20 July 2017
EMA/COMP/294665/2017
Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 10-12 May 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

10 May 2017, 09:00-19:00, room 2F

11 May 2017, 08:30-19:00, room 2F

12 May 2017, 08:30-12:00, room 2F

Disclaimers

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

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

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

Note on access to documents

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified.

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

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 10-12 May 2017 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 10-11 April 2017 were adopted with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/005/17

Treatment of glioma

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

In the light of the findings from scientific report by Allen et al, Sci Transl Med. 2016 Aug 31;8(354), the sponsor was invited to justify the validity and relevance of the preclinical xenograft model for establishing medical plausibility. In this context, the sponsor was invited to expand on the study methodology and outcome of the non-clinical data presented in the application.

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The COMP acknowledges the current evidence and considers that the current level of evidence is not sufficient to support significant benefit.

The sponsor was requested to elaborate on the results from the preclinical xenograft model to justify the assumption of significant benefit over temozolomide. It seems that temozolomide was more effective in this experiment.

The sponsor was requested to provide additional preclinical or preliminary clinical evidence with the proposed product to support the proposed significant benefit claims:

– synergistic efficacy of the proposed product with temozolomide

– improved efficacy due to continuous oral dosing throughout the entire 28-day cycle

– improved convenience due to oral administration

– improved efficacy and major contribution to patient care in patients that cannot tolerate existing therapies, e.g. elderly patients

Please note, that 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.

Finally, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor further elaborated on the issues raised. It was argued that the preclinical model presented is extensively used in the literature as relevant for the proposed condition. The COMP acknowledged the presented argumentation and considered the preclinical model to be relevant for the justification of medical plausibility in the sought indication.

Regarding prevalence, the COMP accepted the presentation on a more detailed prevalence calculation, taking into consideration regulatory guidance documents; the COMP accepted the justification of the sponsor.

Regarding significant benefit, the sponsor did not present new data but expanded on the data that had been submitted already. The COMP considered the outcome of the comparative preclinical studies to be insufficient to conclude on significant benefit on the basis of an improved efficacy. Furthermore, it was clarified to the sponsor that without further clinical evidence the preclinical safety data was not adequate to support the arguments on improved safety. Finally, the claim on major contribution to patient care for patients that cannot tolerate existing therapies, e.g. elderly patients was not supported with

additional evidence. Therefore, the COMP did not consider that the significant benefit of the proposed product had been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 May 2017, prior to final opinion.

2.1.2. - EMA/OD/017/17

Treatment of cystic fibrosis

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

- Intention to diagnose, prevent or treat

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

– the clinical relevance of the apparently modest effect of the combination of the proposed product and tobramycin in the chronic infection model of *P. aeruginosa* in artificial sputum media and in the nasopharynx migration model.

– In this context, the sponsor should present currently missing P values of the effects of tobramycin alone to further elucidate any significant differences;

– the methodology of the chronic infection study and of the nasopharynx migration study, including in relation to the timing of administration;

– the results of the infected silicone tubes model study, as the difference between tobramycin and the combination of tobramycin and the proposed product seems to be driven by an outlier.

- Significant benefit

In absence of an established medical plausibility the significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor further elaborated on the issues raised. It was stressed that the product has a novel mechanism of action that is assumed to control bacteria in biofilm infection. It was argued that there are no chronic infection preclinical models available in which to test the effect of the product on *P. aeruginosa* infections in a cystic fibrosis environment. It was also argued that the available *in vivo* models of cystic fibrosis do not recapitulate the characteristics of human disease. For this reason the sponsor has used alternative models to mimic *P. aeruginosa* lung infection of cystic fibrosis. The COMP considered that in the absence of clinically relevant outcomes in models of the condition or in affected patients, it would be difficult to establish the criteria of medical plausibility and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 May 2017, prior to final opinion.

2.1.3. - EMA/OD/324/16

Treatment of spinal cord injury

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

- Intention to diagnose, prevent or treat

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

– the variability of the outcome on the BBB score observed in the preclinical model and how the small effect size could predict clinically meaningful benefit. Furthermore, the sponsor should provide additional data on other important functional outcomes, e.g. biomarkers (e.g. justifying the claimed anti-inflammatory effect) or data on other aspect of neurologic improvement (e.g. improvement of spasticity or reflexes, sensorium)

– the similarities and differences between the proposed product and the products that have been studied in the scientific literature and have been provided by the sponsor to support medical plausibility

– a more in depth discussion of the results from presented literature overview with other similar products

- Significant benefit

The proposed arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. However, this argumentation is not supported by evidence. The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on any preclinical or clinical data to justify the assumption of significant benefit over all authorised medicinal products for the proposed orphan indication including methylprednisolone and the authorised products for spasticity and neuropathic pain.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor further elaborated on the available preclinical data with the proposed product and also discussed additional clinical data with other similar products.

The COMP considered that more data could have been presented to understand the mechanism of action and that the presented data was not collected in an adequate preclinical model of the particular target disease setting. The Committee was of the opinion that further data would be needed to support medical plausibility for the purpose of orphan designation.

Regarding significant benefit *versus* authorised products including symptomatic treatments and steroids, the sponsor confirmed its position that the proposed product has a novel mechanism of action with the assumed potential to improve mobility and mortality in patients affected by the condition. It was also outlined that methylprednisolone was not considered to be the best standard of care in the scientific community. The COMP noted that an alternative mechanism of action *per se* is not sufficient for the justification of significant benefit, and that a data-driven comparative discussion *versus* all authorised products would be expected; this was still outstanding.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 May 2017, prior to final opinion.

2.1.4. Synthetic glucagon analogue modified to contain 7 amino acid substitutions - EMA/OD/002/17

Zealand Pharma A/S; Treatment of congenital hyperinsulinism

COMP coordinator: Kerstin Westermark/Vallo Tillmann

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

- Intention to diagnose, prevent or treat

The sponsor described data in preclinical models of the condition but has provided very little detail on the models used, methodology and outcomes observed. In addition, the sponsor presented clinical data in healthy volunteers and patients with type I diabetes, which are of little relevance in this application, which is for treatment of a different condition.

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

– the results obtained *in vivo* in preclinical models in the treatment of congenital hyperinsulinism,

– the relevance of the preclinical models used for the treatment of congenital hyperinsulinism, and the interpretation of the results obtained in the experiments,

– the methodology used in the preclinical studies as well as the results from these studies and its relevance for the development of the product in the condition,

– the relevance of the clinical data used for the acute treatment of hypoglycaemia in type I diabetes in the context of the need for a chronic hypoglycaemia treatment in congenital hyperinsulinism.

- Significant benefit

Glucagon is used as a standard of care to manage hypoglycaemia in congenital hyperinsulinism patients and as such may be viewed as a satisfactory method of treatment.

The sponsor is requested to discuss the arguments for significant benefit and to elaborate on the results from preclinical and clinical studies to justify the assumption of significant benefit over commonly used methods of treatment of hypoglycaemia (e.g. containing glucagon).

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

In the written response, the sponsor provided details of non-clinical studies performed with the use of the product. Although no genetic models of the condition were used, the committee considered that acute hypoglycaemia models were relevant for this application in view of similar underlying pathophysiology. In addition, the sponsor provided a retrospective analysis of treatments received by patients affected by the condition. Glucagon containing products were used only in 1% of such patients due to significant

problems with the stability of currently authorised products, which are readily forming fibrils and aggregates and therefore cannot be administered continuously. The sponsor provided data in the original application in which it appears that the proposed product will be of improved stability and quality. The committee accepted these arguments in favour of significant benefit and the oral hearing was cancelled.

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

The intention to treat the condition with the medicinal product containing synthetic glucagon analogue modified to contain 7 amino acid substitutions was considered justified based on clinical data demonstrating hyperglycaemic effect of the product.

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

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

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 synthetic glucagon analogue modified to contain 7 amino acid substitutions will be of significant benefit to those affected by the condition. The sponsor has provided retrospective clinical data that demonstrate that the use of existing products containing glucagon via continued infusion is limited due to significant stability and quality limitations. The sponsor demonstrated that this problem could be solved with the use of the proposed product, which is characterised by extended stability and does not form fibrils or aggregates. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic glucagon analogue modified to contain 7 amino acid substitutions, for treatment of congenital hyperinsulinism, was adopted by consensus.

2.1.5. Recombinant human Factor IX protein modified with three point mutations - EMA/OD/018/17

Voisin Consulting S.A.R.L.; Treatment of haemophilia B

COMP coordinator: Karri Penttila/Martin Možina

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

Regarding the proposed argument on improved efficacy, the sponsor is reminded that an improved PK profile *per se* is not considered sufficient to support significant benefit. The sponsor is requested to provide additional data *versus* authorised long acting FIX products.

In order to discuss the proposed argument on major contribution to patient care related to subcutaneous administration, the COMP invites the sponsor to substantiate by data that the product has comparable efficacy and safety to other long-acting FIX products.

In the written response, and during an oral explanation before the Committee on 11 May 2017, the sponsor provided further background on the product and its development explaining that it is developed for daily subcutaneous administration. Furthermore, the sponsor provided more details on the preclinical studies and the modelling approach that contextualised the outcome with the efficacy data of currently authorised products. The COMP accepted the argumentation but expressed a strong recommendation for protocol assistance with a significant benefit question to the COMP in order to discuss the strategy to demonstrate significant benefit with clinical data at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing recombinant human factor IX protein modified with three point mutations was considered justified based on preclinical data from valid disease models demonstrating that treatment improved coagulation.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury.

The condition was estimated to be affecting approximately 0.25 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 factor IX protein modified with three point mutations will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the proposed product can improve blood coagulation by daily subcutaneous administration in the same range as currently authorised products. In contrast, currently authorised products are administered via non-daily intravenous injections. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for recombinant human factor IX protein modified with three point mutations, for treatment of haemophilia B, was adopted by consensus.

2.1.6. Sildenafil - EMA/OD/304/16

Avivia Beheer BV; Treatment of congenital diaphragmatic hernia

COMP coordinator: Armando Magrelli/Mario Ricciardi

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

- Proposed condition

The sponsor is invited to discuss the proposed condition in the context of the classification of paediatric pulmonary hypertensive vascular disease (Cerro et al, Pulmonary circulation 2011 1; 2).

The sponsor is also requested to discuss all risk factors for persistent pulmonary hypertension of the newborn, and with regards to congenital diaphragmatic hernia, discuss the risk level to develop the condition.

- 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 arterial pulmonary hypertension, the sponsor should further elaborate on the envisioned scheme of administration in which the product is going to be used, including dose, route, time of initiation of treatment, criteria for definition of the individuals to be administered with the product.

The sponsor is also invited to discuss the relevance of the proposed *in vivo* model and the results obtained, in particular with regards to the absence of observations after birth.

- 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition and provide an updated calculation taking into consideration the entirety of the population at risk.

The sponsor is also invited to provide a prevalence estimate for congenital diaphragmatic hernia as such, in the context of a treatment indication.

In the written response, the sponsor proposed to amend the applied indication to "treatment of congenital diaphragmatic hernia" on the rationale that the diagnosis of the condition must be made before pharmacological intervention can commence. It was clarified that the majority of congenital diaphragmatic hernia cases are diagnosed prenatally, and that there is an important correlation with up to approximately 94% of embryos developing perinatal pulmonary vascular maladaptation associated with the condition. As regards the proposed administration of the product, the applicant is proposing maternal sildenafil administration to foetuses with predicted severe or moderate pulmonary hypoplasia. In this population, the occurrence of persistent pulmonary hypertension of the newborn is expected to be higher than 65%. Congenital diaphragmatic hernia is usually diagnosed at around 20 weeks, and the sponsor anticipates that treatment will start in the window between 20 and 25 weeks. The proposal is to administer an oral formulation of sildenafil to the mother, and it is stated that this is feasible because a) sildenafil crosses the placenta and b) the use of sildenafil in pregnant population such as in the context of preeclampsia has not identified any safety concerns. The Committee acknowledged that the change of indication was thus appropriate.

With regards to the medical plausibility, the applicant elaborated on the relevance of the preclinical settings used, reporting that the subjects have impaired airway and vascular development, pathologic lung compliance, airway resistance, tissue damping and elastance, mimicking the clinical phenotype. An article was also cited (Russo et al, Thorax, 2016;0: 1–9.) reporting thickness improvements in peripheral pulmonary vessels, pulmonary vascular resistances, terminal bronchiolar density, lung mechanics. Furthermore, a nitrofen-induced model of the condition (Luong et al, Circulation. 2011;123:2120-2131.) was also discussed, where antenatal sildenafil improves pathological features of persistent pulmonary hypertension of the newborn, including lung morphometry, capillary density, PA medial wall thickness, right ventricular hypertrophy. The COMP considered that the medical plausibility is thus considered acceptable.

As regards the prevalence calculation for the new proposed indication, the applicant is proposing 0.03 per 10,000, calculated on the basis of a birth-prevalence of 2.8/10,000,

assuming as well that 82% would survive and have duration of condition of days or weeks (less than a year). The COMP considered information from one Member State, where an estimation of the point prevalence in 2013 was estimated to be 1.3 in 10,000.

The Committee also considered that the pathophysiology of congenital diaphragmatic hernia is a combination of lung hypoplasia and immaturity associated with persistent pulmonary hypertension of newborn and cardiac dysfunction. With advances in the management of the condition, the overall survival has improved and has been reported to be 70-90% in non-ECMO infants and up to 50% in infants who undergo ECMO. (Chandrasekharan et al, Matern Health Neonatol Perinatol. 2017 Mar 11;3:6.)

Based on these considerations, the oral explanation was cancelled as all raised issues have been considered addressed.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of congenital diaphragmatic hernia.

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

The intention to treat the condition with the medicinal product containing sildenafil was considered justified based on non-clinical data in an *in vivo* model of the proposed condition, supporting branching, thickness and ejection dynamics improvements in the pulmonary vasculature.

The condition is life-threatening and chronically debilitating due to persistent pulmonary hypertension of the newborn and cardiac dysfunction. The overall survival has been reported as low as 50% in infants who are in need of extracorporeal membrane oxygenation.

The condition was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for sildenafil, for treatment of congenital diaphragmatic hernia, was adopted by consensus.

2.1.7. - EMA/OD/001/17

Prevention of rejection following solid organ transplantation

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

- Proposed condition

The sponsor is invited to reword the proposed indication to “treatment of solid organ transplantation” in line with the exceptional circumstances discussed in the updated guideline ENTR/6283/00 Rev 04. Updated sections for the chronically debilitating/life-threatening nature and prevalence calculation are invited as needed.

- Intention to diagnose, prevent or treat

In order to justify the medical plausibility, data with the specific product in either preclinical models or in affected patients are expected. In the cited preliminary clinical observations, the proposed active substance is used in the context of induced chimerism in kidney transplant recipients, following combined kidney and bone marrow transplantation.

The applicant is invited to discuss to what extent the reported effects may be attributed to the proposed product and not to stem cell immunomodulation.

- Significant benefit

In the absence of a justified medical plausibility, significant benefit is a contradictory argument. In case the sponsor presents data to justify medical plausibility, further justifications will be needed for the assumption of significant benefit.

The sponsor is invited to provide a data-driven comparative discussion versus all authorised products in the context of the proposed condition.

In the written response, and during an oral explanation before the Committee on 11 May 2017, the sponsor accepted to amend the indication, but did not provide any further data or updated seriousness and prevalence sections as it had been requested by the COMP. The COMP had also asked for a data-driven comparison for the purpose of justifying significant benefit, which was not provided either.

During the oral explanation, it was asserted that the chimerism induced by the concomitant bone marrow transplantation was transient, and not the main driver for immune-tolerance. The applicant also informed that preclinical data in a model supporting the proposal are available. The settings of these experiments and the results obtained were not presented in detail to allow the COMP to draw any conclusions.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 May 2017, prior to final opinion.

2.1.8. - EMA/OD/248/16

Prevention of arteriovenous access dysfunction in haemodialysis patients

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

For the purposes of orphan medicinal product designation, arteriovenous access dysfunction in haemodialysis patients should be justified as a distinct medical entity or a valid subset; the sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The condition could be viewed as a complication resulting from treatment of an underlying condition or as an integral procedure of a treatment modality which is haemodialysis.

In addition, the sponsor presented data with the use of unspecific (surrogate) models of vascular inflammation, which are not accurately representing the proposed condition.

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of arteriovenous access dysfunction in haemodialysis patients, the sponsor should further elaborate on:

– the relevance of the preclinical models used for the prevention of arteriovenous access dysfunction in haemodialysis patients, and the interpretation of the results obtained in the experiments,

– the methodology used in the preclinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

- Number of people affected

The sponsor proposed a prevalence estimate based on valid sources but including only patients undergoing vascular access surgery. Patients at risk of such intervention seem not to be included in the calculation.

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 and to provide contemporary prevalence estimate based on most up-to-date data. The sponsor should describe and justify the methodology used for the prevalence calculation. The sponsor is asked to provide both incident haemodialysis patients and patients undergoing haemodialysis being at risk of access dysfunction as complementation to the approach based on surgical procedures.

The sponsor should re-calculate the prevalence estimate based on relevant and recent 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.

In the written response, and during an oral explanation before the Committee on 11 May 2017, the sponsor insisted that the patient population for which the treatment is intended are only patients with arteriovenous fistula or arteriovenous graft, therefore consideration of patients on haemolysis as a whole would not be appropriate. The committee questioned these assumptions in the view of a systemic nature of the proposed treatment and the potential pharmacodynamic activity of the product also in other patients on haemolysis. In addition, incidence of the condition was discussed in view of the sponsor's new calculations. The sponsor provided data to show that the incidence of haemolysis in the EU is above 5 in 10,000 and thus does not fall under the ceiling for prevalence criterion for an orphan drug designation. It was also discussed, whether patients with arteriovenous access would have to have the procedure repeated throughout their chronic treatment. It appeared that a need of retreatment was likely, and the prevalence calculation of AV access surgeries provided by the sponsor (3.5 in 10,000) would not take into account the need of repeated surgery in a proportion of patients. The Committee also considered that the condition constituted an unacceptable subset of a broader condition, defined by a treatment modality of 'haemodialysis'. However haemodialysis as a whole is not rare in the orphan context.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 May 2017, prior to final opinion.

2.1.9. Tripotassium citrate monohydrate and potassium hydrogen carbonate - EMA/OD/016/17

Advicenne Pharma SA; Treatment of distal renal tubular acidosis

COMP coordinator: Olimpia Neagu

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

For the purposes of orphan medicinal product designation, distal renal tubular acidosis should be justified as a distinct medical entity or a valid subset; the sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). In particular, the sponsor was requested to justify the exclusion of some secondary forms of renal tubular acidosis from the proposed indication.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life-threatening nature of the condition by providing mortality/survival data.

- 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should recalculate the estimate taking into consideration all cases of secondary distal renal tubular acidosis.

- Significant benefit

The arguments on significant benefit are based on a claim of major contribution to patient care and improved safety over the authorised products.

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

It is well known that extrapolation from 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.

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

Additionally, the sponsor is invited to discuss any documented difficulties such as palatability issues with the currently existing formulations *vis-à-vis* the proposed medicinal product subject of this application.

In the written response, the sponsor addressed the raised issues of prevalence and significant benefit.

With regards to delineating the proposed indication, the main point discussed by the sponsor in favour of distal renal tubular acidosis was a distinct pathophysiology involving ineffective H+-ATPase and/or AE1 transporters in the α-intercalated cells of the distal renal tubule (due to either mutations of or auto-antibodies against the renal transporters). This in turn leads to the unique biochemical combination of high urine pH, low blood bicarbonate and low blood potassium. As regards the covered population it is argued that for the

acquired forms of distal renal tubular acidosis, the confirmed, plausible cases and cases without specific information as well were encompassed based on the supposition that the pathophysiological mechanism is shared for all the forms of this autoimmune disease (i.e. autoantibodies directed against the AE1/H+-ATPase transporters). The life-threatening nature was also discussed, with a citation of literature studies pointing that the condition can lead to death up to approximately 10% of inherited distal renal tubular acidosis cases. This can be considered acceptable.

As regards the prevalence, the sponsor further clarified how the estimate for primary distal renal tubular acidosis was calculated, on the basis of publications and consultations from national reference centres. As regards the acquired cases, it is asserted that its prevalence is driven by primary Sjogren, with 2.6% to 5.3% of Sjogren patients developping the condition. The sponsor stressed that prevalence in secondary Sjogren syndrome (SS) is covered in the specific associated autoimmune diseases, and Systemic lupus erythematosus, primary biliary cirrhosis and autoimmune hepatitis are considered for the purpose of calculating prevalence for secondary distal renal tubular acidosis. The overall conclusion was thus not revised and reached up to 2.1 per 10,000.

As for the raised issue of the significant benefit, the sponsor further elaborated on the results of the crossover clinical study, discussing that while the study was of non-inferiority design, the results show improved efficacy of the product *versus* standard of care, which was shown to be statistically significant. The applicant also submitted a discussion of the “ease of administration” and “palatability” of the product *versus* other existing treatments.

The COMP considered that the condition and prevalence have been adequately delineated based on the above justifications provided. As regards significant benefit, the claim on major contribution to patient care was not endorsed because the documented and serious issues with the already available products were not presented. However, the crossover study presented supports an assumption of improved efficacy *versus* standard of care. Therefore, a clinically relevant advantage was considered justified. The committee accepted these arguments in favour of significant benefit and the oral hearing was cancelled.

The Committee agreed that the condition, distal renal tubular acidosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tripotassium citrate monohydrate and potassium hydrogen carbonate was considered justified based on preliminary clinical data showing restoration of serum bicarbonate levels in affected patients.

The condition is chronically debilitating due to sensorineural hearing loss, restricted growth, rickets and nephrolithiasis and life-threatening with mortality reported as high as approximately 10% for some groups of affected patients.

The condition was estimated to be affecting approximately 2.1 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 tripotassium citrate monohydrate and potassium hydrogen carbonate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support restoration of

serum bicarbonate levels, which compare favourably to existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tripotassium citrate monohydrate and potassium hydrogen carbonate, for treatment of distal renal tubular acidosis, was adopted by consensus.

2.1.10. - EMA/OD/014/17

Treatment of ovarian cancer

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

- Significant benefit

The sponsor presented non-clinical data demonstrating added effect of the proposed product when used in combination with paclitaxel and cisplatin. No comparative data *vis-à-vis* bevacizumab was presented.

The arguments on significant benefit are based on the new mechanism of action leading to the potential improved efficacy in the condition and improved safety over bevacizumab.

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

The sponsor is invited to elaborate on any clinical data available to date.

In the written response, and during an oral explanation before the Committee on 11 May 2017, the sponsor elaborated on non-clinical studies in which the product was shown to be of improved efficacy in comparison with the chemotherapy combination treatment using carboplatin and paclitaxel. The sponsor also clarified that there are several positions in the therapeutic algorithm for ovarian cancer where the product could show significant benefit, as in neoadjuvant setting in advanced (stage 3-4) ovarian cancer. In addition, the sponsor provided initial data from the ongoing clinical study, which is meant to evaluate the safety of the product. The sponsor appraised the positive safety results so far and argued that in neoadjuvant setting the product would compare favourably to bevacizumab, which cannot be used right before the surgery. Patients enrolled in the presented study are few, therefore arguments of improved safety of the product *vs.* bevacizumab were considered premature. In addition, patients enrolled did not represent the intended clinical setting of the product, and no efficacy data were available at this point. The Committee also considered that all products authorised for the front line treatment of advanced ovarian cancer have to be taken into consideration when demonstrating significant benefit. It was considered that the assumption of significant benefit over all authorised products cannot be made at this point in time and the sponsor was invited to consider resubmitting in the future when more data become available that would allow a comparative discussion.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 May 2017, prior to final opinion.

2.1.11. - EMA/OD/311/16

Treatment of neonatal abstinence syndrome

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

- Proposed condition

For the purposes of orphan medicinal product designation, neonatal Abstinence Syndrome should be justified as a distinct medical entity or a valid subset; the sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor was invited to delineate the scope of the proposed indication *vis a vis* other abstinence and addiction syndromes.

- 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 neonatal abstinence syndrome, the sponsor should further elaborate on the scope of the proposed indication, and elaborate on how the product will be administered.

In the sought settings, the sponsor was invited to submit any preclinical study or preliminary clinical observations, and present clinically relevant outcomes to justify the intention to treat.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition can be defined as being life-threatening or chronically debilitating.

- 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 justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation, and include the severity stages of the proposed condition.

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

- Significant benefit

The sponsor was invited to provide a significant benefit justification *versus* all authorised products with indications encompassing the sought orphan condition.

In the absence of data in the sought indication medical plausibility and significant benefit may not be considered by the COMP.

The sponsor formally withdrew the application for orphan designation, on 26 April 2017, prior to responding to the list of issues.

2.1.12. - EMA/OD/020/17

Treatment of subarachnoid haemorrhage

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 subarachnoid haemorrhage, the sponsor should further elaborate on the results obtained in the preclinical model and how this data can predict clinically meaningful benefits for patients affected by the condition. The sponsor should clarify if additional preclinical or preliminary clinical data with the proposed product is available. It would be useful to obtain more information on the ongoing study/planned development.

- 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 aim to provide a more accurate prevalence estimate for subarachnoid haemorrhage; the current proposal is lower than the previously designated orphan condition aneurysmal subarachnoid haemorrhage. The sponsor should revisit the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action leading to the potential improved efficacy in the condition as single therapy or as add-on therapy. The current argumentation cannot be considered sufficient to establish significant benefit. The sponsor is requested to provide a data-driven comparative discussion on significant benefit *versus* nimodipine.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, and during an oral explanation before the Committee on 11 May 2017, the sponsor presented additional published preclinical data on behavioural outcomes to support medical plausibility. Further *in vitro* data was also supplied on the proposed mechanism of action of the product. The COMP acknowledged the data and accepted this level of evidence for the assumption of medical plausibility for the purpose of orphan designation.

Regarding significant benefit, the sponsor mainly argued that there was still an unmet medical need while acknowledging that there was not yet any preclinical or clinical data on the proposed product *versus* or on top of the authorised product nimodipine. The COMP

concluded that further data was necessary to determine significant benefit *versus* authorised treatments.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 May 2017, prior to final opinion.

2.1.13. Sirolimus - EMA/OD/007/17

Vale Pharmaceuticals Limited; Treatment of tuberous sclerosis

COMP coordinator: Bożenna Dembowska-Bagińska/Daniel O'Connor

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

- Significant benefit

The sponsor has not considered topical hospital formulations of sirolimus and other commonly used methods in the treatment of the condition.

The sponsor should further elaborate on the potential clinically relevant advantage their product will have using clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of these patients.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, the sponsor produced data for two different topical formulations (0.1% and 1%) which they have been preparing. They have produced stability data analysis of their formulations and have compared it to formulations which have been prepared by another source for both concentrations and at different temperatures.

Their higher concentration formulation showed better stability at 6 months than the comparator when kept at room temperature. The COMP accepted that the higher concentration showed adequate stability which could support the basis of a major contribution to patient care as a more stable formulation at 1% sirolimus (the upper limit of the currently available sirolimus topical hospital preparations). The Committee agreed that the condition, tuberous sclerosis, is a distinct medical entity and meets the criteria for orphan designation. The committee accepted the arguments in favour of significant benefit and the oral hearing was cancelled.

The intention to treat the condition with the medicinal product containing sirolimus was justified based on published clinical studies of topical formulations of sirolimus demonstrating positive clinical outcomes on cutaneous angiofibromas.

The condition is chronically debilitating due to facial disfigurement and severe neurodevelopmental symptoms and life-threatening due to the formation of multiple tumours.

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 sirolimus will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data

demonstrating that the proposed topical formulation offers better stability and could translate into long-term efficacy. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for sirolimus, for treatment of tuberous sclerosis, was adopted by consensus.

2.1.14. Decitabine and tetrahydrouridine - EMA/OD/008/17

Ulrich Muehlner; Treatment of sickle cell disease

COMP coordinator: Karri Penttila

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

- Number of people affected

The sponsor proposed a calculation of prevalence based on the incidence of sickle cell gene in the population and the probability of children born with the disease. This is an indirect approach and no data with actual prevalence of identified sickle cell disease cases were given.

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 including studies on patients with the diagnosis as opposed to probability studies.

In the written response, the sponsor provided a calculation of prevalence based on data from 10 national registries in the EU. Although the value proposed, 1.26 in 10,000 is significantly lower than previously accepted conservative estimates of the prevalence of sickle cell disease, the Committee found the methodology and sources used acceptable. The prevalence of approximately 1.3 in 10,000 was considered plausible based on the data provided.

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

The intention to treat the condition with the medicinal product containing decitabine and tetrahydrouridine was considered justified based on clinical data demonstrating a clinically relevant increase in the production of foetal haemoglobin.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival.

The condition was estimated to be affecting approximately 1.3 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 decitabine and tetrahydrouridine will be of significant benefit to those affected by the condition. The sponsor has provided clinical data

that demonstrate that patients who have not responded adequately to treatment with hydroxyurea achieved a clinically relevant increase in foetal haemoglobin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for decitabine and tetrahydrouridine, for treatment of sickle cell disease, was adopted by consensus.

2.1.15. Ibutamoren mesilate - EMA/OD/013/17

Richardson Associates Regulatory Affairs Ltd; Treatment of growth hormone deficiency

COMP coordinator: Vallo Tillmann/Kerstin 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:

- Number of people affected

The sponsor has submitted a prevalence calculation which is based on publications from 1977 to 2006. There are more recent publications and data in the EU. The sponsor is therefore invited to recalculate the prevalence with more current data. 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".

In the written response, the sponsor provided an updated prevalence calculation using recent registry data and publications to address the limitations of the first calculation. The concerns expressed by the COMP on a possible improved patient outcome were addressed by the sponsor using the data from registries. The COMP accepted this approach and agreed that 4.6 in 10,000, which was the upper limit of the prevalence calculation, could be used for the purpose of designation, and that there was no risk that the prevalence could be over 5 in 10,000.

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

The intention to treat the condition with the medicinal product containing ibutamoren mesilate was considered justified based on preliminary clinical data showing acceptable growth rates in patients with the condition.

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

The condition was estimated to be affecting approximately 4.6 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 ibutamoren mesilate will be of significant benefit to those affected by the condition. The sponsor's product is an oral formulation acting through an alternative mode of action to growth hormone treatment. Preliminary clinical data demonstrate that acceptable growth rates can be achieved. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

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

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/023/17

Treatment of sudden sensorineural hearing loss

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 June meeting.

2.2.2. Asp-Arg-Val-Tyr-Ile-His-Pro - EMA/OD/031/17

Envigo Pharma Consulting Limited; Treatment of epidermolysis bullosa

COMP coordinator: Pauline Evers

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 Asp-Arg-Val-Tyr-Ile-His-Pro was considered justified based on improvements observed in mitten deformities and fibrosis, in an *in vivo* model of the condition.

The condition is life-threatening and chronically debilitating due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

The condition was estimated to be affecting approximately 0.7 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 Asp-Arg-Val-Tyr-Ile-His-Pro, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.3. Avacopan - EMA/OD/028/17

ChemoCentryx Limited; Treatment of C3 glomerulopathy

COMP coordinator: Annie Lorence

The Committee agreed that the condition, C3 glomerulopathy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing avacopan was considered justified based on preliminary clinical data showing an improvement in renal function.

The condition is life-threatening and chronically debilitating due to the development of nephrotic syndrome and end-stage kidney disease leading to renal failure.

The condition was estimated to be affecting approximately 0.8 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 avacopan, for treatment of C3 glomerulopathy, was adopted by consensus.

2.2.4. - EMA/OD/295/16

Treatment of invasive candidiasis

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 June meeting.

2.2.5. - EMA/OD/029/17

Treatment of neuroblastoma

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

2.2.6. - EMA/OD/032/17

Treatment of myotonic disorders

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 June meeting.

2.2.7. - EMA/OD/263/16

Treatment of neonatal abstinence syndrome

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

2.2.8. - EMA/OD/325/16

Treatment of spinal cord injury

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 June meeting.

2.2.9. Pentamer formyl thiophene acetic acid - EMA/OD/034/17

NeuroScios GmbH; Treatment of Creutzfeldt-Jakob disease

COMP coordinator: Michel Hoffmann/Dinah Duarte

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

The intention to treat the condition with the medicinal product containing pentamer formyl thiophene acetic acid was considered justified based on data from models of the condition demonstrating reduced prion protein aggregation and improved survival.

The condition is life-threatening due to rapid disease progression with median survival of 14 months and chronically debilitating due to rapid neurological degeneration that produces muscle spasms and progressive loss of mental function, reduced muscular coordination, personality changes, impaired memory and impaired vision.

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 pentamer formyl thiophene acetic acid, for treatment of Creutzfeldt-Jakob disease, was adopted by consensus.

2.2.10. - EMA/OD/030/17

Treatment of amyotrophic lateral sclerosis

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

2.2.11. - EMA/OD/024/17

Treatment of mastocytosis

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

2.2.12. - EMA/OD/025/17

Treatment of pachyonychia congenita

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 June meeting.

2.2.13. - EMA/OD/033/17

Treatment of ischemic optic neuropathy

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 June meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

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

COMP coordinators were appointed for 2 applications submitted

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of haemophilia A

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

3.1.2. -

Treatment of myasthenia gravis

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

3.1.3. -

Prevention of graft-versus-host disease

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

3.1.4. -

Treatment of mercury toxicity

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

3.1.5. -

Treatment of soft tissue sarcoma

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

3.2. Finalised letters

3.2.1. -

Treatment of Wolfram syndrome

The finalised letter was circulated for information.

3.2.2. -

Treatment of Wolfram syndrome

The finalised letter was circulated for information.

3.2.3. -

Treatment of beta-thalassemia intermedia and major

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of acute hepatic porphyria

The new request was noted.

3.3.2. -

Treatment of Prader-Willi syndrome

The new request was noted.

3.3.3. -

Treatment of plasminogen deficiency

The new request was noted.

3.3.4. -

Treatment of graft-versus-host disease

The new request was noted.

4. Review of orphan designation for orphan medicinal products for marketing authorisation

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

4.1.1. Cuprior - trientine tetrahydrochloride – EMEA/H/C/004005/000, EMA/OD/001/15, EU/3/15/1471

GMP-Orphan SA; Treatment of Wilson's disease

COMP coordinator: Martin Možina / Annie Lorence

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:

To support the arguments for significant benefit over marketed trientine formulation, the sponsor claimed an improved availability and compliance.

The sponsor presented the analysis of countries in which the availability of trientine may be limited. The sponsor is requested to further elaborate on the data regarding availability issues, including compassionate use programs, named patient basis use as well local preparations as alternative ways through which patients may access trientine.

No data with the use of Cuprior was presented to support the compliance arguments and the arguments were based on assumptions emerging from a survey conducted among trientine users. The sponsor should further elaborate on any data with the use of their product that would support improved compliance claims. In the absence of data with the product in the condition, the arguments of improved compliance will not be possible to establish.

In its written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor elaborated on the availability of trientine in EU member states and on the results from the survey of patients' preference and reasons for missing a dose. The COMP concluded that:

The proposed therapeutic indication, treatment of Wilson's disease in patients intolerant of D-Penicillamine therapy falls entirely within the scope of the orphan indication of the designated orphan medicinal product for treatment of Wilson's disease.

The prevalence of Wilson's disease (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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.

Satisfactory methods of treatment of the condition have been authorised in the European Union; however, the assumption that Cuprior may be of potential significant benefit to those affected by the orphan condition does not hold. The analysis performed by the sponsor to

substantiate the lack of availability of trientine in the EU was not satisfactory. In addition, the sponsor's claim of significant benefit due to improved compliance was rejected because of the methodology used by the sponsor to support this claim, as no patients had actually received the improved formulation of trientine - Cuprior. In the absence of data with the use of the product it is not possible to confirm the assumption of improved compliance.

An opinion recommending the removal of Cuprior, trientine tetrahydrochloride (EU/3/15/1471) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.1.2. Besponsa - inotuzumab ozogamicin – EMEA/H/C/004119, EMA/OD/194/12, EU/3/13/1127

Pfizer Limited; Treatment of B-cell acute lymphoblastic leukaemia

COMP coordinator: Karri Pentilla / Bozenna Dembowska-Baginska

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 sponsor is invited to present and discuss any available clinical data supporting the significant benefit of the proposed product as compared to all medicinal products currently authorized for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia. This would include both Ph- and Ph+ patients as in the sponsor studies, and would include all authorised products including Blincyto.

Grounds of significant benefit can be based on a clinical advantage or a major contribution to patient care (e.g. ease of use) *vs.* the existing authorised medicinal products. Any claim of significant benefit needs to be supported by clinical data.

In its written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor discussed the significant benefit of Besponsa in the two groups of patients for which MA has been granted, i.e. Ph- and Ph+ adult patients with relapsed of refractory acute lymphoblastic leukaemia.

It was considered that Ph- patients constitute the majority (approximately 75%) of adult acute lymphoblastic leukaemia cases. The standard treatment for relapsing or refractory Ph- acute lymphoblastic leukaemia is standard chemotherapy. A range of different chemotherapy regimens are available, including induction therapy based on a backbone of vincristine, corticosteroids, and anthracyclines (e.g., doxorubicin, daunorubicin), hyper-cyclophosphamide, doxorubicin (adriamycin), and dexamethasone (hyper-CVAD), cytarabine-based regimens such as high dose cytarabine (HIDAC), fludarabine/cytarabine/granulocyte colony-stimulating factor (FLAG) +/- idarubicin, and other chemotherapy. More recently, blinatumomab (Blincyto), a bispecific anti-CD3/CD19 monoclonal antibody, was approved by the EMA.

The phase III study at the base of the MA in the Ph- indication was extensively discussed by the sponsor to support the clinical advantages of Besponsa in relation to the chemotherapy agents commonly used (investigators' choice) in this setting. As no direct comparative data with Blincyto were available, the sponsor performed an indirect comparison with a Matching Adjusted Indirect Comparison analysis, matching single-patient data from the Phase III

Besponsa study with aggregated data from the main study of Blincyto in the same indication.

In the Phase III study there were statistically significant differences in favour of Besponsa in terms of Complete Remission (CR), Complete Remission with incomplete haematological recovery (CRi), Minimal Residual Disease (MRD) for patients with CR/CRi, and median Progression Free Survival (PFS). Median Overall Survival (OS) was also mildly significant (p = 0.0407), with higher statistical significance at an updated analysis of the ITT population with cut-off date at January 2017. The COMP noted that the survival curves of standard chemotherapy and Besponsa show no difference until after 15 months of treatment, with a clinical advantage applicable only to the population surviving after 15 months (approximately 30% of the initial study population). A significant benefit in relation to standard chemotherapy, although modest, was acknowledged.

As regards the Matching Adjusted Indirect Comparison analysis (MAIC), the sponsor used Besponsa individual patient data, and aggregated data from the phase III trial of Blincyto. The baseline variables used in the MAIC included age, gender, maximum of central/local bone marrow blasts, peripheral blasts, white blood cell (WBC) at baseline/diagnosis, salvage status, primary refractory, refractory to salvage, and prior hematopoietic stem cell transplantation (HSCT). The most relevant finding from the MAIC analysis was the higher HSCT rate in Besponsa treated patients *vs.* Blincyto (Odds Ratio 2.3; CI: 1.4-3.8), meaning that a higher number of patients in the Besponsa study were able to be bridged to HSCT. Additional analysis on overall survival and comparisons of long-term survival produced less clear-cut results, and the latter was limited by the few number of patients assessed at later time points. The COMP considered that with the data presented it was difficult to identify a clear relevant clinical advantage of Besponsa vs. Blincyto. On the other hand, a favourable comparison was considered by the Committee in relation to the dosing schedule of Besponsa, 1-hour infusion once a week in 3-4 week cycles, and to the fact that the administration does not require patients to be hospitalized following treatment, as also reported in the SPC. This was considered to represent a major contribution to patient care compared to Blincyto, administered for 2 cycles each of which requiring 4 weeks of continuous infusion, with a rather complex management of the infusion bag. Data presented by the sponsors on hospitalizations due to a variety of causes on the study drug dosing days in the phase III study showed much lower hospitalization rates even compared to standard chemotherapy.

The COMP also discussed the potential significant benefit of Besponsa in Ph+ ALL in relation to the currently authorized products for the relapsing refractory population. The first line treatment of Ph+ acute lymphoblastic leukaemia consists of TKI inhibitors (currently imatinib, dasatinib, and ponatinib). As the authorized therapeutic indication of Besponsa is for adult patients with Ph+ relapsed or refractory B cell precursor acute lymphoblastic leukaemia that have failed treatment with at least 1 TKI, one clinically relevant advantage of Besponsa is that it can be used also once TKIs have failed. Since TKIs different from the ones used in first line may also be used in refractory/relapsing patients, the sponsor also presented some indirect comparison data (not modelled) showing favourable results of Besponsa on Complete Remission (CR) and Complete Remission with incomplete haematological recovery (CRi) in relation to imatinib, dasatinib and ponatinib. The COMP was of the opinion that the last line use of Besponsa after one or more failed TKis could be considered a relevant advantage.

The COMP concluded that:

The proposed therapeutic indication, 'treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)' falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of B-cell acute lymphoblastic leukaemia.

The prevalence of B-cell acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukaemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Besponsa may be of potential significant benefit to those affected by the orphan condition is confirmed. This is based on data from a phase 3 study showing better efficacy of Besponsa on acute lymphoblastic leukaemia relapsed or refractory from previous treatments as compared to the currently authorised chemotherapy agents for the same indication. Compared to blinatumomab (Blincyto), also authorised for this indication, Besponsa showed a more advantageous dosing schedule requiring fewer hospitalization days.

An opinion not recommending the removal of Besponsa, inotuzumab ozogamicin (EU/3/13/1127) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

4.1.3. Spinraza - nusinersen – EMEA/H/C/004312, EMA/OD/141/11, EU/3/12/976

Biogen Idec Ltd; Treatment of 5q spinal muscular atrophy

COMP coordinator: Pauline Evers / Ingeborg Barisic

The COMP concluded that:

The proposed therapeutic indication, treatment of 5q Spinal Muscular Atrophy falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of 5q spinal muscular atrophy.

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

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

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of Spinraza, antisense oligonucleotide targeted to the SMN2 gene, nusinersen (EU/3/12/976) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its April meeting and upon adoption of CHMP opinion.*]

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

4.2.1. Oxervate - cenegermin - EMEA/H/C/004209, EMA/OD/143/15, EU/3/15/1586

Dompe farmaceutici s.p.a.; Treatment of neurotrophic keratitis

COMP coordinator: Geraldine O'Dea / Frauke Naumann-Winter; Expert: Ségolène Ayme

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:

Prevalence:

The sponsor is invited to further elaborate on the prevalence calculation and include data on the milder forms of neurotrophic keratitis which would be identified using the Mackie classification and therefore be more representative of the potential broader population. The sponsor is also invited to further elaborate on the prevalence of the condition in very common situations (e.g. drug toxicity causes of the condition, surgical interventions, the impact of aging among others).

In its written response, and during an oral explanation before the Committee on 10 May 2017, the sponsor did not submit any new data following the question that was raised but further elaborated on the prevalence calculation that they initially submitted.

The sponsor was asked several questions pertaining to the size of the mild forms of the condition and the low reporting of the literature of this form. The sponsor acknowledged that the milder forms could be under reported and that the assumptions made were based on the declarations by the ophthalmologists the sponsor had questioned. The sponsor highlighted that in the literature the moderate and severe forms are reported to have a prevalence of 1.6 in 10,000. They stated that these forms represent a third of all the cases and that they were informed that mild forms represent the remaining two thirds of the cases. Using this reasoning the sponsor proposed 4.1 in 10,000.

The COMP questioned the sponsor on the reasoning for the milder forms and highlighted that this could be larger. The other question raised was the duration of the condition which was not easy to address as the sponsor noted this is not clearly described in the literature. A collection of epidemiological data during the development phase would have introduced more certainty on the actual number.

The COMP accepted the methodology and conservative nature of the submitted prevalence calculation. As there has been no major change in the public domain since the original prevalence calculation submitted for the initial orphan designation the COMP was of the opinion that at this time the proposed prevalence calculation of 4.1 in 10,000 could be

acceptable for the purpose of the maintenance of the orphan designation. The COMP recommended granting the maintenance of the orphan designation.

The COMP concluded that:

The proposed therapeutic indication, treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of neurotrophic keratitis.

The prevalence of neurotrophic keratitis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 4.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to progressive damage of corneal epithelium and stroma leading to loss of vision. Corneal ulceration, infection and perforation can also occur.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of Oxervate, recombinant human nerve growth factor, cenegermin (EU/3/15/1586) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

[*Post-meeting note: The COMP adopted the opinion by written procedure following its May meeting and upon adoption of CHMP opinion.*]

4.2.2. - ciclosporin – EMEA/OD/106/05, EU/3/06/360, EMEA/H/C/004411

Santen Oy; Treatment of vernal keratoconjunctivitis

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 June meeting.

4.2.3. Raxone (idebenone) - Type II variation – EMEA/OD/077/06, EU/3/07/437, EMEA/H/C/003834/II/0003

Santhera Pharmaceuticals (Deutschland) GmbH; Treatment of Duchenne muscular dystrophy

CHMP rapporteur: John Joseph Borg; CHMP co-rapporteur: Andrea Laslop

The status of the procedure at CHMP was noted.

4.2.4. Masipro – masitinib - EMEA/OD/062/04, EU/3/04/242, EMEA/H/C/004159

AB Science; Treatment of Mastocytosis

The status of the procedure at CHMP was noted.

4.2.5. Qinprezo - vosaroxin – EMA/OD/158/11, EU/3/12/990, EMEA/H/C/004118

Sunesis Europe Ltd; Treatment of acute myeloid leukaemia

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.5. Public Summary of Opinions

The draft public summaries of the COMP opinions adopted last month were endorsed for publication on the EMA website.

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

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

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

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

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

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meetings

None

7.1.2. Protocol Assistance Working Group

The working group on Protocol Assistance met on 10 May 2017.

7.1.3. Preclinical Models Working Group

The working group on Preclinical Models met on 11 May 2017.

7.1.4. Impact of Brexit to COMP

The impact of Brexit on the activities of EMA and its Committees was presented.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 11 May 2017.

7.2.2. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes April 2017

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

Revision of the Commission Regulation (EC) No 847/2000 of April 2000 laying down the provisions for implementation of the Criteria for designation of a medicinal product as an orphan medicinal product and definitions of the Concept 'similar medicinal product and 'clinical superiority'
Scope: Review of comments received from the public consultation

The comments received during public consultation on the EC consultation document "Concept of 'similar medicinal product' in the context of the orphan legislation: adaptation to technical progress" were presented.

Document(s) tabled:
2016_07_EC_consultation_paper

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

The draft Agenda of EMA/FDA teleconference on Orphan Medicines April 18, 2017 is available in MMD for information.

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

Documents were circulated in MMD.

Document(s) tabled:
COMP Work Plan 2017

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 10-12 May 2017 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Katerina Kopeckova	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	
Melinda Sobor	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
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	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Ségolène Ayme	Expert - via telephone*	Expert recommended by EMA	No restrictions applicable to this meeting	.
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
OD: Orphan Designation
PA: Protocol Assistance
PDCO: Paediatric Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SA: Scientific Advice
SAWP: Scientific Advice Working Party

Orphan Designation (*section 2 Applications for orphan medicinal product designation*)

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance (*section 3 Requests for protocol assistance with significant benefit question*)

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation (*section 4 Review of orphan designation for orphan medicinal products for marketing authorisation*).

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/