7 November 2018
EMA/COMP/701293/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 9-11 October 2018

Chair: Violeta Stoyanova-Beninska

09 October 2018, 08:30-20:15, room 02-F

10 October 2018, 08:30-20:45, room 02-F

11 October 2018, 08:30-18:00, room 02-F

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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

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 and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for COMP agenda for 9-11 October 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 11-13 September 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/086/18

Treatment of hepatocellular carcinoma

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

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

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

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor discussed relevant non-clinical or clinical data to support a significant benefit vs sorafenib and reginaferib. Two additional products, lenvatinib and cabozantinib, recently approved by CHMP were also identified. The COMP discussed the potential for significant benefit based on a clinically relevant advantage in patient population targeted by the proposed product as well as sorafenib and reginaferib, and now also includes lenvatinib and cabozantinib. The sponsor could not provide further data in this patient population to show the significant benefit over all four products currently authorised. The COMP therefore could not recommend granting the orphan designation for this product at this point in time.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.2. - EMA/OD/085/18

Treatment of hepatocellular carcinoma

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

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

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

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor discussed relevant non-clinical or clinical data to support a significant benefit vs sorafenib and reginaferib. Two additional products, lenvatinib and cabozantinib, recently approved by CHMP were also identified. The COMP discussed the potential for significant benefit based on a clinically relevant advantage in patient population targeted by the proposed product as well as sorafenib and reginaferib, and now also includes lenvatinib and cabozantinib. The sponsor could not provide further data in this patient population to show the significant benefit over all four products currently authorised. The COMP therefore could not recommend granting the orphan designation for this product at this point in time.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.3. Anetumab ravtansine - EMA/OD/258/17

Bayer AG; Treatment of ovarian cancer

COMP coordinator: Tim Leest

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 sponsor should provide a 5-year prevalence estimate taking into consideration the updated incidence figure from ECIS 2018.

- Significant benefit

The sponsor is requested to provide a data-driven discussion of significant benefit over authorised products in R/R platinum resistant patients other than pegylated liposomal doxorubicin (PLD), including bevacizumab.

In the written response, the sponsor provided additional indirect comparisons to support a significant benefit on the grounds of clinically relevant advantage. The presented indirect comparisons were based on the published overall response rate data from authorised products and the preliminary clinical data that has been collected for the proposed product in combination with pegylated liposomal doxorubicin. The indirect comparisons of efficacy data suggest that the proposed product could lead to improved overall response rates in subjects with mesothelin-expressing platinum-resistant recurrent ovarian, fallopian tube, or primary peritoneal cancer. The COMP considered that this is sufficient evidence to support significant benefit for the purpose of orphan designation. The oral explanation was cancelled. The COMP recommends to seek protocol assistance and to discuss the demonstration of significant benefit via a significant benefit question addressed to the COMP.

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

The intention to treat the condition with the medicinal product containing anetumab ravtansine was considered justified based on preliminary clinical data demonstrating responses in patients affected by the condition.

The condition is chronically debilitating due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing anetumab ravtansine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in patients affected by the condition. Indirect comparisons show that the observed response rate compares favourably to published data from currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for anetumab ravtansine, for treatment of ovarian cancer, was adopted by consensus.

2.1.4. Autologous human adipose perivascular stromal cells genetically modified to secrete soluble tumor necrosis factor-related apoptosis-inducing ligand - EMA/OD/110/18

Rigenerand S.r.l.; Treatment of pancreatic cancer

COMP coordinator: Brigitte Bloechl-Daum

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

- Significant benefit

The sponsor was requested to discuss the envisaged clinical positioning of the proposed product and provide adequate arguments for significant benefit in line with current treatment guidelines.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor explained that the future clinical positioning of the proposed product will be in patients affected by locally advanced non-metastatic pancreatic cancer in combination with currently authorised products gemcitabine and Nab-paclitaxel. In addition, the sponsor provided the results of non-clinical studies that have tested the proposed product either on top of gemcitabine or Nab-paclitaxel. The data suggests that the proposed product had a small but statistically significant add-on effect on top of those two authorised treatments. The COMP considered that this is sufficient evidence to support significant benefit for the purpose of orphan designation. The COMP recommends to seek protocol assistance and to discuss the demonstration of significant benefit via a significant benefit question addressed to the COMP.

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

The intention to treat the condition with the medicinal product containing autologous human adipose perivascular stromal cells genetically modified to secrete soluble tumour necrosis factor-related apoptosis-inducing ligand was considered justified based on non-clinical data from valid models suggesting that treatment impairs tumour growth.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival of about 6 months.

The condition was estimated to be affecting approximately 2.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous human adipose perivascular stromal cells genetically modified to secrete soluble tumour necrosis factor-related apoptosis-inducing ligand will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data from valid models suggesting that treatment impairs tumour growth. Treatment in combination with currently authorised products led to better efficacy

when compared to efficacy of authorised products in monotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous human adipose perivascular stromal cells genetically modified to secrete soluble tumour necrosis factor-related apoptosis-inducing ligand, for treatment of pancreatic cancer, was adopted by majority (22 out of 26 votes).

The divergent positions (*Brigitte Blöchl-Daum; Armando Magrelli; Frauke Naumann-Winter; Daniel O'Connor; Ingrid Wang)* were appended to this opinion.

2.1.5. Cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L--glutamyl-L-threonyl]acetate - EMA/OD/106/18

Santhera Pharmaceuticals (Deutschland) GmbH; Treatment of cystic fibrosis

COMP coordinator: Eva Malikova

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cystic fibrosis (CF), the sponsor should further elaborate on the relevance of the methodology and results of the non-clinical studies to the intended clinical use of the product, and in particular:

- the rationale for administering the product before the challenges in all models tested, and the translatability to the clinical setting where treatment is started after the CF pathology has been established;

- similarities and differences of airway inflammation between the non-clinical models used in this application and the type of inflammation pathognomonic of CF;

- The translatability of the results from the models of this application, all characterized by acute inflammation apart from the semi-chronic smoke model, to the chronic airways inflammation in CF;

the translatability of the observed results to the disease-relevant endpoints in CF, taking into account the current study of Wagner *et al*, 2016 (PMID: 27456476)

The sponsor was also invited to present any data on inflammatory biomarkers or any other activity marker from the phase I study in CF patients.

- Significant benefit

The sponsor was invited to further discuss potential clinical advantages of the proposed product that could justify a claim of significant benefit over the authorised medicines for the treatment of CF in the EU.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor explained that the use of neutrophil elastase in preventive setting, i.e. before the challenge in the non-clinical models, can be justified by the fact that neutrophil inflammation is a continuous process in cystic fibrosis and therefore the effect in reducing neutrophil infiltration in the lungs can be extrapolated from a preventive to a treatment

setting. The sponsor then discussed the relevance to CF of the non-clinical models used to support the medical plausibility, highlighting the importance of the airways neutrophil component, which was present in the models and is one of the most relevant features of airways inflammation in CF. Finally the sponsor clarified that the results of the non-clinical study and the product's mechanism of action are relevant from the perspective of the pathogenesis of several key features of CF-like lung disease. The COMP accepted the medical plausibility.

The sponsor also discussed the potential significant benefit of the proposed product, based on the anti-inflammatory activity demonstrated in the non-clinical models. As currently no anti-inflammatory treatments are authorized in CF, the COMP concluded that the proposed product may be of potential significant benefit.

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

The intention to treat the condition with the medicinal product containing cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl]acetate was considered justified based on non-clinical data showing reduction of anti-inflammatory mediators and cells in different models of airway inflammation.

The condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-glutamyl-L-threonyl]acetate salt will be of significant benefit to those affected by the condition. The sponsor has provided non clinical and preliminary clinical data showing anti-inflammatory activity of the proposed product. This would allow use in combination with the currently authorized treatments for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl]acetate, for treatment of cystic fibrosis, was adopted by consensus.

2.1.6. Imlifidase - EMA/OD/093/18

Hansa Medical AB; Treatment of anti-glomerular basement membrane disease

COMP coordinator: Dinah Duarte

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 anti-glomerular basement membrane disease, the sponsor should further elaborate on:

- the settings used in the non-clinical model, with the product administered before the onset of the condition.
- the available preliminary clinical data, with regards to the population studied, any concomitant treatments received and the results obtained in detail.

- Number of people affected

The sponsor was invited to elaborate on the duration of the condition, in order to justify the use of yearly incidence, instead of point prevalence for the estimation of the number of affected patients.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the presented non-clinical and clinical studies, in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. A comparative data-driven discussion of the effects of the product versus the effects of cyclophosphamide in the target condition is expected in that regard.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor further elaborated on the *in vivo* model, in which species non-specific product had to be used to elicit effects. The COMP considered that the non-clinical model would not allow for the extrapolation of observations to justify the medical plausibility. Further, clinical effects of the products in patients affected by the condition were also discussed. The COMP considered that the use of concomitant treatments was a limitation to the assessment of the effects that can be attributed to the product. However, the reported effects appeared favourable when compared to effects of standard of care reported in the literature.

With regards to prevalence, the issues of onset/development and duration of the established impairment are conflated. The applicant stated that anti-GBM (anti-glomerular basement membrane) disease evolves very rapidly within months, with an average duration of less than 1 year. The COMP accepted that yearly incidence would suffice for the purpose of orphan designation.

Finally, significant benefit was argued on the basis of the mechanism of action. The COMP considered that a mechanism of action per se would not suffice to justify significant benefit, but that the considerations of the medical plausibility (as described above) would also suffice for assuming a favourable comparison to the standard of care.

The Committee agreed that the condition, anti-glomerular basement membrane disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing imlifidase was considered justified based on preliminary clinical observations supporting improvements in estimated glomerular filtration rate and reductions in serum IgG (immunoglobulin G) levels in affected patients.

The condition is chronically debilitating and life-threatening, in particular because of complications such as glomerulonephritis leading to kidney failure and pulmonary haemorrhage.

The condition was estimated to be affecting approximately 0.02 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 imlifidase will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting improvements in estimated glomerular filtration rate and reductions in serum IgG levels in affected patients, as compared to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for imlifidase, for treatment of anti-glomerular basement membrane disease, was adopted by consensus.

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

2.1.7. Glucagon - EMA/OD/108/18

Pharma Gateway AB; Treatment of noninsulinoma pancreatogenous hypoglycaemia syndrome

COMP coordinator: 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:

- 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 noninsulinoma pancreatogenous hypoglycaemia syndrome, the sponsor was asked to further elaborate on the relevance of the preliminary clinical data used for the treatment of noninsulinoma pancreatogenous hypoglycaemia syndrome, and the interpretation of the results obtained with particular attention to hypoglycaemia, defined by plasma glucose less than 3.3 milimoles per litre.

In the written response, the sponsor provided additional data on patients who were included in the study described by Laguna, Sanz *et al*, 2018 publication. The COMP was of the opinion that this preliminary data was sufficient to support the basis of medical plausibility for the purpose of an orphan designation.

The Committee agreed that the condition, noninsulinoma pancreatogenous hypoglycaemia syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing glucagon was considered justified based on preliminary clinical data showing a reduction or elimination of hypoglycemic episodes.

The condition is life-threatening and chronically debilitating due to the repetitive nature of the associated hypoglycaemia which can be severe leading to neuroglycopenia resulting in

dangerous and life-threatening outcomes, such as seizures, loss of consciousness and brain damage.

The condition was estimated to be affecting approximately 3.7 in 10,000 persons in the European Union, at the time the application was made.

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 glucagon, for treatment of noninsulinoma pancreatogenous hypoglycaemia syndrome, was adopted by consensus.

2.1.8. - EMA/OD/128/18

Treatment of graft-versus-host disease

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of graft-versus-host disease, the sponsor should further elaborate on:

  - the interpretation of the results obtained in the preliminary clinical observations
  - the relevance of the presented corneal injury non-clinical model
  - present any other available outcomes in either relevant non-clinical models or preliminary clinical settings.

- Significant benefit

The arguments on significant benefit are based on the discussion of a retrospective analysis of a cohort of patients affected by the proposed condition.

The sponsor was invited to further elaborate on a) the extent of the effects given the uncontrolled settings of the study, the post-hoc nature of the analyses and the low number of observations b) the effects of the other concomitant treatments on those 12 weeks of treatment and the justification of attribution of effects to the product in question and c) the absence of a comparative discussion for all authorised products including cyclosporine which is authorised for prevention and treatment of the broader indication.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor the applicant elaborated on the non-clinical model discussed in the application. The sponsor noted that the model recapitulates lacrimal dysfunction and infiltration of immune cells into the lacrimal glands, corneal inflammation and loss of goblet cells that are also characteristic features of ocular graft versus host disease. The scarcity of the available non-clinical models was also discussed, and their inapplicability for this product testing e.g. due to the rapid evolution of ulceration. No additional data was presented in the supplementary responses. The COMP did not consider the non-clinical model relevant in the absence of graft-versus-host disease (GVHD) setting.

In addition, the clinical study that had already been presented in the initial application was discussed again. The COMP considered that a detailed discussion of any concomitant

treatments and their effects was missing and this made it difficult to consider the medical plausibility to be justified.

Significant benefit was argued based data from the clinical study in which the addition of the product to topical and systemic immune-suppressive medicines led to an improvement in both symptoms of ocular discomfort and clinical signs. However, detailed discussion of the concomitant therapies (including the timing and changes), as well as the effects of such therapies in the control groups were missing. Therefore the COMP considered that the applicant had not advanced his position and that the comparison versus the available products did not justify a clinically relevant advantage or a major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2018, prior to final opinion.

2.1.9. 3-(3-(3,5-dimethyl-1H-pyrazol-4- yl)propoxy)-4- fluorobenzoic acid - EMA/OD/096/18

Pharma Gateway AB; Treatment of ATTR amyloidosis

COMP coordinator: Dinah Duarte

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

While the authorised products refer to polyneuropathy patients, the applicant has studied the effects of the proposed product in subjects with symptomatic cardiomyopathy. The applicant was invited to comment on the relevance of the endpoints of the ongoing clinical study specifically for this manifestation in the context of ATTR amyloidosis.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor discussed the mechanism of action of the product in the context of the pathophysiology of the condition and focused on the available preliminary clinical observations from the ongoing clinical study in symptomatic cardiomyopathy associated with ATTR amyloidosis (ATTR-CM) patients. In that study clinically relevant improvement were observed in patients with cardiomyopathy. These effects were put into context of other clinical studies in which cardiac worsening was observed. The COMP considered that the preliminary clinical observations in symptomatic ATTR CM patients would support a significant benefit versus the authorised treatments because the latter are currently authorised only for polyneuropathy patients.

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

The intention to treat the condition with the medicinal product containing 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid was considered justified based on preliminary clinical observations in ATTR-cardiomyopathy patients, showing improvements in serum prealbumin.

The condition is life-threatening and chronically debilitating in particular due to the development of polyneuropathy and cardiomyopathy.

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

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 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in ATTR-amyloidosis patients with cardiomyopathy, who responded to treatment with stabilization of transthyretin and increase of serum concentration of transthyretin. The authorised products are indicated for polyneuropathy manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 3-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)-4-fluorobenzoic acid, for treatment of ATTR amyloidosis, was adopted by consensus.

2.1.10. Larotrectinib - EMA/OD/116/18

Bayer AG; Treatment of glioma

COMP coordinator: Brigitte Bloechl-Daum

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

- 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 glioma, the sponsor should further elaborate on:

— the co-existence of neurotrophic tyrosine receptor kinase fusion (NTRK-fusion) positive and negative tumour sites within one patient. The sponsor was asked to explain how often this has been observed and discuss the impact of this in terms of the efficacy of the therapy.

— the currently available preliminary clinical data. The sponsor was asked to present more detailed information on each individual patient, their previous treatments (focus on authorised products), and their outcome. In terms of outcomes, please clarify the significance of a best response of stable disease in the majority of patients.

- Significant benefit

For the demonstration of significant benefit, the sponsor was invited to provide more detailed information on the presented patients, on their previous treatments (authorised products) and their outcome. If patients did not fail currently authorised products, the sponsor was asked to provide indirect comparison versus authorised products to demonstrate significant benefit.

The sponsor was invited to submit any additional non-clinical or preliminary clinical data of relevance for the condition, which could be used for the demonstration of significant benefit.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor stressed the extreme heterogeneity of cancer, which reflects a continuously evolving population of tumour cells. The sponsor reported on the current experience from the clinical development and inferred that the vast majority of tumours

treated had minimal intratumoural heterogeneity. However, a number of patients were identified to have presented with heterogenic tumours.

The sponsor provided more details regarding the glioma patients that have been treated with the product across various protocols. The results demonstrate that the vast majority achieved stable disease as their best outcome after failing best standard of care including authorised products. The COMP discussed that more mature data on progression free survival and overall survival could have been useful to contextualise the clinical relevance of stable disease in a very heterogeneous patient population. Nevertheless, when taking into consideration the totality of evidence, it was considered that a high level of disease control in patients that failed authorised treatments was sufficient evidence to support the assumptions of medical plausibility and significant benefit for the purpose of orphan designation.

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 larotrectinib was considered justified based on preliminary clinical data showing disease control in patients affected by the condition.

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 larotrectinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing disease control in patients affected by the condition, who have failed the current best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for larotrectinib, for treatment of glioma, was adopted by consensus.

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

2.1.11. Larotrectinib - EMA/OD/117/18

Bayer AG; Treatment of papillary thyroid cancer

COMP coordinator: Bożenna Dembowska-Bagińska

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 papillary thyroid cancer, the sponsor should further elaborate on

- the co-existence of neurotrophic tyrosine receptor kinase fusion (NTRK-fusion) positive and negative tumour sites within one patient. The sponsor was asked to explain how often this has been observed and discuss the impact of this in terms of the efficacy of the therapy.
- the currently available preliminary clinical data. The sponsor was asked to clarify the significance of a best response of stable disease in the majority of patients and the duration of responses. The sponsor was also asked to discuss the relevance of data in patients without measurable disease at time of enrolment.

- Significant benefit

For the demonstration of significant benefit, the sponsor iwas invited to provide more detailed information on the presented patients, on their previous treatments (authorised products) and their outcome. In this context, the sponsor was asked to clarify the reason for discontinuation of the previous treatments. If patients did not fail currently authorised products, the sponsor was asked to provide indirect comparison versus authorised products to demonstrate significant benefit.

The sponsor was invited to submit any additional non-clinical or preliminary clinical data of relevance for the condition, which could be used for the demonstration of significant benefit.

In the written response, and during an oral explanation before the Committee on 9 October 2018, the sponsor acknowledged that cancer can be extremely heterogeneous in nature within any given patient, reflecting a continuously evolving population of tumour cells. The sponsor reported on its current experience form the clinical development and infers that the vast majority of tumours treated had minimal intratumoural heterogeneity. However, a number of patients were identified to have presented with heterogenic tumours.

The sponsor provided updated results (new data cut-off) and more details regarding the papillary thyroid cancer patients that have been treated with the product across various protocols. In general, enrolled patients failed best standard of care. The preliminary results demonstrated that the vast majority of patients achieved partial or complete responses as their best outcome. When taking into consideration the totality of evidence, the COMP considered that there was sufficient evidence to support the assumptions of medical plausibility and significant benefit for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing larotrectinib was considered justified based on preliminary clinical data showing that patients respond to treatment.

The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment and in case of development of metastasis with wide spread of the tumour.

The condition was estimated to be affecting approximately 3.3 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 larotrectinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients, who have failed the current best standard of care including authorised products, respond to treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for larotrectinib, for treatment of papillary thyroid cancer, was adopted by consensus.

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

2.1.12. - EMA/OD/118/18

Treatment of anaplastic thyroid 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 anaplastic thyroid cancer, the sponsor should further elaborate on:

- the co-existence of neurotrophic tyrosine receptor kinase fusion (NTRK-fusion) positive and negative tumour sites within one patient. Please explain how often this has been observed and discuss the impact of this in terms of the efficacy of the therapy.
- the currently available preliminary clinical data. Please make sure to present all available evidence from the clinical studies.

- Significant benefit

For the demonstration of significant benefit, the sponsor was invited to provide more detailed information on the presented patients, on their previous treatments (authorised products) and their outcome. If patients did not fail currently authorised products (i.e. doxorubicin), please provide indirect comparison versus authorised products to demonstrate significant benefit.

The sponsor was invited to submit any additional non-clinical or preliminary clinical data of relevance for the condition, which could be used for the demonstration of significant benefit.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor provided updated results and more details regarding a very limited number of anaplastic thyroid cancer patients that have been treated with the proposed product across various protocols. The outcomes showed a response in 50% of patients. While the patients have failed previous treatments, none of these patients received the currently authorised product doxorubicin. When taking into consideration the totality of evidence, the COMP considered that there was not yet sufficient evidence to support the

assumptions of medical plausibility and significant benefit for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.13. - EMA/OD/111/18

Treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukemic/disseminated)

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

Medical plausibility is mainly argued on the basis of clinical observations in anaplastic large cell lymphoma (ALCL) patients, an indication for which the product is already marketed. The applicant was invited to provide any further available data in other peripheral T cell lymphomas, in either non-clinical models or in affected patients. In case of an amended indication, data in that specific setting will be expected to justify medical plausibility.

- Prevalence

In case of an amended indication, the sponsor was invited to provide a revised estimate for the number of patients affected by that condition.

- Significant Benefit

The applicant was requested to further elaborate on the issue of significant benefit by providing a data-driven comparative discussion versus all authorised products, including Adcetris in peripheral T-cell lymphoma settings. Available data in non-ALCL settings would be helpful in that regard.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor acknowledged that their product has a Market Authorisation for a subtype of the proposed indication however they provided an argument for the compatibility of the proposed indication based on the “spirit” of the Orphan regulation. Since this interpretation rests outside of the scientific scope of evaluation, the broad peripheral T-cell lymphoma condition would be difficult to accommodate and the indication needs to be revised. In evaluation of the submitted responses it was the scientific opinion of the COMP that the sought indication included a subset for which the sponsor already had an orphan designation and a marketing authorisation, and that the proposed condition was not acceptable for the same product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.14. - EMA/OD/122/18

Treatment of transplant-associated thrombotic microangiopathy following Haematopoietic Stem Cell Transplantation

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

- Condition

The proposed condition is widely discussed in the literature as a complication of haematopoietic stem cell transplantation (HSCT) (e.g. Cho *et al*. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic haematopoietic stem-cell transplantation. Transplantation 2010;90(8):918-926, Jodele *et al*, Refined diagnostic and risk criteria for HSCT-associated thrombotic micro-angiopathy: a prospective study in children and young adults Blood, 124 (2014), pp. 645-65).

The committee considered that the proposed complication cannot be considered separately of the treatment modality of HSCT, and as such the indication of "treatment in haematopoietic stem cell transplantation"(emphasis added) should be the subject of this application.

- Intention to diagnose, prevent or treat

Notwithstanding of the indication issue as described above, in order to establish correctly if there exists a scientific rationale for the development of the proposed product the sponsor should further elaborate on the cited clinical studies, in particular with regards to the effects of concomitant treatments, and duration of the responses observed.

- Significant benefit

The sponsor was requested to provide a comparative discussion of the proposed treatment versus the standard of care, taking into consideration the available treatments used in HSCT. It is also noted that the proposed product already has a market authorisation in HSCT, as it is indicated "for the treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) in haematopoietic stem cell transplantation (HSCT) therapy".

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor accepted the proposed amendment of the indication. It was stated that there is no agreement regarding the standard of care for transplantation associated microangiopathy, and as such, the effects of concomitant treatments are unknown. With regards to the issue of duration of the effects observed, it was further stated that no patient level data existed that could provide insight on the duration of responses. Therefore, the medical plausibility was not established if it is not clear whether and to what extent the reported effects may be attributed to treatments other than the proposed product.

The sponsor discussed also the different classes of treatments used in HSCT, but did not provide a comparison of their effects the proposed product. A table was provided reporting the efficacy of the product in various thrombotic microangiopathies. A favourable safety profile was also alluded to in particular with regards to nephrotoxicity. However, a comparative discussion based on data versus the authorised counterparts was not presented. Therefore the COMP considered that the medical plausibility and significant benefit issues could not be established.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 October 2018, prior to final opinion.

2.1.15. - EMA/OD/129/18

Prevention of graft versus host disease

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

- 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 was requested to provide data to support the argumentation for improved efficacy and provide a comparative discussion over all authorised products.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor provided further argumentation in support of significant benefit. Significant benefit over currently authorised anti-thymocyte globulin was argued on the grounds of improved safety. Even though no clinical data with the proposed product have been generated in the proposed orphan indication, it was claimed that the safety profile of the proposed compound is well-known due to a large safety-database in other indications. No significant benefit argumentation was provided regarding cyclosporin. The sponsor hypothesised that there could be an add-on effect, however it was acknowledged that there currently is no data to support this hypothesis. When taking into consideration the totality of evidence, the COMP considered that there was not yet sufficient evidence to support the assumptions of significant benefit for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.16. - EMA/OD/084/18

Prevention of bronchopulmonary dysplasia

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 prevention of Bronchopulmonary dysplasia, the sponsor should further elaborate on:

1) the preeclampsia and chorioamnionitis models and in particular the relevance of these full-term models to the target condition bronchopulmonary dysplasia;

The sponsor was also invited to present and discuss in detail any additional data from these studies that may support the medical plausibility in bronchopulmonary dysplasia.

2) the relevance of non-clinical endpoints measured to the clinical manifestations and clinical course of bronchopulmonary dysplasia;

The sponsor was also invited to discuss to which non-clinical study they refer when citing the paper from Albertine, 2015, as this paper does not seem to contain the data reported by the sponsor in this application.

3) The results from the clinical study in retinopathy of prematurity and their relevance for the treatment of bronchopulmonary dysplasia (BPD). This should also include a discussion on the background therapy and safety signals identified in the study, including higher incidence of necrotizing enterocolitis (NEC) and higher mortality in the treated arm.

4) The sponsor is asked to present all the data in a graphical form with the statistics included, as such presentation was omitted in the initial application and is needed for proper data evaluation.

- Number of people affected

The sponsor should provide a prevalence estimate as number of persons in 10,000 in the EU.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor provided more detailed information than in the initial application, as well as graphic representations of the results. The sponsor discussed all used non-clinical models and their relevance for the prevention of bronchopulmonary dysplasia. The COMP questioned the applicant on the lack of lung functional data in the model deemed most relevant and the sponsor reported that it is possible that lung function data have been measured, but those data were not available at the moment. The sponsor also reported increased alveolar formation and capillary surface density in that model. It was considered that this is difficult to establish from the histology figure provided by the applicant. Thus the results of the study were considered encouraging but overall non conclusive.

The COMP then questioned the sponsor's clinical data, in particular in relation to the adverse events reported in the study, including a number of deaths, especially in the treated group. The sponsor explained that the severity of the condition improved in the treatment arm as compared to the placebo but overall differences between study arm sizes were so significant that the comparison of effects was difficult to make. Overall, the COMP concluded that it was not possible to reach a clear conclusion on the clinical benefit of the product on BPD from this study.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

2.1.17. Humanized IgG1 monoclonal antibody against GD2 - EMA/OD/126/18

Y-mAbs Therapeutics A/S; Treatment of neuroblastoma

COMP coordinator: Brigitte Bloechl-Daum

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

- Significant benefit

For the establishment of significant benefit the sponsor was requested to further elaborate on:

- the rationale as to why improved efficacy with the proposed product could be expected in light of the same mechanism of action as dinutuximab beta
- the provided crude indirect comparisons regarding dinutuximab beta from the SmPC. The sponsor was asked to provide the baseline characteristics of the compared patient populations in order to justify the validity of the indirect comparison. Furthermore, the sponsor was asked to provide indirect comparisons for the individual trials of dinutuximab beta in R/R patients (see studies Study APN311-202 and APN311-303 in Qarziba EPAR).

- if there were patients enrolled, who failed Qarziba treatment, but responded to the proposed product.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor provided more details on the preliminary clinical data that has been generated with the proposed product and the crude indirect comparison with data that was generated with the currently authorised product Qarziba. The COMP considered that at this point in time, the provided indirect comparisons could not establish a significant benefit claim of improved efficacy due to the low patient numbers and due to potential differences in studied patient populations. In the absence of a clinically relevant advantage, the sponsor also attempted to claim a major contribution to patient care. The currently authorised product Qarziba is administered in combination with IL-2 (interleukin-2), which can be associated with adverse reactions. Furthermore, the posology of Qarziba outlines IV administration for 10 days consecutively, or for five daily 8 hour long infusions. The proposed product was able to achieve clinical responses with three 30 min IV (intravenous) infusions of high doses every second day. This could be considered as a more convenient administration, which might allow for a higher degree of out-patient therapy. The COMP considered that the provided evidence is sufficient to support the assumption for a major contribution to patient care for the purpose of orphan designation. The assumption of significant benefit will have to be confirmed at the time of marketing authorisation when the justification should include a quantitative element that allows the COMP to measure magnitude of effect as compared with the already authorised product(s). A strong recommendation is given to seek EMA protocol assistance and discuss the demonstration of significant benefit with the COMP via a significant benefit question.

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

The intention to treat the condition with the medicinal product containing humanised IgG1 monoclonal antibody against GD2 was considered justified based on preliminary clinical data showing responses in patients affected by the condition.

The condition is life threatening and chronically debilitating due to its aggressive nature and frequency of metastatic disease. It accounts for almost 15% of childhood cancer fatalities. The likelihood of survival is dependent on the age of the patient, the stage and biological characteristics of the disease. The poorest prognosis is seen in children diagnosed at older age (>18 months), those diagnosed at advanced stages of disease, and those positive for certain molecular biological markers such as oncogene-neuroblastoma derived amplification.

The condition was estimated to be affecting approximately 1.1 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 humanised IgG1 (inmunoglobulin G1) monoclonal antibody against GD2 will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing similar responses compared to the currently authorised products, when provided in a reduced administration schedule. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for humanised IgG1 monoclonal antibody against GD2, for treatment of neuroblastoma, was adopted by consensus.

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

2.1.18. Lisocabtagene maraleucel - EMA/OD/124/18

Celgene Europe Limited; Treatment of primary mediastinal large-B-cell lymphoma

COMP coordinator: Frauke Naumann-Winter

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

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available non-clinical or clinical studies to justify the assumption of significant benefit in particular over Yescarta.

A direct or indirect comparative discussion to justify either a clinically relevant advantage or major contribution to patient care is expected.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor discussed arguments for the justification of significant benefit versus Yescarta. Firstly, an improved safety profile was claimed in particular on the basis of occurrence of cytokine release syndrome. Data from the ZUMA-1 study of Yescarta were juxtaposed to the data from sponsor's study. It was reported that cytokine release syndrome occurred in 93% of relapsed/refractory Non-Hodgkin lymphoma patients in ZUMA-1 versus 40% in relapsed/refractory primary mediastinal large-B-cell lymphoma patients in the sponsor's study. The COMP considered that the number of patients with relapsed/refractory primary mediastinal large-B-cell lymphoma was low, but that safety extrapolations could be made on the basis of comparisons of the cytokine release syndrome rates observed in the relapsed/refractory Non-Hodgkin lymphoma populations. This assumption was considered acceptable for the purposed of justifying significant benefit.

The second argument of improved safety was made in relation to the mechanism of action for the proposed product. However, this argument was only a theoretical at this time and its validity remains to be explored in future studies. The COMP did not accept this line of argument in the absence of data showing the claimed effect.

The sponsor also proposed an improved efficacy but no data comparison was provided to support this claim. The Committee agreed that the condition, primary mediastinal large-B-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 lisocabtagene maraleucel was considered justified based on clinical observations in relapsed/refractory patients who responded to treatment with the proposed product.

The condition is life-threatening due to relapses in 20-30% of patients who have poor prognosis and chronically debilitating in particular due to superior vena cava syndrome, night sweats, fever and weight loss.

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 lisocabtagene maraleucel will be of significant benefit to those affected by the condition. The sponsor has provided clinical data in heavily pretreated relapsed refractory patients, who responded to treatment with the proposed product. Moreover, the rates of cytokine release syndrome in the treated patients were reported to be lower in comparison to the currently authorised chimeric antigen receptor cell product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lisocabtagene maraleucel, for treatment of primary mediastinal large-B-cell lymphoma, was adopted by consensus.

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

2.1.19. Apraglutide - EMA/OD/115/18

IQVIA RDS Ireland Limited; Treatment of Short Bowel Syndrome

COMP coordinator: Dinah Duarte

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 Short Bowel Syndrome, the sponsor should further elaborate on the non-clinical results obtained in the surgical piglet models that do not support a significant improvement in weight gain. This is considered by the COMP to be the most relevant endpoint for establishing medical plausibility in non-clinical models.

- 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 sponsor should discuss the current prevalence figure and clarify if all short bowel syndrome (SBS) patients are covered by the assumptions including patients that do not or no longer receive home parental nutrition (HPN). Furthermore, adequate disease duration should be defined based on scientific literature and used for the estimation of prevalence.

- Significant benefit

The sponsor was invited to present additional non-clinical data from valid models or preliminary clinical data from SBS patients to demonstrate significant benefit versus Teduglutide.

In the written response, and during an oral explanation before the Committee on 10 October 2018, the sponsor provided an updated prevalence calculation of 0.6 per 10,000, which was accepted by the COMP.

Regarding medical plausibility and significant benefit, additional preliminary clinical data were presented from two short bowel syndrome patients. The data demonstrate that treatment can improve metabolic balance and can lead to weight gain. The proposed

product was administered once weekly via SC. In comparison, the currently authorised product Revestive has to be administered daily via SC. The weekly administration with the proposed product could be considered to be more convenient for patients affected by the condition. The COMP considered that the currently provided evidence is sufficient to support the assumption for a major contribution to patient care for the purpose of orphan designation. The assumption of significant benefit will have to be confirmed at the time of marketing authorisation, when the justification should include a quantitative element that allows the COMP to measure magnitude of effect as compared with the already authorised product(s). A strong recommendation is given to seek EMA protocol assistance and discuss the demonstration of significant benefit with the COMP via a significant benefit question.

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

The intention to treat the condition with the medicinal product containing apraglutide was considered justified based on preliminary clinical data showing improvements in metabolic balance and weight gain.

The condition is chronically debilitating due to severe nutritional deficiency, metabolic and/or septic complications and life-threatening liver failure and end stage renal disease.

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 apraglutide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that administration of the proposed product once weekly led to improvements in metabolic balance and weight gain. The currently authorised product has to be administered once daily. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for apraglutide, for treatment of short bowel syndrome, was adopted by majority (30 out of 33 votes).

The divergent positions (*Brigitte Blöchl-Daum; Vallo Tillmann; Geraldine O'Dea)* were appended to this opinion.

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

2.1.20. - EMA/OD/121/18

Treatment of follicular 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 21 September 2018, prior to responding to the list of issues.

2.1.21. - EMA/OD/097/18

Treatment of alcohol-dependence

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 21 September 2018, prior to responding to the list of issues.

2.1.22. - EMA/OD/119/18

Treatment of large hemispheric infarction

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 proposed condition is argued to be a valid subset (in the sense of ENTR/6283/00) of a broader distinct medical entity.

The COMP considers this to be insufficiently justified in the context of the EU Orphan Medicinal Product designation framework (O'Connor *et al*, Nat Rev Drug Discov. 2018 Sep 12.). This is because hypoperfusion, SUR1-TRPM4 expression and oedema do not only occur in the subset of Large hemispheric Infarction (LHI), but also in other types of strokes. Therefore pharmacodynamic actions cannot be excluded outside the severe subset proposed for designation.

The applicant is invited to reconsider the proposed indication, and provide qualitative arguments for exclusion of pharmacodynamic effects if a subset is to be proposed.

- Intention to diagnose, prevent or treat

Notwithstanding the above issue on the proposed condition, the sponsor was invited to elaborate on the possible reasons that the primary endpoint of the cited clinical study was not met, and provide any further non-clinical or clinical observations to justify the intention to treat the condition.

- 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".

Notwithstanding the above issue on the proposed condition, 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 (e.g. total incidence of strokes, ratio of LHI), the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

Notwithstanding the above issue on the proposed condition, the applicant was invited to specifically state the authorised products in the sought indication, and provide a data driven comparative discussion to justify either a clinically relevant advantage or a major contribution to patient care.

In the written response, and during an oral explanation before the Committee on 11 October 2018, the sponsor elaborated on the proposed condition and argued that there is a lack of continuity with other types of strokes, on the grounds of the underlying pathophysiology. In particular, there is a lesion volume threshold, below which oedema a

symptom that does not cause further damage. It was also stated that there is a consensus according to which treating subclinical oedema will not improve outcomes, and pointed to non-clinical models where craniotomy for all lesions may be ineffective. During the oral hearing the sponsor was further invited to delineate the proposed threshold of the lesion, and elaborate on the newly added argument of the effects on potassium channels. In evaluation of the responses, the COMP considered that the exclusion of effects solely in large hemispheric infarction was not sufficiently justified in light of literature supporting effects in broader stroke. The COMP also noted that significant oedema may also occur in cerebellar strokes, and that the product may have beneficial effects in those types as well. Overall, the exclusion of pharmacodynamic effects outside of the proposed subset was not considered justified.

With regards to prevalence it was argued based on clinical therapeutic considerations that the duration of the large hemispheric infarction itself, is up to approximately 10 days and the tissue repair process is complete within about 2 months. This definition of duration is different to the notion of people affected by (large hemispheric infarction) stroke, as per the "points to consider" document duration can exist the window where an intervention is deemed possible. The prevalence calculation was therefore not accepted.

Significant benefit was discussed with reference to the clinical study, but no new data were submitted. The limitations originally identified therefore hold. In conclusion, the COMP considered that the criteria for designation could not be met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 October 2018, prior to final opinion.

2.1.23. Propagermanium - EMA/OD/103/18

Quality Regulatory Clinical Ireland Limited; Treatment of Focal Segmental Glomerulosclerosis

COMP coordinator: Tim Leest

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 prevalence calculation has only been provided for primary forms of the condition and has not included the secondary forms. The sponsor should recalculate the prevalence including the secondary forms as well.

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 the new mechanism of action and the potential improved efficacy in the condition.

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

In the written response, the sponsor provided a revised prevalence calculation for the basis of a correction for the increase in the African population in Europe who are known to be at greater risk of the condition. A correction for secondary forms of the condition was also provided. This increased the prevalence to 2.63 in 10,000 which the COMP considered acceptable.

The sponsor explained the clinically relevant advantage of using the proposed product in the condition where only cyclosporine is used. The sponsor highlighted that the response to intervention is initially effective in approximately 50% of patients and is associated with frequent relapses and significant long-term toxicity. The sponsor highlighted that there was a need in the other 50% of patients who have no alternative to cyclosporin. The sponsor provided additional data with the product in several non-clinical studies using other non-clinical models of the condition. The COMP also noted that there were publications in the public domain which supported the effects of the proposed product in different non-clinical models of the condition. The results from these additional studies supported the findings of the study used in the submission as well as showing additional promise in reducing fibrosis.

The COMP considered that the additional data supported the recommendation to grant the orphan designation.

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

The intention to treat the condition with the medicinal product containing propagermanium was considered justified based on preliminary non-clinical data in a model of the condition which showed a reduction in the number of podocytes lost and an improvement in proteinuria.

The condition is life-threatening and chronically debilitating due to the development of end-stage kidney disease.

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 propagermanium will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate the product could offer an alternative in patients who are refractory to cyclosporin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for propagermanium, for treatment of Focal Segmental Glomerulosclerosis, was adopted by consensus.

2.1.24. 5-{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride - EMA/OD/040/18

Takeda Pharma A/S; Treatment of Kabuki syndrome

COMP coordinator: Tim Leest

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 a limited prevalence calculation based on a limited literature search and assumptions offering a range for the prevalence which does not appear to reflect the current understanding in Europe. The sponsor was invited to recalculate the prevalence with more current information available in the public domain concerning the European Economic Area.

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 provided a revised prevalence calculation offering a clearer view of the current situation in Europe. It includes a mix of publications, registry data and personal expert statements which offer a current view of the European situation. The sponsor notes that the data reported in the registries are probably an under representation of the current situation in these Member States and this was supported by expert statements from some of these Member State. The sponsor accounted for these assumptions and provided a revised prevalence of 1 in 10,000. The COMP considered that this prevalence calculation was acceptable.

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

The intention to treat the condition with the medicinal product containing 5-{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride was considered justified based on non-clinical *in vivo* data in which the sponsor showed an improvement in relevant surrogate end-points as well as functional outcomes.

The condition is chronically debilitating due to several neurological, motor and cardiac deficiencies which will affect the well-being of the patients. The most salient of the deficiencies are those associated with neurological functioning associated with the hippocampus producing a distinctive neuropsychological deficit such as deficits in nonverbal skills associated with executive dysfunction and deficits in language abilities, phonological and morphosyntactic deficits as well as oromotor ones such as dysarthria and dyspraxia. Deficits in motor skill and visuomotor integration abilities have also been noted. Patients can also have epilepsy and cardiac defects.

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 5-{(1R,2R)-2-[(cyclopropylmethyl)amino]cyclopropyl}-N-(tetrahydro-2H-pyran-4-yl)thiophene-3-carboxamide monohydrochloride, for treatment of Kabuki syndrome, was adopted by consensus.

2.1.25. - EMA/OD/130/18

Treatment of severe combined immunodeficiency

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 20 September 2018, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/150/18

Treatment of pseudomyxoma peritonei

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee November meeting.

2.2.2. - EMA/OD/140/18

Treatment of congenital adrenal hyperplasia

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/141/18

Treatment of Fanconi anaemia

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee November meeting.

2.2.4. Allogeneic Faecal Microbiota, pooled - EMA/OD/123/18

MaaT PHARMA; Treatment of graft-versus-host disease

COMP coordinator: Frauke Naumann-Winter

The Committee agreed that the condition, graft-versus-host-disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with allogeneic faecal microbiota, pooled was considered justified based on bibliographic clinical data from the published literature demonstrating that faecal microbiota transplantations can reduce manifestations of intestinal graft-versus-host disease.

The condition is life-threatening and chronically debilitating due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

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 allogeneic faecal microbiota, pooled will be of significant benefit to those affected by the condition. The sponsor has provided bibliographic clinical data demonstrating that faecal microbiota transplantations can reduce manifestations of intestinal graft-versus-host disease. In these published case series, faecal microbiota transplantations were given either on top of best standard of care including authorised products or in patients that no longer respond to currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic faecal microbiota, pooled, for treatment of graft-versus-host-disease, was adopted by consensus.

2.2.5. - EMA/OD/144/18

Treatment of pseudomyxoma peritonei

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee November meeting.

2.2.6. - EMA/OD/131/18

Treatment of epidermolysis bullosa

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.

2.2.7. Etamsylate - EMA/OD/135/18

Consejo Superior de Investigaciones Cientificas (CSIC); Treatment of hereditary hemorrhagic telangiectasia

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing etamsylate was considered justified based on preliminary clinical data showing a reduction in epistaxis.

The condition is life-threatening and chronically debilitating due to arteriovenous malformations in different organs, leading to recurrent bleeding from the nasal mucosa with development of severe anaemia, and to potentially fatal bleeding in the stomach, gut, brain, liver and lungs.

The condition was estimated to be affecting approximately 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 etamsylate, for treatment of hereditary haemorrhagic telangiectasia, was adopted by consensus.

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

2.2.8. *ex vivo* fused normal allogeneic human myoblast with another normal allogeneic human myoblast - EMA/OD/134/18

Dystrogen Therapeutics S.A.; Treatment of Duchenne muscular dystrophy

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing *ex vivo* fused normal allogeneic human myoblast with another normal allogeneic human myoblast was considered justified based on non-clinical data, showing improved muscle force and function in a valid model of the condition.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing *ex vivo* fused normal allogeneic human myoblast with another normal allogeneic human myoblast will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data supporting functional effects in subjects with different dystrophin genotypes. In contrast, the authorised product only targets the subset of nonsense mutated patients, and as such the product is expected to target a wider population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *ex vivo* fused normal allogeneic human myoblast with another normal allogeneic human myoblast, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

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

2.2.9. *ex vivo* fused normal allogeneic human myoblast with autologous human myoblast derived from Duchenne muscular dystrophy affected donor - EMA/OD/133/18

Dystrogen Therapeutics S.A.; Treatment of Duchenne muscular dystrophy

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing *ex vivo* fused normal allogeneic human myoblast with autologous human myoblast derived from Duchenne muscular dystrophy affected donor was considered justified based on non-clinical data, showing improved muscle force and function in a valid model of the condition.

The condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

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

medicinal product containing *ex vivo* fused normal allogeneic human myoblast with autologous human myoblast derived from Duchenne muscular dystrophy affected donor will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data supporting functional effects in subjects with different dystrophin genotypes. In contrast, the authorised product only targets the subset of nonsense mutated patients, and as such the product is expected to target a wider population. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *ex vivo* fused normal allogeneic human myoblast with autologous human myoblast derived from Duchenne muscular dystrophy affected donor, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

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

2.2.10. H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-2Thi-Gly-Leu-Met(O2)-NH2-DOTA-213-Bismuth - EMA/OD/145/18

Dr. Regenold GmbH; Treatment of glioma

COMP coordinator: Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-2Thi-Gly-Leu-Met(O2)-NH2-DOTA-213-Bismuth was considered justified based on preliminary clinical data showing improved survival in recurrent glioblastoma 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 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-2Thi-Gly-Leu-Met(O2)-NH2-DOTA-213-Bismuth will be of significant benefit to those affected by the condition/to the population at risk of developing the condition. The sponsor has provided preliminary clinical that demonstrate an improvement in survival in patients with recurrent glioblastoma compared to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for containing H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-2Thi-Gly-Leu-Met(O_2)-NH_2-DOTA-213-Bismuth, for treatment of glioma, was adopted by consensus.

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

2.2.11. - EMA/OD/136/18

Treatment of spinal muscular atrophy

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.

2.2.12. Human apotransferrin - EMA/OD/109/18

Sanquin Plasma Products B.V.; Treatment of beta-thalassemia intermedia and major

COMP coordinator: Ingeborg Barisic

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 human apotransferrin was considered justified based on nonclinical data that demonstrate that treatment with the proposed product improves red blood cell counts, splenomegaly and iron deposition in models of the condition.

The condition is life-threatening and chronically debilitating due to the severe anaemia and the need for blood transfusions.

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 human apotransferrin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate that treatment with the proposed product improves red blood cell counts, splenomegaly and iron deposition in models of the condition. In contrast, the available medicinal products are chelating agents that target iron overload. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human apotransferrin, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

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

2.2.13. Ile-Ser-Ile-Thr-Glu-Ile-Lys-Gly-Val-Ile-Val-His-Arg-Ile-Glu-Thr-Ile-Leu-Phe-Lys-Lys-Lys-Lys-Glu-Met-Pro-Ser-Glu-Glu-Gly-Tyr-Gln-Asp - EMA/OD/146/18

United Neuroscience Limited; Treatment of multiple system atrophy

COMP coordinator: Darius Matusevicius

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

The intention to treat the condition with the medicinal product containing ile-Ser-Ile-Thr-Glu-Ile-Lys-Gly-Val-Ile-Val-His-Arg-Ile-Glu-Thr-Ile-Leu-Phe-Lys-Lys-Lys-Lys-Glu-Met-Pro-

Ser-Glu-Glu-Gly-Tyr-Gln-Asp was considered justified based on non-clinical data demonstrating a reduction in the motor function deterioration.

The condition is chronically debilitating due to autonomic failure, parkinsonism and cerebellar ataxia and life-threatening with median life expectation of 8.5 years following the onset of symptoms.

The condition was estimated to be affecting less than 0.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for ile-Ser-Ile-Thr-Glu-Ile-Lys-Gly-Val-Ile-Val-His-Arg-Ile-Glu-Thr-Ile-Leu-Phe-Lys-Lys-Lys-Lys-Glu-Met-Pro-Ser-Glu-Glu-Gly-Tyr-Gln-Asp, for treatment of multiple system atrophy, was adopted by consensus.

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

2.2.14. - EMA/OD/139/18

Treatment of cystic fibrosis

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

2.2.15. - EMA/OD/137/18

Treatment of cystic fibrosis

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

2.2.16. Fidanacogene elaparvovec - EMA/OD/112/18

Pfizer Europe MA EEIG; Treatment of haemophilia B

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing fidanacogene elaparvovec was considered justified based on preliminary clinical observations in a cohort of treated patients, supporting long term improvement in Factor IX (FIX) levels, reduction of annualised bleeding rates and exogenous FIX use.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury; bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening.

The condition was estimated to be affecting approximately 0.3 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 fidanacogene elaparvovec will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in a cohort of affected patients, supporting long term improvement in FIX levels and a reduction in annualised bleeding rates as well as exogenous FIX use. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fidanacogene elaparvovec, for treatment of haemophilia B, was adopted by consensus.

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

2.2.17. Setmelanotide - EMA/OD/143/18

TMC Pharma Services Ltd; Treatment of leptin receptor (LEPR) deficiency

COMP coordinator: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on early clinical data showing significant reductions in hunger score and body weight in patients.

The condition is life-threatening and chronically debilitating due to unrelenting hunger leading to morbid obesity and related comorbidities such as cardiovascular, metabolic, respiratory and orthopaedic impairments.

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

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

A positive opinion for setmelanotide, for treatment of leptin receptor deficiency, was adopted by consensus.

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

2.2.18. - EMA/OD/142/18

Treatment of biliary tract 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.

2.2.19. - EMA/OD/148/18

Treatment of autosomal dominant polycystic kidney disease (ADPKD)

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 eighteen applications submitted applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

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

The status of the procedure was noted.

3.1.2. -

Treatment of ovarian cancer

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

3.1.3. -

Treatment of spinal cord injury

The status of the procedure was noted.

3.2. Finalised letters

3.2.1. -

Treatment of glioma

The finalised letter was circulated for information.

3.2.2. -

Treatment of glioma

The finalised letter was circulated for information.

3.2.3. -

Treatment of glioma

The finalised letter was circulated for information.

3.2.4. -

Prevention of graft rejection following solid organ transplantation

The finalised letter was circulated for information.

3.2.5. -

Treatment of transthyretin-mediated amyloidosis

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

4.1.1. Jivi - Pegylated B-domain-deleted sequence-modified recombinant human factor VIII – EMEA/H/C/004054, EMA/OD/128/10, EU/3/10/847

Bayer AG; Treatment of haemophilia A

CHMP rapporteur: Greg Markey; CHMP co-rapporteur: Hanne Lomholt Larsen

A list of issues was adopted on 13 September 2018.

An oral explanation was held on 9 October 2018.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 October 2018, prior to final opinion.

4.1.2. Poteligeo - mogamulizumab – EMEA/H/C/004232, EMA/OD/091/16, EU/3/16/1756

Kyowa Kirin Limited; Treatment of cutaneous T-cell lymphoma

CHMP rapporteur: Paula Boudewina van Hennik; CHMP co-rapporteur: Daniela Melchiorri

A list of issues was adopted on 13 September 2018.

An oral explanation was held on 11 October 2018.

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

An opinion recommending not to remove Poteligeo 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. 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

CAT rapporteur: Christiane Niederlaender; CAT co-rapporteur: Sol Ruiz

A list of issues was adopted on 19 July 2018.

An oral explanation was held on 12 September 2018.

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

An opinion recommending not to remove Luxturna 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.

4.2. [Post-meeting note: The COMP adopted opinion by written procedure following its September meeting.]Orphan designated products for discussion prior to adoption of CHMP opinion

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

Shire Pharmaceuticals Ireland Limited; Treatment of hereditary angioedema

CHMP rapporteur: Kristina Dunder; CHMP co-rapporteur: Joseph EmmerichPatient expert: Laura Szutowicz

A list of issues was adopted on

An oral explanation was held on 10 October 2018

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

An opinion recommending not to remove TAKHZYRO from the EC Register of Orphan Medicinal Products was adopted by majority majority (26 out of 29 votes).

The divergent positions (*Brigitte Blöchl-Daum; Elisabeth Penninga; Fernando Mendez Hermida)* were appended to this opinion.

The Orphan Maintenance Assessment Report will be publicly available on the EMA website.

4.2.2. - mexiletine hcl – EMEA/H/C/004584, EMA/OD/074/14, EU/3/14/1353

LUPIN (EUROPE) LIMITED; Treatment of myotonic disorders

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for two applications

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

5.1.1. Venclyxto – Venetoclax – Type II variation – EMEA/H/C/004106/II/0008, EMA/OD/124/12, EU/3/12/1080

AbbVie Limited; Treatment of chronic lymphocytic leukaemia

CHMP rapporteur: Filip Josephson;

A list of issues was adopted on 13 September 2018.

An oral explanation was held on 11 October 2018.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 October 2018, prior to final opinion.

5.2. Prior to adoption of CHMP opinion

5.2.1. Imnovid – pomalidomide - Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G

Celgene Europe Limited; Treatment of multiple myeloma

CHMP rapporteur: Robert James Hemmings

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 December meeting.

5.2.2. Translarna - Ataluren - Type II variation – EMEA/H/C/002720/II/0047, EMEA/OD/106/04, EU/3/05/278

PTC Therapeutics International Limited; Treatment of duchenne muscular dystrophy

CHMP rapporteur: Johann Lodewijk Hillege

5.2.3. The status of the procedure at CHMP was noted.Opsumit - Macitentan - Type II variation – EMEA/H/C/002697/II/0029, EMA/OD/023/11, EU/3/11/909

Actelion Registration Limited; Treatment of pulmonary arterial hypertension

CHMP rapporteur: Concepcion Prieto Yerro

5.3. The status of the procedure at CHMP was noted.Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for one application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

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

Document was circulated in MMD.

Documents tabled:
Draft Agenda for SRLM SAWP-COMP in Vienna 2018

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 9 October 2018.

7.1.3. Election of COMP Vice-Chairperson

The European Medicines Agency's (EMA) Committee for Orphan Medicinal Products (COMP) has elected Dr Armando Magrelli as its new vice-chair for a three-year mandate.

7.1.4. Prevalence Working Group

The working group on Prevalence met on 10 October 2018.

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 September 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

The topic was postponed to November meeting.

Document(s) tabled:
Draft COMP Work Plan 2019

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. IRIS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

Presentation was given to the Committee.

8.2. Concepts of significant benefit (follow-up to COMP Work Plan 2017)

The topic was postponed to November meeting.

8.3.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 9-11 October 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Elena Kaisis	Member	Cyprus	No interests declared	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Angelo Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	EMA/OD/124/18Treatment of primary mediastinal large-B-cell lymphomaEMA/OD/121/18Treatment of follicular lymphomaImnovid – pomalidomide - Type II variation – EMEA/OD/053/09, EU/3/09/672, EMEA/H/C/002682/II/0031/G; Celgene Europe Limited; Treatment of multiple myeloma
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Laura Szutowicz	Patient expert - in person*		No restrictions applicable to this meeting	TAKHZYRO - lanadelumab – EMEA/H/C/004806, EMA/OD/075/15, EU/3/15/1551 Shire Pharmaceuticals Ireland Limited;

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Treatment of hereditary angioedema
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.

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/