19 March 2015
EMA/COMP/25297/2015
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 10-12 February 2015 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because 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).

Contents

1. Introduction 2

2. Applications for orphan medicinal product designation 2

2.1. For opinion 2
2.2. For discussion / preparation for an opinion 15
2.3. Revision on the COMP opinions 28
2.4. Appeal procedure 29
2.5. Evaluation on-going 29
2.6. Validation on-going 29

3. Requests for protocol assistance 29

4. Overview of applications 30

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation 30

5.1. Orphan designated products for which CHMP opinions have been adopted 30
5.2. Orphan designated products for discussion prior to adoption of CHMP opinion 31
5.3. On-going procedures 31

6. Procedural aspects 33

7. Any other business 34

List of participants 35

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

1.1 Adoption of the agenda, EMA/COMP/25295/2015

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 7-9 January 2015 EMA/COMP/780484/2014

The minutes were adopted with no amendments.

1.3 Declaration of conflicts of interest

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). K. Kubáčková declared a potential conflict of interest on agenda point 2.2.27.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Product for treatment of eosinophilic oesophagitis - EMA/OD/243/14
[COMP co-ordinator: A. Corrêa Nunes]

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

Regulation (EC) No.141/2000 states that a sponsor may apply for designation at any stage of development prior to applying for marketing authorisation. The sponsor is invited to clarify at which stage of development the proposed product is. Any sponsor-generated data with the proposed product should be clearly delineated.

- Prevalence

For the calculation and presentation of the prevalence estimate it 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, describe and justify the methodology used for the prevalence calculation. The sponsor is requested to discuss the apparent continuing increase in the prevalence of the condition, and provide an updated calculation at the time the application is made.

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

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

In the written response, and during an oral explanation before the Committee on 10 February 2015, the sponsor elaborated on the two issues raised.

With regards to the stage of development, it was reported that a limited number of patients were treated with the proposed formulation through a compassionate use program. It was reported that within four months all patients had some evidence of symptomatic improvement and that most of them had a complete eosinophilic and histological resolution. It was thus concluded by the COMP that the development of the proposed product for designation had commenced.

With regards to the prevalence issue, the sponsor acknowledged that there has been a recent rise in the incidence of the condition but commented that such reports may be biased and that the rise in rates is largely due to awareness and the increase in endoscopies and oesophageal biopsies. It was argued that the heterogeneity of available data globally necessitates the calculation of prevalence based on European studies, and refered to a Spanish, a Swiss and a Dutch studies, which were used as a basis to project incidence for the year the application was submitted. The sponsor used regression analysis to project the incidence for 2014, and then used this incidence as a basis to calculate prevalence. It was presented that for Spain, the figure may be as high as 6.1 per 10,000, but the sponsor presented a weighted average of the above three countries, yielding a 4.929/10,000 figure for the purpose of designation.

The COMP noted that the level of uncertainty with regards to respecting the provisioned prevalence threshold would not allow to conclude that the prevalence criterion had been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.2 **6-Ethoxy-7-methoxy-2-(2-methylsulfanylphenyl)-3,1-benzoxazin-4-one** for treatment of Netherton syndrome, Sixera Pharma AB - EMA/OD/264/14

[COMP co-ordinator: A. Andrić]

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 Netherton syndrome, the sponsor should further elaborate on:

- the results obtained in chosen and other available preclinical models of the condition, in particular further available outcome measures, such as improvement of skin lesions, scratching behaviour, etc. to support medical plausibility;
- the possibility of effects of the vehicle on the skin lesions and include an untreated control group in the analysis.

In the written response, the sponsor presented more detailed data on transepidermal water loss in the preclinical model studied, and emphasized that the proposed product improves skin barrier. The sponsor argued that this is the most relevant outcome measure for the condition since impaired skin barrier function is the primary defect in Netherton syndrome. It was also clarified that scratching behaviour was not assessed due to the small area treated in the experiments and histological analyses have not been undertaken due to the short treatment course. The sponsor has also confirmed that the

vehicle shows no effects on transepidermal water loss. The Committee agreed that the condition, Netherton syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 6-ethoxy-7-methoxy-2-(2-methylsulfanylphenyl)-3,1-benzoxazin-4-one was considered justified based on data from preclinical models of the condition showing improvement in the impaired skin barrier function upon topical administration of the product.

The condition is chronically debilitating and life-threatening due to dehydration, recurrent infections, failure to thrive and malnutrition especially during the neonatal period, and cutaneous infections, increased risk for skin cancer, alteration of physical appearance, and psychological burden on patients later in life.

The condition was estimated to be affecting approximately 0.05 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6-ethoxy-7-methoxy-2-(2-methylsulfanylphenyl)-3,1-benzoxazin-4-one may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product reduces transepidermal water loss, a measure of the impaired skin function, which is a key characteristic of the condition and is not treated by currently authorised medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6-ethoxy-7-methoxy-2-(2-methylsulfanylphenyl)-3,1-benzoxazin-4-one, for treatment of treatment of Netherton syndrome, was adopted by consensus.

2.1.3 Product for treatment of idiopathic noncirrhotic portal hypertension - EMA/OD/269/14

[COMP co-ordinator: A. Corrêa Nunes]

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 5 February 2015, before responding to the list of issues.

2.1.4 Product for treatment of biliary tract cancer - EMA/OD/252/14

[COMP co-ordinator: A. Magrelli]

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 biliary tract cancer, the sponsor should further elaborate on:

- the rationale behind using allogeneic rather than autologous mesenchymal stem cells;
- the relevance of the preclinical model used for the treatment of biliary tract cancer, and the interpretation of the results obtained in the experiments;
- the methodology used in the pre-clinical studies, in particular whether the active substance used is the product as applied for designation.

- Number of people affected

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

The proposed prevalence estimate is lower than figures previously adopted. The sponsor is asked to present a revised prevalence calculation using on the most conservative estimates.

- Significant benefit

The sponsor should further elaborate on any further available data strengthening the argument for improved efficacy over standard of care. In the absence of data supporting medical plausibility significant benefit cannot be assessed.

In the written response, and during an oral explanation before the Committee on 10 February 2015, the sponsor highlighted that the starting material can be obtained from healthy young donors with no limitation of amount, and that the product would be ready as an "off the shelf product". In order to justify the preclinical model chosen, the sponsor argued that although of pancreatic origin, it is the best available animal model for the condition, as tumours of the pancreatic as well as the bile duct stem from the same anatomical structure during embryogenesis. The sponsor presented immunofluorescence staining of tumour sections in preclinical models, supporting the tumour specific homing of the active substance.

With regards to the prevalence, the sponsor proposed a revised estimate of 0.9 in 10,000, based on incidence data from EUCAN 2012 and a survival time below 12 months.

As for significant benefit, the sponsor further elaborated on preliminary clinical data obtained in one patient with cholangiocarcinoma, and further emphasised the good tolerability in contrast to gemcitabine, although the COMP had already questioned the validity of the latter argument due to the early stage of development.

Having discussed the application with the sponsor and internally the COMP concluded that the sponsor failed to provide data with the proposed product as applied for designation in either a valid preclinical models of the condition or in preliminary clinical settings in patients affected by the condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.5 Product for treatment of pancreatic cancer - EMA/OD/242/14

[COMP co-ordinator: B. Bloechl-Daum]

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 19 January 2015, before responding to list of issues.

2.1.6 Product for treatment of Huntington's disease - EMA/OD/255/14

[COMP co-ordinator: A. Andrić]

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 for improved efficacy in the condition, versus authorised symptomatic treatments.

The sponsor is requested to further discuss the improvement in motor behaviour in the preclinical model, vis a vis the effects in motor behaviour of authorised products for the condition.

The sponsor is also requested to document any further aspects of the condition that may be improved with the proposed product, and discuss these effects in the context of authorised counterparts.

In the written response, and during an oral explanation before the Committee on 10 February 2015, the sponsor did not provide new data, but argued that the motor improvements seen in the preclinical model are broader than the ones improved by anti-choreic agents, since the results indicate improvement in voluntary movements. A potential for improving memory was also proposed, but none of these claims was supported by any data.

The COMP considered that the preclinical invertebrate model used could not be extrapolated to draw conclusions for improvements in conscious voluntary movements in patients affected by the condition. In the absence of data to support the significant benefit, the designation would not be considered acceptable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.7 Nalbuphine hydrochloride for treatment of uremic pruritus, Trevi Therapeutics Limited - EMA/OD/265/14
[COMP co-ordinator: J. Torrent-Farnell] [Expert: Pieter de Graeff]

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

Uremic pruritus should be justified as a distinct medical entity or a valid subset. The sponsor is requested to justify the reasoning behind proposing uremic pruritus as a distinct medical entity, and not a symptom occurring in patients with end stage renal disease.

Note that this is for the purposes of orphan medicinal product designation; your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of uremic pruritus, the sponsor should further elaborate on:

  - the methodology used and results obtained in the clinical study. In particular, the sponsor should justify the inclusion of mildly affected patients in the proof of concept clinical study (VAS < 4), while such patients were excluded from the sponsor's prevalence calculation, concomitant anti-pruritic treatments, and the large inter-individual variability of treatment results within treatment groups.

- Number of people affected

For the calculation and presentation of the prevalence estimate it 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 has excluded part of the population affected by the proposed condition, namely patients with mild uremic pruritus. The sponsor should justify the exclusion of this population based on available classification systems or internationally recognized definitions. Note that for the purpose of orphan medicinal product designation, clinical considerations, such as need for therapy or severity, are not accepted for defining a subset. The sponsor should also justify why not all patients with end stage renal disease, who may suffer from uremic pruritus, were considered in their prevalence calculation. Given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should also perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 11 February 2015, the sponsor argued that uremic pruritus has a distinct profile of inflammatory markers, elevated levels of serum beta-endorphin, and heightened dermal nociceptor sensitization among uremic patients with pruritus versus those without. The COMP considered that the sponsor has not justified that uremic pruritus has distinct pathophysiological, histopathological and clinical signs and symptoms delineating uremic pruritus and distinguishing uremic pruritus from pruritus as a consequence of other conditions. The sponsor also failed to establish clear diagnostic criteria for uremic pruritus based on international classifications or consensus guidelines from professional bodies. Uremic pruritus could therefore not be considered a valid condition for designation.

The sponsor also discussed the COMP's question on medical plausibility and clarified details of the proof of concept clinical study. It was stated that exploratory pharmacodynamic effects of nalbuphine was analysed in 14 haemodialysis patients with all grades of severity of pruritus, while treatment efficacy (proof of concept) was only evaluated in the 8 patients with moderate to severe pruritus, as only those 8 patients meet the diagnostic criteria for uremic pruritus. These 8 patients with a VAS > 4 reported a mean reduction of -4 points from baseline (SD -2 to -6) over the tested dose range, with 1/8 subjects showing no to minimal change in VAS over the study duration. Data on concomitant medication were also provided, along with justifications of inter-individual variability of treatment results. Notwithstanding that the uremic pruritus was not considered as a valid condition for orphan designation, the COMP considered that intention to treat uremic pruritus with nalbuphine hydrochloride was considered plausible based on clinical data showing reductions in pruritus intensity measured by vascular analogue score.

With regards to the COMP's question on prevalence, the sponsor emphasised that in their view they did not exclude parts of the publication because "the sponsor does not accept that 'mild uremic pruritus' by definition even exists, since moderate to severe and persistent itch is a pre-requisite for the diagnosis of uremic pruritus". Hence the sponsor was of the opinion that proposed prevalence of 2.5 in 10,000, based in a prevalence of dialysis in the EU of 6.2 per 10,000 population with 41% of these patients having uremic pruritus (Pisoni *et al* 2006), comprises all patients with uremic pruritus in the EU. The sponsor also presents a prevalence calculation including all patients indicating any severity of pruritus symptoms (all patients except those who were "not bothered"), 71% of the DOPPS population, resulting in a prevalence of 4.4 in 10,000. The sponsor further calculated that more than 80% of dialysis patients would have to have uremic pruritus for the prevalence to exceed 5 in 10,000. Notwithstanding that the uremic pruritus was not considered as a valid condition for orphan designation, the COMP considered that uremic pruritus was affecting approximately 4.4 in 10,000 persons.

The COMP considered that:

The sponsor has failed to justify that uremic pruritus has distinct pathophysiological, histopathological and clinical signs and symptoms delineating uremic pruritus and distinguishing uremic pruritus from pruritus as a consequence of other conditions.

The intention to treat uremic pruritus with the medicinal product containing nalbuphine hydrochloride was considered justified based on clinical data showing reductions in pruritus intensity measured by vascular analogue score (VAS).

Uremic pruritus is chronically debilitating due to its negative impact of quality of life, sleep disturbances, higher odds of feeling drained and depression. Uremic pruritus in haemodialysis patients was also associated with a higher mortality risk, and can therefore be considered life-threatening.

Uremic pruritus was affecting approximately 4.4 in 10,000 persons in the European Union, at the time the application was made.

No satisfactory method of treatment exists in the European Union for patients affected by uremic pruritus.

The sponsor has failed to justify that uremic pruritus is a distinct medical entity or a valid subset with reference of the guideline on the format and content of the applications for orphan medicinal product designation ENTR/6283/00 Rev 04. Consequently a condition subject of this application in the sense of Regulation (EC) No.141/2000 cannot be identified.

Post-meeting note:

A negative opinion on orphan medicinal product designation for Nalbuphine hydrochloride, for treatment of uremic pruritus, was adopted by consensus via written procedure on 27 February 2015.

2.1.8 Recombinant human club cell 10 KDa protein for prevention of bronchopulmonary dysplasia, RLM Consulting - EMA/OD/270/14
[COMP co-ordinator: K. Westermark] [Expert: Ninna Gullberg]

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

- the interpretation of the results obtained in the clinical study, in particular effects of the product on endogenous CC10 production, the impact of infections, antibiotics- and other concomitant treatments, and respiratory morbidity during the first 3 days of life on observed short term outcomes, as well as more details on long term outcomes, such as season of follow-up period, parental smoking, RSV-prophylaxis, concomitant (respiratory) medication, long term supplemental oxygen, concomitant conditions and reasons for drop-outs.

In the written response, and during an oral explanation before the Committee on 11 February 2015, the sponsor addressed the points that had been raised by the COMP and elaborated in detail on clinical characteristics of the study population of the phase I clinical study. The major obstacle in the sponsor's interpretation of the clinical outcomes however, is the small sample size per group at follow up visits which hamper interpretation of statistical analyses. The COMP acknowledged that the cited study was not designed to demonstrate efficacy.

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

The intention to prevent the condition with the medicinal product containing recombinant human club cell 10 KDa protein was considered justified based on data showing anti-inflammatory effects, diminished damage to pulmonary tissues, and reduced surfactant turnover in preclinical models of the condition.

The condition is chronically debilitating and life-threating due to inflammation and scarring in the lungs, resulting in necrotizing bronchiolitis and alveolar septal injury, which compromises the oxygenation of blood.

The condition was estimated to be affecting between 1 and 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 prevention that has been authorised in the European Union for patients affected by the condition.

A positive opinion for containing recombinant human club cell 10 KDa protein, for prevention of bronchopulmonary dysplasia, was adopted by consensus.

2.1.9 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/262/14

[COMP co-ordinator: E. Kaisi]

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

- Intention to diagnose, prevent or treat

The proposed product is targeting a sole manifestation of ALS (drooling/sialorrhea) and not the condition ALS itself. In the context of this application and for the purposes of an orphan designation in the entire population of ALS, the sponsor is invited to discuss the clinical relevance of drooling in the condition ALS.

Drooling presents as a symptom to a number of different conditions (including other neuromuscular diseases, anatomic abnormalities, *etcetera*). The sponsor is invited to clarify the rationale for restricting the use of the proposed product to ALS.

The sponsor did not present any data in the proposed condition supporting the medical plausibility.

In order to establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ALS, the sponsor should further elaborate on the relevance of the studies on healthy volunteers and Parkinson disease to drooling in ALS.

The endpoints of the studies include the measurement of saliva production and saliva secretion rate. Given that increased salivary production is not considered to be a main contributor to the pathophysiology of drooling in patients with neurodegenerative diseases, the correlation between the suppression of whole saliva production and saliva secretion rate with the reduction in drooling in ALS should be further elaborated upon.

In addition the sponsor is invited to elaborate on the scientific rationale of reducing Ach release and inhibiting its uptake, taking into account the importance of ACh in the neurotransmission in ALS.

In absence of data in the proposed condition the medical plausibility cannot be assessed.

- Significant benefit

The sponsor did not discuss the significant benefit of the proposed product *vs*. riluzole, currently authorized for the treatment of ALS.

In addition, the sponsor is invited to discuss the significant benefit *vis a vis* all available treatments that represent the current standard of care for drooling, including medicinal products and treatment methods (*e.g.* radiotherapy). The sponsor is also invited to further substantiate the claims of improved safety.

The sponsor is reminded that in absence of a discussion on significant benefit and of data supporting the assumed advantages of the proposed product, the significant benefit cannot be evaluated by the Committee.

In the written response, and during an oral explanation before the Committee on 11 February 2015, the sponsor elaborated on the raised issues and argued that chronic drooling seen in ALS patients is difficult to treat and that the authorised treatment for this condition does not treat this symptom. They also referred to preliminary clinical data in healthy volunteers and patients with Parkinson disease.

The COMP considered that the sponsor has not justified that sialorrhea in ALS would be different than sialorrhea seen in other conditions, and that in the absence of data with the product in specific ALS settings the medical plasubility and significant benefit cannot be considered.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 February 2015, prior to final opinion.

2.1.10 Product for treatment of Wilson disease - EMA/OD/241/14
[COMP co-ordinator: K. Westermark]

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 Wilson's disease, the sponsor should further elaborate on:

  - the results obtained in preclinical studies in models of Wilson's disease, in particular evidence for copper excretion

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action, namely the product's feature of specifically targeting hepatocytes and its selectivity for copper, and the potential improved efficacy and safety in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from preclinical studies to justify the assumption of significant benefit, in particular the assumption of improved efficacy, over authorised medicinal products for the proposed orphan indication.

It is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments in most cases.

In the written response, and during an oral explanation before the Committee on 10-12 February 2015, the sponsor elaborated on the in vitro studies presented in the original application and the

effects of the product versus penicillamine in a preclinical model of the condition. With regards to the COMP's question on evidence for copper excretion, the sponsor stated that sample collection was not possible at late time-points, and further clarified that there was no increase in plasma copper levels observed. The COMP was of the opinion that in order to accept medical plausibility, proof of actual copper clearance from the body would be necessary.

With regards to significant benefit, the sponsor proposed that the product may be of improved safety and efficacy based on preclinical studies, and proposed a different mechanism of copper excretion than D-Penicillamine, namely excretion via the bile. No specific data in support of this hypothesis were presented.

The COMP concluded that even though there is room to consider the concept that the proposed product can chelate copper and decrease copper liver levels, the sponsor failed to provide evidence for copper secretion. Therefore the medical, plausibility could not be accepted based on the available data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.11 Product for treatment of creatine transporter deficiency - EMA/OD/239/14

[COMP co-ordinator: A. Moraiti]

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

- Intention to diagnose, prevent or treat

The Guideline on the Format and Content of Applications ENTR/6283/00, expects data with the specific product as proposed for designation in specific models or patients affected by the condition.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of creatine transporter deficiency, the sponsor should further elaborate on:

- the relevance of the preclinical settings used for the treatment of creatine transporter deficiency, and the interpretation of the results obtained in the experiments;
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition;
- any available studies with the specific product in relevant models of the condition or in affected patients.

The sponsor is also invited to clarify the stage of development of the product, and present any available data with the product proposed for designation.

In the written response, and during an oral explanation before the Committee on 11 February 2015, the sponsor further clarified the stage of development of the product and discussed the available in vitro studies, but did not provide any data with the product in specific in vivo models of the condition. The COMP considered that in the absence of data is specific models of the condition or in patients affected by the condition, the consideration of medical plausibility would not be possible.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.12 Product for treatment of Smith-Magenis syndrome - EMA/OD/260/14
[COMP co-ordinators: G. Capovilla/ I. Bradinova]

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 Smith-Magenis syndrome, the sponsor should further elaborate on:

  - any available data with the product in valid models of the condition, or a justification why validated models of the condition were not used;
  - any available data with the product as applied for designation in patients with the condition.

In the absence of data with the product in valid preclinical models or patients with the condition orphan designation cannot be granted.

In the written response, and during an oral explanation before the Committee on 11 February 2015, the sponsor stressed that one of the most common and prominent features of the condition is the sleep disorder that is characterized by the abnormal daytime circadian rhythm of melatonin secretion, and argued that the product has a circadian regulatory effect and was expected to aid the patient in sleeping at the desired time. The COMP considered that in the absence of data is specific models of the condition or in patients affected by the condition subject of this application the consideration of medical plausibility would not be possible.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 February 2015, prior to final opinion.

2.1.13 Human plasma-derived alpha-1 proteinase inhibitor for treatment of graft versus host disease, Richardson Associates Regulatory Affairs Ltd - EMA/OD/267/14
[COMP co-ordinator: F. 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:

- Intention to diagnose, prevent or treat

Given that the preclinical evidence presented in the application pertains to preventive models, the sponsor is requested to present data in curative /treatment settings, either in models or in patients affected by the GvHD. In particular with regards to the ongoing phase I/II study in corticosteroid refractory patients, the sponsor is requested to present the data referred to and provide any updated results available, including any follow-up observations to this point in time.

In the absence of data in the proposed treatment settings the orphan designation will not be acceptable.

- Number of people affected

For the calculation and presentation of the prevalence estimate it 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 re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the

assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

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

The sponsor is requested to further elaborate on the preliminary clinical data presented, and discuss the potential significant benefit versus all authorised products for the treatment of the condition.

In the absence of data in the proposed treatment settings the orphan designation will not be acceptable.

In the written response, the sponsor addressed the issues by providing an interim report from the ongoing phase 1/2 clinical trial, which encompassed haematological malignancies patients that received transplants from HLA-matched siblings or cord blood following myeloablative or reduced-intensity conditioning.

The observations discussed pertained to patients who previously received cyclosporine and mycophenolate mofetil for GVHD prophylaxis and developed acute GVHD of grades III-IV that was corticosteroid resistant. In these patients treatment with the product resulted in favourable changes in stool volume, and reduced protein-losing enteropathy. The COMP acknowledged the medical plausibility on the basis of these data.

With regards to the justification of significant benefit, the sponsor argued that for these patients the standard of care would be corticosteroids and stressed again that the patients included in the phase I/II study were corticosteroid resistant. The COMP noted that all patients received cyclosporine and mycophenolate mofetil for GVHD prophylaxis, and after appearance of GVHD methylprednisolone was instituted. Based on responses seen in these patients, the significant benefit was considered as an add-on to standard of care.

Finally, with regards to the prevalence issue, the sponsor provided an updated calculation.

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

The intention to treat the condition with the medicinal product containing human plasma-derived alpha-1 proteinase inhibitor was considered justified based on preliminary clinical data in patients affected by the condition who responded to treatment by improvements in gastrointenstinal manifestations of the condition.

The condition is chronically debilitating and life-threatening in particular 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 less than 1 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human plasma-derived alpha-1 proteinase inhibitor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with the condition who were refractory to treatment with corticosteroids during cyclosporine prophylaxis. These

patients responded to treatment by improvement of gastrointestinal manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human plasma-derived alpha-1 proteinase inhibitor, for treatment of graft-versus-host disease, was adopted by consensus.

2.1.14 Tideglusib for treatment of fragile X syndrome, QRC Consultants Ltd. - EMA/OD/253/14
[COMP co-ordinator: I. Bradinova]

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 fragile X syndrome, the sponsor should further elaborate on:

  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition, in particular any available biochemical data from preclinical in vivo models substantiating the mode of action as well as data on long-lasting effects of the proposed product.

In the written response, and during an oral explanation before the Committee on 12 February 2015, the sponsor brought forward arguments for assessing behavioural parameters shortly after administration of the product based on published literature with other substances (Franklin *et al* 2014, Min *et al* , 2009) as well as after chronic administration (Guo *et al* , 2012, Yuskaitis *et al* 2010). The sponsor bridged characteristics of these other active substances and proposed that effects of the proposed product would be apparent on acute administration and would not show tolerance. The COMP considered that while the sponsor's argument on effects after single administration were acceptable based on the literature and their own experimental data, the argument on lack of tolerance development will require further research due to contradictory reports in the literature. With regards to biochemical testing, the sponsor presented new data of brain and lymphocyte levels of pERK and pAkt by Western blot and flow-cytometry, respectively, as well as detection of total and phosphorylated GSK3beta levels in a preclinical model of the condition. The Committee agreed that the condition, fragile X syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tideglusib was considered justified based on data in preclinical models of the condition showing acute improvements in neurobehavioural outcomes and neuronal pathology.

The condition is chronically debilitating due to developmental delay, severe neurobehavioural and neurocognitive complications.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for tideglusib, for treatment of fragile X syndrome, was adopted by consensus.

2.1.15 5'-$A_SC_SA_ST_SC_SA_SG_ST_SC_ST_SG_SA_SU_SA_SA_SG_SC_ST_SA$-3'for treatment of Alport syndrome, CTI Clinical Trial and Consulting Services Europe GmbH - EMA/OD/238/14
[COMP co-ordinator: A. Corrêa Nunes]

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 it 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 describe and justify the methodology used for the prevalence calculation, in particular how the proposed prevalence estimate of 2 in 10,000 was calculated and which data source(s) it was derived from.

In the written response, the sponsor elaborated on the two European studies on birth prevalence of Alport Syndrome (Pajari *et al*, 1006, Persson *et al*, 2005) and the most frequently cited prevalence estimate of about 2 in 10,000 coming from an observational study of families that transmit XLAS in Utha and southern Idaho, USA (Hasstedt *et al*, 1983). The sponsor argued that although not performed in Europe, the study examined a population of mostly European descent. The COMP acknowledged that published data is scarce due to the rarity of the disease, and adopted the sponsor's proposed prevalence of 2 in 10,000 as a conservative estimate.

The Committee agreed that the condition, Alport 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'-$A_SC_SA_ST_SC_SA_SG_ST_SC_ST_SG_SA_SU_SA_SA_SG_SC_ST_SA$-3' was considered justified based on data in preclinical models of the condition showing improvements in parameters of renal dysfunction and increased survival.

The condition is life-threatening and chronically debilitating due to progressive renal failure and end stage kidney disease usually occurring in the second to the sixth decade of life, rendering patients dependent on haemodialysis and/or kidney transplantation. Progressive sensorineural hearing loss can lead to deafness. Ophthalmologic complications include cataracts, lenticonus, kerataconus, as well as retinal flecks in the macula and mid periphery.

The condition was estimated to be affecting not more than 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for 5'-$A_SC_SA_ST_SC_SA_SG_ST_SC_ST_SG_SA_SU_SA_SA_SG_SC_ST_SA$-3', for treatment of Alport syndrome, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 Product for treatment of trigeminal neuralgia - EMA/OD/244/14
[COMP co-ordinator: A. Corrêa Nunes]

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 March meeting.

2.2.2 [5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6 trifluoromethyl-pyridin-3-ylmethyl)-amine hydrochloride for treatment of tenosynovial giant cell tumour, localised and diffuse type, Daiichi Sankyo Development Ltd - EMA/OD/279/14
[COMP co-ordinator: D. O'Connor]

The Committee agreed that the condition, tenosynovial giant cell tumour, localised and diffuse type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine hydrochloride was considered justified based on preliminary clinical data showing reduction in tumour size in treated patients affected by the condition.

The condition is chronically debilitating due to the progressive course of the disease that results in the destruction of joints.

The condition was estimated to be affecting not more than 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for [5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-pyridin-2-yl]-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine hydrochloride, for treatment of tenosynovial giant cell tumour, localised and diffuse type, was adopted by consensus.

2.2.3 Product for treatment of cryptococcosis - EMA/OD/300/14
[COMP co-ordinator: A. Lorence]

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 March meeting.

2.2.4 Product for the treatment of tularemia - EMA/OD/301/14
[COMP co-ordinator: A. Lorence]

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 March meeting.

2.2.5 Product for treatment of invasive candidiasis - EMA/OD/294/14
[COMP co-ordinator: N. Sypsas]

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 March meeting.

2.2.6 5,10,15,20-tetrakis(2,6-difluoro-3-N-methylsulfamoylphenyl)bacteriochlorin for treatment of cholangiocarcinoma, Luzitin S.A. - EMA/OD/305/14
[COMP co-ordinator: K. Kubáčková]

Following review of the application by the Committee, it was agreed to rename the indication to "biliary tract cancer".

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

The intention to treat the condition with the medicinal product containing 5,10,15,20-tetrakis(2,6-difluoro-3-N-methylsulfamoylphenyl)bacteriochlorin was considered justified based on preclinical models of the condition showing significant reduction of tumour size.

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

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5,10,15,20-tetrakis(2,6-difluoro-3-N-methylsulfamoylphenyl)bacteriochlorin may be of significant benefit to those affected by the condition. This is based on a different mechanism of action that specifically targets the tumour site and allows the use in combination with the current 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 5,10,15,20-tetrakis(2,6-difluoro-3-N-methylsulfamoylphenyl)bacteriochlorin, for treatment of biliary tract cancer, was adopted by consensus.

2.2.7 Gallium (^{68}Ga)-edotreotide for diagnosis of gastro-entero-pancreatic neuroendocrine tumours, Advanced Accelerator Applications SA - EMA/OD/219/14
[COMP co-ordinator: K. Kubáčková]

The Committee agreed that the condition, gastro-entero-pancreatic neuroendocrine tumours, is a distinct medical entity and meets the criteria for orphan designation.

The intention to diagnose the condition with the medicinal product containing gallium (^{68}Ga)-edotreotide was considered justified based on pre-clinical in vivo data using a valid model of the condition showing good resolution for the purpose of diagnosis of the condition.

The condition is chronically debilitating and life-threatening, in particular due to the debilitating symptoms and the poor prognosis in patients with localised advanced or metastatic disease.

The population of patients eligible for diagnosis of the condition was estimated to be approximately 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gallium (^{68}Ga)-edotreotide may be of significant benefit to those affected by the

condition. The sponsor has provided preclinical data that demonstrate that better imaging of neuroendocrine neoplasm manifestations offering a better specificity and sensitivity which is more clinically relevant than somatostatin-receptor scintigraphy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for gallium (^{68}Ga)-edotreotide, for diagnosis of gastro-entero-pancreatic neuroendocrine tumours, was adopted by consensus.

2.2.8 Adeno-associated viral vector serotype 9 containing the human glucocerebrosidase gene for treatment of Gaucher disease, Gauchers Association - EMA/OD/303/14
[COMP co-ordinator: A. Corrêa Nunes]

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human glucocerebrosidase gene was considered justified based on data in preclinical models of the disease showing improvements in cerebral and visceral pathology as well as improved survival.

The condition is chronically debilitating in particular due to hepatosplenomegaly, thrombocytopenia, anemia, bone disease, as well as neurological manifestations in the neuronopathic form of the condition, and life-threatening with reduced life expectancy.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 9 containing the human glucocerebrosidase gene may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that treatment with the product has the potential to be curative. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 containing the human glucocerebrosidase gene, for treatment of Gaucher disease, was adopted by consensus.

2.2.9 Product for treatment of acute respiratory distress syndrome - EMA/OD/290/14
[COMP co-ordinator: J. Torrent-Farnell]

The sponsor formally withdrew the application for orphan designation, on 27 January 2015.

2.2.10 Autologous adipose tissue-derived stromal vascular fraction cells for treatment of systemic sclerosis, Assistance Publique Hôpitaux de Marseille - EMA/OD/296/14
[COMP co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing autologous adipose tissue-derived stromal vascular fraction cells was considered justified based on preclinical and on preliminary clinical data showing efficacy of the product on relevant endpoints.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure.

The condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous adipose tissue-derived stromal vascular fraction cells may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing an effect on relevant endpoints in patients that had not responded to previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by systemic sclerosis.

A positive opinion for autologous adipose tissue-derived stromal vascular fraction cells, for treatment of systemic sclerosis, was adopted by consensus.

2.2.11 Product for treatment of Duchenne muscular dystrophy - EMA/OD/257/14
[COMP co-ordinator: P. Evers]

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 March meeting.

2.2.12 Chimeric 2'-O-(2-methoxyethyl) / DNA modified oligonucleotide targeted to huntingtin RNA for treatment of Huntington's disease, Isis USA Ltd - EMA/OD/256/14
[COMP co-ordinator: V. Stoyanova]

Following review of the application by the Committee, it was agreed to rename the indication to "chimeric 2'-O-(2-methoxyethyl) modified oligonucleotide targeted to huntingtin RNA".

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chimeric 2'-O-(2-methoxyethyl) modified oligonucleotide targeted to huntingtin RNA was considered justified based on data in preclinical models of the condition showing improvements in motor skills and anxiety.

The condition is chronically debilitating due to progressive motor dysfunction, severe behavioural and cognitive disturbances, and life-threatening with a median survival time reported in the range of 15 to 18 years after onset.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal

product containing chimeric 2'-O-(2-methoxyethyl) modified oligonucleotide targeted to huntingtin RNA may be of significant benefit to those affected by the condition. The sponsor has provided data showing that the product acts through inhibition of expression of the huntingtin gene, which may lead to improvements in several aspects of the condition, including survival, behaviour and movement disorders, as supported by preclinical data. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for chimeric 2'-O-(2-methoxyethyl) modified oligonucleotide targeted to huntingtin RNA, for treatment of Huntington's disease, was adopted by consensus.

2.2.13 Product for treatment of follicular lymphoma - EMA/OD/275/14
[COMP co-ordinator: B. Bloechl-Daum]

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 March meeting.

2.2.14 Product for treatment of Stargardt's disease - EMA/OD/295/14
[COMP co-ordinator: K. Westermark]

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 March meeting.

2.2.15 Enoxacin for treatment of amyotrophic lateral sclerosis, Impasara Ltd - EMA/OD/283/14
[COMP co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing enoxacin was considered justified based on beneficial effects on motor function and disease progression in preclinical models of the disease.

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

The condition was estimated to be affecting not more 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing enoxacin may be of significant benefit to those affected by the condition. The sponsor has provided data that demonstrate that the product delays the onset of symptoms and improves motor function in preclinical models of the condition. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.16 Ex vivo expanded autologous human keratinocytes containing epidermal stem cells transduced with a COL17A1 encoding retroviral vector for treatment of epidermolysis bullosa, Chiesi Farmaceutici S.p.A. - EMA/OD/299/14
[COMP co-ordinator: A. Matulevičienė]

The Committee agreed that the condition, epidermolysis bullosa, 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-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *COL17A1*-encoding retroviral vector was considered justified based on pre-clinical data.

The condition is chronically debilitating and life-threatening, in particular due to severe generalised blistering resulting in poor quality of life and shortened life expectancy.

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.

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

A positive opinion for ex-vivo-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *COL17A1*-encoding retroviral vector, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.17 Ex vivo expanded autologous human keratinocytes containing epidermal stem cells transduced with a COL7A1 encoding retroviral vector for treatment of epidermolysis bullosa, Chiesi Farmaceutici S.p.A. - EMA/OD/298/14
[COMP co-ordinator: A. Matulevičienė]

The Committee agreed that the condition, epidermolysis bullosa, 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-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *COL7A1*-encoding retroviral vector was considered justified based on pre-clinical data.

The condition is chronically debilitating and life-threatening, in particular due to severe generalised blistering resulting in poor quality of life and shortened life expectancy.

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.

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

A positive opinion for ex-vivo-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *COL7A1*-encoding retroviral vector, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.18 Ex vivo expanded autologous human keratinocytes containing epidermal stem cells transduced with a LAMB3 encoding retroviral vector for treatment of epidermolysis bullosa, Chiesi Farmaceutici S.p.A. - EMA/OD/297/14
[COMP co-ordinator: J. Torrent-Farnell]

The Committee agreed that the condition, epidermolysis bullosa, 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-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *LAMB3*-encoding retroviral vector was considered justified based on preliminary clinical data in patients with the condition showing stable skin engraftment.

The condition is chronically debilitating and life-threatening, in particular due to severe generalised blistering resulting in poor quality of life and shortened life expectancy.

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.

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

A positive opinion for ex-vivo-expanded autologous human keratinocytes containing epidermal stem cells transduced with a *LAMB3*-encoding retroviral vector, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.19 Product for diagnosis of glioma - EMA/OD/280/14
[COMP co-ordinator: B. Bloechl-Daum]

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

2.2.20 Product for treatment of pancreatic cancer- EMA/OD/302/14
[COMP co-ordinator: B. Bloechl-Daum]

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 March meeting.

2.2.21 Human reovirus type 3 Dearing strain for treatment of ovarian cancer, Oncolytics Biotech (UK) Limited - EMA/OD/304/14
[COMP co-ordinator: B. Bloechl-Daum]

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 human reovirus type 3 Dearing strain was considered justified based on preclinical models of the condition showing improved survival, reduced ascites formation and reduction in tumour volume in treated subjects.

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 not more than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human reovirus type 3 Dearing strain may be of significant benefit to those affected by the condition. This was considered justified based on a novel mechanism of action that may translate into improved efficacy, as supported by preclinical and preliminary clinical data that report responses in patients who have relapsed following previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human reovirus type 3 Dearing strain, for treatment of ovarian cancer, was adopted by consensus.

2.2.22 Humanized anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 for treatment of ovarian cancer, ImmunoGen Europe Limited - EMA/OD/281/14

[COMP co-ordinator: B. Bloechl-Daum]

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 humanized anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 was considered justified based on studies performed on valid preclinical models and preliminary clinical data showing antitumour activity.

The condition is chronically debilitating in particular 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 not more than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved effects in reduction of tumour burden when used in combination with existing treatments as well as preliminary clinical data in patients who have relapsed or are refractory to authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised anti-folate receptor 1 monoclonal antibody conjugated to maytansinoid DM4, for treatment of ovarian cancer, was adopted by consensus.

2.2.23 Product for treatment of congenital venous malformations - EMA/OD/282/14

[COMP co-ordinator: D. Krievins]

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 March meeting.

2.2.24 Product for treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue - EMA/OD/286/14
[COMP co-ordinator: K. Kubáčková]

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

2.2.25 Product for treatment of nodal marginal zone lymphoma - EMA/OD/284/14
[COMP co-ordinator: K. Kubáčková]

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

2.2.26 Product for treatment of splenic marginal zone lymphoma - EMA/OD/285/14
[COMP co-ordinator: K. Kubáčková]

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

2.2.27 Lenvatinib for treatment of hepatocellular carcinoma, Eisai Europe Limited - EMA/OD/287/14
[COMP co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing lenvatinib was considered justified based on pre-clinical in vivo models of the condition and preliminary clinical data in patients with the condition.

The condition is life-threatening because it is often discovered in advanced phase, and survival following diagnosis is approximately 6 to 20 months. The main chronically debilitating manifestations include abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lenvatinib may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo and clinical data that demonstrate that patients with advanced metastatic hepatocellular carcinoma have partial response or stable disease following treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lenvatinib, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2.28 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/278/14
[COMP co-ordinator: V. Stoyanova]

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 March meeting.

2.2.29 Melphalan flufenamide for treatment of plasma cell myeloma, Oncopeptides AB - EMA/OD/293/14 *[COMP co-ordinator: K. Kubáčková]*

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

The intention to treat the condition with the medicinal product containing melphalan flufenamide was considered justified based on preclinical data in relevant models of the condition showing prolongation of survival and preliminary clinical data showing responses in patients who had relapsed or were refractory to previous treatment.

The condition is chronically debilitating in particular due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years.

The condition was estimated to be affecting approximately 3.6 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing melphalan flufenamide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that show clinical responses in patients who had relapsed or were refractory to previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for melphalan flufenamide, for treatment of plasma cell myeloma, was adopted by consensus.

2.2.30 Recombinant human monoclonal antibody binding to vascular adhesion protein-1 for treatment of primary sclerosing cholangitis, Biotie Therapies Corp - EMA/OD/288/14
[COMP co-ordinator: A. Corrêa Nunes]

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

The intention to treat the condition with the medicinal product containing recombinant human monoclonal antibody binding to vascular adhesion protein-1 was considered justified based on pre-clinical in vivo data showing a reduction of hepatic inflammation and fibrosis.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure, and the increased risk of developing hepatocellular cancer. Common findings include pruritus which may be very distressing, usually occurring at night, hyperlipidaemia, hypothyroidism, deficiency of fat-soluble vitamins and osteopaenia.

The condition was estimated to be affecting approximately 1.6 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human monoclonal antibody binding to vascular adhesion protein-1 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate a reduction in hepatic fibrosis. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human monoclonal antibody binding to vascular adhesion protein-1, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2.31 Product for prevention of organ rejection following solid organ transplantation - EMA/OD/308/14
[COMP co-ordinator: K. Westermark]

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 March meeting.

2.2.32 Product for treatment of Duchenne muscular dystrophy - EMA/OD/307/14
[COMP co-ordinator: P. Evers]

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 March meeting.

2.2.33 Product for treatment of Ebola virus disease - EMA/OD/310/14
[COMP co-ordinator: A. Lhoir]

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 March meeting.

2.2.34 Product for treatment of Leber congenital amaurosis - EMA/OD/309/14
[COMP co-ordinator: A. Magrelli]

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 March meeting.

2.2.35 Sodium; 3- [(4aR, 6R, 7R, 7aS)-7-hydroxy-2-oxido-2-sulfanylidene-4a, 6, 7, 7a-tetrahydro-4H-furo [3, 2-d] [1, 3, 2] dioxaphosphinin-6-yl] -2-bromo-6-phenyl-5H-imidazo [1, 2-a] purin-9-one for treatment of retinitis pigmentosa, Universitätsklinikum Tübingen (UKT) - EMA/OD/289/14
[COMP co-ordinator: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing sodium 3-[(4aR,6R,7R,7aS)-7-hydroxy-2-oxido-2-sulfanylidene-4a,6,7,7a-tetrahydro-4H-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-2-bromo-6-phenyl-5H-imidazo[1,2-a]purin-9-one was considered justified based on preclinical data in

relevant models of the condition supporting improved survival of photoreceptors and improvement of retinal function.

The condition is chronically debilitating due to the development of nyctalopia (night blindness) and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting less than 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for sodium 3-[(4aR,6R,7R,7aS)-7-hydroxy-2-oxido-2-sulfanylidene-4a,6,7,7a-tetrahydro-4H-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-2-bromo-6-phenyl-5H-imidazo[1,2-a]purin-9-one, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.36 Product for treatment of systemic sclerosis - EMA/OD/306/14
[COMP co-ordinator: K. Westermark]

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 March meeting.

2.2.37 Trientine tetrahydrochloride for treatment of Wilson's disease, GMP-Orphan SAS - EMA/OD/001/15
[COMP co-ordinator: K. Westermark]

The Committee agreed that the condition, Wilson's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing trientine tetrahydrochloride was considered justified based on preliminary clinical data.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later on in the brain. The liver disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing trientine tetrahydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided data showing that trientine 2HCl is only authorized in one EU country and further elaborated on the lack of availability, resulting in an unmet medical need for the patients in the community. Therefore, the availability of trientine tetrahydrochloride in the whole of EU could be of significant benefit. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for trientine tetrahydrochloride, for treatment of Wilson's disease, was adopted by consensus.

2.3. Revision on the COMP opinions

2.3.1 Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of adenovirus infection following haematopoietic stem cell transplantation, Miltenyi Biotec GmbH - EMA/OD/245/14
[Co-ordinators: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus was considered justified based on clinical reports showing reduction of viral load and favourable clinical outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to interstitial pneumonitis, hepatitis, haemorrhagic cystitis or nephritis, haemorrhagic colitis, central nervous system disease and disseminated disease. Mortality rate is up to 67%.

The condition was estimated to be affecting less than 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus, for treatment of adenovirus infection following haematopoietic stem cell transplantation, was re-adopted by consensus.

2.3.2 Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of Epstein-Barr virus infection following haematopoietic stem cell transplantation, Miltenyi Biotec GmbH - EMA/OD/247/14
[Co-ordinators: B. Dembowska-Bagińska]

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of Epstein-Barr virus infection following haematopoietic stem cell transplantation".

The intention to treat the condition with the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus was considered justified based on clinical reports showing reduction of viral load and favourable clinical outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to the development of enteritis with multiple ulcers, hepatitis, encephalitis and extensive lymphadenopathy; EBV infections do progress to post-transplant lymphoproliferative disease in about 10% of cases.

The condition was estimated to be affecting less than 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus, for treatment of Epstein-Barr virus infection following haematopoietic stem cell transplantation, was re-adopted by consensus.

2.4. Appeal procedure

None.

2.5. Evaluation on-going

The Committee noted that evaluation was on-going for 16 applications for orphan designation.

2.6. Validation on-going

The Committee was informed that validation was on-going for 50 applications for orphan designation.

3. Requests for protocol assistance

3.1 For treatment of African trypanosomiasis [Coordinator: B. Bloechl-Daum]

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

3.2 For treatment of Stargardt's disease [Coordinator: K. Westermark]

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

3.3 For treatment of pancreatic cancer [Coordinator: B. Bloechl-Daum]

The Committee was briefed on the significant benefit issues.

3.4 For treatment of amyloid light-chain amyloidosis [Coordinator: K. Westermark]

The Committee was briefed on the significant benefit issues.

3.5 For treatment of Pemphigus [Coordinator: B. Bloechl-Daum]

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

3.6 For treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis [Coordinator: B. Bloechl-Daum]

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

3.7 For treatment of mastocytosis [Coordinator: K. Westermark]

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

3.8 For treatment of active ulcerative colitis [Coordinator: K. Westermark]

The Committee was briefed on the significant benefit issues.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for 1 application submitted and 21 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

An updated overview of orphan applications for Marketing Authorisation was circulated.

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

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

5.1.1 Levofloxacin hemihydrate for treatment of cystic fibrosis; Aptalis Pharma SAS (EU/3/08/566)

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

The potential advantages and assumed clinical benefit(s) of the proposed product in relation to the current standard of maintenance antibiotic care of chronic Pseudomonas a. infection in cystic fibrosis, with particular focus on the authorised products for inhalation use.

The potential benefits, in terms of clinically relevant advantage and/or major contribution to patient care, that Quinsair would bring to the treatment of cystic fibrosis.

The sponsor was invited to present and discuss any available clinical data supporting the claims of significant benefit.

In its written response, and during an oral explanation before the Committee on 10 February 2015, the sponsor discussed the available data that supported the marketing authorisation application and positioned the product in the context of other existing satisfactory treatments for the proposed condition. The sponsor produced arguments on both a clinically relevant advantage and a major contribution to patient care.

With regards to the clinically relevant advantage, the sponsor argued that on the basis of the pivotal trial, the proposed product was non-inferior to Tobi inhalation solution, and had a sustained effect on lung function and a reduction in the percentage of patients who require both administration of anti-pseudomonal antibacterials and hospitalization for respiratory symptoms. An improved safety profile over other existing treatments was also argued. The COMP considered that there were no data to confirm the significant benefit assumption and that non-inferiority would not suffice to justify significant benefit.

A major contribution to patient care was also argued on the basis of a more convenient administration scheme, a shorter nebulization time and the absence of a need for reconstitution or refrigeration. The COMP considered that these advantages were at this point in time assumptive as there was no data of the clinical consequences of the claimed improved convenience.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the product from the registry of orphan medicinal products, on 12 February 2015.

5.1.2 Ruxolitinib for treatment of polycythaemia vera; Novartis Europharm Limited (EU/3/14/1244)

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 March meeting.

Post-meeting note:

The sponsor formally withdrew the product from the EC Register of Orphan Medicinal Products, on 17 February 2015, prior to responding to the list of issues.

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

5.2.1 Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175)

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 March meeting.

5.2.2 Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

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

5.3. On-going procedures

5.3.1 Blinatumomab for treatment of acute lymphoblastic leukaemia; Amgen Europe B.V. (EU/3/09/650)

5.3.2 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

5.3.3 Isavuconazonium sulfate; Basilea Medical Ltd:

a) treatment of invasive aspergillosis (EU/3/14/1284)

b) treatment of mucormycosis (EU/3/14/1276)

5.3.4 Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

5.3.5 Cysteamine hydrochloride for treatment of cystinosis; Lucane Pharma (EU/3/14/1341)

5.3.6 Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

5.3.7 Efmoroctocog alfa for treatment of haemophilia A; Biogen Idec Ltd (EU/3/10/783)

5.3.8 Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

5.3.9 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

5.3.10 Ibrutinib for treatment of lymphoplasmacytic lymphoma; Janssen-Cilag International NV (EU/3/14/1264)

5.3.11 Ketoconazole for treatment of Cushing's syndrome; Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (EU/3/12/1031)

5.3.12 Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

5.3.13 Recombinant human parathyroid hormone for treatment of hypoparathyroidism; NPS Pharma UK Ltd (EU/3/13/1210)

5.3.14 Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

5.3.15 Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

5.3.16 Lenalidomide for treatment of mantle cell lymphoma; Celgene Europe Limited (EU/3/11/924)

5.3.17 Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

5.3.18 L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

5.3.19 Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

5.3.20 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

5.3.21 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.22 Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

6. Procedural aspects

6.1 Significant Benefit Working group

Meeting was postponed to March.

6.2 Draft Minutes of Italian CHMP/CAT/COMP Presidency meeting

The minutes were adopted with no amendments.

6.3 Update from the European Commission

The European Commission representative gave an update on the activities undertaken by the European Commission.

6.4 NCA/COMP Consultation on proposed process improvements for Orphan procedures (review and reconnect) – Workshop

The workshop took place on 12 February 2015.

6.5 EMA communication on public consultation on application of transparency rules of EU Clinical Trial Regulation

- Questions and answers - Public consultation on implementation of transparency requirements of the European Clinical Trial Regulation
- Press release - Public consultation on application of transparency rules of EU Clinical Trial Regulation
- Fax cover message - EMA communication on Public consultation on application of transparency rules of EU Clinical Trial Regulation

The documents were circulated for information.

6.6 Draft Agenda - PCWP and HCPWP joint meeting – 4 March 2015

The agenda was circulated for information.

6.7 Draft Agenda - PCWP and HCPWP joint meeting - Information session on Biosimilars – 5 March 2015

The agenda was circulated for information.

6.8 Minutes of the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) meeting with all eligible organisations - 26 November 2014

The minutes were circulated for information.

7. Any other business

7.1 Change of meeting dates for July, September and December 2015

The COMP agreed on the revised meeting dates for July, September and December.

7.2 Presidency Hosted 'Strategic Review and Learning Meetings' for 2015 – Proposal for the COMP

No Strategic Review and Learning Meeting are scheduled for the COMP and PDCO under the Latvian and Luxembourger Presidencies of the Council of the European Union (first half and second half of 2015 respectively). The Chair called for a volunteering Member State to organise a joint COMP/PDCO Strategic Review and Learning Meeting during the second half of the year. Alternatively a joint meeting can be organised at the EMA in the margin of the COMP and PDCO plenary meetings.

7.3 COMP involvement in strategy and pilot phase for patient registries

The Chair asked COMP members to volunteer to join the advisory group on Strategy and pilot phase for patient registries (see the presentation given in October 2014 under A.O.B.). The advisory group mostly meets by TC and held its first meeting on 23rd January.

7.4 Rare Diseases Day 2015 (http://www.rarediseaseday.org)

The COMP was informed that the Rare Disease Day 2015 would take place on 28 February. All COMP participants were invited to join a raised hands photo session.

7.5 Ruling of the General Court TEVA vs. EMA/EC

The EMA presented the outcome of the court case.

Date of next COMP meeting: 17-19 March 2015

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 February 20105 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Elena Kaisi	Member	Cyprus	No interests declared	
Katerina Kubacková	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Albert Vincenti	Member	Malta	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Lars Gramstad	Member	Norway	No interests declared	
Bożenna Dembowska-	Member	Poland	No restrictions applicable to this	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bagińska			meeting	
Ana Corrêa Nunes	Member	Portugal	No interests declared	
Flavia Saleh	Member	Romania	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	Member	Sweden	No restrictions applicable to meetings	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No restrictions applicable to meetings	
Aikaterini Moraiti	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Observer	Eurordis	Participation in the meeting as observer allowed	
Ninna Gullberg	Expert - in person*	PDCO member	Direct interests declared	
Pieter de Graeff	Expert - via telephone*	CHMP member	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.