunter syndrome)

The Committee was briefed on the significant benefit issues. Further discussion is expected next meeting.

3.1.3. -

Treatment of hepatocellular carcinoma

The Committee was briefed on the significant benefit issues. Further discussion is expected next meeting.

3.1.4. -

Treatment of diffuse large B-cell lymphoma

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. -

Prevention of ischaemia reperfusion injury associated with solid organ transplantation

The finalised letter was circulated for information.

3.2.2. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of Duchenne muscular dystrophy

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

4.1.1. SARCLISA - isatuximab – EMEA/H/C/004977, EMA/OD/198/13, EU/3/14/1268, EMA/OD/0000019553

Sanofi-Aventis Groupe; Treatment of plasma cell myeloma

COMP Rapporteurs: Karri Penttila; Elisabeth Johanne Rook

A list of issues was adopted on 20 February 2020.

An oral explanation was held on 22 April 2020.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 23 April 2020, prior to final opinion.

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

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

4.2.1. - luspatercept

Celgene Europe BV;

a) Treatment of beta-thalassaemia intermedia and major, EMEA/H/C/004444, EMA/OD/047/14, EU/3/14/1300, EMA/OD/0000008931

The status of the procedure at CHMP was noted.

b) Treatment of myelodysplastic syndromes, EMEA/H/C/004444, EMA/OD/048/14, EU/3/14/1331, EMA/OD/0000009353

The status of the procedure at CHMP was noted.

4.2.2. – glasdegib - EMEA/H/C/004878, EMA/OD/106/17, EU/3/17/1923, EMA/OD/0000020246

Pfizer Europe MA EEIG; Treatment of acute myeloid leukaemia

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

*[Post-*meeting *note: The COMP adopted the list of issues by written procedure following its April meeting.]*

4.2.3. – imlifidase - EMEA/H/C/004849, EMA/OD/237/16, EU/3/16/1826, EMA/OD/0000005755

Hansa Biopharma AB; Prevention of graft rejection following solid organ transplantation

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for three 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

5.1.1. Adcetris - brentuximab vedotin - Type II variation - EMEA/H/C/002455/II/0070, EMA/OD/072/08, EU/3/08/595, EMA/OD/0000007448

Takeda Pharma A/S; Treatment of peripheral T-cell lymphoma

CHMP Rapporteur: Paula Boudewina van Hennik; CHMP Co-Rapporteur: Jan Mueller-Berghaus

A list of issues was adopted on 19 March 2020.

An oral explanation was held on 22 April 2020.

The Committee confirmed that all issues previously identified in this application had been addressed.

An opinion recommending not to remove Adcetris (brentuximab vedotin) 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.

5.2. Prior to adoption of CHMP opinion

5.2.1. Imbruvica – ibrutinib - Type II variation - EMEA/H/C/003791/II/0059, EMA/OD/156/11, EU/3/12/984, EMA/OD/0000026247

Janssen-Cilag International NV; Treatment of chronic lymphocytic leukaemia

CHMP Rapporteur: Filip Josephson; CHMP Co-Rapporteur: Sinan B. Sarac

The status of the procedure at CHMP was noted.

5.2.2. Kyprolis – carfilzomib - Type II variation - EMEA/H/C/003790/II/0045, EMA/OD/120/07, EU/3/08/548, EMA/OD/0000030043

Amgen Europe B.V.; Treatment of multiple myeloma

CHMP Rapporteur: Jorge Camarero Jiménez; CHMP Co-Rapporteur: Alexandre Moreau

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

[Post-meeting note: The reassessment of the orphan designation will be further discussed in the next meeting]

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 meeting – COMP, 12-14 February 2020, Zagreb, Croatia

The COMP adopted the minutes of the Strategic Review & Learning meeting which was held on 12-14 February 2020 in Zagreb.

7.1.2. Strategic Review & Learning meeting – joint COMP/CAT/PDCO, 21-22 November 2019, Helsinki, Finland

The topic was postponed.

7.1.3. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 21 April 2020.

7.1.4. Committee for Orphan Medicinal Products Rules of Procedure

Following-up on the comments received during the March meeting, the updated COMP Rules of Procedure were presented and discussed.

The amendments to the RoP were required to enable COMP to continue their work in a virtual setting while adapting to the measures in place to contain the COVID19 outbreak, as well as to ensure the validity of the various decisions that the committee will adopt.

To add flexibility to the system, the possibility to give a proxy vote to another member who is present at the relevant meeting of the body concerned has been introduced.

COMP adopted the updated Rules of Procedure by consensus. The document will be available on the EMA website.

7.1.5. Reassessment of the Orphan criteria

The Committee reviewed and discussed the criteria for reassessment of extensions of indication within an already approved orphan condition in accordance with the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products.

The COMP agreed to set up a drafting group to further review the criteria.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

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)

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 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 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

8.1.1. Working Party with Patients' and Consumers' Organisations (PCWP) and Working Party with Healthcare Professionals' Organisations (HCPWP)

The COMP delegate to HCPWP and COMP delegate to PCWP presented a report from the joint March 2020 PCWP/HCPWP meeting.

9. 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/

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 21-23 April 2020 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	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No interests declared	
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 Kovarova	Member	Czech Republic	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	
Frauke Naumann-Winter	Member	Germany	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	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Elisabeth 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 interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovakia	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	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	4.2.1 - luspatercept
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert	Patients' Organisation	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
		Representative		
	Patient expert	Germany	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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