13 September 2018
EMA/COMP/425925/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 17-19 July 2018

Chair: Bruno Sepodes

17 July 2018, 08:30-20:30, room 2F

18 July 2018, 08:30-20:30, room 2F

19 July 2018, 08:00-13:00, room 2F

Disclaimers

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

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 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 17-19 July 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 19-21 June 2018 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/058/18

Treatment of progressive supranuclear palsy

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 progressive supranuclear palsy, the sponsor should further elaborate on the relevance of the non-clinical model used for the treatment of progressive supranuclear palsy, and the interpretation of the results obtained in the experiments. The absence of effects in functional endpoints was noted, and the relevance of endpoints studied should be further discussed.

In the written response, and during an oral explanation before the Committee on 17 July 2018, the sponsor explained a) that the available model was selected based on recapitulation of the pathophysiology and commercial availability, and not the functional manifestations of the proposed condition; b) that the functional impairment in that model results from spinal cord and not brain lesions and that c) oral treatment with the proposed product for 3.5 months was shown to biochemically reduce pathological tau throughout the cortex and in the dentate gyrus area of the hippocampus. The COMP reflected on the relevance of the endpoints studied and the absence of functional improvements. It was considered that the targeted pathology was common to a plethora of neurological conditions and that functional assessments of cognitive behaviour could also have been performed. In the absence of functional improvements *in vivo*, the Committee considered that the medical plausibility could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2018, prior to final opinion.

2.1.2. - EMA/OD/046/18

Treatment of eosinophilic oesophagitis

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 9 July 2018, prior to responding to the list of issues.

2.1.3. 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt - EMA/OD/051/18

Pharm Research Associates (UK) Limited; Treatment of acute myeloid leukaemia

COMP rapporteur: Daniel O'Connor

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

It is noted that the proposed product is positioned into the treatment algorithm in patients relapsed/refractory to standard intensive induction chemotherapy and in patients not eligible for intensive chemotherapy. The sponsor should further discuss the positioning of their product in these treatment lines and provide a data-driven discussion on significant benefit versus all authorised products including azacitidine, decitabine and salvage regimens. The COMP generally prefers non-clinical *in vivo* and preliminary clinical data in support of significant benefit.

In the written response, the sponsor further elaborated on the justification of the significant benefit of the product over authorised counterparts. The positioning of the product in the treatment algorithm was supported by preliminary clinical data confirming that the product will be developed for patients relapsed/refractory to standard intensive induction chemotherapy and in patients not eligible for intensive chemotherapy. The currently available non-clinical data from valid models was highlighted, suggesting that the proposed product in combination of low-dose cytarabine could reduce tumour growth leading to better survival compared to low-dose cytarabine alone. The COMP was of the opinion that this

evidence was sufficient to support the assumption of significant benefit for orphan designation and therefore the oral explanation was cancelled. The 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 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt was considered justified based on non-clinical data demonstrating that treatment can reduce tumour growth and improve survival.

The condition is chronically debilitating in particular due to intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also life-threatening with overall 5-year relative survival with the currently available treatments of approximately 20%.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrated that treatment in combination with a non-intensive first line chemotherapy medicine can reduce tumour growth and improve survival compared to monotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide fumarate salt, for treatment of acute myeloid leukaemia, was adopted by consensus.

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

2.1.4. - EMA/OD/072/18

Treatment of follicular lymphoma

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 has provided an under-estimate of the prevalence of the condition which does not reflect currently reported numbers discussed in more recent papers such as Provencio et al 2017.

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

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

- Significant benefit

The arguments on significant benefit are based on an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor should further elaborate on the previous therapies used in the patient population and elaborate in detail the results of the main clinical study to support the significant benefit assumption in the context of the current therapeutic management of these patients.

In the written response, and during an oral explanation before the Committee on 17 July 2018, the COMP noted that the sponsor has not adequately compared the proposed active substance to idelalisib in the proposed indication. Only vague assumption such as "the proposed active substance may provide comparable efficacy to idelalisib while providing a differentiated and markedly improved safety and tolerability profile" are provided in the original application. In addition, the sponsor has not provided any argumentation against obinutuzumab. As these treatments are deemed to play a significant role in the management of these patients the COMP considered that there was not enough data for them to establish significant benefit and as such could not recommend granting of the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2018, prior to final opinion.

2.1.5. Adeno-associated viral vector serotype hu68 containing the human *SMN1* gene - EMA/OD/065/18

Biogen Idec Limited; Treatment of spinal muscular atrophy

COMP rapporteur: Fernando Méndez Hermida

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

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available studies to justify the assumption of significant benefit over authorised medicinal product for the proposed orphan indication.

It is well known that extrapolation from non-clinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases.

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of the current authorised medicinal product for the same condition.

In the written response, the sponsor presented an additional claim for significant benefit on the basis of improved efficacy. This assumption was based on a comparison of survival observations in the SMNΔ7 non-clinical model versus bibliographical studies in the same model. Treatment with a single intracerebroventricular (ICV) injection of the proposed product on the first day of life provided a "median survival of 60-65 days" (250% net increase). It was argued that this compares favourably with *in vivo* results from a publication of Passini et al. (Sci Transl Med; 3 (72): 72ra18) where ICV administration of nusinersen at the day of birth increased survival up to approximately day 26. The applicant attributes this improvement to the new mechanism of action that does not rely on the SMN2 copies. The Committee considered that it is difficult to make indirect comparisons in non-clinical models, but acknowledged that the control groups in both experiments had a comparable life span. Therefore, the assumption for improved efficacy was eventually considered for the purpose of orphan designation and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype hu68 containing the human *SMN1* gene was considered justified based on improvements in survival and motor function in a valid non-clinical model of the condition.

The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype hu68 containing the human *SMN1* gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data supporting improvements in survival in a model of the condition that compare favourably with the effects of the authorised product in the same settings. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype hu68 containing the human *SMN1* gene, for treatment of spinal muscular atrophy, was adopted by consensus.

2.1.6. somapacitan - EMA/OD/041/18

Novo Nordisk A/S; Treatment of growth hormone deficiency

COMP rapporteur: Vallo Tillmann

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 is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The proposed prevalence estimate is underlined by assumptions. The sponsor was requested to provide more details on the methodology for prevalence calculation, justification of assumption and a sensitivity analysis of the reported calculations. Especially a sensitivity analysis for adult onset patients should be provided taking into consideration a longer disease duration, i.e. 35-40 years.

- Significant benefit

The sponsor was requested to further elaborate on the results from trial to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. The sponsor was asked to discuss:

- the results on protocol deviations, showing that treatment with the proposed product led to a higher number of protocol deviations regarding compliance,
- the patient-reported outcome (PRO) results suggesting that treatment with the proposed product improved convenience. Why did overall satisfaction not improve in line with convenience?
- the PRO results in light of a potential bias in patient recruitment with a lower global satisfaction score in the treatment arm at the time of enrolment.

In the written response, and during an oral explanation before the Committee on18 July 2018 the sponsor further elaborated on the justification of the prevalence and the significant benefit of the product over authorised counterparts.

Regarding the prevalence, the sponsor has provided a calculation that combined incidence data with disease duration to estimate the current prevalence. The sponsor has also performed sensitivity analyses taking into account higher disease durations adjusting the adult onset growth hormone deficiency (GHD) disease duration to 25 years. This results in an overall prevalence estimate of 4.9 per 10,000. The COMP accepted the methodology, but adjusted the prevalence by taking into account a slightly lower incidence in accordance with previous orphan designation applications. The COMP adopted a prevalence estimate of 4.7 per 10,000.

Regarding significant benefit, the sponsor provided further information on the data collected in a clinical trial comparing the proposed long-acting growth hormone product somapactian with a short-acting growth hormone product nortitropin. It was clarified that the treatment with the long-acting growth hormone product was not associated with higher protocol deviations on compliance, and that overall the adherence rates on both treatment arms were comparable and slightly better in the somapacitan arm. Also the presented patient reported outcome (PRO) data collected with the “Treatment Satisfaction Questionnaire for Medication - 9 items” (TSQM-9) were further discussed. The sponsor confirmed that patients receiving somapactian reported on a better convenience compared to patients receiving norditropin. This analysis reached statistical significance. The level of improvement however was difficult to contextualise. Furthermore, there were no observed improvements in the other two domains of TSQM-9, i.e. effectiveness and overall satisfaction. The COMP was of the opinion that the currently limited data-set on patient reported outcomes could potentially translate into a major contribution to patient care. The presented evidence therefore could support the assumption of a significant benefit for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing somapacitan was considered justified based on preliminary clinical data showing insulin like growth factor (IGF-I) response upon treatment.

The condition is life-threatening and chronically debilitating due to the psychosocial impact, the cardiovascular risk, and risk of decreased bone mass and fractures.

The condition was estimated to be affecting approximately 4.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing somapacitan will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that treatment with the proposed long-acting growth hormone product was more convenient for patients compared to patients receiving currently authorised growth hormone products. The Committee considered that the reported patient centred outcomes could potentially translate into a major contribution to patient care.

A positive opinion for somapacitan, for treatment of growth hormone deficiency, was adopted by consensus.

2.1.7. Tilorone - EMA/OD/039/18

Professor Marjukka Myllärniemi; Treatment of idiopathic pulmonary fibrosis

COMP rapporteur: Eva Malikova

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

- Significant benefit

In order to justify the significant benefit the sponsor was invited to further discuss the indirect comparison with pirfenidone and nintedanib, taking into account the different methodologies of these studies, and the difficulties of comparing the silica with the bleomycin model.

The sponsor was also invited to further justify the assumption of major contribution to patient care based on the formulation for inhalation, since no data is available with this formulation in humans.

In the written response, and during an oral explanation before the Committee on 18 July 2018 the sponsor further discussed the indirect comparison of proposed product and authorised product in the bleomycin model and the silica- induced models to support the assumption of significant benefit. Both silica models and bleomycin models are considered valid models of lung fibrosis. Based on the arguments presented by the sponsor the COMP accepted the indirect comparison between silica model studies of tilorone and bleomycin model studies of other compounds. While the data presented by the sponsor do not show better efficacy of tilorone as compared to pirfenidone and nintedanib, a similar level of efficacy can be established.

Regarding potential advantages of the formulation for inhalation, including the assumption of better safety linked to lower systemic absorption, the sponsor discussed data just published from another group (Usmani et al, 2018) showing peripheral distribution of Tc-labeled small (1,5 µm) sized particles in fibrotic lungs. This provides the first evidence in humans that administration via inhalation of particle of respirable size may be efficacious in IPF, which is a disease of the lung interstititium, where traditionally tissue penetration of drugs by inhalation was considered poor. The particles of the formulation developed by the sponsor fall within the lower half of the respirable range and therefore the assumption that they will penetrate in the peripheral lung is supported. The potential availability of a medicinal product with anti-fibrotic activity via inhalation route, therefore with lower systemic absorption, may constitute a clinically relevant advantage in view of the very frequent adverse events (nausea, diarrhea, phototoxicity and rash in up to 90% of the patients in some trials) of the currently authorised products, both given by oral route. The COMP expressed a positive opinion on the orphan designation.

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

The intention to treat the condition with the medicinal product containing tilorone was considered justified based on non-clinical data showing reduction of fibrosis in valid models of the condition.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung ventilator function, heavily limiting exercise capability and decreasing quality of life and leading in many cases within months or a few years to the need of oxygen therapy. Pulmonary hypertension usually develops. Median survival is less than five years.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tilorone will be of significant benefit to those affected by the condition. The sponsor has provided non clinical data showing that the product has comparable efficacy to the currently authorised products for the treatment of the condition. In addition it can significantly reduce fibrosis when given by inhalation. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

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

2.1.8. - EMA/OD/057/18

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 28 June 2018, prior to responding to the list of issues.

2.1.9. Recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 - EMA/OD/044/18

Omeros London Limited; Treatment in haematopoietic stem cell transplantation

COMP rapporteur: Karri Penttila

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

- Proposed condition

The COMP has noted that the scope of the application pertains to a complication of haematopoietic stem cell transplantation (HSCT) (Cho *et al*. Transplantation 2010;90(8):918-926, Jodele *et al*, Blood, 124 2014: 645-65). The sponsor is requested to elaborate on the demarcation of the proposed condition as a distinct medical entity for the purpose of the orphan medicinal product designation.

A discussion of the distinct etiologic, histological, clinical characteristics that would differentiate the condition from non-HSCT associated thrombotic microangiopathies, is also expected. Consensus diagnostic criteria and classification systems should be discussed.

In the written response, the sponsor made the following two points as differentiating qualities of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HCT-TMA): (a) the target condition has a distinct pathogenesis, focusing on endothelial injury from immunosuppression, induction chemotherapy, graft-versus host disease and infection; and (b) the involvement is mainly limited or focused to the kidney, its duration is longer than other TMAs, and the relative frequency of genetic mutations in HCT-TMA is different than in other thrombotic micro-angiopathies. The COMP considered that the proposed differences are not qualitatively distinct and that the features are ultimately dependent on the underlying procedure of HSCT. Therefore the proposed indication was considered amendable to the “treatment in HSCT”, which is a treatment modality that has exceptionally been subject of orphan designation procedures and the oral explanation was cancelled.

Given the change in the indication, significant benefit would need to be justified. The COMP acknowledged that the comparison performed by the applicant versus literature studies captures the conventional management of HCT-TA affected patients. Therefore, the sponsor had provided clinical data that the product improves survival of patients affected by this complication of HSCT versus existing treatments. This was considered to constitute a clinically relevant advantage.

Following review of the application by the Committee, it was agreed to rename the indication to treatment in haematopoietic stem cell transplantation.

The Committee agreed that the condition, haematopoietic stem cell transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 was considered justified based on improved survival in treated patients with haematopoietic stem cell transplantation-associated thrombotic microangiopathy, compared to historical controls.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease and haematopoietic stem cell transplantation-associated thrombotic microangiopathy.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improved survival in treated patients with haematopoietic stem cell transplantation-associated thrombotic microangiopathy, compared to historical controls. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.10. - EMA/OD/063/18

Treatment of ovarian cancer

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 ovarian cancer, the sponsor should further elaborate on the presented preliminary clinical results and justify that the effect shown in ovarian cancer patients can be attributed to the product.

- Number of people affected

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

The prevalence discussion could benefit from a justification on the choice of the epidemiological index (e.g. complete prevalence/ 10 year partial prevalence/ 5 year partial prevalence) and duration of the condition, consideration of more sources for the final prevalence estimate (e.g. RARECARE), as well as discussion on survival and incidence trends overtime.

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to provide a concise structured data driven comparative discussion of the product against the authorised and indicated for the same targeted patient population counterparts.

In the written response, and during an oral explanation before the Committee 18 July 2018, the sponsor provided an updated estimate of the prevalence of the condition (4.5 per 10,000), which was accepted by the Committee. The applicant also elaborated on the results of the clinical study and expanded on the arguments made to support the significant benefit of the product over authorised counterparts. The sponsor, however, failed to provide an adequately substantiated, structured, data-driven comparative discussion of the product against the authorised and indicated for the same targeted patient population counterparts. As a result, the COMP could not substantiate the claim of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 July 2018, prior to final opinion.

2.1.11. (3R,3aS,9R,9aS,9bS)-3-((dimethylamino)methyl)-9-hydroxy-6,9-dimethyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one fumarate - EMA/OD/060/18

IQVIA RDS Ireland Limited; Treatment of glioma

COMP rapporteur: Dinko Vitezic

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 the treatment of glioma, the sponsor should further elaborate on:

- the relevance of the non-clinical model used for the treatment of glioma, and the interpretation of the results obtained in the experiments,
- the relevance of the findings in the preliminary clinical data submitted by the sponsor to support the potential efficacy of the product in the condition.

- Significant benefit

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

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

The sponsor should further elaborate on the relevance of the results of the preliminary clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor provided further elaboration on the non-clinical evidence to support the potential efficacy of the active substance in glioma with data from studies in two well-established models of glioblastoma (C6 and U87-GL xenografts). Tumour growth was measured in both models, and survival was recorded in the C6 Wistar rat model.

The sponsor also highlighted preliminary clinical data from patients with progressive disease, who were non-responders to temozolomide (TMZ) without expectation of response to any available therapies. The majority of patients achieved stable disease after one cycle with the proposed product. The COMP accepted data to support the basis of medical plausibility for the purpose of orphan designation. Furthermore, the COMP considered that the preliminary clinical data showing an acceptable response in patients who were non-responders to TMZ supported significant benefit on the basis of a clinically relevant advantage. The oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing (3R,3aS,9R,9aS,9bS)-3-((dimethylamino)methyl)-9-hydroxy-6,9-dimethyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one fumarate was considered justified based on preliminary clinical data showing improvement in response in relapsed or refractory patients.

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

The condition was estimated to be affecting approximately 2.7 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 (3R,3aS,9R,9aS,9bS)-3-((dimethylamino)methyl)-9-hydroxy-6,9-dimethyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one fumarate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improved response in patients with relapsed or refractory glioma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (3R,3aS,9R,9aS,9bS)-3-((dimethylamino)methyl)-9-hydroxy-6,9-dimethyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one fumarate, for treatment of glioma, was adopted by consensus.

2.1.12. - EMA/OD/066/18

Treatment of heregulin-positive non-small cell lung cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 29 June 2018, prior to responding to the list of issues.

2.1.13. - EMA/OD/037/18

Treatment of idiopathic pulmonary fibrosis

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

- Significant benefit

In order to justify the significant benefit the sponsor was invited to provide further details on the additive effect between the proposed product and pirfenidone in the bleomycin model study and provide a discussion on the clinical relevance of this finding.
Comparative data on the reduction of mRNA of profibrotic markers versus pirfenidone and nintedanib should also be presented.

In the written response, and during an oral explanation before the Committee on 18 July 2018, the sponsor further discussed the data on collagen expression with the proposed product alone or in combination with pirfenidone and nintedanib. It was noted that there was a modest additive effect when added to pirfenidone but not to nintedanib. This result on its own would not be sufficient to support the significant benefit due to the small effect size. Of note, nintedanib seemed to have a more pronounced effect than the proposed product. The applicant also described more in detail the results of the messenger RNA (mRNA) expression of fibrotic (collagen) and pro-fibrotic (connective tissue growth factor [CTGF] and interleukin-6 [IL-6]) markers in lungs. The addition of the proposed product to pirfenidone or nintedanib increased the reduction of collagen and IL-6 mRNA however to an extent the clinical translation of which is not clear.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 July 2018, prior to final opinion.

2.1.14. Copanlisib - EMA/OD/071/18

Bayer AG; Treatment of marginal zone lymphoma

COMP rapporteur: Karri Penttila

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

- Number of people affected

The sponsor appears to have provided an over calculation of the prevalence of the condition in Europe. The sponsor has used limited bibliographical sources to establish the prevalence.

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

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

In the written response, the sponsor presented an updated prevalence calculation resulting in 0.5 in 10,000. The COMP considered that the revised prevalence calculation was adequate to recommend granting of the orphan designation.

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

The intention to treat the condition with the medicinal product containing copanlisib was considered justified based on preliminary clinical data showing improved outcomes in patients with relapsed or refractory marginal zone lymphoma.

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 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 copanlisib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improvement in outcomes in patients with relapsed or refractory disease. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.15. - EMA/OD/070/18

Treatment of pulmonary arterial hypertension

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 27 June 2018, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. 1-(3-Methylbutanoyl)-L-aspartyl-L-threonyl-L-histidyl-L-phenylalanyl-L-prolyl-(L-cystinyl-L-isoleucyl-[(N6-(S)-4-carboxy-4-palmitamidobutanoyl)-L-lysinyl]-L-phenylalanyl-L-glutamyl-L-prolyl-L-arginyl-L-serinyl-L-lysinyl-L-glycinyl-L-cystinyl)-L-lysinamide, disulfide, Acetate - EMA/OD/099/18

IQVIA RDS Ireland Limited; Treatment of beta thalassaemia intermedia and major

COMP rapporteur: Armando Magrelli

The Committee agreed that the condition, beta-thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1-(3-methylbutanoyl)-L-aspartyl-L-threonyl-L-histidyl-L-phenylalanyl-L-prolyl-(L-cystinyl-L-isoleucyl-[(N6-(S)-4-carboxy-4-palmitamidobutanoyl)-L-lysinyl]-L-phenylalanyl-L-glutamyl-L-prolyl-L-arginyl-L-serinyl-L-lysinyl-L-glycinyl-L-cystinyl)-L-lysinamide, disulfide, acetate was considered justified based on non-clinical data showing improvement in anaemia and reduction in iron concentration in spleen and liver.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 1-(3-methylbutanoyl)-L-aspartyl-L-threonyl-L-histidyl-L-phenylalanyl-L-prolyl-(L-cystinyl-L-isoleucyl-[(N6-(S)-4-carboxy-4-palmitamidobutanoyl)-L-lysinyl]-L-phenylalanyl-L-glutamyl-L-prolyl-L-arginyl-L-serinyl-L-lysinyl-L-glycinyl-L-cystinyl)-L-lysinamide, disulfide, acetate will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that the treatment with the proposed product was able to improve ineffective erythropoiesis and chronic anaemia. These effects were not observed when testing currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-(3-methylbutanoyl)-L-aspartyl-L-threonyl-L-histidyl-L-phenylalanyl-L-prolyl-(L-cystinyl-L-isoleucyl-[(N6-(S)-4-carboxy-4-palmitamidobutanoyl)-L-lysinyl]-L-phenylalanyl-L-glutamyl-L-prolyl-L-arginyl-L-serinyl-L-lysinyl-L-glycinyl-L-cystinyl)-L-lysinamide, disulfide, acetate, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.2. (S)-(−)-3-(4-aminophenyl)-2-methoxypropanoic acid - EMA/OD/075/18

Nogra Pharma Limited; Treatment of idiopathic pulmonary fibrosis

COMP rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing (S)-(−)-3-(4-aminophenyl)-2-methoxypropanoic acid was considered justified based on non-clinical data showing reduction of fibrosis and improved survival in valid models of the condition.

The condition is chronically debilitating due to progressive dyspnoea and loss of lung ventilator function, heavily limiting exercise capability and decreased quality of life of the affected patients and leading in many cases within months or a few years to the need of oxygen therapy. Pulmonary hypertension usually develops. Median survival is less than five years. Death ultimately occurs due to respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-(−)-3-(4-aminophenyl)-2-methoxypropanoic acid will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing better survival when compared to pirfenidone and greater reduction of fibrosis as compared with nintedanib, the two medicinal products currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (S)-(−)-3-(4-aminophenyl)-2-methoxypropanoic acid, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.3. Acetylleucine - EMA/OD/095/18

IntraBio Ltd; Treatment of spinocerebellar ataxia

COMP rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on preliminary clinical data suggesting improvements in patients on relevant disease-specific clinical assessment scales.

The condition is chronically debilitating due to slowly progressive incoordination of gait which is often associated with poor coordination of hands, speech, and eye movements.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for acetylleucine, for treatment of spinocerebellar ataxia, was adopted by consensus.

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

2.2.4. Autologous glioma tumour cells treated with antisense molecule directed against the insulin-like growth factor type 1 receptor - EMA/OD/049/18

Pharma Gateway AB; Treatment of glioma

COMP rapporteur: Dinko Vitezic

Following review of the application by the Committee, it was agreed to rename the active substance to autologous glioma tumour cells treated with antisense molecule directed against the insulin-like growth factor type 1 receptor.

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

The intention to treat the condition with the medicinal product containing autologous glioma tumour cells treated antisense molecule directed against the insulin-like growth factor type 1 receptor was considered justified based on preliminary clinical data in patients with the condition showing improvements in progression free survival and overall survival.

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

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the

medicinal product containing autologous glioma tumour cells treated with antisense molecule directed against the insulin-like growth factor type 1 receptor will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data where their product was used before the initiation of standard of care in patients with grade IV glioblastoma multiform (GBM). An improvement in overall survival and progression free survival in these patients was reported as compared to patients who only received standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous glioma tumour cells treated with antisense molecule directed against the insulin-like growth factor type 1 receptor, for treatment of glioma, was adopted by consensus.

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

2.2.5. - EMA/OD/079/18

Treatment of mastocytosis

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 September meeting.

2.2.6. Bertilimumab - EMA/OD/098/18

IQVIA RDS Ireland Limited; Treatment of bullous pemphigoid

COMP rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing bertilimumab was considered justified based on preliminary clinical data demonstrating a reduction of skin lesions.

The condition is life-threatening due to treatment induced immunosupression and chronically debilitating due to tense blisters, erythema, urticarial plaques, skin erosions and crusts, severe pruritus and oral lesions.

The condition was estimated to be affecting approximately 2.5 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 bertilimumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that indicate a steroid sparing effect of the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for bertilimumab, for treatment of bullous pemphigoid, was adopted by consensus.

2.2.7. CD34+ haematopoietic stem and progenitor cells with CD3+ T-cells - EMA/OD/088/18

IQVIA RDS Ireland Limited; Treatment in solid organ transplantation

COMP rapporteur: Fernando Méndez Hermida

Following review of the application by the Committee, it was agreed to rename the indication to treatment in solid organ transplantation.

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

The intention to treat the condition with the medicinal product containing CD34+ haematopoietic stem and progenitor cells with CD3+ T-cells was considered justified based on preliminary data in kidney transplant patients who have shown improvement in graft survival.

The condition is chronically debilitating and life-threatening due to complications such as ischemia - reperfusion injury, delayed graft function, and graft rejection.

The population of patients eligible for treatment of the condition was estimated to be approximately 0.7 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 CD34+ haematopoietic stem and progenitor cells with CD3+ T-cells will be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in the use of immunosuppressive therapy in patients who have received a solid organ transplant. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for CD34+ haematopoietic stem and progenitor cells with CD3+ T-cells, for treatment in solid organ transplantation, was adopted by consensus.

2.2.8. - EMA/OD/087/18

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

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 September meeting.

2.2.9. - EMA/OD/090/18

Treatment of Fanconi anemia

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 September meeting.

2.2.10. - EMA/OD/089/18

Treatment of neuronal ceroid lipofuscinosis

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 September meeting.

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

2.2.11. - EMA/OD/094/18

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 September meeting.

2.2.12. - EMA/OD/081/18

Prevention of graft-versus-host 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 September meeting.

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

2.2.13. - EMA/OD/042/18

Treatment of osteosarcoma

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 September meeting.

2.2.14. - EMA/OD/077/18

Treatment of acute radiation 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 September meeting.

2.2.15. - EMA/OD/074/18

Treatment of polycythemia vera

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 September meeting.

2.2.16. Obiltoxaximab - EMA/OD/080/18

SFL Regulatory Services GmbH; Treatment of anthrax

COMP rapporteur: Eva Malikova

Following review of the application by the Committee, it was agreed to broaden the indication to treatment of anthrax.

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

The intention to treat the condition with the medicinal product containing obiltoxaximab was considered justified based on non-clinical data showing increased survival with the proposed product in valid models of the condition.

The condition is life-threatening due to development of pleural effusions, haemorrhagic mediastinitis and haemorrhagic meningitis, linked to a fatality rate of 45% up to 100%.

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.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obiltoxaximab will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing improved survival when the product was used in addition to levofloxacin and ciprofloxacin, currently authorised for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for obiltoxaximab, for treatment of anthrax, was adopted by consensus.

2.2.17. Pemigatinib - EMA/OD/038/18

Incyte Biosciences Distribution B.V.; Treatment of biliary tract cancer

COMP rapporteur: Daniel O'Connor

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

The intention to treat the condition with the medicinal product containing pemigatinib was considered justified based on *in vivo* data in a model of the condition supporting inhibition of tumour growth, and preliminary clinical observations reporting responses in affected patients.

The condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

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.

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 pemigatinib, for treatment of biliary tract cancer, was adopted by consensus.

2.2.18. - EMA/OD/091/18

Treatment of multiple myeloma

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 September meeting.

2.2.19. - EMA/OD/078/18

Treatment of acute liver failure

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 September meeting.

[*Post-meeting note: The COMP adopted the list of issues by written procedure following its 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 coordinators were appointed for twenty applications submitted.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of bronchiolitis obliterans syndrome

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 glioma

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.1.3. -

Treatment of glioma

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.1.4. -

Treatment of glioma

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.1.5. -

Prevention of graft rejection following solid organ transplantation

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.1.6. -

Treatment of transthyretin-mediated amyloidosis

The Committee was briefed on the significant benefit issues in preparation of the September meeting.

3.1.7. -

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.

3.2. Finalised letters

3.2.1. -

Treatment of Fabry disease

The finalised letter was circulated for information.

3.2.2. -

Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

The finalised letter was circulated for information.

3.2.3. -

Treatment of congenital hyperinsulinism

The finalised letter was circulated for information.

3.2.4. -

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

The finalised letter was circulated for information.

3.2.5. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.2.6. -

Treatment of graft-versus-host disease

The finalised letter was circulated for information.

3.2.7. -

Treatment of hairy cell leukaemia

The finalised letter was circulated for information.

3.3. New requests

None

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. Kymriah - tisagenlecleucel – EMEA/H/C/004090

Novartis Europharm Limited;

a) Treatment of diffuse large B-cell lymphoma EMA/OD/087/16, EU/3/16/1745

b) Treatment of B-lymphoblastic leukaemia/lymphoma EMA/OD/187/13, EU/3/14/1266

COMP rapporteurs: Frauke Naumann-Winter / Karri Penttila; CAT rapporteur: Rune Kjeken; CAT co-rapporteur: ;

A list of issues was adopted on 24 May 2018.

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

An opinion recommending not to remove Kymriah, autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19, tisagenlecleucel, from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Yescarta - axicabtagene ciloleucel - EMEA/H/C/004480

Kite Pharma EU B.V.

a) Treatment of primary mediastinal large B-cell lymphoma EMA/OD/078/15, EU/3/15/1553

b) Treatment of follicular lymphoma EMA/OD/135/15, EU/3/15/1579

c) Treatment of diffuse large B cell lymphoma EMA/OD/171/14, EU/3/14/1393

COMP rapporteurs: Karri Penttila / Fernando Méndez Hermida; CAT rapporteur: Jan Mueller-Berghaus; CAT co-rapporteur: Claire Beuneu

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 17 July 2018.

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

An opinion recommending not to remove Yescarta from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.3. Veyvondi - vonicog alfa – EMA/OD/055/10, EU/3/10/814, EMEA/H/C/004454

Baxalta Innovations GmbH; Treatment of von Willebrand disease

A list of issues was adopted on 24 May 2018.

An oral explanation was held on 17 July 2018.

The COMP noted the removal of the orphan designation from the EC Register of Orphan Medicinal Products.

4.1.4. Lenvima - Lenvatinib – Type II variation - EMEA/H/C/003727/II/0011/G, EMA/OD/287/14, EU/3/15/1460

Eisai Ltd; Treatment of hepatocellular carcinoma

CHMP rapporteur: Bart Van der Schueren; CHMP co-rapporteur: Robert James Hemmings

A list of issues was adopted on 31 October 2017.

An oral explanation was held on 17 July 2018.

The COMP noted the removal of the orphan designation from the EC Register of Orphan Medicinal Products.

4.1.5. Cablivi - caplacizumab - EMEA/OD/109/08, EU/3/09/629, EMEA/H/C/004426

Ablynx NV; Treatment of thrombotic thrombocytopenic purpura

Action: For adoption

A list of issues was adopted on 17 July 2018.

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

The orphan maintenance 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. Symkevi - tezacaftor / ivacaftor – EMEA/H/C/004682, EMA/OD/156/16, EU/3/17/1828

Vertex Pharmaceuticals (Europe) Ltd.; Treatment of cystic fibrosis

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 17 July 2018.

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

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

4.2.2. Apealea – paclitaxel - EMEA/OD/061/06, EU/3/06/422, EMEA/H/C/004154

Oasmia Pharmaceutical AB; Treatment of ovarian cancer

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 19 July 2018.

The COMP noted the removal of the orphan designation from the EC Register of Orphan Medicinal Products.

4.2.3. Onpattro - patisiran – EMEA/H/C/004699, EMA/OD/142/10, EU/3/11/857

Alnylam UK Limited; Treatment of familial amyloid polyneuropathy

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 19 July 2018.

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

An opinion recommending not to remove Onpattro from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.4. Luxturna - voretigene neparvovec - EMEA/H/C/004451

Spark Therapeutics Ireland Ltd

a) Treatment of retinitis pigmentosa EMA/OD/040/15, EU/3/15/1518

b) Treatment of Leber's congenital amaurosis EMA/OD/150/11, EU/3/12/981

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 September meeting.

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

4.2.5. - lanadelumab – EMEA/H/C/004806, EMA/OD/075/15, EU/3/15/1551

Shire Pharmaceuticals Ireland Limited; Treatment of hereditary angioedema

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP rapporteurs were appointed for one application.

4.5. Orphan Maintenance Reports

Documents were circulated in MMD.

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. Kalydeco – Ivacaftor - Type II variation - EMEA/H/C/002494/II/0063/G, EMEA/OD/010/08, EU/3/08/556

Vertex Pharmaceuticals; Treatment of cystic fibrosis

CHMP rapporteur: Concepcion Prieto Yerro

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 17 July 2018.

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

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

5.2.2. Darzalex - Daratumumab – Type II variation - EMEA/H/C/004077/II/0011, EMA/OD/038/13, EU/3/13/1153

Janssen-Cilag International N.V.; Treatment of plasma cell myeloma

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

A list of issues was adopted on 21 June 2018.

An oral explanation was held on 18 July 2018.

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

An opinion recommending not to remove Darzalex from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

5.2.3. Blincyto - blinatumomab - Type II variation – EMEA/OD/029/09, EU/3/09/650, EMEA/H/C/003731/II/0011

Amgen Europe BV - The Netherlands; Treatment of acute lymphoblastic leukaemia

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

The COMP noted status of the procedure at the CHMP.

5.2.4. Rubraca - rucaparib - Type II variation – EMEA/H/C/004272/II/0001, EMA/OD/085/12, EU/3/12/1049

Clovis Oncology UK Limited; Treatment of ovarian cancer

CHMP rapporteur: Jorge Camarero Jiménez

The COMP noted status of the procedure at the CHMP.

5.2.5. Ravicti - glycerol phenylbutyrate - Type II variation – EMEA/H/C/003822/II/0019

Horizon Pharma Ireland Limited;

a) Treatment of ornithine carbamoyltransferase deficiency EMA/OD/002/10, EU/3/10/734

b) Treatment of citrullinaemia type 1 EMA/OD/003/10, EU/3/10/735

c) Treatment of argininosuccinic aciduria EMA/OD/004/10, EU/3/10/736

d) Treatment of hyperargininaemia EMA/OD/005/10, EU/3/10/737

e) Treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) EMA/OD/006/10, EU/3/10/738

f) Treatment of carbamoyl-phosphate synthase-1 deficiency EMEA/OD/124/09, EU/3/10/733

CHMP rapporteur: Greg Markey

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is not needed.

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings, 23-24 October 2018, Vienna, Austria

Action: For information

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 17 July 2018

7.1.3. Election of COMP Chairperson

Action: For information

The Committee was informed on the election process of COMP Chairperson. Election will take place at the September COMP plenary meeting.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes June 2018

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. The 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 2018

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2018 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

Document was circulated in MMD.

Document tabled:
Q2/2018 Update of the Business Pipeline report for the human scientific committees

8.2. EMA relocation to Amsterdam, the Netherlands - update

Update on EMA relocation to Amsterdam was given.

Document tabled:
Presentation

8.3. EMA-EUnetHTA bilateral

Scope: Significant Benefit (SB) and Relative Effectiveness Assessment (REA) for Orphan Medicinal Products (OMP)

EMA gave update on progress made so far.

Document tabled:
ppt EMA-EUnetHTA bilateral 5 July 2018

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 July 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	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 restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No participation in final deliberations and voting on:	Lenvima - Lenvatinib – Type II variation - EMEA/H/C/003727/II/0011/G, EMA/OD/287/14, EU/3/15/1460; Eisai Ltd; Treatment of hepatocellular carcinoma
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	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	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	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Nicolas Giraud	Patient expert - in person*		No restrictions applicable to this	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			meeting	
Mario Ricciardi	Patient expert - via telephone*		No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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/