London, 19 August 2016
EMA/532759/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Carbaglu

carglumic acid

Procedure no: EMEA/H/C/000461/P46/033

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Introduction

On 02JUN2016, the MAH submitted a completed paediatric study for Hyperammonemia in Organic Acidemia Decompensation, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study title and number is a stand alone study:

Retrospective Observational Study of Hyperammonemia in Organic Acidemia Decompensation Episodes in Patients Treated with Carbaglu® with/or without Ammonia Scavengers versus Ammonia Scavengers Alone.

2.2. Information on the pharmaceutical formulation used in the study

No information was provided regarding the pharmaceutical formulation used in the study. However the drug product / name was “Carglumic acid (Carbaglu®) “ thus it is assumed that it is the one marketed in EU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- OE-CGA001-OA2009 and OE-CGA001-OA2012; "Retrospective Observational Study of Hyperammonemia in Organic Acidemia Decompensation Episodes in Patients Treated with Carbaglu® with/or without Ammonia Scavengers versus Ammonia Scavengers Alone" (study code: OE-CGA001-OA2009/ 0E-CGA001-OA2012)
- exploratory analysis of the pooled results of these 2 retrospective observational studies (OE-CGA001-OA2009 and OE-CGA001-OA2012);

Resumé

In 2009, a retrospective observational study (OE-CGA001-OA2009) was submitted to the EMA to support the claim of an extension of the indication of Carbaglu in the treatment of hyperammonemia due to organic acidemias (Methyl-Malonic academia/MMA, Propionic Acidemia/PA, Isovaleric Acidemia/IVA). The new indication for Carbaglu was approved in the European Union in May 2011.

Clinical study report (dated 31 August 2015)

Later in 2012, Orphan Europe wanted to also extend the indication of Carbaglu in US. For this purpose, it was advised to Orphan Europe to add a comparative arm to study OE-CGA001-OA2009 by conducting a retrospective observational study to evaluate hyperammonemia in OA decompensation episodes in patients treated with NH3 scavengers without carglumic acid.

This study, with protocol number OE-CGA001-OA2012, is considered as the control arm of study OE-CGA001-OA2009. Study OE-CGA001-OA2012 was set up and conducted in the closest possible conditions to study OE-CGA001-OA2009, particularly regarding the type of study, the selected sites, the period of data collection and the data collected. The data from the two studies were pooled; an analysis by treatment group was performed. This analysis supports the efficacy and safety of carglumic acid (Carbaglu) for the treatment of hyperammonemia due to PA, MMA and IVA. This study showed that the reduction of plasma NH3 level occurred faster in patients treated with carglumic acid with or without NH3 scavengers. This reduction was particularly marked during the first hours of the acute hyperammonemic metabolic decompensation i.e. when it is critical to rapidly decrease the plasma NH3 level to limit potential neurological sequelae.

Addendum to clinical study report (dated 21 September 2015)

An addendum to this CSR written later and dated 21 September 2015 is also included. It summarizes the exploratory analysis of the pooled results of these 2 retrospective observational studies (OE-CGA001-OA2009 and OE-CGA001-OA2012) in 3 separate treatment groups: carglumic acid only (Study OE-CGA001-OA2009), carglumic acid + NH3 scavengers (Study OE-CGA001-OA2009), and NH3 scavengers only (Study OE-CGA001-OA2012). Ammonia level data were censored at the time of extracorporeal detoxification initiation. The purpose of this exploratory analysis is to examine the effect of carglumic acid without the effect of NH3 scavengers or extracorporeal detoxification (HD/HF/PD) in patients with OA following episodes of hyperammonemic decompensation. Use of carglumic acid alone does not reflect clinical practice since the primary goal of treatment is to adequately treat patients as soon as possible using all available medications to reduce NH3 levels quickly.

Depending on NH3 levels, NH3 detoxification usually occurs through the use of a combination of pharmacological treatments to eliminate NH3 excess (e.g., NH3 scavengers: sodium benzoate or sodium phenylbutyrate) and/or through extracorporeal detoxification, such as Hemodialysis, Hemofiltration or Hemodiafiltration, or Peritoneal dialysis in severely decompensated patients. Due to their invasive nature, extracorporeal detoxification is usually initiated when other measures fail to control hyperammonemia. The age of the patient, local facilities, and center experience orient the choice of extracorporeal detoxification method. At present, none of these NH3 scavengers are approved for the treatment of hyperammonemia associated with propionic acidemia (PA), methyl-malonic acidemia (MMA), or isovaleric acidemia (IVA) in the European Union (nor in US).

2.3.2. Clinical study

Clinical study number and title

OE-CGA001-OA2009/ OE-CGA001-OA2012: Retrospective Observational Study of Hyperammonemia in Organic Acidemia Decompensation Episodes in Patients Treated with Carbaglu® with/or without Ammonia Scavengers versus Ammonia Scavengers Alone

Description

Studies OE-CGA001-OA2009 and OE-CGA001-OA2012 were retrospective observational studies conducted to evaluate hyperammonemia in OA decompensation episodes in patients treated with carglumic acid with or without NH3 scavengers (Study OE-CGA001-OA2009: treatment group) and NH3 scavengers only (Study OE-CGA001-OA2012: control group). Data regarding decompensation episodes from 01 January 1995 until 31 October 2009 were recorded in as many patients as possible

enrolled in key experienced European hospitals in Italy, France, Spain, and the United Kingdom (Studies OE-CGA001-OA2009 and OE-CGA001-OA2012) and Germany, the Netherlands, and Turkey (Study OE-CGA001-OA2009).

The pooled results of these 2 retrospective observational studies (OE-CGA001-OA2009 and OE-CGA001-OA2012) is summarized in 3 separate treatment groups: carglumic acid only (Study OE-CGA001-OA2009), carglumic acid + NH3 scavengers (Study OE-CGA001-OA2009), and NH3 scavengers only (Study OE-CGA001-OA2012). Ammonia level data were censored at the time of extracorporeal detoxification initiation. The purpose of this exploratory analysis is to examine the effect of carglumic acid without the effect of NH3 scavengers or extracorporeal detoxification (HD/HF/PD) in patients with OA following episodes of hyperammonemic decompensation.

Use of carglumic acid alone does not reflect clinical practice since the primary goal of treatment is to adequately treat patients as soon as possible using all available medications to reduce NH3 levels quickly.

Depending on NH3 levels, NH3 detoxification usually occurs through the use of a combination of pharmacological treatments to eliminate NH3 excess (e.g., NH3 scavengers: sodium benzoate or sodium phenylbutyrate) and/or through extracorporeal detoxification, such as HD, HF, or PD in severely decompensated patients. Due to their invasive nature, extracorporeal detoxification is usually initiated when other measures fail to control hyperammonemia. The age of the patient, local facilities, and center experience orient the choice of extracorporeal detoxification method.

At present, none of these NH3 scavengers are approved for the treatment of hyperammonemia associated with propionic acidemia (PA), methyl-malonic acidemia (MMA), or isovaleric acidemia (IVA) in the US or Europe.

Methods

Objective(s)

The post-hoc exploratory analyses discussed in this addendum were performed in 3 treatment groups:

- Carglumic acid only (Study OE-CGA001-OA2009)
- Carglumic acid + NH3 scavengers (Study OE-CGA001-OA2009)
- NH3 scavengers only (Study OE-CGA001-OA2012)

Data related to demographics, other baseline characteristics, and efficacy are presented by episode of decompensation and data related to safety are presented by episode and patient. For some patients, data from several episodes were collected. Since these episodes may have been treated differently, data related to them, despite being from the same patient, may have been included in different treatment groups.

Study design

This was a pooling of retrospectively acquired data in studies OE-CGA001-OA2009 and OE-CGA001-OA2012.

The rationale for these post-hoc analyses (3 treatment groups and censored data) was to better assess the isolated effect of carglumic acid in lowering NH3 levels over time by removing 2 main confounding NH3-reducing factors: NH3 scavengers and HD/HF/PD.

Study population /Sample size

The safety set (SS) included all decompensation episodes from patients enrolled in 1 or both studies who received at least 1 dose of study treatment (carglumic acid, NH3 scavengers).

The full analysis set (FAS) included all decompensation episodes from patients enrolled in 1 or both studies who received at least 1 dose of study treatment (carglumic acid, NH3 scavengers) and had a confirmed diagnosis of OA (PA, MMA, or IVA) by the treating physician.

The post-hoc exploratory analyses were conducted on the FAS population. For the efficacy analyses, NH3 data was censored at the time of HD/HF/PD initiation.

The post-hoc exploratory analyses were limited to:

• Demographic summary with descriptive statistics only: Demography, Baseline characteristics, Study treatment dosing and Concomitant medications.

Treatments

Outcomes/endpoints

Efficacy summaries:

- Summary of daily plasma NH3 levels by 12-hour periods from 0 to 48 hours and by 24-hour periods from Day 2 to Day 5

  The highest NH3 levels by period were summarized using descriptive statistics. The mean ratio to baseline was calculated and compared between treatment groups (in pairs) using the Wilcoxon test.

- Success rate

  Success rate was defined as achieving a plasma NH3 level <= 60 µmol/L (in the absence of death, initiation of HD/HF/PD, or withdrawal from treatment for safety reasons): the proportion of success in each treatment group was computed with its 95% confidence interval (CI) using the Clopper-Pearson method; the 2 proportions were compared using the Fisher's exact test.

- Time to success

  Kaplan-Meier survival curves for time to success (in the absence of death, initiation of HD/HF/PD, or withdrawal from treatment for safety reasons) were produced for each treatment group. The 3 treatment groups were compared using the log-rank test.

- Summary of clinical symptoms and markers at baseline and endpoint

- Change in the number of clinical symptoms and markers: analyzed from baseline to endpoint with descriptive statistics

- Shift in clinical symptoms and markers (symptoms versus no symptoms): analyzed from baseline to endpoint

Safety summaries:

- Adverse event (AE) summaries with descriptive statistics

Statistical Methods

General Considerations

Continuous variables were summarized using descriptive statistics: mean, standard deviation (SD), median, interquartile range (Q1 - Q3), range of values (i.e., minimum and maximum values), and number of patients and/or number of episodes.

Categorical data were presented using counts and percentages. Percentages were calculated according to the number of patients/episodes for whom/which data were available.

For safety analyses, descriptive statistics were used to summarize safety parameters by treatment group. Adverse events were summarized at the patient and episode level with regard to number of AEs per patient, and presented as a summary. Adverse events were also summarized at the event level with regard to the relationship to treatment, action taken, and outcome, and presented in tabular form. Finally, the number and percentage of episodes/patients experiencing each AE within each body system were summarized overall in tabular form.

Post-hoc statistical analyses were performed on the database locked on 02 July 2014. All analyses were produced using the Statistical Analysis Systems (SAS®) software versions 9.2/9.3, (SAS Institute, Cary, Northern Carolina, USA) and Adclin® software version TPF 3.2.2 (Adclin SA, Paris, France).

Handling of Dropouts or Missing Data

With regard to dropouts and missing data, the same rules as in the full CSR were applied for the post-hoc analyses. No imputations were performed on missing plasma NH3 data.

Multiple Comparisons/Multiplicity

No correction to nominal p-values for multiple comparisons was applied. All tests were considered significant at the 5% significance level (i.e., $p \leq 0.05$). These post-hoc analyses should be considered exploratory, and inferences made based on p-values should be interpreted with caution. Statistical tests should be considered to be descriptive/suggestive rather than conclusive.

Results

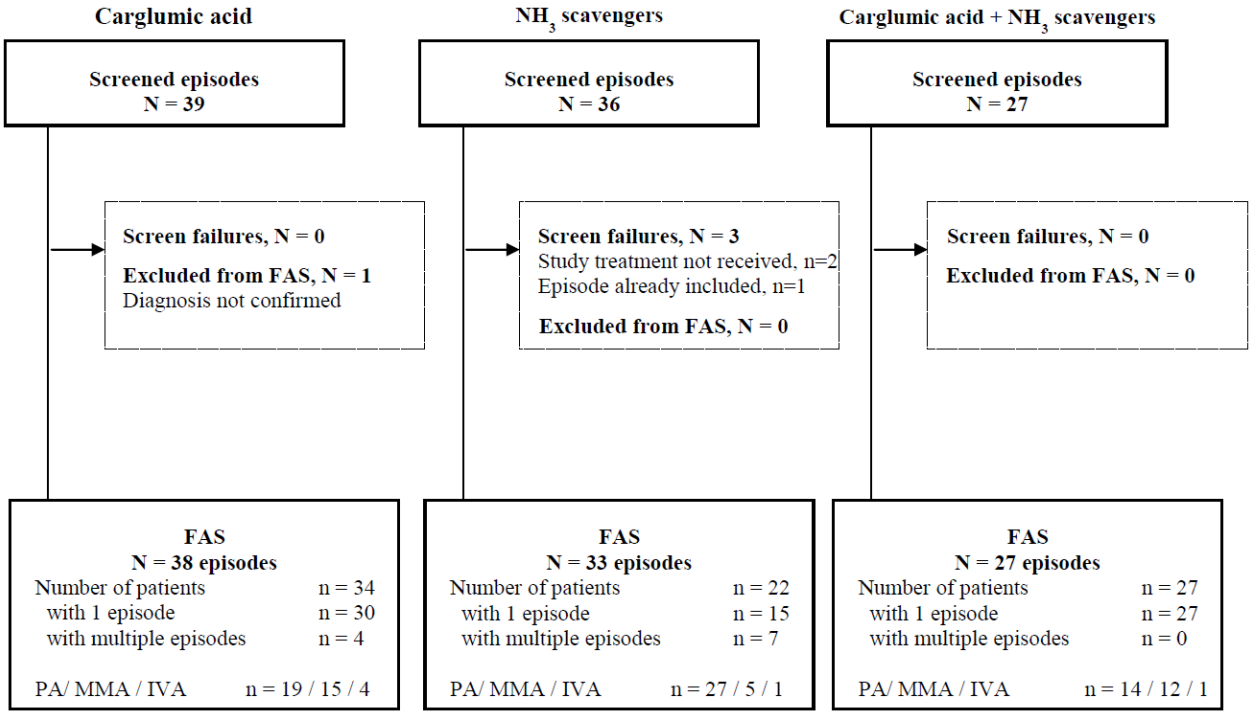
Recruitment / Number analysed

A consort chart by episode is presented in Figure 1. Note that the same patient may have had several episodes that were treated differently which explains the difference between the number of patients and the number of episodes in each treatment group.

A total of 102 episodes were collected: 39 episodes in the carglumic acid group, 36 episodes in the NH3 scavengers group, and 27 episodes in the carglumic acid + NH3 scavengers group.

Among the 102 episodes collected, 3 episodes were considered screen failures (study treatment not received [n=2] and episode already included [n=1]). All 99 episodes were included in the SS. A total of 98 episodes from 83 patients were included in the FAS; 1 episode was excluded due to a diagnosis other than OA.

Figure 1 – Consort Chart by Episode



Baseline data

Demographic Data

Demographic data by episode for patients included in the FAS are presented in Table below.

The majority of episodes in all treatment groups occurred in patients with a confirmed diagnosis of PA although the proportion was higher in the NH3 scavengers group than the other 2 groups (50.0% in the carglumic acid group, 81.8% in the NH3 scavengers group, and 51.9% in the carglumic acid + NH3 scavengers group).

Episodes occurred in a relatively even number of females and males in all treatment groups and median gestational age of patients was 39.0 weeks in all groups.

Table 1 – Demography - FAS (N = 98 Episodes)

Description		Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
		Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
Confirmed diagnosis				
PA	n (%) of episodes	19 (50.0)	27 (81.8)	14 (51.9)
MMA	n (%) of episodes	15 (39.5)	5 (15.2)	12 (44.4)
IVA	n (%) of episodes	4 (10.5)	1 (3.0)	1 (3.7)
Gender				
Female	n (%) of episodes	16 (42.1)	17 (51.5)	15 (55.6)
Male	n (%) of episodes	22 (57.9)	16 (48.5)	12 (44.4)
Gestational age (weeks)	N	37	28	26
	Missing	1	5	1
	Mean (SD)	38.78 (1.65)	38.32 (2.14)	38.46 (1.94)
	Q1/Median/Q3	38.0/39.0/40.0	38.0/39.0/40.0	37.0/39.0/40.0
	Min, Max	34.0, 41.0	34.0, 41.0	35.0, 41.0

FAS = full analysis set; IVA = isovaleric acidemia; Max = maximum; Min = minimum; MMA = methyl-malonic acidemia; N/n = number; NH_3 = ammonia; PA = propionic acidemia; Q = quartile; SD = standard deviation

History of the Disease

The median age at diagnosis was 13.0 days (Q1 - Q3 = 5.0 - 33.0 days) in the carglumic acid group, 9.5 days (Q1 - Q3 = 5.0 - 19.5 days) in the NH3 scavengers group, and 8.0 days (Q1 - Q3 = 5.0 - 15.0 days) in the carglumic acid + NH3 scavengers group.

A family history of OA was reported in a greater proportion of episodes in the NH3 scavengers group (48.5%) than in the carglumic acid (15.8%) or the carglumic acid + NH3 scavengers (7.4%) groups. Likewise, consanguinity of parents was reported in a greater proportion of episodes in the NH3 scavengers group (69.7%) than in the carglumic acid (42.1%) or the carglumic acid + NH3 scavengers (29.6%) groups.

Summary of Episodes

Summary of episodes data are presented in Table 2.

The median number of days between the start of the episode and the start of treatment was 1 day in all treatment groups. More than 80% of the episodes ended within 15 days, with a median duration of episodes of 6.0 days in the carglumic acid and carglumic acid + NH3 scavengers groups, and 8.5 days in the NH3 scavengers group.

The median duration of treatment was 4.0 days in the carglumic acid and NH3 scavengers groups, and 5.0 days in the carglumic acid + NH3 scavengers group.

End of the treatment was due to the end of the episode in 31 out of 35 (88.6%) episodes in the carglumic acid group, 16 out of 31 (51.6%) episodes in the NH3 scavengers group, and 25 out of 27 (92.6%) episodes in the carglumic acid + NH3 scavengers group.

End of the treatment was due to death in 3 out of 35 (8.6%) episodes in the carglumic acid group, 3 out of 31 (9.7%) episodes in the NH3 scavengers group, and none of the episodes in the carglumic acid + NH3 scavengers group.

Switched to long-term treatment was reported only in the NH3 scavengers group (10 out of 31 episodes, 32.3%). No episode reported lack of efficacy or AE as a reason for the end of treatment.

Table 2 – Summary of Episodes - FAS (N = 98 Episodes)

Description		Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
		Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
Time between start of episode and start of treatment (days)	N	38	33	27
	Missing	0	0	0
	Mean (SD)	2.8 (5.0)	1.3 (2.3)	2.8 (7.9)
	Median (range)	1.0 (0, 24)	1.0 (0, 12)	1.0 (0, 41)
Episode duration	N	38	33	27
	Missing	0	0	0
Episode ended ≤ 15 days	n (%)	33 (86.8)	27 (81.8)	24 (88.9)
Episode ongoing > 15 days - end date available	n (%)	3 (7.9)	3 (9.1)	2 (7.4)
Episode ongoing > 15 days - no episode end date	n (%)	2 (5.3)	3 (9.1)	1 (3.7)
Duration of ended episodes (days)	N	36	30	26
	Missing	2	3	1
	Mean (SD)	7.6 (6.0)	10.4 (8.5)	7.9 (8.3)
	Median (range)	6.0 (2, 26)	8.5 (4, 48)	6.0 (2, 43)
Duration of treatment (days)	N	38	33	27
	Missing	0	0	0
	Mean (SD)	5.7 (5.1)	7.8 (7.7)	5.4 (4.1)
	Median (range)	4.0 (1, 16)	4.0 (1, 37)	5.0 (1, 16)
Reason for end of treatment	N	35	31	27
	Missing	3	2	0
End of episode	n (%)	31 (88.6)	16 (51.6)	25 (92.6)
Death	n (%)	3 (8.6)	3 (9.7)	0 (0)
Other: other	n (%)	1 (2.9)[1]	2 (6.5)[2]	2 (7.4)[3]
Other: switched to long-term treatment	n (%)	0 (0)	10 (32.3)	0 (0)
Lack of efficacy	n (%)	0 (0)	0 (0)	0 (0)
AE	n (%)	0 (0)	0 (0)	0 (0)

[1] Normalization of NH_3 plasma levels.

[2] Improvement of hyperammonemia and parent refusal.

[3] Dramatic decreases of NH_3 plasma levels and adequate response to treatment by other drugs.

AE = adverse event; FAS = full analysis set; N/n = number; NH_3 = ammonia; SD = standard deviation

Baseline Characteristics of Episode

Baseline characteristics of episodes included in the FAS are presented in Table 3.

The median age at the start of the episode was lower in the carglumic acid + NH3 scavengers group (0.2 months or 5.0 days) than in the carglumic acid group (1.7 months or 50.5 days) or the NH3 scavengers group (2.2 months or 68.0 days).

The median baseline NH3 level was higher in the carglumic acid + NH3 scavengers group (270.9 µmol/L) than in the carglumic acid group (199.0 µmol/L) or the NH3 scavengers group (122.0 µmol/L).

Table 3 – Baseline Characteristics of Episode - FAS (N = 98 Episodes)

Description		Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
		Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
Age at start of episode (months)	N	38	33	27
	Missing	0	0	0
	Mean (SD)	34.3 (64.8)	24.6 (32.6)	19.9 (46.9)
	Q1/Median/Q3	0.1/1.7/39.3	0.1/2.2/48.8	0.1/0.2/2.0
	Min, Max	0, 267	0, 97	0, 194
NH_3 level at baseline (µmol/L) FAS (NH_3 data censored at HD/HF/PD initiation)	N	37	30	26
	Missing	1	3	1
	Mean (SD)	257.0 (268.4)	226.8 (287.8)	345.6 (274.7)
	Mean (xULN)	4.9	4.4	5.9
	Q1/Median/Q3	125.0/199.0/295.0	91.0/122.0/191.0	160.0/270.9/429.0
	Min, Max	21, 1633	36, 1434	77, 1200

FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; Max = maximum; Min = minimum; N/n = number; NH_3 = ammonia; PD = peritoneal dialysis; Q = quartile; SD = standard deviation; ULN = upper limit of normal

Prior and Concomitant Medications

Prior medications included ongoing treatment at the time of enrollment and before the start of study treatment.

As expected, most of the prior and concomitant medications corresponded to treatment used to treat and monitor the metabolic decompensation and to prevent life-threatening complications. An overview of the treatments of interest initiated to treat the episode by treatment group is presented in Table 4. The most common treatment in all treatment groups was carnitine (90 out of 98 episodes, 91.8%). Carnitine is given to compensate for secondary carnitine deficiency caused by urinary loss of carnitine bound to organic acids. Carnitine seems to contribute to the reduction of hyperammonemia in PA patients and to demonstrate antioxidant capacity

Table 4 – Medications of Interest during the Episode - FAS

Treatment	Carglumic acid		NH_3 scavengers		Carglumic acid + NH_3 scavengers	
	Number of Medications	Episodes n (%)	Number of Medications	Episodes n (%)	Number of Medications	Episodes n (%)
Any carnitine	51	32 (84.2)	38	33 (100)	32	25 (92.6)
Any arginine	0	0 (0)	5	5 (15.2)	6	6 (22.2)
Any cobalamin (vitamin B_{12})	16	12 (31.6)	7	7 (21.2)	15	14 (51.9)
Any glucose	2	2 (5.3)	21	20 (60.6)	3	3 (11.1)
Any biotin (vitamin B_8)	9	9 (23.7)	9	9 (27.3)	12	10 (37.0)
Any thiamine (vitamin B_1)	6	5 (13.2)	1	1 (3.0)	3	2 (7.4)
Any riboflavin (vitamin B_2)	1	1 (2.6)	1	1 (3.0)	3	2 (7.4)

FAS = full analysis set; n = number; NH_3 = ammonia

Hemodialysis/Hemofiltration/Peritoneal Dialysis

Extracorporeal detoxification methods data by episode for patients included in the FAS are presented in Table 5.

The percentage of episodes treated with HD/HF/PD was similar in the carglumic acid group (13.2%) and the carglumic acid + NH3 scavengers group (11.1%), less than half of the percentage in the NH3 scavengers group (30.3%).

In the majority of episodes for which data was collected, the patients did not receive HD/HF/PD treatment (80 out of 98 episodes, 81.6%).

Table 5 – Hemodialysis, Hemofiltration, and Peritoneal Dialysis - FAS

Description	Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
	Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
Any HD/HF/PD			
Yes, n (%)	5 (13.2)	10 (30.3)	3 (11.1)
No, n (%)	33 (86.8)	23 (69.7)	24 (88.9)

FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; N/n = number; NH_3 = ammonia; PD = peritoneal dialysis

Efficacy results

Daily Plasma NH3 Levels

A summary of the change in maximum daily NH3 levels over time for episodes included in the FAS (NH3 data censored at HD/HF/PD initiation) is presented in Table 6. Data are presented at baseline and after initiation of treatment by period of treatment up to and including 120 hours (5 days) of treatment, corresponding to the acute phase of the hyperammonemic metabolic decompensation

episode. Note that median duration of treatment was 4.0 days in the carglumic acid and NH3 scavengers groups and 5.0 days in the carglumic acid + NH3 scavengers group.

In addition, a summary of mean ratio in NH3 levels to baseline over time for episodes included in the FAS (NH3 data censored at HD/HF/PD initiation) is presented in Figure 2 by 12-hour periods from 0 to 48 hours and Figure 3 by 24-hour periods from Day 1 to Day 5.

Change from baseline was calculated as the maximum NH3 level during the given time period minus the last NH3 value prior to treatment initiation. Ratio to baseline was calculated as the maximum NH3 levels during the given time period divided by the last NH3 value prior to treatment initiation. Reduction from baseline was calculated as 1 - [ratio to baseline] x 100.

During the first 12 hours after treatment initiation, the mean ratio to baseline in the carglumic acid + NH3 scavengers group was 0.731; this corresponds to a mean reduction from baseline of -26.9% which is statistically significantly different (p=0.0238) from the NH3 scavengers group (mean ratio to baseline = 1.116, mean reduction from baseline = +11.6%). During the same time period, the mean ratio to baseline in the carglumic acid group was 0.866 which corresponds to a mean reduction from baseline of -13.4% which, when compared to the mean reduction from baseline in the NH3 scavengers group, was just above the statistical significance level limit (p=0.0576).

From 12 to 24 hours after treatment initiation, there was no statistically significant difference between the mean reduction from baseline in the carglumic acid + NH3 scavengers group (-51.9%) and the NH3 scavengers group (-21.5%; p=0.0806) or the carglumic acid group (-46.8%) and the NH3 scavengers group (p=0.1821), although the mean reductions were more than double in the carglumic acid-containing groups.

From 24 to 36 hours after treatment initiation, there were statistically significant differences between the mean reduction from baseline in the carglumic acid + NH3 scavengers group (-71.2%) and the NH3 scavengers group (-6.6%; p=0.0003) and the carglumic acid group (-43.8%) and the NH3 scavengers group (p=0.0183). During the same time period, there was also a statistically significant difference between the mean reduction from baseline in the carglumic acid group and the carglumic acid + NH3 scavengers group (p=0.0120).

From 36 to 48 hours after treatment initiation, there were statistically significant differences between the mean reduction from baseline in the carglumic acid + NH3 scavengers group (-63.6%) and the NH3 scavengers group (-15.2%; p=0.0274) and the carglumic acid group (-62.5%) and the NH3 scavengers group (p=0.0348).

From 48 to 72 hours after treatment initiation, there continued to be statistically significant differences between the mean reduction from baseline in the carglumic acid + NH3 scavengers group (-75.6%) and the NH3 scavengers group (-16.3%; p=0.0011) and the carglumic acid group (-65.9%) and the NH3 scavengers group (p=0.0054). There were statistically significant differences between the mean reduction from baseline in the carglumic acid + NH3 scavengers group and the NH3 scavengers from 72 to 96 hours after treatment initiation (p=0.0136) and from 96 to 120 hours after treatment initiation (p=0.0184), both in favor of the combination group.

Table 6 – Summary of Ammonia Levels - FAS (NH3 data censored at HD/HF/PD initiation)

Description	Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
	Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
Baseline, n (episode)	37	30	26
Mean/median NH_3 level (µmol/L)	257 / 199	227 / 122	346 /271
Min, Max NH_3 level (µmol/L)	21, 1633	36, 1434	77, 1200
0-12 hours, n (episode)	28	15	18
Mean/median NH_3 level (µmol/L)	204 / 132	128 / 115	261 / 200
Min, Max NH_3 level (µmol/L)	37, 657	56, 352	75, 870
Mean/median change from baseline[1] (µmol/L)	-27 / -30	-14 / 0	-151 / -96
Mean reduction from baseline[2] (%)	-13.4%	+11.6%	-26.9%
p-value[3]	0.4508 (vs CGA+SCA)	0.0576 (vs CGA)	0.0238* (vs SCA)
12-24 hours, n (episode)	24	18	19
Mean/median NH_3 level (µmol/L)	117 / 99	99 / 90	147 / 96
Min, Max NH_3 level (µmol/L)	32, 580	20, 311	35, 536
Mean/median change from baseline[1] (µmol/L)	-163 / -108	-53 / -34	-222 / -178
Mean reduction from baseline[2] (%)	-46.8%	-21.5%	-51.9%
p-value[3]	0.5655 (vs CGA+SCA)	0.1821 (vs CGA)	0.0806 (vs SCA)
24-36 hours, n (episode)	18	11	15
Mean/median NH_3 level (µmol/L)	138 / 81	101 / 75	91 / 79
Min, Max NH_3 level (µmol/L)	25, 683	47, 276	34, 296
Mean/median change from baseline[1] (µmol/L)	-156 / -111	-23 / -39	-312 / -236
Mean reduction from baseline[2] (%)	-43.8%	-6.6%	-71.2%
p-value[3]	0.0120* (vs CGA+SCA)	0.0183* (vs CGA)	0.0003* (vs SCA)

Table 6 – Summary of Ammonia Levels - FAS (NH3 data censored at HD/HF/PD initiation) (Continued)

Description	Carglumic acid	NH_3 scavengers	Carglumic acid + NH_3 scavengers
	Episodes (N = 38)	Episodes (N = 33)	Episodes (N = 27)
36-48 hours, n (episode)	14	13	13
Mean/median NH_3 level (µmol/L)	88 / 54	76 /74	90 / 59
Min, Max NH_3 level (µmol/L)	36, 249	31, 139	33, 283
Mean/median change from baseline[1] (µmol/L)	-259 / -171	-77 / -43	-252 / -272
Mean reduction from baseline[2] (%)	-62.5%	-15.2%	-63.6%
p-value[3]	0.4520 (vs CGA+SCA)	0.0348* (vs CGA)	0.0274* (vs SCA)
48-72 hours, n (episode)	13	16	16
Mean/median NH_3 level (µmol/L)	67 / 65	93 / 84	65 / 53
Min, Max NH_3 level (µmol/L)	27, 121	26, 255	18, 224
Mean/median change from baseline[1] (µmol/L)	-257 / -118	-58 / -47	-312 / -241
Mean reduction from baseline[2] (%)	-65.9%	-16.3%	-75.6%
p-value[3]	0.0832 (vs CGA+SCA)	0.0054* (vs CGA)	0.0011* (vs SCA)
72-96 hours, n (episode)	4	15	10
Mean/median NH_3 level (µmol/L)	112 / 113	58 / 50	47 / 34
Min, Max NH_3 level (µmol/L)	62, 159	24, 108	16, 82
Mean/median change from baseline[1] (µmol/L)	-449 / -133	-100 / -56	-296 / -222
Mean reduction from baseline[2] (%)	-57.6%	-49.9%	-81.0%
p-value[3]	0.1039 (vs CGA+SCA)	0.7263 (vs CGA)	0.0136* (vs SCA)

Table 6 – Summary of Ammonia Levels - FAS (NH3 data censored at HD/HF/PD initiation) (Continued)

Description	Carglumic acid Episodes (N = 38)	NH_3 scavengers Episodes (N = 33)	Carglumic acid + NH_3 scavengers Episodes (N = 27)
96-120 hours, n (episode)	8	7	6
Mean/median NH_3 level (µmol/L)	66 / 59	71 / 74	36 / 32
Min, Max NH_3 level (µmol/L)	42, 95	26, 137	18, 75
Mean/median change from baseline[1] (µmol/L)	-267 / -76	-65 / -70	-245 / -242
Mean reduction from baseline[2] (%)	-55.0%	-38.3%	-82.1%
p-value[3]	0.0814 (vs CGA+SCA)	0.6854 (vs CGA)	0.0184* (vs SCA)

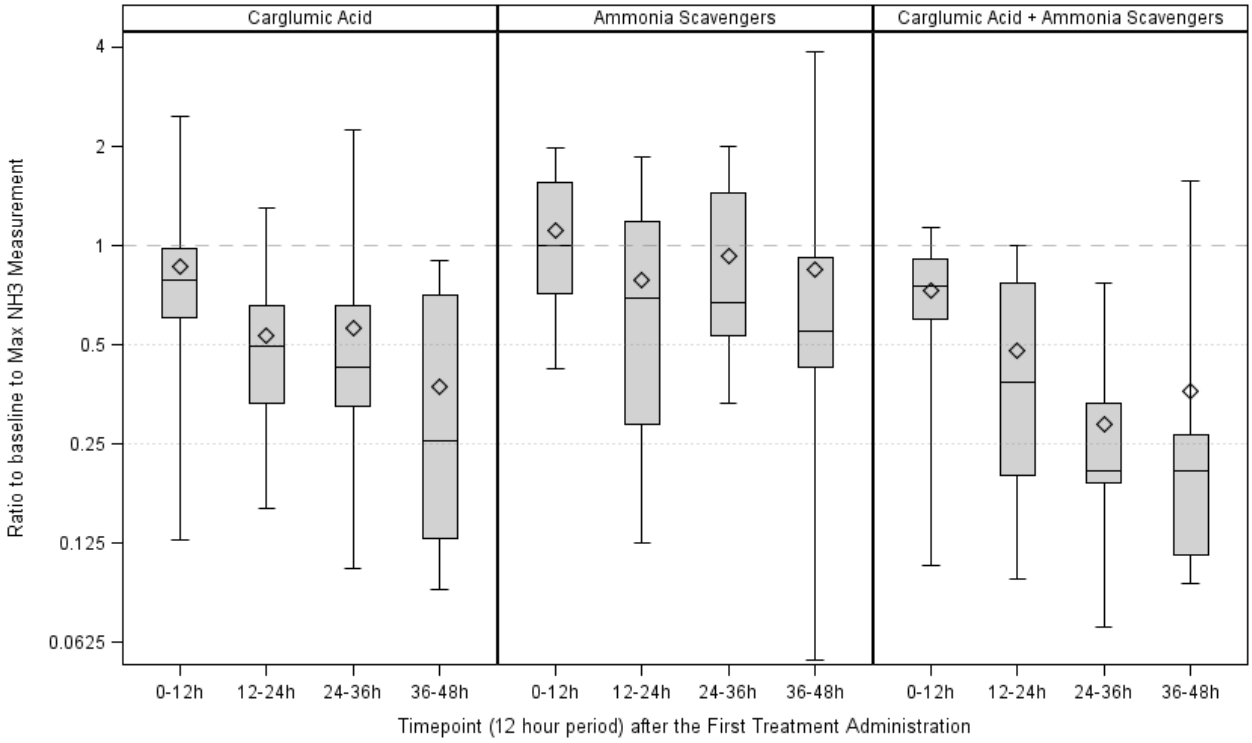
* = denotes statistical significance; CGA = carglumic acid; FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; Max = maximum; Min = minimum; N/n = number of episodes; NH_3 = ammonia; PD = peritoneal dialysis; SCA = NH_3 scavengers

[1] Change from baseline was calculated as the maximum NH_3 level during the given time period minus the last NH_3 value prior to treatment initiation.

[2] Reduction from baseline was calculated as 1 minus the ratio to baseline, multiplied by 100.

[3] The statistical significance of the difference in the mean ratio to baseline was tested between groups as indicated using the Wilcoxon test.

Figure 2 – Box and Whisker Plot of Ratio to Baseline in Ammonia Levels by 12-hour Period - FAS (NH3 data censored at HD/HF/PD initiation)



Ratio to baseline was calculated as the maximum NH3 level during the given time period divided by the last NH3 value prior to treatment initiation.

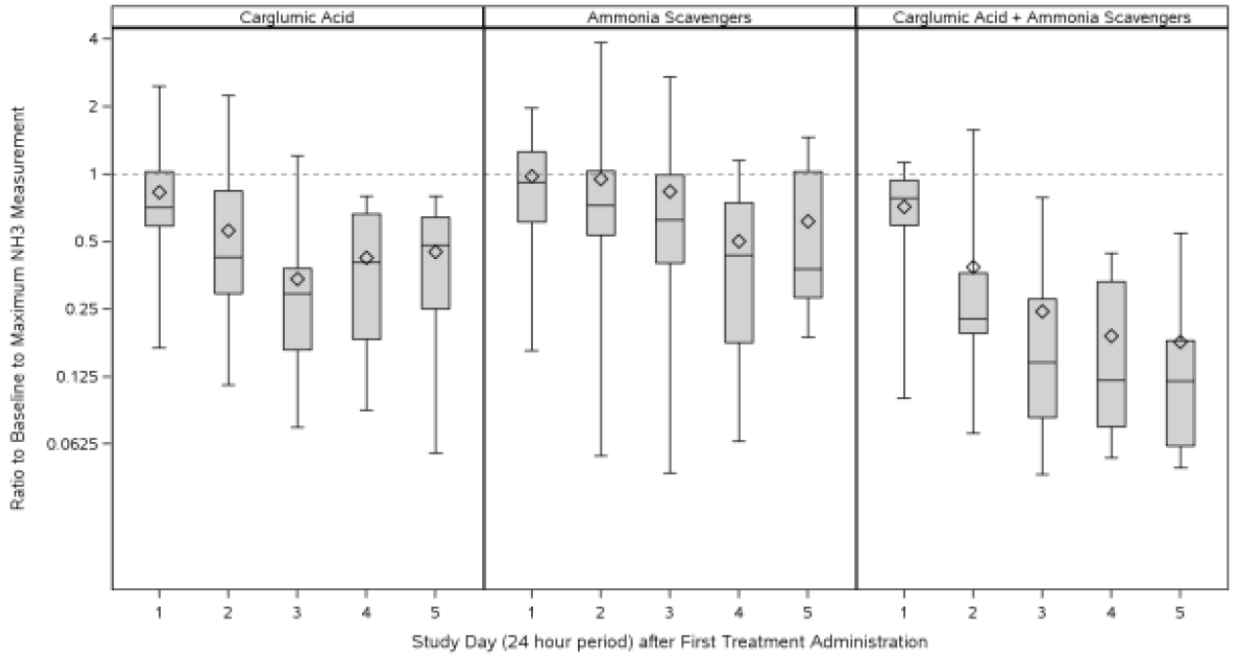
Y axis: log scale

Box limits = Q1 and Q3; ◇ = mean; line within box = median; lines outside box = minimum and maximum values

0-12 h 12-24 h 24-36 h 36-48 h

	0-12 h	12-24 h	24-36 h	36-48 h
Carglumic acid:	n = 28 episodes	n = 24 episodes	n = 18 episodes	n = 14 episodes
NH_3 scavengers:	n = 15 episodes	n = 18 episodes	n = 11 episodes	n = 13 episodes
Carglumic acid + NH_3 scavengers:	n = 18 episodes	n = 19 episodes	n = 15 episodes	n = 13 episodes

Figure 3 – Box and Whisker Plot of Ratio to Baseline in Ammonia Levels by Study Day -FAS (NH3 data censored at HD/HF/PD initiation)



Ratio to baseline was calculated as the maximum NH3 level during the given time period divided by the last NH3 value prior to treatment initiation.

Y axis: log scale

Box limits = Q1 and Q3; ◇ = mean; line within box = median; lines outside box = minimum and maximum values

	Day 1	Day 2	Day 3	Day 4	Day 5
Carglumic acid:	n = 32 episodes	n = 22 episodes	n = 13 episodes	n = 4 episodes	n = 8 episodes
NH_3 scavengers:	n = 22 episodes	n = 17 episodes	n = 16 episodes	n = 15 episodes	n = 7 episodes
Carglumic acid + NH_3 scavengers:	n = 21 episodes	n = 18 episodes	n = 16 episodes	n = 10 episodes	n = 6 episodes

Success/Failure

Success was defined as 2 consecutive measures of plasma NH3 level equal to or below the threshold of 60 µmol/L without i) HD/HF/PD started after the initiation of treatment by carglumic acid or NH3 scavengers, ii) death, or iii) treatment withdrawal for safety reasons. Improvement without success confirmed was defined as the last post-baseline NH3 assessment equal to or below 60 µmol/L without i) HD/HF/PD treatment initiated after the first day of treatment, ii) death, or iii) treatment withdrawal for safety reasons. The proportion of success and improvement without success confirmed in each

treatment group was computed with its 95% CI using the Clopper-Pearson method. In the carglumic acid group, 10 out of 38 episodes (26.3%) were treated with success and improvements were seen with treatment in 11 out of 38 episodes (28.9%). There was no statistically significant difference between treatment groups (p = 1.0000).

Time to Success/Failure

The time to success/improvement was calculated as the time from the first treatment administration to the time of the first value of NH3 equal to or below 60 µmol/L after treatment initiation. The 3 treatment groups were compared using the log-rank test for homogeneity between strata.

In the carglumic acid group, it took 34 hours to achieve success/improvement in 25% of episodes. There was no statistically significant difference between treatment groups in the time to success/improvement (p = 0.7380).

Changes in Clinical Symptoms and Markers

Table 7 summarizes the neurological findings and feeding difficulties observed in >10% of episodes in any treatment group at baseline as these 2 parameters are most relevant at the onset of metabolic decompensation.

The number of episodes with clinical symptoms and markers in all categories was generally higher in all treatment groups at baseline than at endpoint.

Table 7 – Summary of Neurological Findings and Feeding Difficulties Observed in >10% of Episodes in any Treatment Group at Baseline - FAS (NH3 data censored at HD/HF/PD initiation)

Symptoms		Carglumic Acid Episodes (N = 38)		NH_3 scavengers Episodes (N = 33)		Carglumic acid + NH_3 scavengers Episodes (N = 27)	
		Baseline, n episodes (%)	Endpoint, n episodes (%)	Baseline, n episodes (%)	Endpoint, n episodes (%)	Baseline, n episodes (%)	Endpoint, n episodes (%)
Neurological Findings:	Abnormal movements	10 (26.3)	1 (2.6)	3 (9.1)	1 (3.0)	5 (18.5)	1 (3.7)
	Coma	6 (15.8)	1 (2.6)	1 (3.0)	0	3 (11.1)	2 (7.4)
	Lethargy	16 (42.1)	4 (10.5)	11 (33.3)	2 (6.1)	17 (63.0)	2 (7.4)
	Muscle hypotonia	15 (39.5)	7 (18.4)	12 (36.4)	1 (3.0)	19 (70.4)	4 (14.8)
	Neurological development impairment	2 (5.3)	1 (2.6)	4 (12.1)	3 (9.1)	0	0
	Seizures	2 (5.3)	0	4 (12.1)	1 (3.0)	3 (11.1)	0
	Somnolence/Asthenia	18 (47.4)	3 (7.9)	8 (24.2)	1 (3.0)	21 (77.8)	2 (7.4)
	Visual impairment	4 (10.5)	3 (7.9)	1 (3.0)	1 (3.0)	1 (3.7)	2 (7.4)[1]
Feeding Difficulties:	Poor feeding	15 (39.5)	4 (10.5)	13 (39.4)	0	18 (66.7)	1 (3.7)
	Vomiting	19 (50.0)	7 (18.4)	19 (57.6)	3 (9.1)	10 (37.0)	1 (3.7)

FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; N/n = number; NH_3 = ammonia; PD = peritoneal dialysis

[1] Note that for Patient #20201, neurological status at baseline was erroneously marked as normal despite that the patient had an ongoing medical history of blindness recorded at screening. The patient's neurological status at endpoint correctly identified visual impairment.

Overall, shifts in findings from symptoms at baseline to no symptoms at endpoint occurred for the majority of categories.

Table 8 summarizes the shift in the number of episodes in which patients displayed neurological findings and feeding difficulties.

At baseline, in most episodes (86% to 100%) across all 3 treatment groups, patients presented with neurological findings. The shift from neurological findings at baseline to normal neurological status at endpoint occurred for 9 out of 18 (50%), 4 out of 11 (36%), and 5 out of 11 (45%) episodes in the carglumic acid group, the NH3 scavengers group, and the combination group, respectively.

Rarely, patients with no neurological symptoms at baseline developed symptoms at endpoint; this occurred in 1 (5%) episode in the carglumic acid group, 1 (8%) episode in NH3 scavengers group, and no episode in the carglumic acid + NH3 scavengers group.

Similarly, at baseline, in most episodes (86% to 100%) across all 3 treatment groups, patients presented with feeding difficulties. The shift from feeding difficulties at baseline to normal feeding at endpoint occurred for 11 out of 19 (58%), 9 out of 12 (75%), and 8 out of 10 (80%) episodes in the carglumic acid group, the NH3 scavengers group, and the combination group, respectively.

No patient in any treatment group developed feeding difficulties at endpoint when the symptom was not present at baseline.

Table 8 – Shift Table of Neurological Findings and Feeding Difficulties - FAS (NH3 data censored at HD/HF/PD initiation)

	ENDPOINT	BASELINE								
		Carglumic acid, n (%)			NH_3 scavengers, n (%)			Carglumic acid + NH_3 scavengers, n (%)		
		No symptoms	Symptoms	All	No symptoms	Symptoms	All	No symptoms	Symptoms	All
Neurological Findings:	No symptoms	2 (10)	9 (43)	**11 (52)**	0 (0)	4 (33)	**4 (33)**	0 (0)	5 (45)	**5 (45)**
	Symptoms	1 (5)	9 (43)	**10 (48)**	1 (8)	7 (58)	**8 (67)**	0 (0)	6 (55)	**6 (55)**
	All	**3 (14)**	**18 (86)**	21 (100)	**1 (8)**	**11 (92)**	12 (100)	**0 (0)**	**11 (100)**	11 (100)
Feeding Difficulties:	No symptoms	2 (10)	11 (52)	**13 (62)**	2 (14)	9 (64)	**11 (79)**	0 (0)	8 (80)	**8 (80)**
	Symptoms	0 (0)	8 (38)	**8 (38)**	0 (0)	3 (21)	**3 (21)**	0 (0)	2 (20)	**2 (20)**
	All	**2 (10)**	**19 (90)**	21 (100)	**2 (14)**	**12 (86)**	14 (100)	**0 (0)**	**10 (100)**	10 (100)

FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; n = number; NH_3 = ammonia; PD = peritoneal dialysis

Table 9 summarizes the number, as well as the change from baseline, of neurological findings and feeding difficulties.

The median change in the number of neurological findings from baseline to endpoint was -2.0 in the carglumic acid + NH3 scavengers group and -1.0 in both the carglumic acid and the NH3 scavengers groups. The median change in the number of feeding difficulties from baseline to endpoint was -1.0 in all 3 treatment groups.

Overall, the number of clinical findings, including clinical, laboratory, neurological, psychiatric, and respiratory findings and feeding difficulties, from baseline to endpoint, decreased in all treatment groups.

Table 9 – Number of Neurological Findings and Feeding Difficulties - FAS (NH3 data censored at HD/HF/PD initiation)

		Carglumic acid		NH_3 scavengers		Carglumic acid + NH_3 scavengers	
		Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
Neurological Findings:	n	36	21	30	12	26	12
	Mean / Median	2.6 / 2.0	1.3 / 0	1.9 / 2.0	1.3 / 1.0	3.0 / 3.0	1.5 / 1.0
	Min, Max	0, 8	0, 5	0, 5	0, 4	1, 6	0, 4
	Change from baseline						
	Mean / Median	-	-1.3 / -1.0	-	-0.3 / -1.0	-	-1.6 / -2.0
	Min, Max	-	-5, 3	-	-2, 3	-	-4, 2
Feeding Difficulties:	n	36	21	30	13	26	10
	Mean / Median	1.0 / 1.0	0.5 / 0	1.1 / 1.0	0.2 / 0	1.1 / 1.0	0.2 / 0
	Min, Max	0, 2	0, 2	0, 2	0, 1	0, 2	0, 1
	Change from baseline						
	Mean / Median	-	-0.6 / -1.0	-	-0.8 / -1.0	-	-0.8 / -1.0
	Min, Max	-	-2, 1	-	-2, 0	-	-1, 0

FAS = full analysis set; HD = hemodialysis; HF = hemofiltration; Max = maximum; Min = minimum; n = number; NH_3 = ammonia; PD = peritoneal dialysis

Safety results

Extent of exposure

In the carglumic acid group, all episodes (n = 38) were orally treated with carglumic acid; the mean (SD) daily dose of carglumic acid during the first 24 hours of treatment was 152.2 (123.1) mg/kg for patients in the FAS. Likewise, in the carglumic acid + NH3 scavengers group, all episodes (n = 27) were orally treated with carglumic acid; the mean (SD) daily dose of carglumic acid during the first 24 hours of treatment was 171.2 (94.7) mg/kg for patients in the FAS. Twenty (74.1%) of the episodes in this treatment group were treated concomitantly with 1 NH3 scavenger and 7 (25.9%) of the episodes in this treatment group were treated concomitantly with 2 NH3 scavengers.

Treatment with NH3 scavengers was given intravenously in 72% of episodes. Sodium benzoate was the most popular concomitant NH3 scavenger used (alone in 66.7% of episodes and in combination with sodium phenylbutyrate in 25.9% of episodes); the median (range) dose of sodium benzoate was 257.8 (149-790) mg/kg . Sodium phenylbutyrate was used alone in 7.4% of episodes and in combination with sodium benzoate in 25.9% of episodes; the median (range) dose of sodium phenylbutyrate was 282.0 (169-5625) mg/kg.

The median doses of the NH3 scavengers in the combination group were similar to the median doses in the NH3 scavengers group. In the NH3 scavengers group, the median (range) dose of sodium benzoate during the first 24 hours of treatment was 250.0 (81-1000) mg/kg and the median (range) dose of sodium phenylbutyrate during the first 24 hours of treatment was 277.8 (58-971) mg/kg.

Adverse events

Brief Summary of AEs

A summary of AEs for patients/episodes included in the FAS is presented in Table 10.

In total, 61 AEs were experienced by 17 (50.0%) patients during 19 (50.0%) episodes in the carglumic acid group, 97 AEs were experienced by 15 (68.2%) patients during 19 (57.6%) episodes in the NH3 scavengers group, and 21 AEs were experienced by 11 (40.7%) patients during 11 (40.7%) episodes in the carglumic acid + NH3 scavengers group. Patients in the NH3 scavengers group experienced the greatest number of treatment-emergent AEs (TEAEs; n = 85), serious TEAEs (n = 31), severe TEAEs (n = 34), deaths (n = 14), and treatment-emergent deaths (n = 13).

Patients in the carglumic acid group experienced the greatest number of drug-related TEAEs (n = 18) and drug-related serious TEAEs (n = 5).

In the carglumic acid + NH3 scavengers group, 6 TEAEs and 1 serious TEAE were considered drug-related. Drug-relatedness in the combination treatment group was assessed as related to carglumic acid treatment exclusively and not to treatment with NH3 scavengers.

Overall, the AEs reported in the study were largely related to the disease/condition (i.e., metabolic decompensation) rather than drug toxicity.

Table 10 – Summary of AEs – FAS

Description	Carglumic acid			NH_3 scavengers			Carglumic acid + NH_3 scavengers		
	n	Episodes (N = 38)	Patients (N = 34)	n	Episodes (N = 33)	Patients (N = 22)	n	Episodes (N = 27)	Patients (N = 27)
AEs, n (%)	61	19 (50.0)	17 (50.0)	97	19 (57.6)	15 (68.2)	21	11 (40.7)	11 (40.7)
TEAEs, n (%)	54	17 (44.7)	15 (44.1)	85	17 (51.5)	13 (59.1)	18	10 (37.0)	10 (37.0)
Drug-related TEAEs[1,2], n (%)	18	6 (15.8)	6 (17.6)	1	1 (3.0)	1 (4.5)	6	3 (11.1)	3 (11.1)
Serious TEAEs, n (%)	13	8 (21.1)	8 (23.5)	31	8 (24.2)	8 (36.4)	7	4 (14.8)	4 (14.8)
Drug-related serious TEAEs[1,2], n (%)	5[3]	4 (10.5)	4 (11.8)	0	0 (0)	0 (0)	1	1 (3.7)	1 (3.7)
Severe TEAEs, n (%)	15	8 (21.1)	8 (23.5)	34	8 (24.2)	8 (36.4)	6	4 (14.8)	4 (14.8)
AE leading to death, n (%)	3	3 (7.9)	3 (8.8)	14[4]	5 (15.2)	5 (22.7)	6	3 (11.1)	3 (11.1)
TEAE leading to death, n (%)	3	3 (7.9)	3 (8.8)	13	4 (12.1)	4 (18.2)	6	3 (11.1)	3 (11.1)

AE = adverse event; FAS = full analysis set; N/n = number; NH_3 = ammonia; TEAE = treatment-emergent adverse event

[1] Categories for relatedness were as follows: related or unknown in Study OE-CGA001-OA2009 and certainly, probably/likely, possibly, conditionally, or unassessable in Study OE-CGA001-OA2012.

[2] Drug-relatedness in the combination group refers exclusively to carglumic acid treatment and not NH_3 scavenger treatment.

[3] The relationship to study drug was initially reported as unknown by the physician for all 5 TEAEs and was upgraded by the sponsor to related as a conservative pharmacovigilance measure.

[4] One AE led to death but as the aggravation of the health status started before treatment initiation, the event was not considered treatment-emergent.

Display and Analysis of AEs

A summary of TEAEs for patients/episodes included in the FAS is presented by system organ class (SOC) and preferred term (PT) in Table 11.

In the carglumic acid group, 54 TEAEs were experienced by 15 patients (44.1%) during 17 episodes (44.7%); the most frequently reported TEAEs by SOC were general disorders and administration site conditions (n = 10) and blood and lymphatic system disorders (n = 9).

In the NH3 scavengers group, 85 TEAEs were experienced by 13 patients (59.1%) during 17 episodes (51.5%); the most frequently reported TEAEs by SOC were metabolism and nutrition disorders (n = 26) and blood and lymphatic system disorders (n = 16).

In the carglumic acid + NH3 scavengers group, 18 TEAEs were experienced by 10 patients (37.0%) during 10 episodes (37.0%); the most frequently reported TEAEs by SOC were blood and lymphatic system disorders (n = 3).

Table 11 – Treatment-emergent Adverse Events in > 5% of Episodes in any Treatment Group by System Organ Class and Preferred Term – FAS

Description	Carglumic acid			NH_3 scavengers			Carglumic acid + NH_3 scavengers		
	n	Episodes (N = 38)	Patients (N = 34)	n	Episodes (N = 33)	Patients (N = 22)	n	Episodes (N = 27)	Patients (N = 27)
Any TEAE, n (%)	54	17 (44.7)	15 (44.1)	85	17 (51.5)	13 (59.1)	18	10 (37.0)	10 (37.0)
Blood and lymphatic system disorders, n (%)	9	6 (15.8)	6 (17.6)	16	10 (30.3)	10 (45.5)	3	2 (7.4)	2 (7.4)
Anaemia	2	2 (5.3)	2 (5.9)	2	2 (6.1)	2 (9.1)	2	1 (3.7)[1]	1 (3.7)[1]
Coagulopathy	1	1 (2.6)[1]	1 (2.9)[1]	6	5 (15.2)	5 (22.7)	0	0 (0)	0 (0)
Thrombocytopenia	2	2 (5.3)[1]	2 (5.9)[1]	7	7 (21.2)	7 (31.8)	1	1 (3.7)	1 (3.7)
Cardiac disorders, n (%)	3	3 (7.9)	3 (8.8)	4	4 (12.1)	4 (18.2)	1	1 (3.7)	1 (3.7)
Cardiac failure	0	0 (0)	0 (0)	3	3 (9.1)	3 (13.6)	0	0 (0)	0 (0)
Gastrointestinal disorders, n (%)	5	5 (13.2)	5 (14.7)	6	3 (9.1)	3 (13.6)	2	2 (7.4)	2 (7.4)
Diarrhea	2	2 (5.3)[1]	2 (5.9)[1]	1	1 (3.0)	1 (4.5)	1	1 (3.7)[1]	1 (3.7)[1]
Vomiting	2	2 (5.3)[1]	2 (5.9)[1]	2	1 (3.0)	1 (4.5)	0	0 (0)	0 (0)
General disorders and administration site conditions, n (%)	10	8 (21.1)	8 (23.5)	5	5 (15.2)	5 (22.7)	1	1 (3.7)	1 (3.7)
Hyperthermia	2	2 (5.3)[1]	2 (5.9)[1]	0	0 (0)	0 (0)	0	0 (0)	0 (0)
Hypothermia	2	2 (5.3)	2 (5.9)	0	0 (0)	0 (0)	0	0 (0)	0 (0)
Multi-organ failure	1	1 (2.6)	1 (2.9)	2	2 (6.1)	2 (9.1)	0	0 (0)	0 (0)
Pyrexia	3	3 (7.9)[2]	3 (8.8)[2]	2	2 (6.1)	2 (9.1)	0	0 (0)	0 (0)

Table 11 – Treatment-emergent Adverse Events in > 5% of Episodes in any Treatment Group by System Organ Class and Preferred Term - FAS (Continued)

Description	Carglumic acid			NH_3 scavengers			Carglumic acid + NH_3 scavengers		
	n	Episodes (N = 38)	Patients (N = 34)	n	Episodes (N = 33)	Patients (N = 22)	n	Episodes (N = 27)	Patients (N = 27)
Infections and infestations, n (%)	6	6 (15.8)	6 (17.6)	7	6 (18.2)	5 (22.7)	1	1 (3.7)	1 (3.7)
Sepsis	2	2 (5.3)[1]	2 (5.9)[1]	1	1 (3.0)	1 (4.5)	0	0 (0)	0 (0)
Investigations, n (%)	4	4 (10.5)	4 (11.8)	1	1 (3.0)	1 (4.5)	1	1 (3.7)	1 (3.7)
Oxygen saturation decreased	2	2 (5.3)	2 (5.9)	0	0 (0)	0 (0)	0	0 (0)	0 (0)
Metabolism and nutrition disorders, n (%)	6	5 (13.2)	5 (14.7)	26	11 (33.3)	9 (40.9)	1	1 (3.7)	1 (3.7)
Hyperglycaemia	1	1 (2.6)	1 (2.9)	6	5 (15.2)	4 (18.2)	1	1 (3.7)	1 (3.7)
Hypocalcaemia	1	1 (2.6)[1]	1 (2.9)[1]	4	4 (12.1)	4 (18.2)	0	0 (0)	0 (0)
Hypokalaemia	1	1 (2.6)	1 (2.9)	6	6 (18.2)	6 (27.3)	0	0 (0)	0 (0)
Hypomagnesaemia	0	0 (0)	0 (0)	2	2 (6.1)	2 (9.1)	0	0 (0)	0 (0)
Metabolic acidosis	0	0 (0)	0 (0)	2	2 (6.1)	2 (9.1)	0	0 (0)	0 (0)
Nervous system disorders, n (%)	4	4 (10.5)	4 (11.8)	6	3 (9.1)	3 (13.6)	1	1 (3.7)	1 (3.7)
Convulsion	1	1 (2.6)	1 (2.9)	3	3 (9.1)	3 (13.6)	0	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders, n (%)	1	1 (2.6)	1 (2.9)	8	5 (15.2)	5 (22.7)	2	2 (7.4)	2 (7.4)
Respiratory distress	0	0 (0)	0 (0)	4	4 (12.1)	4 (18.2)	0	0 (0)	0 (0)

[1] Considered drug-related in 1 episode/patient

[2] Considered drug-related in 2 episodes/patients

FAS =full analysis set; N/n = number; NH_3 = ammonia; TEAE = treatment-emergent adverse event

DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Listing of Deaths, other SAEs and other Significant AEs

Deaths

A total of 22 fatal TEAEs occurred in 10 patients/episodes: 3 fatal TEAEs occurred in 3 patients (8.8%) during 3 episodes (7.9%) in the carglumic acid group, 13 fatal TEAEs occurred in 4 patients (18.2%) during 4 episodes (12.1%) in the NH3 scavengers group, and 6 fatal TEAEs occurred in 3 patients (11.1%) during 3 episodes (11.1%) in the carglumic acid group + NH3 scavengers group.

Other SAEs

A total of 51 serious TEAEs occurred in 20 patients/episodes: 13 serious TEAEs (5 considered drug-related) occurred in 8 patients (23.5%) during 8 episodes (21.1%) in the carglumic acid group, 31 serious TEAEs (none considered drug-related) occurred in 8 patients (36.4%) during 8 episodes (24.2%) in the NH3 scavengers group, and 7 serious TEAEs (1 considered related to carglumic acid) occurred in 4 patients (14.8%) during 4 episodes (14.8%) in the carglumic acid group + NH3 scavengers group.

2.3.3. Discussion on clinical aspects

Efficacy

In this very exploratory analysis, the efficacy of treatment with carglumic acid compared to NH3 scavengers was assessed through comparisons of plasma NH3 levels during hyperammonemia in OA decompensation episodes prior to or not treated with extracorporeal detoxification (HD/HF/PD) in order to examine the effect of carglumic acid without confounding NH3-reducing treatments.

This comparison, based on paired retrospective comparison, yields very low quality or strength. Yet, given the rareness of the condition, the scarce population and the risks of non treatment within a short period of time, this approach may be the only one valuable in the near future.

The following conclusions may be understood from the study:

- During the 12-hour periods from treatment initiation to 48 hours and the 24-hour periods thereafter until 120 hours, the mean reduction in NH3 levels from baseline in the carglumic acid + NH3 scavengers group and the carglumic acid group were greater than in the NH3 scavengers group despite that both groups had higher NH3 levels at baseline. Overall, NH3 reductions from baseline were greatest in the carglumic acid + NH3 scavengers group.
- Differences between the combination group and the NH3 scavengers group were statistically significant in favor of the combination group during all time periods except from 12 to 24 hours after treatment initiation even though the mean reduction from baseline in the combination group was more than double that in the NH3 scavengers group.
- There was no statistically significant difference between treatment groups in rate of success/improvement (p = 1.0000) or time to success/improvement (p = 0.7380).
- Overall, the number of clinical findings, including clinical, laboratory, neurological, psychiatric, and respiratory findings and feeding difficulties, from baseline to endpoint, decreased in all treatment groups. The median change in the number of findings from baseline to endpoint was

-4.0 in the carglumic acid group and -3.0 in both the carglumic acid + NH3 scavengers and the NH3 scavengers groups.

- An overall shift in findings from symptoms at baseline to no symptoms at endpoint occurred for the majority of findings, including the neurological findings and feeding difficulties categories. The shift from neurological findings at baseline to normal neurological status at endpoint occurred for 9 out of 18 (50%), 4 out of 11 (36%), and 5 out of 11 (45%) episodes in the carglumic acid group, the NH3 scavengers group, and the combination group, respectively. Simarly the shift from feeding difficulties at baseline to normal feeding at endpoint occurred for 11 out of 19 (58%), 9 out of 12 (75%), and 8 out of 10 (80%) episodes in the carglumic acid group, the NH3 scavengers group, and the combination group, respectively.
- The median change in the number of neurological findings from baseline to endpoint was -2.0 in the carglumic acid + NH3 scavengers group and -1.0 in both the carglumic acid and the NH3 scavengers groups. The median change in the number of feeding difficulties from baseline to endpoint was -1.0 in all treatment groups.
- Median duration of treatment was 4.0 days in the carglumic acid and NH3 scavengers groups and 5.0 days in the carglumic acid + NH3 scavengers group. More than 80% of the episodes ended within 15 days; the median duration of episodes was 6.0 days in the carglumic acid and carglumic acid + NH3 scavengers groups, and 8.5 days in the NH3 scavengers group.

Safety

Analysis of the safety data in the 3 treatment groups showed that:

- The mean (SD) daily dose of carglumic acid during the first 24 hours of treatment for patients in the FAS was in the same range in the carglumic acid group (152.2 [123.1] mg/kg) and the carglumic acid + NH3 scavengers group (171.2 [94.7] mg/kg).
- Likewise, the median (range) dose of NH3 scavengers (sodium benzoate/sodium phenylbutyrate) during the first 24 hours of treatment for patients in the FAS was similar in the carglumic acid + NH3 scavengers group (257.8 [149-790] mg/kg / 282.0 [169-5625] mg/kg) and the NH3 scavengers group (250.0 [81-1000] mg/kg / 277.8 [58-971] mg/kg).
- Overall, the AEs reported in the study were largely related to the disease/condition (i.e., metabolic decompensation) rather than drug toxicity.
- Patients in the NH3 scavengers group experienced the greatest number of TEAEs (n = 85), serious TEAEs (n = 31), severe TEAEs (n = 34), deaths (n = 14), and treatment-emergent deaths (n = 13). Patients in the carglumic acid group experienced the greatest number of drug-related TEAEs (n = 18) and drug-related serious TEAEs (n = 5).
- The SOC with the greatest number of TEAEs was general disorders and administration site conditions (n = 10) in the carglumic acid group, metabolism and nutrition disorders (n = 26) in the NH3 scavengers group, and blood and lymphatic system disorders (n = 3) in the carglumic acid + NH3 scavengers group.
- A total of 3 fatal TEAEs occurred in 3 patients (8.8%) during 3 episodes (7.9%) in the carglumic acid group, 13 fatal TEAEs occurred in 4 patients (18.2%) during 4 episodes (12.1%) in the NH3 scavengers group, and 6 fatal TEAEs occurred in 3 patients (11.1%) during 3 episodes (11.1%) in the carglumic acid group + NH3 scavengers group.

This report presents the exploratory analysis of data collected in 2 different retrospective studies from patients hospitalized due to metabolic hyperammonemic decompensation episodes in OA (PA, MMA and IVA). Propionic acidemia, MMA and IVA are rare inherited metabolic diseases which are characterized by a dysfunction of a specific step in amino acid catabolism, leading to accumulation of organic acids in blood and urine as well as high NH3 concentrations. Hyperammonemia is one of the most severe, life-threatening symptoms in metabolic decompensation episodes. High NH3 levels are neurotoxic [Butterworth, 1998] and it has been shown that longer durations and higher values of hyperammonemia are associated with poorer neurological outcomes [Bachmann, 2003]. Prompt management of the disease, by using all pharmacological treatments and methods available, is required to avoid, or at least limit, the potential neurological sequelae encountered in OA patients.

In the full CSR (dated 31 August 2015), patients/episodes were divided into 2 treatment groups: those treated with carglumic acid with or without NH3 scavengers (Study OE-CGA001-OA2009) and those treated with NH3 scavengers only (Study OE-CGA001-OA2012). In this Addendum, patients/episodes were divided into 3 treatment groups: those treated with carglumic acid only (Study OE-CGA001-OA2009), those treated with carglumic acid + NH3 scavengers (Study OE-CGA001-OA2009), and those treated with NH3 scavengers only (Study OE-CGA001-OA2012). In addition, NH3 data presented were censored at the time of HD/HF/PD initiation in order to further isolate the potential effects of carglumic acid without other NH3-reducing treatments.

3. Rapporteur's overall conclusion and recommendation

Data from a total of 98 episodes were included in the FAS; 60 of these episodes occurred in patients with a diagnosis of PA (61.2%), 32 of these episodes occurred in patients with a diagnosis of MMA (32.7%), and 6 of these episodes occurred in patients with a diagnosis IVA (6.1%). The relatively small number of IVA patients is consistent with the frequency observed in clinical practice.

The median age at the start of the episode was lower in the carglumic acid + NH3 scavengers group (0.2 months or 5.0 days) than in the carglumic acid group (1.7 months or 50.5 days) or the NH3 scavengers group (2.2 months or 68.0 days). Furthermore, mean NH3 levels at baseline were higher in the carglumic acid + NH3 scavengers group (346 µmol/L) than in the carglumic acid group (257 µmol/L) or the NH3 scavengers group (227 µmol/L).

The patient population included in the carglumic acid + NH3 scavenger group appears slightly more severe taking into consideration 2 key risk factors: younger age and initial levels of ammonemia. In addition, all of the patients whose episodes were treated with the combination of carglumic acid + NH3 scavengers displayed neurological findings and feeding difficulties, the 2 most relevant clinical symptoms in metabolic decompensation, at baseline. On the contrary, patient populations in the carglumic acid and the NH3 scavengers groups were comparable with regard to demographics and risk factors.

The median duration of treatment was 4.0 days in the carglumic acid and NH3 scavengers groups, and 5.0 days in the carglumic acid + NH3 scavengers group. The median duration of episodes was 6.0 days in the carglumic acid and carglumic acid + NH3 scavengers groups, and 8.5 days in the NH3 scavengers group.

During the 12-hour periods from treatment initiation to 48 hours and the 24-hour periods thereafter until 120 hours, the mean reduction in NH3 levels from baseline in the carglumic acid + NH3

scavengers group and the carglumic acid group were greater than in the NH3 scavengers group. Overall, NH3 reductions from baseline were greatest in the carglumic acid + NH3 scavengers group.

Differences between the combination group and the NH3 scavengers group were statistically significant in favor of the combination group during all time periods except from 12 to 24 hours after treatment initiation even though the mean reduction from baseline in the combination group was more than double that in the NH3 scavengers group.

Overall, the number of clinical findings, including clinical, laboratory, neurological, psychiatric, and respiratory findings and feeding difficulties, from baseline to endpoint, decreased in all treatment groups. The median change in the number of findings from baseline to endpoint was -4.0 in the carglumic acid group and -3.0 in both the carglumic acid + NH3 scavengers and the NH3 scavengers groups. In addition, an overall shift in findings from symptoms at baseline to no symptoms at endpoint occurred for the majority of findings, including the neurological findings and feeding difficulties categories, in all treatment groups.

A greater percentage of episodes in the NH3 scavengers group (30.3%) were treated with extracorporeal detoxification (HD/HF/PD) than in the carglumic acid (13.2%) or the carglumic acid + NH3 scavengers groups (11.1%). Since NH3 levels are one of the main biological parameters that trigger the decision to start these procedures, it is possible that the more rapid reduction in NH3 levels seen in episodes treated with carglumic acid may have lead to a decision not to initiate HD/HF/PD.

This exploratory analysis, attempting to examine the isolated effect of carglumic acid, the data may suggest that carglumic acid is effective in reducing NH3 levels. Whether it may be more rapidly than NH3 scavengers, especially during the first hours that are critical to limit potential unfavorable neurological outcomes remains to be confirmed in a more powerful seting. Acute hyperammonemia is a medical emergency, which may require HD/HF/PD for rapid removal of NH3, with adjunctive pharmacological treatment and protein restriction to prevent serious neurological sequelae. The use of NH3 scavengers, is still debated in MMA and PA as there is the theoretical risk of increasing intramitochondrial accumulation of coenzyme A (CoA) esters and of further depleting free CoA availability The mean daily dose of carglumic acid during the first 24 hours of treatment for patients in the FAS treated with carglumic acid + NH3 scavengers (171.2 mg/kg) and carglumic acid only (152.2 mg/kg) was in the same range. Likewise, the median dose of NH3 scavengers (sodium benzoate/sodium phenylbutyrate) during the first 24 hours of treatment for patients in the FAS was similar in the carglumic acid + NH3 scavengers group (257.8 mg/kg / 282.0 mg/kg) and the NH3 scavengers group (250.0 mg/kg / 277.8 mg/kg).

Overall, there were fewer AEs in the carglumic acid + NH3 scavengers group (n = 21) than in the carglumic acid group (n = 61) or the NH3 scavengers group (n = 97). Most AEs/SAEs appeared related to the disease/condition (i.e., metabolic decompensation) rather than drug toxicity. The carglumic acid group had the greatest number of drug-related TEAEs (n = 18 versus n = 6 in the carglumic acid + NH3 scavengers group, and n = 1 in the NH3 scavengers group). It is, however, worthwhile to note that the categories of drug-relatedness were different in the 2 studies and that relatedness referred exclusively to carglumic acid in the combination treatment group.

In line with the reasoning of the MAH, and consistent with the results of the full CSR, this analysis apparently support the efficacy and the safety of carglumic acid for the treatment of hyperammonemia due to PA, MMA, and IVA. This exploratory analysis showed that the reduction of plasma NH3 level

occurred faster in episodes treated with carglumic acid with or without NH3 scavengers. This reduction was particularly marked during the first hours of the acute hyperammonemic metabolic decompensation, i.e., when it is critical to rapidly decrease plasma NH3 levels in order to prevent potentially devastating neurological sequelae.

The presented retrospective pooled analysis of studies OE-CGA001-OA2009 and OE-CGA001-OA2012 pretend to consolidate the results of the retrospective study whose analysis has been presented earlier to EMA. This pooling result from US recommendation for granting MA in the indication of Carbaglu in the treatment of hyperammonemia due to organic acidemias (Methyl-Malonic academia/MMA, Propionic Acidemia/PA, Isovaleric Acidemia/IVA).

The pooling of retrospectively acquired data in two different time settings is prone to several bias, and their conclusions must be very cautious. The fact that in some studied efficacy measures there has not been a difference between carglumic acid response and the other group also raise doubts over the efficacy in the medium-long term of Carbaglu treatment. Nevertheless, in some patients, Carbaglu appear to be efficacious in the steep control of hyperammonemia in the studied population.

This PAM has not been a required EMA procedure.

The data provided do not negatively impact the benefit-risk balance of Carbaglu. Therefore no further regulatory action is required.

In the package submitted by the MAH, information on the characteristics of the administered product was not clear. The MAH was informed of this and responded with the following information:

> "In the context of the retrospective nature of the study, the episodes treated with carglumic acid were collected between 1997 and 2009.
>
> The information was not available for all patients/episodes.
>
> > Out of 66 episodes, the information on the carglumic acid formulation used was available for 43 episodes:
> >
> > - 2 episodes treated with carglumic acid powder (between 1997 and 1998)
> > - 41 episodes treated with Carbaglu 200 mg dispersible tablets (marketed in EU) (between 2002 and 2009)
> >
> > For the 23 remaining episodes treated between 2002 and 2009 the information was not reported on the Case Report Form. "

More than 60% of the episodes occurred when under treatment with the EU formulation. The response was considered acceptable.

☒ Fulfilled:

No regulatory action required.