18 July 2019
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Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 18-20 June 2019

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

18 June 2019, 09:00-19:30, room 2A

19 June 2019, 08:30-19:30, room 2A

20 June 2019, 08:30-16:00, room 2A

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 ongoing procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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. 23 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 18-20 June 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The COMP minutes for 21-23 May 2019 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000004238

Treatment of spinal cord injury

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

Spinal cord injury should be further described as a distinct medical entity. 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).

The sponsor aimed to target an aspect of the condition, neuropathic pain, which could also be viewed as a distinct medical entity. The sponsor was invited to elaborate on the inclusion criteria regarding the SCI (spinal cord injury) with neuropathic pain and the description of potential various aetiologies and severities of this condition.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of spinal cord injury the sponsor should further elaborate on:

- the results obtained ex vivo in a model of spinal cord injury,
- the relevance of the spinal nerve injury model used for the treatment of spinal cord injury, and the interpretation of the results obtained in the experiments,
- any clinical data in SCI patients if such data exist.

- Number of people affected

The mean survival of patients suffering from non-traumatic and traumatic SCI differs, but the sponsor assumed only one survival value across all variants of SCI. In addition, inclusion criteria for patients affected by SCI with neuropathic pain were not discussed in the context of the literature used for the estimation of the prevalence of SCI.

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

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registries for the proposed orphan condition and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

- Significant benefit

The arguments on significant benefit were based on the potential for improved safety and efficacy in the condition.

It was noted 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 was required to justify safety arguments in most cases.

The sponsor was requested to further elaborate on the potential risks with the product and how this compared with the safety profile of current authorised medicinal products for the same condition. In addition, the sponsor was requested to comment on any data supporting improved efficacy and to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 18 June 2019, the sponsor insisted that neuropathic pain was a relevant and frequent complication of SCI. The sponsor elaborated on the non-clinical data obtained to date and mentioned that the product was tested in several pain models. The Committee questioned the validity of the spinal nerve injury model for the evaluation of a chronic pain associated with spinal cord injury. The acute versus chronic stages of the condition were discussed in the context of the proposed mechanism of action of the product. The COMP was not convinced, based on the model of a different condition, that the product would have a clinically relevant effect in SCI. The sponsor also described in detail the methodology and sources of data for prevalence

calculation. Finally, the sponsor discussed the arguments for significant benefit which were based mainly on improved efficacy versus pregabalin and improved safety profile versus all other products used in neuropathic pain management. The Committee found the presented arguments too hypothetical and more data was requested, especially to support the efficacy of the proposed product as well as to position the product within the current standard of care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation on 19 June 2019, prior to final opinion.

2.1.2. - EMA/OD/0000003689

Treatment of Gaucher 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:

- 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 Gaucher disease the sponsor was requested to further elaborate on:

- the results obtained *in vitro* on the fibroblast cells from patients and how this would translate into a clinically adequate dose and clinically relevant outcomes in these patients.
- the claim that there are no non-clinical models used for Gaucher disease,
- the relevance of using the results of the clinical study in autophagy-lysosomal system (ALS) in establishing the clinical outcomes in Gaucher disease which was a different condition.

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved capability to target the neurological manifestations associated with the condition as the product crosses the blood brain barrier. To support that claim the applicant provided *in vitro* data using Gaucher disease fibroblasts and bridging data from patients with ALS.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the *in vitro* data and any additional non-clinical and/or clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 18 June 2019, the sponsor did not submit any new data to support the medical plausibility or significant benefit. During the oral explanation the sponsor further elaborated on the *in vitro* and bridging clinical data submitted in the original application. The COMP considered that the argumentation was compelling but not sufficient to recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation on 19 June 2019, prior to final opinion.

2.1.3. - EMA/OD/0000004774

Treatment of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

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 mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like (MELAS) episodes the sponsor should further elaborate on:

– present any available results with the compound as applied for designation, in either relevant non-clinical models or in preliminary clinical observations,

– discuss the extent of the effects presented in the case study, given the uncontrolled nature of observations, the use of concomitant treatments and the relapse-remitting nature of the target condition,

– provide the data of the 6 MELAS patients that were included in the clinical trial.

In the absence of any data with the product as applied for designation in either non-clinical models or patients affected by the condition, the medical plausibility could not be considered justified.

In the written response, and during an oral explanation before the Committee on 18 June 2019, the sponsor elaborated on the currently available data. There were data in non-clinical models to suggest a potential mechanism of action of the proposed product in MELAS. However, the efficacy of the proposed product was not yet studied in non-clinical models of mitochondrial diseases. While the sponsor presented expert opinions outlining an interest in the clinical development of the proposed product, there were currently no published data available on the proposed product in MELAS patients. The COMP concluded that that there was insufficient evidence to support medical plausibility for orphan designation in the absence of efficacy data in non-clinical models or patients affected by the condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 June 2019, prior to final opinion.

2.1.4. - EMA/OD/0000005159

Treatment of non-infectious uveitis

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 was requested to address the reliability of the different national and regional data sets used in the application, taking into consideration the variability of the reported values.

The quoted literature sources were dated from 1977 to 2007, but the sponsor argued that the number of uveitis cases could be assumed to have remained stable year-to-year. The

sponsor was therefore requested to provide more up-to-date data sources and to robustly justify any assumption made on the basis of such data.

Finally, given that the estimates are close to the 5/10,000 limit, the sponsor was invited to perform a sensitivity analysis of all the assumptions used.

- Significant benefit

The sponsor was requested to further discuss the grounds for significant benefit, highlighting any potential clinically relevant advantage of the proposed product in relation to all medicinal products authorized in the EU for the treatment of the condition. Regarding safety, the sponsor was reminded that usually preliminary safety data could not be considered supportive of significant benefit claims, since the full safety profile of the product was not known at that stage.

The sponsor was invited to provide any data with the product in the proposed condition that would allow for a comparison versus the authorised counterparts, in order to justify a clinically relevant advantage or major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 18 June 2019, the sponsor reiterated that they stand by the numbers originally submitted regarding the prevalence, noting that the approach taken was of a conservative nature and discussing the variability of incidence across different sources. The applicant argued that for calculating the prevalence in Europe, they took the most conservative estimate from each country, if more data were available from one country. A conclusion of 4.56 per 10,000 was proposed. The COMP considered that the exercise could have benefited from inclusion of additional articles such as by Bro *et al.* (June 04, 2019) where the authors estimated the incidence of uveitis (infectious and non-infectious) in the region of Jönköping, Sweden, as being around 10.8/10,000. Nevertheless, in light of the established variability of the epidemiology of the condition and the absence of other up-to-date data, the approach and assumptions as followed by the sponsor was acknowledged.

With regards to the significant benefit, the sponsor did not provide new data, and reiterated the claims of major contribution to patient care linked to a claimed long-lasting efficacy and different safety profile compared to existing treatments. The COMP noted that the only available data was the non-clinical experimental uveitis model, which showed activity in the studied context but does not allow for any data-driven comparison versus the authorised counterpart. Therefore the arguments for significant benefit were not considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 June 2019, prior to final opinion.

2.1.5. - EMA/OD/0000006865

Treatment of haematopoietic stem cell 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:

- Significant benefit

The sponsor was invited to provide published scientific data that demonstrate improved efficacy of the proposed product based regimens compared to regimens containing

authorised products busulfan, thiotepa, melphalan, and/or cyclophosphamide. Improved efficacy could be demonstrated via direct or indirect methods.

In the written response, and during an oral explanation before the Committee on 19 June 2019, the sponsor presented an extensive literature overview of efficacy and safety data that has been reported on conditioning regimens with and without the proposed product. The sponsor aimed at providing arguments of improved efficacy and safety of the proposed product as part of standard conditioning therapy regimens over standard regimens containing the currently authorised products via indirect methods. The COMP was of the opinion that the provided literature overview and indirect comparisons were not sufficiently conclusive in supporting the assumption of an improved efficacy or improved safety of the proposed product for the purpose of orphan designation.

In communicating the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 June 2019, prior to final opinion.

2.1.6. recombinant mutated extracellular domain of the human acetylcholine receptor subunit alpha1 - EMA/OD/0000004784

Toleranzia AB; Treatment of myasthenia gravis

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a medical plausibility for the development of the proposed product for treatment of myasthenia gravis the sponsor was asked to further elaborate on:

- the interpretation of the results presented in a well-established and characterized non-clinical model of the condition when the product was administered before the EAMG (experimental autoimmune myasthenia gravis) symptom onset as well as after symptom onset.
- the methodology used in the non-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential for an alternative treatment in patients who are refractory to first line treatment in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical *in vivo* data submitted to justify the assumption of significant benefit over currently authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 19 June 2019, the sponsor submitted additional new non-clinical *in vivo* data using the same validated non-clinical model of the condition to support the basis of the medical plausibility. The data offered further insight into the relevance of the endpoints measured. The COMP indicated that the new data was satisfactory to meet the requirements for the medical plausibility. Further discussion with regards to significant benefit centred on clarifying the

positioning of the product within the current standard of care. The COMP noted that due to late submission of the data a complete assessment could not be made. However the preliminary observation was that the product could be used in first line which would support the disease modifying characteristics of the product.

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

The intention to treat the condition with the medicinal product containing recombinant mutated extracellular domain of the human acetylcholine receptor subunit alpha1 was considered justified based on non-clinical *in vivo* data showing improvement of disease relevant endpoints.

The condition is life-threatening and chronically debilitating due to recurrent crisis characterized by muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment.

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 recombinant mutated extracellular domain of the human acetylcholine receptor subunit alpha1 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data which showed a slowing of the disease progression. The Committee considered that this constituted a clinically relevant advantage for the patients affected by the condition.

A positive opinion for recombinant mutated extracellular domain of the human acetylcholine receptor subunit alpha, for treatment of myasthenia gravis, was adopted by consensus.

2.1.7. 7-ethyl-10-hydroxycamptothecin - EMA/OD/0000005124

Cebiotex S.L.; Treatment of soft tissue sarcoma

COMP Rapporteur: Bozenna Dembowska-BaginskaAs 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 mode of administration and the potential improved efficacy in the condition. The sponsor proposed wide treatment inclusion criteria assuming specific positioning of the product at the time of surgery, prior to the use of first and later line treatments. However, the efficacy of this approach was not discussed in the context of other satisfactory methods of treatment (including radiation).

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. Further contextualisation of the results obtained within the standard of care was needed for the assessment of significant benefit.

In the written response, the sponsor strengthened the arguments to support the positioning of the product in the adjuvant setting in soft tissue sarcoma. The use of the product in a non-clinical model delayed tumour regrowth following surgery as compared to doxorubicin, a standard first line treatment in this condition. The sponsor provided also bibliographic evidence showing that a similar product can be used in conjunction with radiotherapy and various chemotherapy agents. The Committee considered these additional arguments as supportive of the assumption of significant benefit at the time of initial designation. The sponsor was however encouraged to request protocol assistance to support appropriate planning of the clinical trials with this product. In light of the positive outcome of the, discussion, the oral explanation was cancelled.

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 7-ethyl-10-hydroxycamptothecin was considered justified based on non-clinical data in a model of the condition demonstrating slowing down of tumour growth.

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

The condition was estimated to be affecting approximately 3.6 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 provided sufficient justification for the assumption that the medicinal product containing 7-ethyl-10-hydroxycamptothecin will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data that demonstrated that when the product was used at the time of surgery, the growth of tumours was slower in the group treated with the product in combination with doxorubicin as compared to doxorubicin alone. In addition, the sponsor provided bibliographic data showing that the product may be added to chemotherapy or radiotherapy, which is used in some patients following surgery. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for 7-ethyl-10-hydroxycamptothecin, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000002952

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 July meeting.

2.2.2. - EMA/OD/0000003546

Treatment of aneurysmal subarachnoid haemorrhage

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

2.2.3. - EMA/OD/0000003566

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 July meeting.

2.2.4. - EMA/OD/0000003683

Treatment of beta-thalassaemia intermedia and major

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

2.2.5. - EMA/OD/0000004401

Treatment of sarcoidosis

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

2.2.6. - EMA/OD/0000004755

Treatment of neuroblastoma

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

2.2.7. pevonedistat - EMA/OD/0000004845

Takeda Pharma A/S; Treatment of acute myeloid leukaemia

COMP Rapporteur: Frauke Naumann-WinterThe Committee agreed that the condition, acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pevonedistat was considered justified based on non-clinical data in a model of the condition supporting inhibition of tumour growth, as well as preliminary clinical observations reporting clinical responses in affected patients when combined with azacitidine.

The condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

The condition was estimated to be affecting less than 1.8 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 provided sufficient justification for the assumption that the medicinal product containing pevonedistat will be of significant benefit to those affected by

the condition. The sponsor provided preliminary clinical data in treatment-naïve acute myeloid leukaemia patients that support improved survival in combination with azacitidine compared to azacitidine alone. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for pevonedistat, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.8. - EMA/OD/0000004919

Treatment of graft loss in solid organ transplantation

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

2.2.9. - EMA/OD/0000005579

Treatment of cystic 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 July meeting.

2.2.10. - EMA/OD/0000005689

Treatment of haemophilia B

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

2.2.11. - EMA/OD/0000005861

Treatment of myelodysplastic syndromes

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

2.2.12. - EMA/OD/0000005898

Treatment of Huntington’s disease

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

2.2.13. elafibranor - EMA/OD/0000006005

Genfit; Treatment of primary biliary cholangitis

COMP Rapporteur: Dinko VitezicThe Committee agreed that the condition, primary biliary cholangitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing elafibranor was considered justified based on preliminary clinical data demonstrating that treatment can reduce alkaline phosphatase levels in patients affected by the condition.

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

The condition was estimated to be affecting less than 3.9 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 provided sufficient justification for the assumption that the medicinal product containing elafibranor will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data demonstrating that treatment can reduce alkaline phosphatase levels in patients affected by the condition after failing one line of treatment. Indirect comparisons suggested that the proposed product might have improved efficacy compared to the product that was currently authorised for second line therapy. The Committee considered that this constituted a clinically relevant advantage.

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

2.2.14. N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide - EMA/OD/0000006043

Voisin Consulting S.A.R.L.; Treatment of neurofibromatosis type I

COMP Rapporteur: Ingeborg BarisicThe Committee agreed that the condition, neurofibromastosis type 1, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide was considered justified based on non-clinical *in vivo* and preliminary clinical data showing a reduction in tumour size.

The condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms.

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

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

A positive opinion for N-((R)-2,3-dihydroxypropoxyl)-3,4-difluro-2-(2-fluoro-4-iodo-phenylamino)-benzamide, for treatment of neurofibromatosis type 1, was adopted by consensus.

2.2.15. mavorixafor - EMA/OD/0000006091

Voisin Consulting S.A.R.L.; Treatment of WHIM syndrome

COMP Rapporteur: Lyubina Racheva TodorovaThe Committee agreed that the condition, WHIM syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mavorixafor was considered justified based on clinical data demonstrating improvement in absolute neutrophil and leukocyte counts in patients.

The condition is chronically debilitating due to recurring bacterial infections and cutaneous warts.

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

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

A positive opinion for mavorixafor, for treatment of WHIM syndrome, was adopted by consensus.

2.2.16. 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one - EMA/OD/0000006186

Aprea Therapeutics AB; Treatment of myelodysplastic syndromes

COMP Rapporteur: Karri PenttilaThe Committee agreed that the condition, myelodysplastic syndromes, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one was considered justified based on non-clinical data showing inhibition of tumour growth and clinical data showing responses in treated patients in combination with azacitidine.

The condition is life-threatening and chronically debilitating in particular due to anaemia, thrombocytopenia, and neutropenia, as well as transformation into acute myeloid leukemia (AML).

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data in a model of the condition that support improved tumour growth inhibition compared to azacitidine, as well as preliminary clinical data in combination with azacitidine that compare favourably to the expected outcomes with the current treatments. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for 2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one, for treatment of myelodysplastic syndromes, was adopted by consensus.

2.2.17. - EMA/OD/0000006189

Treatment of subarachnoid haemorrhage

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

2.2.18. - EMA/OD/0000006192

Treatment of pneumonia caused by *Pseudomonas aeruginosa*

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

2.2.19. - EMA/OD/0000006314

Treatment of fibromyalgia

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

2.2.20. - EMA/OD/0000006345

Treatment of West syndrome

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

2.2.21. - EMA/OD/0000006379

Treatment of hepatitis D virus infection

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

2.2.22. parsaclisib - EMA/OD/0000006380

Incyte Biosciences Distribution B.V.; Treatment of marginal zone lymphoma

COMP Rapporteur: Karri PenttilaThe 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 parsaclisib was considered justified based on preliminary clinical observations in relapsed/refractory patients who responded to treatment with the proposed product.

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 1.5 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 provided sufficient justification for the assumption that the medicinal product containing parsaclisib will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical observations in relapsed/refractory patients who responded to treatment with the proposed product. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for parsaclisib, for treatment of marginal zone lymphoma, was adopted by consensus.

2.2.23. - EMA/OD/0000006618

Treatment in haematopoietic stem cell transplantation

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

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for twenty applications.

2.7. Evaluation ongoing

The Committee noted that evaluation was ongoing for twenty seven applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

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.

3.1.2. -

Treatment of beta-thalassaemia intermedia and major

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 spinal muscular atrophy

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

3.1.4. -

Treatment of immune thrombocytopenia

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

3.1.5. -

Treatment of multiple myeloma

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

3.1.6. -

Treatment of transthyretin-mediated amyloidosis

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

3.1.7. -

Treatment of medullary thyroid carcinoma

The discussion was postponed.

3.1.8. -

Treatment of acute myeloid leukaemia

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

3.2. Finalised letters

3.2.1. -

Treatment of idiopathic pulmonary fibrosis

The finalised letter was circulated for information.

3.2.2. -

Treatment of tuberculosis

The finalised letter was circulated for information.

3.2.3. -

Treatment of Niemann-Pick disease, type C

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of biliary tract cancer

The new request was noted.

3.3.2. -

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

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. Cufence - trientine dihydrochloride – EMEA/H/C/004111, EMEA/OD/043/03, EU/3/03/172

Univar BV; Treatment of Wilson's disease

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 03 June 2019, prior to responding to the list of issues. The sponsor formally withdrew the orphan designation from the EC register of orphan medicinal products, on 03 June 2019.

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. - larotrectinib - EMEA/H/C/004919

Bayer AG;

a) Treatment of salivary gland cancer EMA/OD/213/17, EU/3/18/1995

b) Treatment of soft tissue sarcoma EMA/OD/184/15, EU/3/15/1606

c) Treatment of glioma EMA/OD/116/18, EU/3/18/2097

d) Treatment of papillary thyroid cancer EMA/OD/117/18, EU/3/18/2098

The status of the procedure at CHMP was noted.

4.2.2. - polatuzumab vedotin – EMEA/H/C/004870, EMA/OD/231/17, EU/3/18/2013, EMA/OD/0000003161

Accelerated assessment

Roche Registration GmbH; 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 July meeting.

4.2.3. - tagraxofusp – EMEA/H/C/005031, EMA/OD/064/15, EU/3/15/1567, EMA/OD/0000004627

Accelerated assessment

TMC Pharma (EU) Limited; Treatment of blastic plasmacytoid dendritic cell neoplasm

The status of the procedure at CHMP was noted.

4.2.4. - Onasemnogene abeparvovec – EMEA/H/C/004750, EMA/OD/028/15, EU/3/15/1509, EMA/OD/0000003028

AveXis Netherlands B.V.; Treatment of spinal muscular atrophy

The status of the procedure at CHMP was noted.

4.2.5. - viable T-cells - EMEA/H/C/002397, EMA/OD/008/16, EU/3/16/1678

Kiadis Pharma Netherlands B.V.; Treatment in haematopoietic stem cell transplantation

The status of the procedure at CHMP was noted.

4.2.6. – cannabidiol - EMEA/H/C/004675

GW Pharma (International) B.V;

a) Treatment of Dravet syndrome EMA/OD/083/14, EU/3/14/1339

b) Treatment of Lennox-Gastaut syndrome EMA/OD/275/16, EU/3/17/1855

The status of the procedure at CHMP was noted.

4.2.7. – enasidenib - EMEA/H/C/004324, EMA/OD/253/15 - EU/3/16/1640, EMA/OD/0000007422

Celgene Europe B.V.; Treatment of acute myeloid leukaemia

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. Ongoing procedures

None

4.5. COMP co-ordinators were appointed for four applications. Orphan Maintenance Reports

The documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Imbruvica – ibrutinib - EMEA/H/C/003791/II/0046, EMA/OD/185/13, EU/3/14/1264, EMA/OD/0000002783

Janssen-Cilag International NV; Treatment of lymphoplasmacytic 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 July meeting.

5.3. Appeal

None

5.4. Ongoing procedures

COMP co-ordinators were appointed for one application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

The COMP received a report for the discussions held during the Romanian presidency meeting held in Rome on 27-28 May. The minutes were circulated for comments.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 18 June 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

The 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 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 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. EMA Business Pipeline activity and Horizon scanning

The document was tabled in MMD for information.

8.2. Handling of competing interests

The EMA Secretariat reminded the Committee of the principles on handling competing interests for Scientific Committees' members and experts as detailed in the corresponding EMA Policy on handling competing interests for Scientific Committees' members and experts (EMA/626261/2014, Rev. 1). In particular, the presentation detailed the types of interests to be declared in the electronic declaration of interests (eDoI) by a member or an expert, the corresponding restrictions in EMA activities if an interest is declared, the requirement to inform the EMA of any intention to become an employee in a pharmaceutical company and the breach of trust procedure in case an interest is not declared intentionally or through gross negligence. In case of any doubt, members and experts are advised to contact EMA for advice before agreeing on any involvement in non-EMA /non-NCAs activities that potentially could be considered as a competing interest and incompatible with involvement in EMA activities.

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 18-20 June 2019 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 Blöchl-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	
Nectaroula Cooper	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	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Elizabeth 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	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Maria Cavaller Bellaubi	Observer	Eurordis	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

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