4 February 2016
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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 8-10 December 2015

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

08 December 2015, 09:00-18:30, room 2F

09 December 2015, 09:30-18:30, room 2F

10 December 2015, 09:00-13:00, room 2F

Disclaimers

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

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

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

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

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

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

1.2. Adoption of agenda

COMP agenda for 8-10 December 2015 was adopted with amendments.

1.3. Adoption of the minutes

COMP minutes for 10-12 November 2015 were adopted with 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/148/15

Treatment of interstitial lung disease in children

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 clarify whether they are seeking designation for the whole group of interstitial lung diseases in children (chILDs) or for the subgroup of surfactant dysfunction mutations and related disorders.

For the purpose of orphan medicinal product designation, the chosen target condition needs to be justified as a distinct medical entity or a valid subset. The sponsor's attention is drawn

to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

In case the chosen condition is chILDs, the sponsor is asked to justify why interstitial lung diseases in children should be designated separately from adult ILDs, by highlighting the uniqueness of the paediatric forms and discussing any overlap with adult ILDs. In case the subgroup of surfactant dysfunction mutations and related disorders is chosen, the sponsor is invited to further justify the rationale of this choice and of excluding other forms of 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 treatment of interstitial lung disease in children, the sponsor should further elaborate on the clinical cases presented to support the medical plausibility.

It seems from these cases that patients treated with the tested product had variable clinical outcomes and more information on these cases, including the ones directly treated by the sponsor, are needed. This includes clearer details on the clinical course of the disease in relation to the periods when the children were exposed to the product, and a comparative discussion taking into account the natural course of untreated disease.

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

- Number of people affected

If the group of surfactant dysfunction mutations and related disorders is chosen as target condition, the sponsor should provide a reliable estimated of the prevalence of this population, based on the available sources (literature, databases, etc.) and expressed as a number in 10,000 people in the EU.

In the written response, and during an oral explanation before the Committee on 8 December 2015, the sponsor confirmed the request for the subgroup of surfactant dysfunction mutations and related disorders and not for the whole group of interstitial lung diseases in children (chILDs) and discussed the genetic and histologic features of these conditions. In order to justify significant benefit, the sponsor described preliminary clinical observations from 5 cases directly treated by the sponsor, but no comparative discussion vs. the natural course of untreated disease was presented. The issue of prevalence was also elaborated.

The COMP considered that the proposed indication has not been justified as a distinct medical entity or a validated subset for the purpose of orphan designation, and that there is a lack of data to support medical plausibility, in the sought indication.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 December 2015, prior to final opinion.

2.1.2. - EMA/OD/160/15

Treatment of soft tissue sarcoma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 1 December 2015, prior to responding to the list of issues.

2.1.3. - EMA/OD/116/15

Treatment of acute myeloid leukemia

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 proposed that their product offers significant benefit based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the very limited nature of the findings from the only pre-clinical *in vivo* study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. The assumption should further elaborate this in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 8 December 2015, the sponsor did not present any new preliminary *in vivo* data which was needed to be able to support the significant benefit. The sponsor attempted to justify the use of *in vitro* cell lines which were derived from patients who have relapsed or have refractory acute myeloid leukaemia. The COMP indicated that for significant benefit the sponsor would need some preliminary *in vivo* data. This was highlighted as the condition has many authorised therapies making it necessary to have tangible data to support the clinically relevant advantage.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 December 2015, prior to final opinion.

2.1.4. - EMA/OD/166/15

Treatment of ovarian cancer

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 20 November 2015, prior to responding to the list of issues.

2.1.5. - EMA/OD/122/15

Treatment of post cardiac arrest 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:

- Intention to diagnose, prevent or treat

For the purpose of orphan medicinal product designation, post cardiac arrest syndrome should be justified as a distinct medical entity or a valid subset. The sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is invited to further elaborate on:

a) Why the proposed condition cannot be viewed as a complication of other underlying diseases that led to arrest and necessitated resuscitation.

b) The overlap of the underlying pathologies that led to the arrest with the pathophysiological features induced by the resumption of spontaneous circulation.

- 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 justify the methodology used for the prevalence calculation. In particular the sponsor is invited to elaborate on:

a) The definition of the condition and of the case for epidemiological considerations, in particular with regards to timing and sustainability of resumption of spontaneous circulation, as well as its relation to the definition of a successful CPR and survival at discharge from hospital.

b) The duration of Post cardiac arrest syndrome in particular with regards to any long term complications. Point prevalence will be needed in case the affected patients are considered to include long-term survivors.

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

- Existing methods

The sponsor is invited to list any products authorised in the EU for indications with broader articulations that encompass the targeted patients of this application. In case of products identified, a significant benefit section will be expected.

In the written response, and during an oral explanation before the Committee on 9 December 2015, the sponsor discussed the following points with regards to the proposed condition: firstly, they referred to the underlying conditions as "risk factors" and drew parallels with another procedure. Secondly, they discerned between causes of cardiac arrest and the events related to ischemia reperfusion after successful resuscitation. During the oral explanation the sponsor also referred to the special considerations of the guideline on the format and content of the applications for orphan designations ENTR/6283/00. With regards to the prevalence calculation, two different definitions are discussed regarding sustained resumption of circulation, i.e. arrival at hospital with pulse for out of hospital arrests, or more than 20 minutes, for in hospital arrests. It was stated that the results of a clinical study aiming to create a registry for out of hospital cardiac arrest in Europe are yet to be published, and three sensitivity analyses were presented, one of which surpasses the provisioned threshold. Finally, the notion that satisfactory methods may exist was rejected by the applicant.

The COMP considered that the proposed condition has not been clearly delineated as a distinct entity and can be viewed in the context of a continuum or complication of the underlying conditions that caused the arrest in the first place. With regards to the

prevalence calculation, given that one analysis breaches the threshold and that European registry data are still not known, the uncertainty of respecting the threshold remains. The sponsor has therefore not addressed the issues raised.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 December 2015, prior to final opinion.

2.1.6. - EMA/OD/155/15

Treatment of myelodysplastic syndromes

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 17 November 2015, prior to responding to the list of issues.

2.1.7. Sodium benzoate - EMA/OD/123/15

Syri Limited; Treatment of arginase deficiency

COMP coordinator: Geraldine O'Dea

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

- 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 hyperargininaemia, the sponsor is invited to present any reports of treated patients or groups of patients that is more recent than the ones presented in the application.

In relation to the cases already presented the sponsor is invited to provide a critical discussion of the assumed clinical efficacy of the product, taking into account the natural course of the disease and the different disease severity in the patients described, the acute vs. chronic use (long term outcomes), the use of concomitant treatments, and any other variable that could have influenced the clinical outcome in these cases.

In the written response, and during an oral explanation before the Committee on 9 December 2015, the sponsor clarified that due to the extreme rarity of the condition the number of cases is very limited, and the cases that have been presented are among the few identified in the past two decades and followed up so far. These cases show evidence of efficacy of sodium benzoate both in acute manifestations of the disease, including reducing acute hyperammonaemia, and chronic manifestations as long term maintenance, when used alone or associated with diet.

The COMP noted that since the list of issues had been answered by the sponsor a medicinal product, Ravicti (glycerol phenylbutyrate) had received EC authorization for the treatment of urea cycle disorders including hyperarginenimia. Based on this the COMP asked the sponsor to justify the significant benefit of sodium benzoate versus glycerol phenylbutyrate. The sponsor based the discussion on the existing guidelines for the treatment of urea cycle disorders from the BIMDG (British Inherited Metabolic Diseases Group) and the Suggested guidelines for the diagnosis and management of urea cycle disorders (Häberle et al. Orphanet Journal of Rare Diseases 2012, 7:32). According to the guidelines both sodium benzoate and sodium phenylbutyrate are indicated for the maintenance treatment.

The COMP noted that Ravicti is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients, ≥2 months of age, with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone, therefore the current indication does not cover the acute episodes. The sponsor suggested that they would intend to develop also an IV formulation of sodium benzoate for the treatment of acute episodes.

In view of the position of sodium benzoate in the current guidelines and the potential of using it in acute episodes of decompensated urea cycle disorders including hyperargininaemia, the COMP considered that the significant benefit of the product was sufficiently justified at this stage and expressed a positive opinion on the designation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of hyperargininaemia.

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

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on case reports showing improvement in serum ammonia, symptoms, and long-term consequences of the condition when the product was administered in a non-controlled way, in the context of dietary treatment.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation such as mental retardation and other types of neurological damage.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium benzoate may be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised product, and in acute forms of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for sodium benzoate, for treatment of hyperargininaemia, was adopted by consensus.

2.1.8. Sodium benzoate - EMA/OD/124/15

Syri Limited; Treatment of argininosuccinate lyase deficiency

COMP coordinator: Geraldine O'Dea

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

- 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 arginosuccinic aciduria, the sponsor is invited to present

any reports of treated patients or groups of patients that is more recent than the ones presented in the application.

In relation to the cases already presented the sponsor is invited to provide a critical discussion of the assumed clinical efficacy of the product, taking into account the natural course of the disease and the different disease severity in the patients described, the acute vs. chronic (long term outcome) use, the use of concomitant treatments, and any other variable that could have influenced the clinical outcome in these cases.

In the written response, and during an oral explanation before the Committee 9 December 2015, the sponsor further discussed the clinical cases presented to support the medical plausibility. The sponsor clarified that due to the extreme rarity of the condition the number of cases is very limited, and the cases that have been presented are among the few identified in the past two decades and followed up so far. These cases show evidence of efficacy of sodium benzoate both in acute manifestations of the disease, including reducing acute hyperammonaemia, and chronic manifestations as long term maintenance, when used alone or associated with diet.

The COMP noted that since the list of issues had been answered by the sponsor a medicinal product, Ravicti (glycerol phenylbutyrate) had received EC authorization for the treatment of urea cycle disorders including argininosuccinic aciduria. Based on this the COMP asked the sponsor to justify the significant benefit of sodium benzoate versus glycerol phenylbutyrate. The sponsor based the discussion on the existing guidelines for the treatment of urea cycle disorders from the BIMDG (British Inherited Metabolic Diseases Group) and the Suggested guidelines for the diagnosis and management of urea cycle disorders (Häberle et al. Orphanet Journal of Rare Diseases 2012, 7:32). According to the latter guidelines, sodium benzoate would be the first choice for the treatment of acute episodes with sodium phenylbutyrate as a potential additional treatment (sodium benzoate +/- sodium phenylbutyrate/ phenylacetate; Häberle et al. 2012). Sodium benzoate is also suggested as first choice for maintenance treatment in the Suggested guidelines, and both sodium benzoate and sodium phenylbutyrate are indicated for the maintenance treatment in the BIMDG guidelines.

The COMP noted that Ravicti is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients, ≥2 months of age, with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone, therefore the current indication does not cover the acute episodes. The sponsor suggested that they would intend to develop also an IV formulation of sodium benzoate for the treatment of acute episodes.

In view of the position of sodium benzoate in the current guidelines and the potential of using it in acute episodes of decompensated urea cycle disorders including argininosuccinic aciduria, the COMP considered that the significant benefit of the product was sufficiently justified at this stage and expressed a positive opinion on the designation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of argininosuccinic aciduria.

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

The intention to treat the condition with the medicinal product containing sodium benzoate was considered justified based on case reports showing improvement in serum ammonia,

symptoms, and long-term consequences of the condition when the product was administered in a non-controlled way, in the context of dietary treatment.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation such as mental retardation and other types of neurological damage.

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.

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 sodium benzoate may be of significant benefit to those affected by the condition. This is based on the potential of the product to be used in combination with the currently authorised products and in acute forms of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for sodium benzoate, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.1.9. - EMA/OD/152/15

Treatment of pulmonary arterial hypertension

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 3 December 2015, prior to responding to the list of issues.

2.1.10. - EMA/OD/164/15

Treatment of non-infectious uveitis

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 non-infectious uveitis, the sponsor should further elaborate on the methodology used in the pre-clinical studies as well as the results from these studies. In particular, the sponsor is invited to discuss the relevance of the study design, which may be interpreted as treatment or prevention. Additional information regarding the length of the study and the stage of product development will be required in order to assess the pharmacokinetics of the sustained release formulation.

- 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".

As it seems that the sponsor has excluded part of the population affected by condition; the sponsor should indicate on which population the prevalence calculation is based on. Note

that the prevalence should be calculated for all patients suffering from non-infectious uveitis, not just a subset, for which the product is being developed.

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

- Significant benefit

The sponsor presents many arguments acknowledging the risks associated with the use of authorised treatments, however it is known that extrapolation from preclinical studies cannot predict the safety of a product in its clinical setting. The efficacy of the product compared to the oral formulation, which is authorized is comparable. It is therefore difficult to translate the presented arguments into a clinically relevant advantage or a major contribution to patient care.

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

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, and during an oral explanation before the Committee on 10 December 2015, the sponsor confirmed that the only available data at this point in time is from a preclinical *in vivo* model in which the product was used concomitantly with the disease induction, reflecting prevention rather than treatment setting. The sponsor also informed the committee about planned further development of the product and the intention to test it in a treatment paradigm in another model, which would substantiate the medical plausibility in the future. The COMP considered that in the absence of data in a treatment setting, the medical plausibility for the sought indication could not be considered justified.

With regards to the prevalence issue the proposed figure was recalculated and the final estimate of 3.8 in 10,000 in the EU was considered acceptable by the Committee.

Moreover, the sponsor argued significant benefit by stressing the drawbacks of the existing treatment regimen and arguing that the product will offer a more favourable benefit/risk ratio compared to the standard of care. The COMP considered that it is not possible to evaluate potential clinical safety based on pre-clinical data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 December 2015, prior to final opinion.

2.1.11. Live attenuated Listeria monocytogenes delta actA/delta inlB strain expressing human mesothelin - EMA/OD/168/15

Medpace Germany GmbH; Treatment of pancreatic cancer

COMP coordinator: Brigitte Bloechl-Daum

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

- Intention to diagnose, prevent, or treat

The sponsor is invited to further clarify the rationale to develop this combination treatment, and in this context discuss the individual efficacy and contributory effect of each of the separate components.

- Number of people affected

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

The sponsor has determined the duration of the condition based on epidemiological data of the untreated metastatic disease, which is 6-10 months. The sponsor is invited to revise its current prevalence calculation to reflect the complete duration of the disease, which is considered to be longer than just the untreated metastatic disease phase.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to further discuss the assumption of significant benefit over all authorised medicinal products based on the results from the presented studies. In this context, the sponsor is invited to provide any further preclinical or preliminary clinical data that might be available to support significant benefit considerations.

In the written response, and during an oral explanation before the Committee on 9 December 2015, the sponsor further elaborated on the issues raised:

Regarding the medical plausibility, the sponsor discussed the combination product under development, and presented results in pre-clinical data models of the sought indication and preliminary clinical data that demonstrated a better overall survival outcome for the combination therapy treatment arm versus the single therapy treatment arm. Regarding the prevalence, the sponsor updated the prevalence estimate to include all stages and severity forms of the proposed condition. As for the issue of significant benefit, the sponsor further discussed the available clinical data and performed an indirect comparison of the clinical results versus published literature studies in similar populations.

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

The intention to treat the condition with the medicinal product containing live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin was considered justified based on preliminary clinical data showing that treatment in combination with a product containing two allogenic irradiated pancreatic tumour cell lines improved overall survival of patients affected by the condition.

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

The condition was estimated to be affecting less than 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 live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data of patients affected by the condition that have failed previous treatments with products authorised for the condition and received the medicinal product in combination therapy with a product containing two allogenic irradiated pancreatic tumour cell lines. The treatment may improve the overall survival of selected patients in relation to published overall survival data of similar patients receiving other available treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin, for treatment of pancreatic cancer, was adopted by consensus.

2.1.12. Two allogenic irradiated pancreatic tumour cell lines - EMA/OD/169/15

Medpace Germany GmbH; Treatment of pancreatic cancer

COMP coordinator: Brigitte Bloechl-Daum

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

- Intention to diagnose, prevent, or treat

The sponsor is invited to further clarify the rationale to develop this combination treatment, and in this context discuss the individual efficacy and contributory effect of each of the separate components.

- Number of people affected

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

The sponsor has determined the duration of the condition based on epidemiological data of the untreated metastatic disease, which is 6-10 months. The sponsor is invited to revise its current prevalence calculation to reflect the complete duration of the disease, which is considered to be longer than just the untreated metastatic disease phase.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to further discuss the assumption of significant benefit over all authorised medicinal products based on the results from the presented studies. In this context, the sponsor is invited to provide any further preclinical or preliminary clinical data that might be available to support significant benefit considerations.

In the written response, and during an oral explanation before the Committee on 9 December 2015, the sponsor further elaborated on the issues raised:

Regarding the medical plausibility, the sponsor discussed the combination product under development, and presented results in pre-clinical data models of the sought indication and preliminary clinical data that demonstrated a better overall survival outcome for the combination therapy treatment arm versus the single therapy treatment arm. Regarding the prevalence, the sponsor updated the prevalence estimate to include all stages and severity forms of the proposed condition. As for the issue of significant benefit, the sponsor further discussed the available clinical data and performed an indirect comparison of the clinical results versus published literature studies in similar populations.

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

The intention to treat the condition with the medicinal product containing two allogenic irradiated pancreatic tumour cell lines was considered justified based on preliminary clinical data showing that treatment in combination with a product containing live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin improved overall survival of patients affected by the condition.

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

The condition was estimated to be affecting less than 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 two allogenic irradiated pancreatic tumour cell lines may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data of patients affected by the condition that have failed previous treatments with products authorised for the condition and received the medicinal product in combination therapy with a product containing live attenuated *Listeria monocytogenes* delta *actA*/delta *inlB* strain expressing human mesothelin. The treatment may improve the overall survival of selected patients in relation to published overall survival data of similar patients receiving other available treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for two allogenic irradiated pancreatic tumour cell lines, for treatment of pancreatic cancer, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate - EMA/OD/184/15

TMC Pharma Services Ltd; Treatment of soft tissue sarcoma

COMP coordinator: Adriana Andrić

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

The intention to treat the condition with the medicinal product containing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-

carboxamide hydrogen sulfate was considered justified based on pre-clinical *in vivo* data and preliminary clinical data showing a reduction in the number of metastasis.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting not more than 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in the number of metastasis in patients with advanced disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.2. - EMA/OD/180/15

Treatment of acute promyelocytic leukaemia

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

2.2.3. Cholesterol-conjugated, acyclic nucleobase analogue-containing synthetic double-stranded oligomer specific to SERPINA1 gene - EMA/OD/178/15

Pharma Gateway AB; Treatment of congenital alpha-1 antitrypsin deficiency

COMP coordinator: Armando Magrelli

Following review of the application by the Committee, it was agreed to rename the active substance to synthetic double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue.

The Committee agreed that the condition, treatment of congenital alpha-1 antitrypsin deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue was considered justified based on preclinical data in relevant models of the condition showing reduction of liver polymer deposits and of liver damage with the proposed product.

The condition is life-threatening and chronically debilitating due to the early development of lung emphysema in adults and liver disease in children and adults. In liver disease, intracellular accumulation of mutant alpha-1 antitrypsin polymers in hepatocytes causes liver inflammation leading to hepatitis with cholestasis, cirrhosis or liver scarring. Liver

cancer may occur later in life. Liver transplant may be required in cases of liver failure; death may occur where transplant is unavailable.

The condition was estimated to be affecting less than 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 double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing a relevant effect of the proposed product on liver histology in liver disease from Z alpha-1 antitrypsin deficiency, a manifestation of congenital alpha1 antitrypsin deficiency for which at present no treatment exists. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for synthetic double-stranded oligomer specific to the *SERPINA1* gene and containing a cholesterol-conjugated, acyclic nucleobase analogue, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

2.2.4. - EMA/OD/132/15

Treatment of Burkitt lymphoma

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 January meeting.

2.2.5. Entolimod - EMA/OD/191/15

TMC Pharma Services Ltd; Treatment of acute radiation syndrome

COMP coordinator: Adriana Andrić

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

The intention to treat the condition with the medicinal product containing entolimod was considered justified based on pre-clinical *in vivo* data which showed improved survival.

The condition is life-threatening due to hematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiorgan dysfunction leading to multiorgan failure and carcinogenesis.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

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 entolimod, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.6. - EMA/OD/188/15

Treatment of dystrophic epidermolysis bullosa

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

2.2.7. - EMA/OD/182/15

Treatment of retinal detachment

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 January meeting.

2.2.8. - EMA/OD/177/15

Treatment of autoimmune haemolytic anaemia

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 January meeting.

2.2.9. - EMA/OD/190/15

Treatment of globoid cell leukodystrophy (Krabbe disease)

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

2.2.10. Live attenuated *Listeria monocytogenes* transfected with plasmids encoding HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O - EMA/OD/161/15

Dr Ulrich Granzer; Treatment of anal cancer

COMP coordinator: Katerina Kubáčková

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

The intention to treat the condition with the medicinal product containing live attenuated *Listeria monocytogenes* transfected with plasmids encoding the HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O was considered justified based on preliminary clinical data showing improved relapse free survival.

The condition is chronically debilitating due to any combination of a mass, non-healing ulcer, pain, bleeding, itching, discharge, faecal incontinence and fistulae and life-threatening due to a 5-year survival which varies between 44% and 66%.

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

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 live attenuated *Listeria monocytogenes* transfected with plasmids encoding HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improved relapse free survival in

patients refractory to treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for live attenuated *Listeria monocytogenes* transfected with plasmids encoding the HPV-16E7 protein fused to a truncated fragment of the Lm protein listeriolysin O, for treatment of anal cancer, was adopted by consensus.

2.2.11. - EMA/OD/183/15

Treatment of gastric cancer

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

2.2.12. - EMA/OD/121/15

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 January meeting.

2.2.13. - EMA/OD/186/15

Prevention of necrotising enterocolitis

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 January meeting.

2.2.14. - EMA/OD/189/15

Treatment of pantothenate kinase associated neurodegeneration

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 January meeting.

2.2.15. - EMA/OD/104/15

Treatment of C3 glomerulopathy

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 January meeting.

2.2.16. - EMA/OD/185/15

Treatment of partial deep dermal and full thickness burns

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 January meeting.

2.3. Revision of the COMP opinions

None

2.4. COMP opinions adopted via written procedure following previous meeting

None

2.5. Appeal

None

2.6. Nominations

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

Action: For adoption

Document tabled:
OMPD applications - appointment of coord. at the 8-10 December 2015 COMP meeting

2.7. Evaluation on-going

Nineteen applications for orphan designation will not be discussed as evaluation is on-going.

Action: For information

Notes:
Cross reference to other agenda point. See 5.8.1. Table 6. Evaluation Ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of ovarian cancer

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

3.1.2. -

Treatment of amyotrophic lateral sclerosis

The Committee was briefed on the significant benefit issues.

[*Post-meeting note: The COMP adopted the final proposed answers on the significant benefit issues via written procedure on 18 December 2015.]*

3.1.3. -

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

The Committee was briefed on the significant benefit issues.

[*Post-meeting note: The COMP adopted the final proposed answers on the significant benefit issues via written procedure on 16 December 2015.]*

3.1.4. -

Treatment of Niemann-Pick disease, type C

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

3.1.5. -

Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity

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

3.1.6. -

Treatment of advanced ovarian cancer

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

3.1.7. -

Treatment of acute myeloid leukaemia

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 glycogen storage disease type II (Pompe's disease)

The finalised letter was circulated for information.

3.2.2. -

Treatment of growth hormone deficiency

The finalised letter was circulated for information.

3.2.3. -

Treatment of Prader-Willi syndrome

The finalised letter was circulated for information.

3.3. New requests

None

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. Wakix - 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride - EMEA/OD/087/06, EU/3/07/459, EMEA/H/C/002616

Bioprojet; Treatment of narcolepsy

COMP coordinators: Josep Torrent-Farnell and Giuseppe Capovilla

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:

- Seriousness

The sponsor is requested to further elaborate on the seriousness of the condition, by providing any available morbidity and mortality data on the basis of current literature.

- Prevalence

The sponsor is requested to provide a calculation of the prevalence of the proposed orphan condition at the time of the review, and vary any assumptions used to provide a sensitivity analysis of the conclusion.

- Significant benefit

The sponsor is requested to provide data to document either a clinically relevant advantage or a major contribution to patient care versus both oxybate and modafinil. A data driven discussion for any of the claimed basis is expected. A discussion of the status and any available data from the clinical study with the product as an add-on to sodium oxybate is also expected.

In its written response, and during an oral explanation before the Committee on 8 December 2015, the sponsor further elaborated on the issues raised:

As for the issue of seriousness of the proposed condition, the sponsor stressed the major detrimental effect on quality of life, supported by literature studies and the COMP acknowledged that the condition is chronically debilitating.

With regards to the prevalence, the sponsor did not advance its initial position and still claimed a “2 to 5” per 10,000 estimate, based on only one literature reference (Longstreth and co-workers). The COMP considered that the sponsor has not established the criterion of prevalence because: a) a systemic overview of the epidemiology of the condition based on available sources has not been provided; more studies are available regarding the epidemiology of the condition including recent ones e.g. Oberle et al, Sleep. 2015 Oct 1;38(10):1619-28; b) the sponsor does not comment on the epidemiology at the time of the review, addressing any issues of trends across time; c) the sponsor does not provide a

sensitivity analysis or alternative methodologies of calculating prevalence to ensure that the provisional threshold is respected.

As regards the significant benefit, the sponsor provided further data in terms of a) a multiple treatment comparison analysis for comparing different treatments of narcolepsy (modafinil, oxybate, pitolisant) and b) data from a clinical study, to argue significant benefit versus oxybate.

In particular, as for the multiple comparison analysis, the sponsor pooled together 13 studies, but a limitation is that the comparability of the populations and settings was not discussed. The sponsor acknowledged a potential methodological bias during the oral explanation in response to a direct question on this issue. Moreover, no statistically significant changes were shown between the proposed product and the other two authorised active substances, in terms of ESS change, MWT change and cataplexy. The COMP agreed that the trends argued could not be considered sufficient to justify the significant benefit due to an absence of statistically significant differences and the methodological limitations of multiple comparison analysis.

As regards the clinical study results presented for the justification of significant benefit, this was a double-blind randomised controlled study to assess the efficacy of pitolisant compared to placebo in add-on to sodium oxybate in the treatment of narcoleptic patients with residual Excessive Daytime Sleepiness. The primary endpoint was ESS change, which was not statistically different versus placebo. The sponsor performed a post-hoc analysis of a “supportive” endpoint, the rate of responders defined by a reduction of 3 points or more (or stabilisation below 10), and also included two patients who withdrew prematurely, to reach a statistically significant difference in the rate of responders. The COMP considered that this study did not provide any data that show significant benefit versus modafinil, and that the data to support the argument over sodium oxybate had the methodological limitation of a post hoc analysis.

In conclusion, the COMP is of the view that the sponsor has not provided sufficient data demonstrating the prevalence remaining below or equal to 5 in 10,000 and, as regards significant benefit, the COMP is of the view that the sponsor did not establish a clinically relevant advantage or major contribution to patient care versus the two authorised products in the condition.

The COMP concluded that:

The proposed therapeutic indication “treatment of narcolepsy with or without cataplexy” falls within the scope of the designated orphan indication which has been worded in broader terms as “treatment of narcolepsy”.

The sponsor has not established that the prevalence of narcolepsy (hereinafter referred to as “the condition”) remains below 5 in 10,000; the applicant has not taken into consideration all the available and most recent epidemiological studies and did not provide a sensitivity analysis as requested by the Committee.
The condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy.

The assumption that Wakix may be of potential significant benefit to those affected by the orphan condition over satisfactory methods of treatment authorised in the EU is not supported as:

- The sponsor has argued a clinically relevant advantage of improved efficacy and improved safety versus modafinil and sodium oxybate, based on trends from a) a multiple treatment comparison and network meta-analysis of literature studies, comparing pitolisant, modafinil, and sodium oxybate and b) clinical data form a study where pitolisant was used as an add-on to sodium oxybate.
- The COMP considered that no significant differences of the product versus the authorised counterparts have been established, with regards to any of the endpoints discussed in the multiple comparison analysis, or with regards to the primary endpoint of the study where the product was used as an add-on to sodium oxybate.

An opinion recommending the removal of Wakix, 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride (EU/3/07/459) from the EC Register of Orphan Medicinal Products was adopted by consensus.

4.1.2. Spectrila - asparaginase – EMA/OD/063/04, EU/3/04/258, EMEA/H/C/002661

Medac Gesellschaft fuer klinische Spezialpraeparate mbH; Treatment of acute lymphoblastic leukaemia

COMP coordinator: Bozenna Dembowska-Bagińska and Frauke Naumann-Winter

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 8 December 2015, prior to responding to the list of issues.

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

4.2.1. Dropcys (CYSTIRANE) – mercaptamine – EMA/OD/106/14, EU/3/14/1341, EMEA/H/C/004038

Lucane Pharma; Treatment of cystinosis

The status of the procedure at CHMP was noted by the COMP.

4.2.2. - migalastat – EMEA/OD/105/05, EU/3/06/368, EMEA/H/C/004059

Amicus Therapeutics UK Ltd; Treatment of Fabry disease

The status of the procedure at CHMP was noted by the COMP.

4.2.3. Neofordex - dexamethasone acetate – EMEA/OD/133/09, EU/3/10/745, EMEA/H/C/004071

LABORATOIRES CTRS; Treatment of multiple myeloma

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

4.2.4. Translarna - 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid – EMEA/OD/107/04, EU/3/05/277, EMEA/H/C/002720/II/0012

PTC Therapeutics International Limited; Treatment of cystic fibrosis

CHMP rapporteur: Johann Lodewijk Hillege; CHMP co-rapporteur: Concepcion Prieto Yerro

The status of the procedure at CHMP was noted by the COMP.

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 1 application.

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. Strategic Review & Learning meetings

During the Dutch EU presidency, the Medicines Evaluation Board will organise a strategic and learning meeting for the CHMP and the COMP in Utrecht, The Netherlands.

The meeting will be held on 30th May 2015 to 1st June 2015 including a joint CHMP/COMP working session.

5.2. Coordination with EMA Scientific Committees or CMDh-v

None

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

5.3.1. Significant Benefit Working Group

The working group on Significant Benefit met on 10 December 2015.

5.3.2. Preclinical Model Working Group

The working group on Preclinical Model met on 9 December 2015.

5.4. Cooperation within the EU regulatory network

5.4.1. European Commission

Report on the Commission Expert Group on Rare Diseases meeting held on 12-13 November 2015

The presentation was postponed to the next COMP meeting.

5.4.2. European Commission

Public consultation on the Commission Notice on the application of Articles 3,5 and 7 of Regulation (EC) NO 141/2000 on Orphan Medicinal Products

The COMP was informed that the Commission Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on Orphan Medicinal Products, replacing the 2003 Communication on orphan medicinal products, had been published for public consultation until 15 February 2016.

5.4.3. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

Report on the ENCePP Plenary meeting held on 24 November 2015

The COMP representative reported from the latest ENCePP meeting.

5.5. Cooperation with International Regulators

None

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

None

5.7. COMP work plan

5.7.1. Draft COMP Work Plan 2016

The Chair presented the latest version of the COMP Work Plan 2016. As discussions regarding cross-committee activities are still ongoing, the final proposal will be circulated after the meeting for adoption by written procedure.

5.8. Planning and reporting

5.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015 were circulated.

5.8.2. Overview of orphan marketing authorisations/applications

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

6. Any other business

6.1.1. Research projects in the Netherlands

ZonMW (The Netherlands Organisation for Health Research and Development) funds health research and stimulates use of the knowledge developed to help improve health and healthcare in the Netherlands.

Among the long list of research supportive programmes there is a call for research proposals under the topic of “Personalized medicine and rare diseases” or “Personalized medicine and oncology”. The first assessment round was in fall 2015 and the Dutch COMP members were part of the evaluating committee.

A selected number of proposals are forwarded to the next stage in which the assessment by external experts is required. COMP members had been invited by their Dutch colleagues to express their interest in being an external expert for this programme.

A list with the titles of the grant proposals was circulated and COMP members signed in for projects they may be interested to assess. The secretariat of ZonMW will contact experts for further details. The Dutch COMP members thanked their COMP colleagues for their interest in this programme.

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 8-10 December 2015 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	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Andri Andreou	Member	Cyprus	No interests declared	
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	
Judit Eggenhofer	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	
Dainis Krievins	Member	Latvia	No restrictions applicable to this meeting	
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	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	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	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Dan Henrohn	Observer	Sweden - MPA	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.