7 November 2019
EMA/COMP/550965/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 8-10 October 2019

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

8 October 2019, 09:00-18:45, room 2A

9 October 2019, 08:45-18:00, room 2A

10 October 2019, 09:00-13:15, 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 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 that no restriction in the involvement of meeting participants in upcoming discussions was identified as included in the pre-meeting list of participants and restrictions.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 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 8-10 October 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 10-12 September 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/0000010228

Treatment of acute myeloid leukaemia

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 17 September 2019, prior to responding to the list of issues.

2.1.2. - EMA/OD/0000006190

Treatment of amyotrophic lateral sclerosis

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 23 September 2019, prior to responding to the list of issues.

2.1.3. replication-incompetent, non-integrating, herpes simplex virus 1 vector expressing the human transglutaminase-1 enzyme - EMA/OD/0000009633

IDEA Innovative Drug European Associates (Ireland) Limited; Treatment of autosomal recessive congenital ichthyosis (ARCI)

COMP Rapporteur: Lyubina Racheva Todorova

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

- Intention to diagnose, prevent or treat

The sponsor was requested to establish correctly if there exists a scientific rationale for the development of the proposed product for Treatment of Autosomal recessive congenital ichthyosis (ARCI) the sponsor should further elaborate on:

- the relevance of the nonclinical model used for the treatment of autosomal recessive congenital ichthyosis (ARCI), and the interpretation of the results obtained in the experiments,
- the absence of data on functional endpoints such as trans-epithelial water loss, and the adequacy of the expressed levels of target protein to elicit a clinically relevant response,
- the envisioned posology and duration of effects of the proposed treatment.

- 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 invited to provide any available in vivo data with the specific product as proposed for designation, to support a comparative discussion versus the authorised products in the respective disease setting. Extrapolation from other products was of limited value in that regard.

In the written response, and during an oral explanation before the Committee on 8 October 2019, the sponsor discussed the feasibility of studying the efficacy of the proposed product on non-clinical in vivo models of the proposed condition. It was pointed out that TGM1 (transglutaminase-1) knockouts display neonatal lethality and that the available xenograft models are characterised by limited number of available grafts and significant biological variability. Furthermore, it was acknowledged by the sponsor that functional endpoints could not have been measured in the BALBC model that had been presented, but parallels are drawn from studies using other TGM1 supplementation therapies (other vectors or recombinant TGM1 delivered via liposomes). With regards to the envisioned dosing scheme, the sponsor discussed an ongoing clinical study with the product in the USA.

Importantly, during the oral explanation the sponsor discussed preliminary clinical observations from the ongoing study in the USA. In particular one enrolled patient was discussed, who received the topical treatment with the proposed product. This patient has been previously receiving authorised acitretin and exfoliation care for several years. Expression of a functional transgene was reported by the sponsor, together with phenotypic improvements and reductions in trans-epithelial water loss.

The COMP considered that the preliminary clinical data would support the assumption that the product may have a beneficial effect in the sought indication. Moreover, and given that therapy was additional to the standard retinoid and exfoliation care, it was considered that

the assumption for a clinically relevant advantage versus the existing authorised products was also justified at this point in time.

The Committee agreed that the condition, treatment of autosomal recessive congenital ichthyosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing replication-incompetent, non-integrating, herpes simplex virus 1 vector expressing the human transglutaminase-1 enzyme was considered justified based on observations in an affected patient supporting expression of transglutaminase-1 and improvements in histology and skin function.

The condition is life-threatening and chronically debilitating in particular due to manifestations such as collodion babies, the development of scales, an impairment of the epidermal barrier resulting in infections and trans epithelial water loss, hyperkeratosis interfering with sweat gland function, ectropion, conductive hearing loss, hair loss, palmoplantar and nail abnormalities, as well as the development of skin malignancies.

The condition was estimated to be affecting less than 0.17 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing replication-incompetent, non-integrating, herpes simplex virus 1 vector expressing the human transglutaminase-1 enzyme will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical observations supporting expression of transglutaminase-1 and improvements in histology and trans epithelial water loss in a patient that has been previously treated with existing products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for replication-incompetent, non-integrating, herpes simplex virus 1 vector expressing the human transglutaminase-1 enzyme, for treatment of autosomal recessive congenital ichthyosis, was adopted by consensus.

2.1.4. ganaxolone - EMA/OD/0000011311

Pharma Gateway AB; Treatment of CDKL5 deficiency disorder

COMP Rapporteur: Giuseppe Capovilla

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for Treatment of CDKL5 deficiency disorder the sponsor should:

- provide more information on the patient characteristics and their disease management (including pharmacological treatment) before enrolling into the trial,
- explain how the add-on efficacy of ganaxolone could be established if the majority of patients was treatment naïve at baseline and initiated concomitant AED therapy at the same time as ganaxolone,

- regarding the indirect comparison, discuss the similarity and differences of patient populations of both trials. Please comment on the overall results of the indirect comparisons, which do not suggest better outcomes when ganaxolone is added to standard AED therapy.

In the written response, the sponsor further elaborated on the preliminary clinical data and the clinical trial design. The sponsor clarified that all enrolled patients were treatment refractory in terms of anti-epileptic therapy (AED). These patients continued to have uncontrolled seizures despite having tried and stopped several AEDs and/or remained uncontrolled despite standard of care AEDs. Per protocol, participants were on a stable regimen of at least two AEDs at baseline. Hence, the clinical trial design allowed measuring the add-on treatment effect of ganaxolone on top of the best standard of care including authorised products. The preliminary clinical data suggest that ganaxolone on top of best standard of care anti-epileptic therapy reduced seizure frequency. The COMP considered that this level of evidence was sufficient to accept medical plausibility and significant benefit.

The Committee agreed that the condition, treatment of CDKL5 deficiency disorder, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ganaxolone was considered justified based on preliminary clinical data suggesting a reduction in seizures upon treatment with the proposed product when used in combination with other anti-epileptic therapy.

The condition is life-threatening and chronically debilitating due to early-onset pharmaco-resistant seizures, global developmental delay, abnormal muscle tone, hand stereotypies, and gastrointestinal and respiratory problems.

The condition was estimated to be affecting approximately 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 ganaxolone will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting a reduction in seizures upon treatment with the proposed product when used in combination with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ganaxolone, for treatment of CDKL5 deficiency disorder, was adopted by consensus.

2.1.5. 4-((E)-(5-(2-(2-((S)-2-((S)-1-(l-threonyl-l-lysyl)pyrrolidine-2-carboxamido)-5-guanidinopentanamido)acetamido)-2-carboxyethyl)-2-hydroxyphenyl)diazenyl)phenyl (2-(trimethylammonio)ethyl) phosphate - EMA/OD/0000009997

Granzer Regulatory Consulting & Services; Treatment of non-infectious uveitis

COMP Rapporteur: Elisabeth Johanne Rook

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the non-clinical in vivo studies 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 8 October 2019, the sponsor offered some further clarification and insight regarding how the proposed product could offer a clinically relevant advantage. The sponsor elaborated on the management of patients and how authorised treatments were used. According to them, three different treatment phases exist and each needs a different management consideration: the acute phase, the chronic phase, and the end-stage phase. The preliminary non-clinical in vivo data provided using cyclosporin as a positive control, shows a significant reduction in ocular inflammation with the proposed product. This would support its use in either the chronic phase and/or the end-stage phase. The COMP considered that the product could show a clinically relevant advantage in the patients with non-infectious uveitis associated with glaucoma and that there was an important need as this represents 20-40% of the patients. The COMP therefore recommended granting the orphan designation.

The Committee agreed that the condition, treatment of non-infectious uveitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 4-((E)-(5-(2-(2-((S)-2-((S)-1-(L-threonyl-L-lysyl)pyrrolidine-2-carboxamido)-5-guanidinopentanamido)acetamido)-2-carboxyethyl)-2-hydroxyphenyl)diazenyl)phenyl (2-(trimethylammonio)ethyl) phosphate was considered justified based on non-clinical in vivo data in a validated model of the condition where ocular inflammation associated with the condition was effectively controlled when compared to the vehicle.

The condition is chronically debilitating due to visual loss, leading to significant visual impairment or legal blindness in up to 35% of patients.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4-((E)-(5-(2-(2-((S)-2-((S)-1-(L-threonyl-L-lysyl)pyrrolidine-2-carboxamido)-5-guanidinopentanamido)acetamido)-2-carboxyethyl)-2-hydroxyphenyl)diazenyl)phenyl (2-(trimethylammonio)ethyl) phosphate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that supports the use of the product in non-infectious uveitis patients with glaucoma not eligible for corticosteroid treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-((E)-(5-(2-(2-((S)-2-((S)-1-(L-threonyl-L-lysyl)pyrrolidine-2-carboxamido)-5-guanidinopentanamido)acetamido)-2-carboxyethyl)-2-hydroxyphenyl)diazenyl)phenyl (2-(trimethylammonio)ethyl) phosphate, for treatment of non-infectious uveitis, was adopted by consensus.

2.1.6. - EMA/OD/0000012715

Treatment of invasive aspergillosis

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

- Intention to diagnose, prevent or treat

The sponsor was asked to establish correctly whether there is a scientific rationale for the development of the proposed product for treatment of invasive aspergillosis. The sponsor was asked to further elaborate on the model used for the treatment of invasive aspergillosis, and the interpretation of the results obtained in the experiments.

In particular, the absence of statistical analyses in all endpoints studied, the lack of data in a pulmonary aspergillosis model, and the comparison of the effects to the standard of care are expected to be discussed. Moreover, the high MIC (minimum inhibitory concentration) values compared to other anti-fungal agents are to be discussed in the context of the proposed mechanism of action.

- 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 provide in vivo data in a model of invasive aspergillosis, where the effects of the product are compared to the authorised medicines, including among others amphotericin and isavuconazole.

In the written response, and during an oral explanation before the Committee on 8 October 2019, the sponsor addressed the raised issues.

Regarding the medical plausibility, the sponsor further elaborated on the materials and methods of the experiments and the newly provided data. The data from the in vivo aspergillus model, suggested improved survival with eradication of CFU (colony forming units) in at least one organ. The COMP noted that only statistically significant results were presented. Regarding significant benefit, the applicant outlined perceived advantages of the product versus authorised medicines that are of theoretical nature. The COMP discussed the presented data and arguments and concluded that the settings and outcomes of the aspergillus models, the low number of studied subjects, as well as the assumptive mechanism of action, would not be robust enough to support the assumption of medical plausibility in the sought indication, nor the assumption of significant benefit over existing authorised products.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2019, prior to final opinion.

2.1.7. - EMA/OD/0000007780

Treatment of mantle cell lymphoma

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 17 September 2019, prior to responding to the list of issues.

2.1.8. camsirubicin - EMA/OD/0000010168

Monopar Therapeutics S.A.R.L; Treatment of soft-tissue sarcoma

COMP Rapporteur: Geraldine O'Dea

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:

- Medical Plausibility

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of soft-tissue sarcoma the sponsor should further elaborate on:

- the phase II clinical trial which has been briefly described. The sponsor was asked to further discuss the methodology aims and duration of the trial as well as the additional results from secondary endpoints. In addition, the sponsor was asked to discuss the validity of the clinical studies used for indirect comparisons of efficacy.

- 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 asked to provide a European 10-year partial prevalence estimate as a proxy of the affected patients, describe and justify the methodology used for the prevalence calculation.

- Significant benefit

The arguments on significant benefit were based on a clinically relevant advantage provided by an analogue of doxorubicin.

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.

It is well known that extrapolation from nonclinical 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.

In the written response, and during an oral explanation before the Committee on 9 October 2019, the sponsor elaborated on the issues that were identified by the COMP. The COMP however accepted the assumptions and limitations regarding the provided prevalence calculation and settled for a prevalence estimation of 3.5 in 10,000.

Regarding medical plausibility, the sponsor reported on two completed trials. A phase 1 dose escalation trial was completed and demonstrated stable disease in the majority of enrolled patients with leiomyosarcoma. There was no evidence of irreversible cardiotoxicity not even for the four patients with prior anthracycline treatments. An open-label, single-arm, phase II study was completed in patients with unresectable or metastatic soft tissue sarcoma and showed that 38% of patients had progression free survival at 6 months. The sponsor provided an indirect comparison to similar studies with doxorubicin showing a similar and potentially more favourable outcome.

Regarding significant benefit, the sponsor argued that their product could offer greater exposure and more cycles of treatment than doxorubicin. It was argued that the better tolerability was supported by the preliminary follow-up data at 1 year indicating that camsirubicin could be used over longer periods and not limited by toxicity. The COMP noted that the sponsor had not established equivalence of effect between doxorubicin and camsirubicin. The sponsor did however indicate that a 1-year follow-up in those patients treated with their product showed no irreversible cardiotoxicity issues. This was further supported by the non-clinical in vivo finding that camsirubicin is associated with less cardiotoxicity than doxorubicin. In totality, the COMP considered sufficient evidence had been provided to support significant benefit and recommended granting the orphan designation.

The Committee agreed that the condition, treatment of 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 camsirubicin was considered justified based on preliminary clinical data showing partial response in patients with advanced unresectable soft tissue sarcoma.

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 3.5 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 camsirubicin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate the potential for enhanced cumulative dosing associated with prolonged exposure which could lead to additional benefits in outcome. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.9. - EMA/OD/0000012626

Treatment of ATTR amyloidosis

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

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 a comprehensive literature search and methodology to provide one conclusive prevalence estimate of the full condition.

- 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 provide evidence to suggest that the novel mechanism of action can translate into an improved efficacy in relation to the currently authorised products.

The sponsor was invited to provide additional evidence to show that that the proposed product can lead to relevant improvements in the ATTR cardiomyopathy pathology or in patients failing currently authorised products.

In the written response, and during an oral explanation before the Committee on 9 October 2019, the sponsor claimed significant benefit in ATTR cardiomyopathy, where there are currently no authorised therapies.

The sponsor acknowledged that there were no data to demonstrate efficacy of the proposed product in adequate non-clinical models of ATTR cardiomyopathy or patients affected by ATTR cardiomyopathy. Hence, the sponsor provided mathematical modelling that aimed at predicting the clinical outcomes in ATTR cardiomyopathy on the basis of the currently available non-clinical PK/PD data. The COMP considered that this degree of evidence was not sufficient in demonstrating that the novel mechanism of action can translate into clinically relevant outcomes in ATTR cardiomyopathy patients.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2019, prior to final opinion.

2.1.10. - EMA/OD/0000012303

Treatment of Duchenne muscular dystrophy

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 23 September 2019, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000004414

Treatment of Sickle cell 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 November meeting.

2.2.2. - EMA/OD/0000007338

Treatment of uveal melanoma

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

2.2.3. - EMA/OD/0000010330

Treatment of immune thrombocytopenia

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 November meeting.

2.2.4. - EMA/OD/0000012386

Treatment of Duchenne muscular dystrophy

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

2.2.5. - EMA/OD/0000012403

Treatment of pancreatic cancer

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 November meeting.

2.2.6. exendin (9-39) - EMA/OD/0000013234

Eigerbio Europe Limited; Treatment of congenital hyperinsulinism

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing exedin (9-39) was considered justified based on clinical data in adult and young patients showing improved fasting glucose levels as well as protein challenge test hypoglycaemia, and an achievement of reduced glucose infusion rate in neonate patients.

The condition is life-threatening due to severe hypoglycaemia and chronically debilitating due to symptoms such as pallor, sweating, tachycardia and neurological effects of chronic hypoglycaemia.

The condition was estimated to be affecting approximately 0.15 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 Exendin (9-39), for treatment of congenital hyperinsulinism, was adopted by consensus.

2.2.7. - EMA/OD/0000013557

Treatment of 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 November meeting.

2.2.8. autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured - EMA/OD/0000013608

Kite Pharma EU B.V.; Treatment of mantle cell lymphoma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured was considered justified based on preliminary clinical data showing favourable survival in patients with mantle cell lymphoma that relapsed after, or were refractory to, several lines of previous treatments.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing improved survival in patients who relapsed from several lines of previous standard of care treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured, for treatment of mantle cell lymphoma, was adopted by consensus.

2.2.9. chimeric fibril-reactive IgG1k monoclonal antibody 11-1f4 - EMA/OD/0000013909

Real Regulatory Limited; Treatment of AL amyloidosis

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing chimeric fibril-reactive IgG1k monoclonal antibody 11-1F4 was considered justified based on preliminary clinical observations showing responses in cardiac outcomes in patients affected by the condition.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

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

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

A positive opinion for chimeric fibril-reactive IgG1k monoclonal antibody 11-1F4, for treatment of AL amyloidosis, was adopted by consensus.

2.2.10. - EMA/OD/0000013983

Treatment of GM1 gangliosidosis

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 November meeting.

2.2.11. (2S,3R,4R,5S)-2-(hydroxymethyl)-1-pentylpiperidine-3,4,5-triol - EMA/OD/0000013997

Idorsia Pharmaceuticals Deutschland GmbH; Treatment of GM2 gangliosidosis

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, treatment of GM2 gangliosidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (2S,3R,4R,5S)-2-(hydroxymethyl)-1-pentylpiperidine-3,4,5-triol was considered justified based on non-clinical data in a model of the condition showing longer survival and improved motor function.

The condition is life-threatening with a reduced life expectancy of 3 to 15 years in infantile and juvenile onset patients, and chronically debilitating due to ataxia, muscle weakness, loss of motor function, sight and hearing, and development of seizures and cognitive impairment.

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

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

A positive opinion for (2S,3R,4R,5S)-2-(hydroxymethyl)-1-pentylpiperidine-3,4,5-triol, for treatment of GM2 gangliosidosis, was adopted by consensus.

2.2.12. - EMA/OD/0000014060

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 November meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for 16 applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 18 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of gastrointestinal stromal tumours

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 graft-versus-host disease

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 Duchenne muscular dystrophy

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 amyotrophic lateral sclerosis

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 congenital adrenal hyperplasia

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 post-polycythaemia vera myelofibrosis

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of glioma

The new request was noted.

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

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

None

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

4.2.1. – Osilodrostat - EMEA/H/C/004821, EMA/OD/099/14, EU/3/14/1345, EMA/OD/0000003092

Novartis Europharm Limited; Treatment of Cushing's syndrome

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

Roche Registration GmbH; Treatment of diffuse large B-cell lymphoma

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Blincyto – blinatumomab – Type II variation – EMEA/H/C/003731/II/0030, EMA/OD/029/09, EU/3/09/650, EMA/OD/0000016144

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

CHMP rapporteur: Alexandre Moreau; CHMP co-rapporteur: Daniela Melchiorri

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

5.2.2. Adcetris - brentuximab vedotin - Type II variation – EMEA/H/C/002455/II/0070 - EMEA/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

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

5.2.3. Darzalex - daratumumab

Janssen-Cilag International NV;

a) EMEA/H/C/004077/II/0029, EMA/OD/038/13, EU/3/13/1153, EMA/OD/0000007195
Treatment of plasma cell myeloma

The status of the procedure at CHMP was noted.

b) EMEA/H/C/004077/II/0030, EMA/OD/038/13, EU/3/13/1153, EMA/OD/0000010020
Treatment of plasma cell myeloma

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

CHMP rapporteur: Sinan B. Sarac Jiménez; CHMP co-rapporteur: Jorge Camarero

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

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

The agenda for the SLRM under the Finish presidency to be held on 21-22 November was presented and topic leads were identified.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 9 October 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

The PRIME eligibility requests 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

The Committee adopted the Work Plan for 2020.

Document tabled:
Draft work plan 2020

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. Drug development for pancreatic cancer

The COMP received and discussed a presentation on the overview of Orphan Designations for pancreatic cancer in Europe.

8.2. EMA's move to the permanent building

The COMP received an update on the EMA's relocation to the permanent building.

8.3. EC guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another

COMP members were reminded to send any comment on the document to EMA.

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 8-10 October 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	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	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	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Elizabeth Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
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	
Daniel O'Connor	Member	United Kingdom	No interests declared	
	Expert - in person*	Medicines Evaluation Board (NL)	No interests declared	
Meeting run with support from relevant EMA staff				

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