Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Carglumic acid

Proprietary Product Name: Carbaglu

Sponsor: Emerge Health Pty Ltd

Date of CER:

First round: 13 April 2014

Second round: 14 September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
µg-eq/g	microgram equivalent per gram
ADP	adenosine diphosphate
ADR	Adverse drug reaction
AE	adverse event
AUC	area under the plasma-concentration time curve
BP	blood pressure
bpm	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CK	creatine kinase
Cmax	maximum plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CPS 1	carbamyl phosphate synthetase 1
CRA	clinical research associate
CRF	Case Report Form
DB	database
DMP	data management plan
DMR	data management report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCP	good clinical practice
HBs	hepatitis B surface antigen

Abbreviation	Meaning
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IEC	Independent Ethics committee
LDH	lactate dehydrogenase
MA	marketing authorization
MAA	marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NAGS	N-acetylglutamate synthase
NDA	new drug application
NH3	ammonia
NPU	named-patient use (program)
OE	Orphan Europe
pH	Acidity (pH)
PK	pharmacokinetics
PK	pharmacokinetics
PR	pulse rate
PV	pharmacovigilance
QC	quality control
QTc	QT interval, corrected for heart rate
SAP	statistical analysis plan
SAS	Statistical Analysis System
SDTM	study data tabulation model
SEC	self-evident correction
SGOT	serum glutamic oxalo-acetic transaminase (same as AST)

Abbreviation	Meaning
SGPT	serum glutamic pyruvic transaminase (same as ALT)
SOC	system organ class
TDD	total daily dose
t_{max}	time to reach maximum plasma concentration
UCD	urea cycle disorder
WHO	World Health Organization
γ-GT	gamma-glutamyl-transpeptidase

1. Introduction

This is a category 1, type submission to register a new chemical entity, carlaglumic acid.

The proposed indications are:

- hyperammonaemia due to N-acetylglutamate synthase primary deficiency.
- hyperammonaemia due to isovaleric acidaemia
- hyperammonaemia due to methymalonic acidaemia
- hyperammonaemia due to propionic acidaemia

The submission proposes registration of the following dosage form and strength:

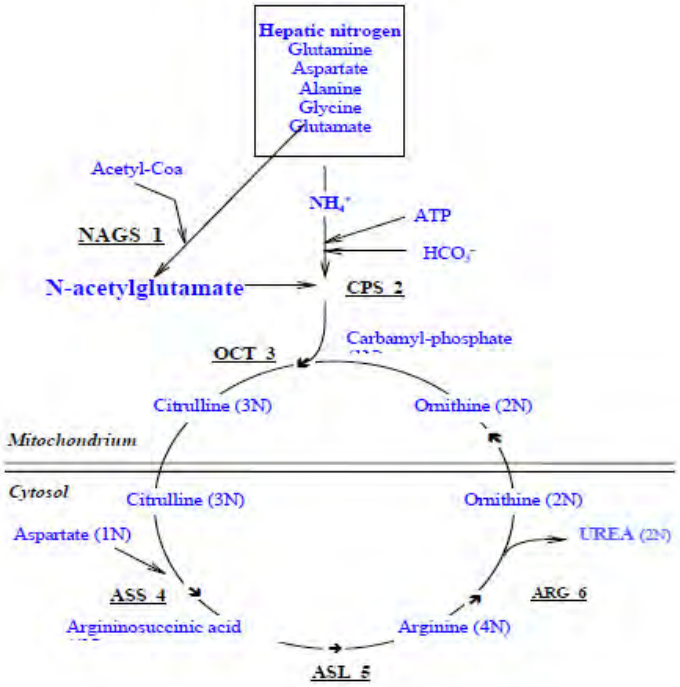
- Carglumic acid 200 mg dispersible tablets

2. Clinical rationale

2.1. The urea cycle

The urea cycle converts nitrogen from peripheral (muscle) and enteral sources (protein ingestion) into urea that is water soluble and can be excreted. Two moles of nitrogen, one from ammonia and one from aspartate, are converted to urea in each cycle (Figure 1). Ammonia nitrogen derives from circulating amino acids, mostly glutamine and alanine. Aspartate is a substrate for argininosuccinic acid synthesis.

Figure 1. The Urea Cycle.



1.NAGS: N-acetylglutamate synthase
2.CPS: carbamoyl phosphate synthetase
3.OTC : ornithinetranscarbamylase
4.ASS: arginosuccinate synthetase
5.ASL : arginosuccinate lyase
6.ARG : arginase

2.2. NAGS deficiency

N-acetyl-glutamate synthase (NAGS) deficiency is a recessive autosomal inherited metabolic disorder. NAGS deficiency is one the most severe and rarest of the hereditary Urea Cycle Disorders. N-acetyl-glutamate synthase is a mitochondrial enzyme, which is essential for the function of the urea cycle converting ammonia into urea in the liver cells and elimination through the kidneys.

The impairment of ammonia detoxication due to NAGS deficiency results in acute and chronic hyperammonaemia, hyperglutaminaemia and, eventually, hypocitrullinaemia. Hyperammonaemia and hyperglutaminaemia are particularly toxic to the central nervous system.

NAGS deficiency represents a serious life threatening clinical condition. Patients with severe complete NAGS deficiency rapidly develop hyperammonaemia soon after birth (between 24 and 48 hours). The clinical course in the neonatal period may be lethal. Left untreated or insufficiently corrected, this condition leads to cerebral oedema, coma and eventually death. For those children who survive, psychomotor retardation is a frequent outcome.

Patients with partial NAGS deficiency (late onset) can present symptoms at almost any time of life because of any stressful triggering event such as an infection, trauma, vaccination, surgery and pregnancy.

2.3. Organic acidaemias

The term ‘organic acidaemia’ or ‘organic aciduria’ (OA) applies to a group of disorders characterised by the excretion of non amino organic acids in urine. Organic acidaemias are the result of dysfunction of specific step/s in amino acid catabolism, usually the result of specific deficient enzyme activity. The majority of the classic organic acid disorders are caused by abnormal amino acid catabolism of branched chain amino acids or lysine. They include maple syrup urine disease (MSUD), propionic acidaemia (PA), methylmalonic acidaemia (MMA), methylmalonic aciduria and homocystinuria, isovaleric acidaemia (IVA), biotin unresponsive 3-methylcrotonyl-CoA carboxylasedeficiency, 3-hydroxy-3-methylglutarylCoA(HMG-CoA) lyase deficiency, ketothiolase deficiency, and glutaric acidaemia type I (GA I).

The first clinical manifestations in all OAs could start in early stage (neonatal period) or in late stage:

- A neonate affected with an OA is usually well at birth and for the first few hours or days of life. The usual clinical presentation is at the time of a metabolic decompensation that leads towards toxic encephalopathy, vomiting, poor feeding, neurologic symptoms such as seizures, abnormal muscle tone, and lethargy, progressing to coma. The earlier the first manifestations, the higher the severity and the poorer the outcome. Prognosis could be improved by early diagnosis and prompt effective treatment.
- In the late onset, older child or adolescent, variant forms of the OAs can present as progressive loss of intellectual functions, ataxia or other focal neurologic signs, Reye-like syndrome, recurrent keto acidosis, or psychiatric symptoms.

2.4. Rationale to develop carglumic acid

The production of urea is mainly regulated by CPS 1 as the first enzyme of the urea cycle. This enzyme catalyses the formation of carbamyl phosphate, the first step of arginine and urea biosynthesis from ammonia, bicarbonate and two molecules of ATP according to the following reaction as shown in Figure 2.

Figure 2. Formation of carbamyl phosphate form ammonia and bicarbonate catalysed by carbamyl phosphate synthetase.

$$2\ ATP + NH_3 + HCO_3^- \rightarrow 2\ ADP + H_2N\ COO\ PO_3^{--} + H_3PO_4$$

CPS 1 is located in the mitochondrial matrix of hepatocytes (Rubio 1981). CPS 1 is absolutely dependent on the presence of N-acetyl glutamate (NAG) to be activated and start the cycle. NAG is an allosteric activator that induces CPS 1 molecule conformational changes.

NAG is synthesized in the mitochondrial matrix from acetyl-CoA and L-glutamate by an enzymatic reaction catalysed by N-acetyl glutamate synthetase (NAGS). The enzymatic activity of NAGS increases the V_{max} of CPS 1 and has no effect on the Km values for the substrates. NAGS activity is regulated by protein intake (Caldovic 2003).

Carglumic acid was used in 1980 for the first time to treat the first clinically diagnosed NAGS deficiency patient based on the process revealed by Grisolia in 1952. Carglumic acid is a structural analogue of NAG, the natural activator of the first enzyme of the urea cycle (carbamylphosphate synthetase). Carglumic acid has been known since the 1970s to be effective in protecting rats against the toxicity of ammonium acetate administered by IV route. Carglumic acid activates in vitro liver CPS 1. Nevertheless, CPS 1 has a lower affinity for carglumic acid than for NAG. Carglumic acid showed a better protective effect in vivo than NAG or L-glutamic acid; therefore, carglumic acid is better drug candidate than NAG. The more effective and longer lasting in vivo effect of carglumic acid is due to a higher permeability of the mitochondria membrane than NAG, and the greater resistance of carglumic acid to hydrolysis by aminocyclase present in the cytosol of hepatocytes.

The biochemical and pharmacological characteristics of carglumic acid make it the only specific treatment of NAGS deficiency in acute as well as in chronic therapeutic approach in NAGS deficiency:

- Carglumic acid is a structural analogue of NAG and also efficiently activates CPS 1 (in vitro).
- It is resistant to hydrolysis by amino-acetylase.
- It is not metabolized.
- It easily enters and remains in the liver.
- It crosses the mitochondrial membrane.

2.5. Rationale to develop Carbaglu

The first carglumic acid available was a simple chemical grade product. The quality and the purity of this chemical did not meet the regulatory standards required for marketing authorization. Based on the knowledge that 5 patients were being treated with a chemical grade product, in 1995 Orphan Europe (OE) took the initiative to develop a medicinal product acceptable for therapeutic use and apply for Marketing Authorization in Europe.

The main steps of that development were:

- Development of the synthesis of a highly purified compound (pharmaceutical grade).
- Development of all testing methods (analytical testing methods, testing in biological fluids).
- Development of a specific formulation allowing the use of a single presentation in both neonates and adults, with a flexible dosage to be adapted to various patients.

This development resulted in a dispersible tablet containing 200 mg of Carglumic acid (CGA), registered by the European Medicines Agency (EMEA) in January 2003. This tablet with 3 score marks can be split in 4 parts each, giving a lot of flexibility in the prescription.

It must be highlighted that the existing chemical grade carglumic acid is for laboratory use only and is labelled 'not for human use'. Nevertheless, this chemical grade product is still used for the treatment of an unknown number of patients, particularly children, on a chronic basis.

2.6. Regulatory background

2.6.1. Australian regulatory history

Orphan drug designation

Carbaglu has previously been designated an Orphan Drug in accordance with sub-regulation 16(2) for the following indication:

Carbaglu is indicated in treatment of

- *hyperammonaemia due to N-acetylglutamate synthase primary deficiency;*
- *hyperammonaemia due to isovaleric acidaemia;*
- *hyperammonaemia due to methymalonic acidaemia;*
- *hyperammonaemia due to propionic acidaemia.*

2.6.2. Overseas regulatory history

The overseas regulatory history is shown in Table 1. It should be noted that the indication approved in the United States does not include the use of Carbaglu for the treatment of organic acidaemia.

2.6.3. Guidance

The following guidances were supplied to the evaluator:

- Clinical Investigation of Medicinal Products for Long Term Use (Directive 75/318/EEC).
- Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate (EMEA/536810/2008).
- Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (EMEA/CHMP/EWP/147013/2004).
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99).
- Reflection Paper Formulations of Choice for the Paediatric Population (EMEA/CHMP/PEG/194810/2005).

2.6.4. Overseas regulatory history

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3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 2 clinical pharmacology studies, both of these provided pharmacokinetic data in normal adult human subjects.

- Several bio-analytical studies.
- There were no population pharmacokinetic analyses.
- Two pivotal efficacy/safety studies.
- No clinical dose-finding studies.
- No other efficacy/safety studies.
- One clinical safety report, one report for the risk of QT prolongation and seven periodic safety update reports.

Extra material

- Belgium and Portugal day 70 regulatory reports for NAGS indication.
- EMEA report for OA indication.

3.2. Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data including in young neonates.

3.3. Good clinical practice

The two pharmacokinetic studies in normal human adults were reported to have complied with GCP.

The retrospective clinical studies did not fully comply with GCP. While the data for the retrospective studies was collected in accordance with GCP principles, the original clinical data entry was not part of a clinical study (it was routine clinical practice) and, hence, not GCP compliant.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 2 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 2. Summaries of pharmacokinetic studies.

Type of study	Study ID	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects Healthy or diagnosis	Duration of treatment
Bioavailability	P991-48 OE 312/PK/99-01	Open, randomized two ways crossover study, single oral dose of 100 mg/kg	Treatment A: 200 mg CGA reference powder (p.o.) Treatment B: 200mg dispersible tablets (p.o.)	12 Healthy male volunteers (18-30 years)	Single dose
Pharmacokineti	026/00 029	Open,	Treatment A:	12	Single dose

Type of study	Study ID	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects Healthy or diagnosis	Duration of treatment
c	OE 312/PK/99-01	randomized two ways crossover study, single oral dose of 100 mg/kg	200 mg CGA reference powder (p.o.) Treatment B: 200mg dispersible tablets (p.o.)	Healthy male volunteers	
Clinical ADME	026/00 080 OE 312/MET/00-01	In vitro study	Radiolabelled carglumic acid	Humans & rats hepatocytes	Incubation form 0.5 to 24 hours
PK	SPC 313-1	Mono-centre, open. Non-placebo-controlled, single-group, single-dose study	Pure powder as oral suspension A single oral dose of 70µCurie ^{14}C labelled carglumic acid (100 mg/kg)	3 Healthy male subjects (40-55 years)	Single dose
PK	026/02/070	Mono-centre, open. Non-placebo-controlled, single-group, single-dose study	100mg/kg of radiolabelled ^{14}C carglumic acid as a single oral dose	Healthy male volunteers	Single dose
PK	026/04 022			Analysis performed on the urine samples received from study 026/02 070	
PK	026/04023			Analysis performed on samples (blood urine faeces) from study 026/02 070	
PK	Data review	A data review of absorption, distribution, metabolism and elimination of carglumic acid in animals and humans – cross species metabolic profile comparison.			
PK	026/01 028		4.8 and 3.5 mg/kg/d or 192 and 119 mg/m^2	Plasma and urine sample s	

Type of study	Study ID	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects Healthy or diagnosis	Duration of treatment
			respectively twice daily	from 2 patients	
PK	026/06 110		Variable dosage regimen prescribed on a case by case basis by the treating physicians to their patients	Blood samples obtained from 10 patients (23 samples analysed)	
PK	026/01 070	Assays of n-carbamyl-L-glutamic acid in plasma samples collected in patients under treatment		One urine sample and 53 plasma samples	
Efficacy and safety	Carbaglu retrospective data review in NAGS deficiency	Retrospective, non-comparative, descriptive review of data collected from NAGS deficiency patients treated with carglumic acid on a long term basis	Carglumic acid The recommended initial daily dose of carglumic acid is 100-250 mg/kg/day Typically treatment is given twice daily Because patients are treated individually and not as a part of a study doses vary quite widely	23 NAGS deficiency patients	
Efficacy and safety	Other study reports – M Tuchman February 2009	Open study	Carbaglu 3 days of treatment Oral or gastrostomy administration of carbamyl glutamic acid at a dose of 100 mg/kg/day for subjects < 25 kg body weight of 2.2 g/m^2/day for subjects ≥ 25 kg body weight	7 patients 2 with NAGS deficiency, 4 with propionic acidaemias and 1 NAGS heterozygote	

Type of study	Study ID	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects Healthy or diagnosis	Duration of treatment
Efficacy and safety	Orphan Europe report (16 March 2009)	Safety report on all patients receiving carglumic acid, regardless of the underlying disease for acute and chronic treatment	Carglumic acid		
Efficacy and safety	Orphan Europe report (20 April 2009)		Carlglumic acid Variable dosage	About 160 Patients 143 including 23 patients with NAGS deficiency and healthy volunteers (15 from 2 clinical trials)	Variable duration
Efficacy and safety	Orphan Europe clinical study report OE-CGA001-OA2009 (September 2010)	A multi-centre observational retrospective data collection and analysis Phase IIIb	Carglumic acid (carbaglu) No dose has been pre-defined. In EU the recommended initial dose is 100-250 mg/kg/day typically given twice or thrice daily	57 patients with hyperammonaemia during decompensation episodes	At the discretion of the treating physician a window evaluation was defined up to a max of 15 days since the first administration of carglumic acid

The PK dataset included the following:

- Single dose pharmacokinetics in 15 normal adult volunteers including 3 subjects as part of a mass balance study.
- A total of 23 samples from 10 patients receiving carglumic acid as part of a follow-up program.
- A total of 53 samples in 20 patients receiving carglumic acid as part of treatment with carglumic acid.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Study OE 312/PK/99-01

Study OE 312 was a comparative pharmacokinetic study in healthy male volunteers after single oral administration. It was a single dose, open label, bioequivalence study between the reference powder and a 200 mg dispersible tablet. The study was conducted in healthy young males. Their demographics were:

- Age: 23.3 ± 3.3 years (range: 18 - 28 years).
- Body weight: 72.1 ± 3.1 kg (range: 65.9 – 75.0 kg).
- Height: 181.5 ± 6.6 cm (range: 171.0 - 190.0 cm).

The primary aims were:

- To determine the relative bioavailability and tolerance of N-carbamyl-L-glutamic acid (carglumic acid) from two OE312 formulations (new dispersible tablet versus the reference powder) administered at the single oral dose of 100 mg/kg in 12 healthy volunteers.
- Evaluation of the pharmacokinetic parameters of carglumic acid by measuring its plasma and urinary levels. The bioequivalence data is of some relevance to the current dossier, in that the powder was used historically for the treatment of hyperammonaemia.

The pharmacokinetic findings are shown below in Figure 3and Table 3.

Figure 3. Mean and S.D. plasma profiles for carglumic acid obtained after single oral administration of 100 mg/kg of OE312 in 12 healthy male volunteers.

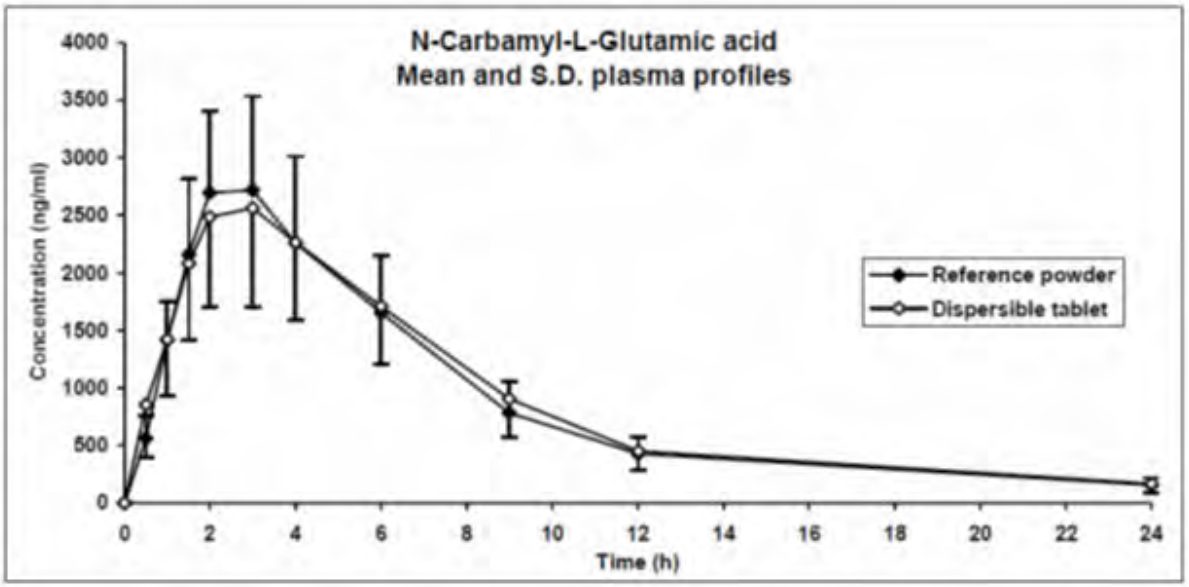


Table 3. Pharmacokinetic parameters of carglumic acid.

N-Carbamyl-L-Glutamic acid	C_{max} (ng.ml)	t_{max} (h)	AUC_{0-t} (ng.ml.h)	$AUC_{0-\infty}$ (ng.ml.h)	$t_{1/2}$ (h)
Treatment A (Reference powder):					
Mean	2943		20850	22414	6.67
S.D.	839	1.5 - 4.0*	5297	5793	1.26
Median	2880	2.0	22085	23693	6.55
Treatment B (Dispersible tablet):					
Mean	2708		21126	22560	6.00#
S.D.	818	2.0 – 4.0*	6580	7019	1.50
Median	2550	3.0	19600	20559	5.56
Analysis of variance	NS (1)	NS (2)	NS (1)	NS (1)	NS (3)
90% confidence intervals	0.83-1.03		0.87-1.16	0.86-1.16	

N-Carbamyl-L-Glutamic acid	MRT (h)	Ae (mg)	CItot/F (ml/min)	Vd/F (L)	Clr (ml/min)
Treatment A (Reference powder):					
Mean	8.36	372	5784	3302	312
S.D.	1.09	82	1864	1114	91
Median	8.04	381	5010	3091	276
Treatment B (Dispersible tablet):					
Mean	8.04	360	5784	2783	295
S.D.	1.53	96	1742	1107	73
Median	7.82	330	5719	2657	290
Analysis of variance	NS (1)	NS (2)	NS (2)	NS (2)	NS (2)

4.2.1.2. Study 026/00 029

Study 026/00 029 was of assays of N-carbamyl-L-glutamic acid in human plasma and urine collected during a kinetic trial. Products: N-carbamyl-L-glutamic acid and hydantoin-5-propionic acid. This report was an addendum to Study OE 312/PK/99-01. The aim of this study was to determine concentrations of N-Carbamyl-L-Glutamic acid and hydantoin-5-propionic acid, which is a degradation product in acidic solution but also a hypothetical metabolite, in human plasma and urine samples collected throughout Study OE 312/PK/99-01.

The report concluded that 2 methodologies were developed and validated for the accurate and precise measurement of N-Carbamyl-L-Glutamic acid and its hypothetic metabolite, hydantoin-5-propionic acid, in human plasma or urine samples. Also stability was shown for both compounds in plasma after 3 freeze/thaw cycles. The main report was produced in March 2001 with an amendment dated September 2001.

4.2.1.3. Study 026/00 080

Evidence of N-Carbamyl-L-Glutamic acid metabolites in human and rat hepatocytes.

This was an in vitro study of the metabolic capacity of N-Carbamyl-L-Glutamic acid in human and rat hepatocytes. The aim was to determine the metabolic pathways of NCLG in rat liver compared with human liver cells. Different hypotheses of metabolism were investigated.

- The first hypothesis of metabolism of N-Carbamyl-L-Glutamic acid is based on the urea cycle. According to this hypothesis, N-Carbamyl-L-Glutamic acid could react with aspartic acid. The resulting compound could liberate fumarate and an intermediate compound. This compound could then be transformed into urea and glutamic acid.

- The possibility of formation of N-Carbamyl-pyroglutamic acid, diaza-l, 3-dione-2, 4-carboxy7-cycloheptane and hydantoin-5-propionic acid resulting from the cyclisation of the parent molecule was also investigated Detection of the hypothetic main metabolites was carried out using a liquid chromatography (LC) coupled with a radiomatic detector (Flo-One). LC/MS was carried out to check and fill out Flo-One results.

The radiolabelled compounds were followed as peaks on the radiochromatograms and results of radioactivity expressed as percentage. In the studied conditions, N-Carbamyl-L-Glutamic acid was not metabolised in either human or rat hepatocytes.

4.2.1.4. Study SPC 313-1

An open label study with ^{14}C labelled carglumic acid to investigate the mass balance, pharmacokinetics and metabolism following a single oral administration to healthy male subjects. This was a single centre, open label, uncontrolled, single dose mass balance study in healthy male subjects, aged between 40 to 55 years. Each subject received a single oral dose of approximately 60 µ Curie ^{14}C labelled carglumic acid (100 mg/kg). Safety measurements (ECG, Vital signs, blood chemistry and haematology) were conducted before and after the study, adverse events were monitored throughout the study. There were two amendments to the report because of mistakes in the original study report. The errors did not alter the overall findings of the study.

Blood samples were taken at the following time points: immediately before the drug administration (0 h) as well as 0.5 h (30 min), 1.0 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, 144 h, and 168 h thereafter.

Urine was collected before the drug administration (0h) then collected from 0 to 2 h, 2 to 4 h, 4 to 8 h, 8 to 12 h, 12 to 24 h and 24 to 36 h, 36 to 48 h after drug administration and thereafter as 24 hour pooled samples.

Breath sampling was performed immediately before the drug administration (0 h) and 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h thereafter. Faecal sampling was before the drug administration (- 24 to 0 h). Thereafter each faecal sample was completely collected for 168 hours and the time of delivery recorded.

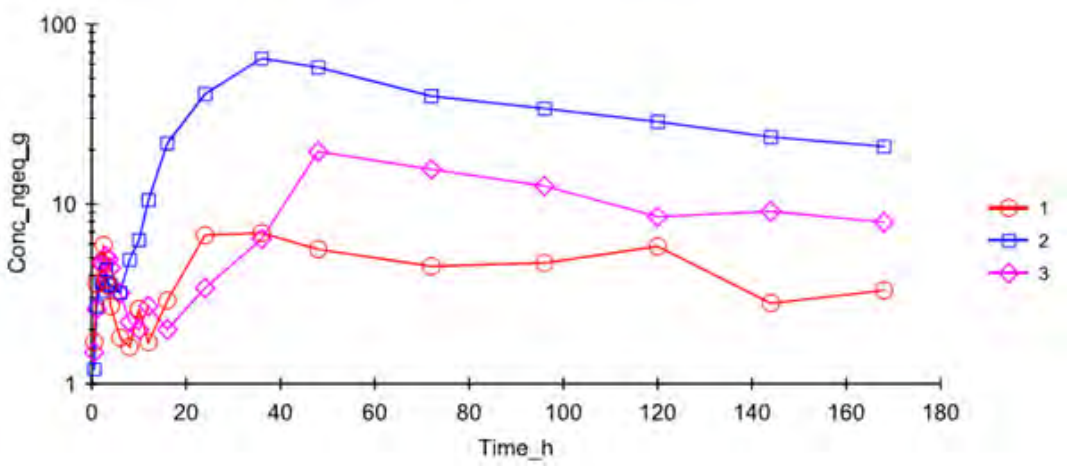
The study found that radioactivity excreted via urine for the three subjects ranged from 8.41 to 9.75 % of the radioactivity administered. Excreted amounts in faeces of subjects 001 and 003 were 71.96 % and 72.67 %, respectively. In faeces of subject 002 only a small amount of the administered radioactivity was recovered (16.45 %).

The blood and plasma concentration profile of radioactivity was characterised by a double peak of radioactivity: after a first peak within the first day after drug administration, a second, higher peak followed with a t_{max} of 36 to 48 h. The terminal phase of all three profiles was characterised by a quite uniform decrease of radioactivity with a mean half-life of approximately 110 to 120 hours with only little variation between the subjects (Table 4). However, subject 002 had substantially higher blood concentrations as compared to the other subjects (Figure 4).

Table 4. Main non compartmental pharmacokinetic parameters for plasma concentrations of radioactivity expressed in µg-eq/g.

Parameter for plasma concentrations (radioactivity expressed in µg-eq/g)	(N = 3)	(N = 3) 24h value subject 002/003 exchanged
AUC (0-inf) [h-µg-eq/g]	4250 ± 3617 (3032) [1399 - 8318]	4277 ± 3900 (2717) [1399 - 8715]
%AUC [%]	38.39 ± 6.26 (36.36) [33.39 – 45.41]	39.13 ± 5.59 (37.26) [34.70 – 45.41]
AUC (0 - tn) [h-µg-eq/g]	2692 ± 2339 (2020) [764 - 5293]	2720 ± 2616 (1705) [764 - 5691]
C_{max} [µg-eq/g]	37.53 ± 29.06 (41.00) [6.90 – 64.70]	30.40 ± 30.38 (19.60) [6.90 – 64.70]
$t_{1/2}$ [h]	107.54 ± 23.17 (100.31) [88.84 – 133.46]	107.54 ± 23.17 (100.31) [88.84 – 133.46]
t_{max} [h]	32.0 ± 6.93 (36.00) [24.0 – 36.0]	40.0 ± 6.93 (36.00) [36.0 – 48.0]

Figure 4. Plasma radioactivity 0-170 hours.



4.2.1.5. Report 026/02 070 (Study SPC 313-1).

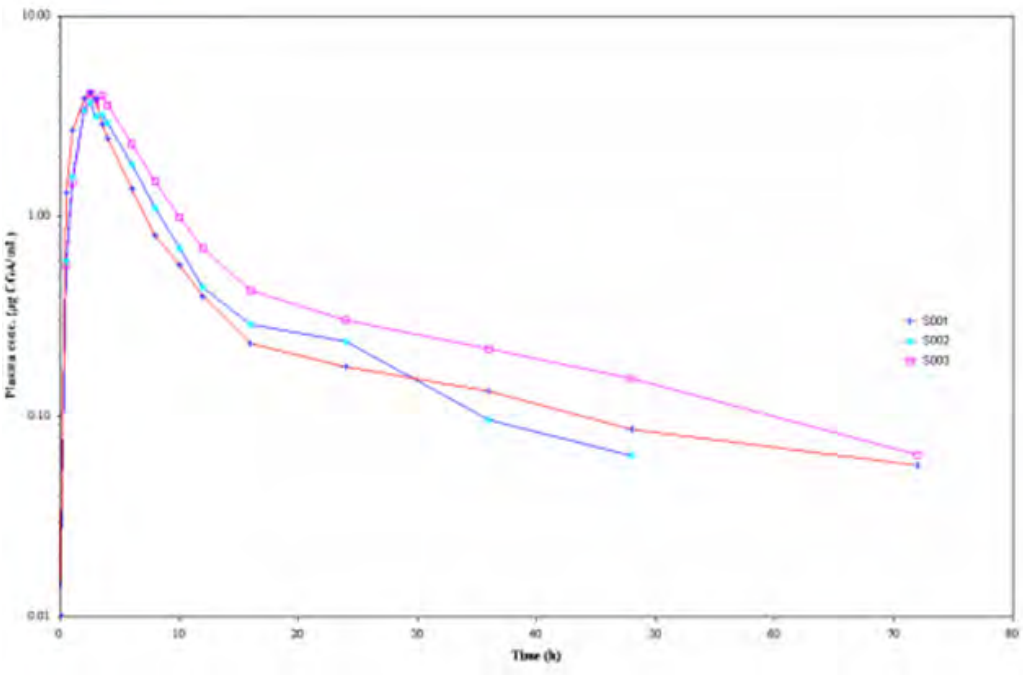
Study SPC 313-1 was a metabolism study of carglumic acid after a single oral administration of [^{14}C] carglumic acid to three human volunteers. An analytical study on samples obtained from Study SPC 313-1. Three volunteers received 100 mg/kg of carglumic acid containing about 2500 KBq of radioactive material as a single oral dose, in the aim to investigate the metabolism of the parent compound. Plasma, urines, faeces and expired CO_2 were collected.

The metabolic capacity of carglumic acid was demonstrated to be limited in at least two out of the three human healthy volunteers. The parent compound assayed specifically by LC/MS-MS was showed to be excreted in large amounts in faeces (approximately 60% in Subjects 001 and 003 but only 8.5% in Subject 002), and to a lesser extent in urine (approximately 8%). These results match the radioactivity amounts excreted in faeces (approximately 72% in Subjects 001 and 003 but only 16.5% in Subject 002) and the radioactivity amounts excreted in urine (approximately 9%) (Table 5 and Figure 5).

Table 5. Pharmacokinetic Parameters (Final Study Report).

Pharmacokinetic parameters for CGA						
Subject Id	T_{max} (h)	C_{max} (µg/mL)	$t_{1/2}$ elim. (h)	AUC_{0-t} (µg.h/mL)	$AUC_{0-infinity}$ (µg.h/mL)	Extrap. (%)
Subject 001	2.5	4.14	27.6	27.4	29.7	7.7
Subject 002	2.5	3.67	12.9	26.4	27.6	4.3
Subject 003	2.5	4.07	21.1	37.1	39.1	5.0
mean	**2.5**	**3.96**	**20.5**	**30.3**	**32.1**	-
sd	-	0.254	7.37	5.91	6.12	-
CV (%)	-	6.4	35.9	19.5	19.06	-
min	2.5	3.67	12.9	26.4	27.6	4.3
max	2.5	4.14	27.6	37.1	39.1	7.7

Figure5. Plasma concentrations of carglumic acid versus time in the three subjects.



4.2.1.6. Report 026/04 022 (Study SPC 313-1)

Report 026/04 022 of Study SPC 313-1 was a validation of assays of carglumic acid in human urine using a low calibration curve. The aim of this study was to validate the assays of carglumic acid in human urine on a low calibration range. The low limit of quantitation previously validated at 20 µg/mL, in human urine (Report No. 026/00 029) needed to be improved in order to quantify on a lower calibration range (4.00 to 100 µg/mL) specimens issued from Study No. 026/02 070. Three volunteers received 100 mg/kg of carglumic acid containing about 2500 KBq of radioactive material as a single oral dose. The results of the 14 urine samples found BLQ in Study No. 026/02 070 and re assayed in the low calibration range are listed in Table 6. Results above BLQ obtained in the previous study (026/02 070) are provided as additional information in the same table and reported in grey shaded cells.

Table 6. Assay results of carglumic acid in human urine with results expressed as µg/mL.

	Subject Number		
Time interval	Subject 001	Subject 002	Subject 003
Predose	BLQ	BLQ	BLQ
0-2h	505	174	545
2-4h	714	418	1532
4-8h	221	172	227
8-12h	54.3	48.8	228
12-24h	60.0	36.0	52.2
24-36h	57.8	22.1	54.1
36-48h	37.2	12.7	67.7
48-72h	18.1	10.1	32.9
72-96h	9.92	BLQ*	28.9
96-120h	8.59	BLQ*	9.04
120-144h	12.6	BLQ*	7.49
144-168h	6.31	BLQ*	6.53

BLQ: Below the Low Limit of Quantitation (20.0 µg/mL)
BLQ: Below the new Low Limit of Quantitation (4.00 µg/mL)*
Results presented in grey shaded cells come from BIOTEC CENTRE study No. 026/02 070 and are given as additional information.

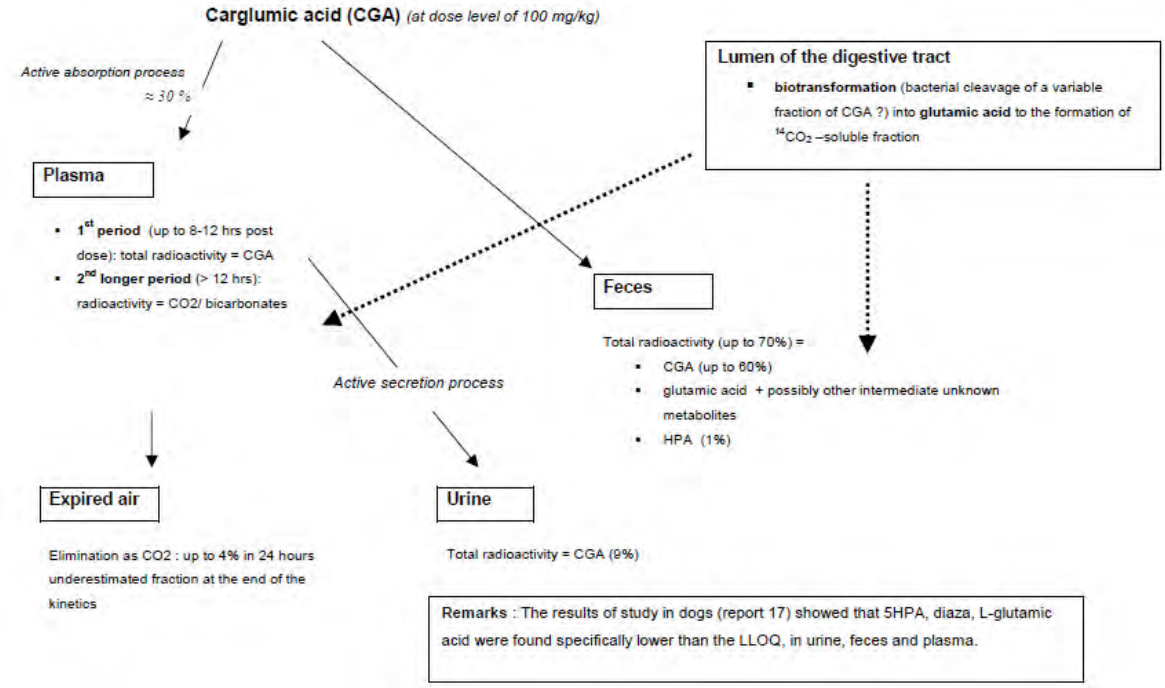
4.2.1.7. Report 026/04 023 (Study SPC 313-1)

Report 026/04 023of Study SPC 313-1 was supplementary research on the metabolism of carglumic acid after a single dose of ^{14}C of carglumic acid to three healthy volunteers. The aim of this study was to check for the presence of $^{14}CO_2$ in the plasma of subjects of Study SPC 313-1. The study also confirmed analysis of faeces from Report 026/02 070 of the same study. Three volunteers received 100 mg/kg of carglumic acid containing about 2500 KBq of radioactive material as a single oral dose, in the aim to investigate the metabolism of the parent compound. The results showed that CO_2 was generated in the plasma of the subjects and that the radioactive compounds in the faeces were stable (not volatile).

4.2.1.8. Data review (Study SPC 313-1)

This study was a data review form Study SPC 313-1 of absorption, distribution, metabolism and elimination of carglumic acid in animals and humans; cross species metabolic profiles comparison. This was a comparative review of the results of Study SPC 313-1 with studies involving rats, rabbits and dogs. There were also comments made on single plasma concentrations of carglumic acid, measured in 11 NAGS patients aged from 1 day to 13 years. The review proposed the following schema for the metabolic pathway and balance of elimination of carglumic acid in humans (Figure 6).

Figure 6. Proposed metabolic pathway and balance of elimination of carglumic acid in humans.



4.2.2. Pharmacokinetics in the target population

4.2.2.1. Report 026/01 028

Report 026/01 028 was of assays of N-Carbamyl-L-Glutamic acid in plasma and urine samples collected in patients under treatment. This report describes the assay development to determine concentrations of N-Carbamyl-L-Glutamic acid and hydantoin-5-propionic acid in human plasma and urine samples. The assay was used to assay samples collected from patients under treatment with N- Carbamyl-L-Glutamic acid.

4.2.2.2. Report 026/06 110

Report 026/06 110 was of Carglumic acid and 5 HPA assays in human plasma specimens collected during a patients' follow-up programme: determination of the presence of diaza (diaza-1, 3-dione -2,4-carboxy-7-cycloheptane) in the specimens. This study was carried out in order to assay carglumic acid and 5 HPA in the plasma of patients under treatment by carglumic acid (Carbaglu) and to qualitatively evaluate the presence of diaza in the same plasma samples.

Carglumic acid was quantified in most plasma samples of patients under Carbaglu treatment, the concentrations ranging from the LOQ (50 ng/ml) to 6123 ng/ml. In the same plasma samples, 5 HPA was quantifiable for two samples and diaza was not detected, except for one sample in which carglumic acid reached a high concentration (3762 ng/ml). These low levels of 5 HPA and diaza determined in a single patient plasma sample reinforce the hypothesis that the traces of 5 HPA and diaza that may be detected in patient's plasma are likely to be generated by the presence of these degradation products in the drug product administered to the patients. The results are shown in Table 7 below.

Table 7. Results of plasma assays in patients who were treated with N-Carbamyl-L-Glutamic acid.

Initials	DOB	City	Country	Last intake of Carbaglu date	Last intake of Carbaglu time	Sample date	Sample time	CGA concentration (ng/mL)	5-HPA concentration (ng/mL)	Diaza concentration (ng/mL)
		Glasgow	UK	NA	NA	17/04/2007	16:15	251	BLQ*	na
		Glasgow	UK	NA	NA	17/04/2007	16:15	276	BLQ*	na
		Lyon	France	15/01/2006	18:00	16/01/2006	11:25	561	BLQ	<LOD
		Lyon	France	15/01/2006	18:00	16/01/2006	12:15	50.7	BLQ	<LOD
¶		Amsterdam	Netherlands	NA	NA	NC	NA	1450	BLQ	<LOD
		Amsterdam	Netherlands	NA	NA	NC	NA	1311	BLQ	<LOD
		Amsterdam	Netherlands	NA	NA	NC	NA	675	BLQ	<LOD
		Lyon	France	07/06/2006	8:30	07/06/2006	12:15	105	BLQ	<LOD
		Lyon	France	13/09/2006	8:30	13/09/2006	11:45	318	BLQ	<LOD
¶		Amsterdam	Netherlands	NA	NA	NC	NA	1077	BLQ	<LOD
		Amsterdam	Netherlands	NA	NA	NC	NA	1253	BLQ	<LOD
		Amsterdam	Netherlands	NA	NA	NC	NA	6123	BLQ*	na
		Amsterdam	Netherlands	NA	NA	NC	NA	1304	BLQ	<LOD
		Amsterdam	Netherlands	NA	NA	NC	NA	BLQ*	BLQ*	na
		Amsterdam	Netherlands	NA	NA	NC	NA	1838	BLQ*	na
		Gottingen	Germany	NA	NA	17/07/2006	8:50	BLQ	BLQ	<LOD
		Gottingen	Germany	NA	NA	16/11/2006	18:50	529	BLQ	<LOD
		Tours	France	NA	NA	07/03/2006	15:30	3762	63.9	>LOD (119 ng/ml)
¶		Rotterdam	Netherlands	NA	NA	24/07/2007	3h/ after 1st dose- NC	118	39.0	<LOD
		Rotterdam	Netherlands	NA	NA	24/07/2007	3h/ after 20h30 -NC	202	BLQ	<LOD
		Rotterdam	Netherlands	NA	NA	25/07/2007	3h/ after dose -NC	235	BLQ*	na
		Rotterdam	Netherlands	NA	NA	25/07/2007	7h/ through -NC	148	BLQ	<LOD
		Lille	France	NA	NA	05/09/2007	NA	6132	BLQ	<LOD

NA = Not Available
na = not applicable, assay volume <500µL
NC = Not Confirmed
BLQ = below the limit of quantification
BLQ* = below the limit of quantification with an assay volume <500 µL
LOD = 31.4 ng/mL

Patient identifiers have been redacted from this figure.

4.2.2.3. Report 026/01 070

Report 026/01 070 was of assays of N-Carbamyl-L-Glutamic acid in plasma and urine samples collected in patients under treatment. This study was carried out in order to assay carglumic acid in human plasma and urine samples using an LC/MS-MS. In human plasma, the method was validated over the range of 50.0 to 10000 ng per mL of plasma for carglumic acid. In human urine, the method was validated over the range of 20.0 to 1000 µg per mL of urine for carglumic acid. The results for urine are shown in Table 8and for plasma in Table 9.

Table 8. Concentrations of carglumic acid in urine.

Subject:	Concentration
* Urine collection between two doses intake	162

*: urine collection between 8h15 and 11h45

Patient identifiers have been redacted from this table.

Table 9. Concentrations of carglumic acid in plasma - Results are expressed as ng/mL.

Initials	DOB	City	Country	Last intake of Carbaglu date	Last intake of Carbaglu time	Sample date	Sample time	Concentration (ng/mL)
		Grenoble	France	29/11/2004	20:00	30/11/2004	NA	59.8
		Colmar	France	NA	NA	03/07/2001	8:15	216
		Colmar	France	NA	NA	03/07/2001	11:45	624
		Lyon	France	30/06/2005	20:00	01/07/2005	12:15	103
		Lyon	France	24/09/2004	9:00	24/09/2004	NA	707
		Lyon	France	07/02/2002	9:30	08/02/2002	12:25	238
		Konstanz	Germany	20/12/2005	20:45	21/12/2005	07:40	79.6
		Konstanz	Germany	21/12/2005	7:45	21/12/2005	09:40	334
		Lyon	France	07/02/2002	21:00-22:00	08/02/2002	08:45	1034
		Lyon	France	18/07/2004	22:30	19/07/2004	09:30	428
		Lyon	France	NA	NA	12/03/2002	07:20	804
		Lyon	France	30/04/2002	06:00	30/04/2002	11:50	1606
		Lyon	France	30/04/2002	12:00	30/04/2002	15:00	2200
		Lyon	France	15/07/2004	21:30	16/07/2004	9:00	197
		Lyon	France	30/06/2005	20:00	01/07/2005	12:00	141
		Glasgow	UK	NA	NA	NC	NA	328
		Glasgow	UK	NA	NA	NC	NA	333
		Stockholm	Sweden	NA	NA	15/06/2003 - NC	9:00	408
		Stockholm	Sweden	NA	NA	15/06/2003 - NC	12:00	1090
		Stockholm	Sweden	NA	NA	20/12/2005	10:00	232
		Stockholm	Sweden	NA	NA	20/12/2005	13:00	477

Table 9 (continued). Concentrations of carglumic acid in plasma - Results are expressed as ng/mL.

Initials	DOB	City	Country	Last intake of Carbaglu date	Last intake of Carbaglu time	Sample date	Sample time	Concentration (ng/mL)
		Lyon	France	25/01/2002	7:00	25/01/2002	12:45	796
		Lyon	France	01/02/2002	7:30	01/02/2002	11:05	310
		Lyon	France	16/07/2004	9:00	16/07/2004	11:00	407
		Lyon	France	05/12/2005	7:30	05/12/2005	11:20	113
		Lyon	France	08/02/2002	6:00	08/02/2002	10:00	448
		Lyon	France	04/07/2004	21:30	05/07/2004	10:30	58.7
		Lyon	France	04/02/2002	7:30	04/02/2002	12:50	1350
		Antwerpen	Netherlands	16/02/2005	7:30/8:00	16/02/2005	11:30	428
		Antwerpen	Netherlands	NA	NA	16/02/2005	15:00	436
		Antwerpen	Netherlands	NA	NA	16/02/2005	7:30	268
		Geinhausen	Germany	NA	NA	02/2002 - NC	NA	2560
		Geinhausen	Germany	NA	NA	02/2002 - NC	NA	1553
		Manchester	UK	12/09/2004	18:00	13/09/2004	12:30	117
		Dresden	Germany	NA	NA	15/11/2003	12:00	3140
		Dresden	Germany	NA	NA	15/11/2003	19:20	5140
		Dresden	Germany	NA	NA	NC	NA	4420
		Dresden	Germany	NA	NA	NC	NA	1398
		Dresden	Germany	NA	NA	NC	NA	1222
		Dresden	Germany	NA	NA	NC	NA	1392
		Dresden	Germany	NA	NA	NC	NA	1260
		Dresden	Germany	NA	NA	NC	NA	1258
		Lyon	France	08/06/2004	12:00	08/06/2004	15:30	917
		Bron	France	04/07/2004	21:30	05/07/2004	10:45	186
			Italy	NA	NA	23/06/2004	8:47	BLQ
			Italy	25/06/2004	NA	25/06/2004	8:56	BLQ
			Italy	NA	NA	26/06/2004	13:15	1323
			Italy	NA	NA	26/06/2004	13:45	1754
			Italy	NA	NA	26/06/2004	14:15	2019
			Italy	NA	NA	26/06/2004	15:15	2050
			Italy	NA	NA	26/06/2004	16:15	1520
			Italy	NA	NA	26/06/2004	23:00	667
			Italy	NA	NA	27/06/2004	21:00	128

NA = Not Available
NC = Not Confirmed

Patient identifiers have been redacted from this table.

4.2.3. Pharmacokinetics in other special populations

No PK studies in other special populations were conducted.

4.2.4. Pharmacokinetic interactions

No PK interaction studies were conducted.

4.3. Evaluator's overall conclusions on pharmacokinetics

The bioequivalence study in 12 normal adult males does define the PK parameters for a single dose of carglumic acid in this population. The study also demonstrated bioequivalence between Carbaglu and the unregistered powder previously available for treatment. The mass balance study in three adult males indicated a significant variation in the disposition of carglumic acid even though all three subjects had similar serum carglumic acid profiles.

The pharmacokinetic data in treated patients were sparse and difficult to interpret. The sponsor only produced raw data and no analysis of these data was presented. There were a range of concentrations seen in treated patients; these being within the range seen in the normal subjects. What is missing is a PK analysis of these data to estimate PK parameters or the likely concentration profile in the treated patients, most of whom were infants and children. The sponsor should have attempted an analysis of these data, for example, using population pharmacokinetic methods. The model could have been informed by the available adult data.

In summary, the pharmacokinetic data are insufficient to support the registration of Carbaglu for use in the target patient population. The evaluator recommends that the sponsor perform further analysis on the available data to investigate whether a satisfactory analysis of these data is possible to better define the pharmacokinetics of Carbaglu in infants and children.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No specific pharmacodynamic studies were submitted in the dossier.

6. Dosage selection for the pivotal studies

There was no rational dose selection for the pivotal studies based upon prior pharmacokinetic studies. The pivotal clinical studies were retrospective clinical case series and the dose administered was determined by the individual treating physician.

7. Clinical efficacy

7.1. Treatment of NAGS deficiency - Pivotal efficacy studies

7.1.1. Study; Carbaglu retrospective data review in NAGS deficiency patients

This study was divided into two parts covering the same patients:

- Part I: Clinical and Biological Responses of Patients with NAGS Deficiency to Acute and Chronic Treatment with Carglumic Acid.
- Part II: Individual Patient Narratives in NAGS Deficiency Patients.

7.1.1.1. Study design, objectives, locations and dates

This retrospective review was based on spontaneous reports following ad hoc guidelines. No study protocol was applied and GCP was not complied with. The review covered a period from 1 January 1991 to 31 December 2007.

Part I: This was a clinical report of the retrospective review of N-acetylglutamate synthase (NAGS) deficiency patients involved in the 'Carbaglu Patient Follow-up Program'. This part of the Clinical Report presents and analyses the clinical and biological responses of patients with NAGS deficiency to acute and long-term treatment with carglumic acid.

Part II: This was a list of individual patient narratives (23 patients), based on the individual Subject Profiles defined in the Data Management Plan that chronologically described the clinical and biological events of each patient, the treatment and evolution of the disease and the adverse events recorded and reported.

7.1.1.1.1. *Primary study objectives*

The primary objective was to review the clinical and biological response of NAGS deficiency patients to carglumic acid within the first 7 days of treatment (short term outcome) and at the last report (long term outcome). For the short term analysis ammonaemia was the primary biomarker supported by glutaminaemia and citrullinaemia results. For the long term analysis all three biomarkers, ammonaemia, glutaminaemia and citrullinaemia, were evaluated.

7.1.1.1.2. *Secondary study objectives*

The secondary objectives were:

- the evaluation of patient clinical development, that is, neurological and psychomotor status, and anthropometric development (growth) parameters;
- the analysis of the implementation of restrictive/free protein diet and concomitant treatment; and
- the analysis of the carglumic doses prescribed as an indirect efficacy parameter and as a definition of the dose response determination.

All the data collected in forms or in any other supportive document of NAGS deficiency patients were taken into account to provide the most complete history of the patients. All the source documents were included as part of the submission and translated into English whenever necessary.

7.1.1.1.3. *Inclusion and exclusion criteria*

Among the 23 confirmed NAGS deficiency patients who have been identified, 18 patients were under long term continuous treatment with carglumic acid at the cut-off date (31st December 2007). One of these patients was previously diagnosed and treated as a patient with CPS 1 deficiency until a recent DNA confirmation of NAGS homozygous mutation.

7.1.1.1.4. *Study treatments*

Patients were treated with carglumic acid, mostly on an mg/kg basis. Both the dose and the schedule of dosing were different for treatment initiation (short term) and for maintenance (long term). The recommended initial daily dose of carglumic acid is 100 to 250 mg/kg/day. Typically, treatment was given twice daily. This dose by weight translates to a minimum single dose of 50 mg and a maximum single dose of 1500 mg in the patients studied (Table 10). Since the data were not from a clinical trial, there were dose modifications, as well as intermittent start and stop periods for treatment, and a few treatment discontinuations. Patients also received alternative treatments for their hyperammonaemia including dialysis (Table 11), which further confounded the results of the study.

Table 10. Dosing schedule.

	Total (N=23)
One dose per day	
< 100 mg/kg	4 (17.4%)
[100-250] mg/kg	1 (4.3%)
> 250 mg/kg	0 (0.0%)
Two doses per day	
< 100 mg/kg	16 (69.6%)
[100-250] mg/kg	2 (8.7%)
> 250 mg/kg	0 (0.0%)
Three doses per day	
< 100 mg/kg	14 (60.9%)
[100-250] mg/kg	10 (43.5%)
> 250 mg/kg	1 (4.3%)
Four doses per day	
< 100 mg/kg	14 (60.9%)
[100-250] mg/kg	12 (52.2%)
> 250 mg/kg	3 (13.0%)
Five doses per day	
< 100 mg/kg	2 (8.7%)
[100-250] mg/kg	0 (0.0%)
> 250 mg/kg	0 (0.0%)
Carglumic acid duration (months)	
n	23
Mean (SD)	97.8 (67.6)
Median	95.1
Q1 - Q3	33.7 - 143.2
Range	7.4 - 248.5
Missing data	0

Table11. Anti-hyperammonemic Concomitant Medications.

	Total (N=23)
Amino acids	1 (4.3%)
Arginine	14 (60.9%)
Carnitine	10 (43.5%)
Citrulline	5 (21.7%)
Hemodialysis	4 (17.4%)
Na-benzoate	16 (69.6%)
Phenylbutyrate	7 (30.4%)

7.1.1.1.5. *Efficacy variables and outcomes*

The efficacy analysis was conducted according to the SAP. The primary efficacy parameters, ammonaemia, glutaminaemia and citrullinaemia, were analysed in the short term (first 7 days from the initiation of carglumic acid treatment) and the long term (last reported visit/evaluation).

7.1.1.1.6. *Randomisation and blinding methods*

Not applicable.

7.1.1.1.7. *Analysis populations*

Twenty three patients were reported in the database. Their demographics are shown in Table 12.

Table 12. Demographic data; Height and weight Z scores and nutrition prior to first dose of carglumic acid.

	Total (N=21)
Height z-score	
n	16
Mean (SD)	-0.3 (1.3)
Median	-0.5
Range	-3.3 - 1.5
Missing data	5
Weight z-score	
n	19
Mean (SD)	-0.9 (1.8)
Median	-1.3
Range	-3.7 - 2.2
Missing data	2
Total protein (g/kg/d)	
n	12
Mean (SD)	1.2 (1.1)
Median	1.4
Range	0.0 - 2.5
Missing data	9
Calories (Kcal/kg/d)	
n	6
Mean (SD)	121.2 (57.5)
Median	106.5
Range	60.0 - 220.0
Missing data	15
Type of diet	
n	13
Free	4 (30.8%)
Restricted	9 (69.2%)
Missing data	8

7.1.1.1.8. *Sample size*

Twenty three patients were included in the report.

7.1.1.2. Statistical methods

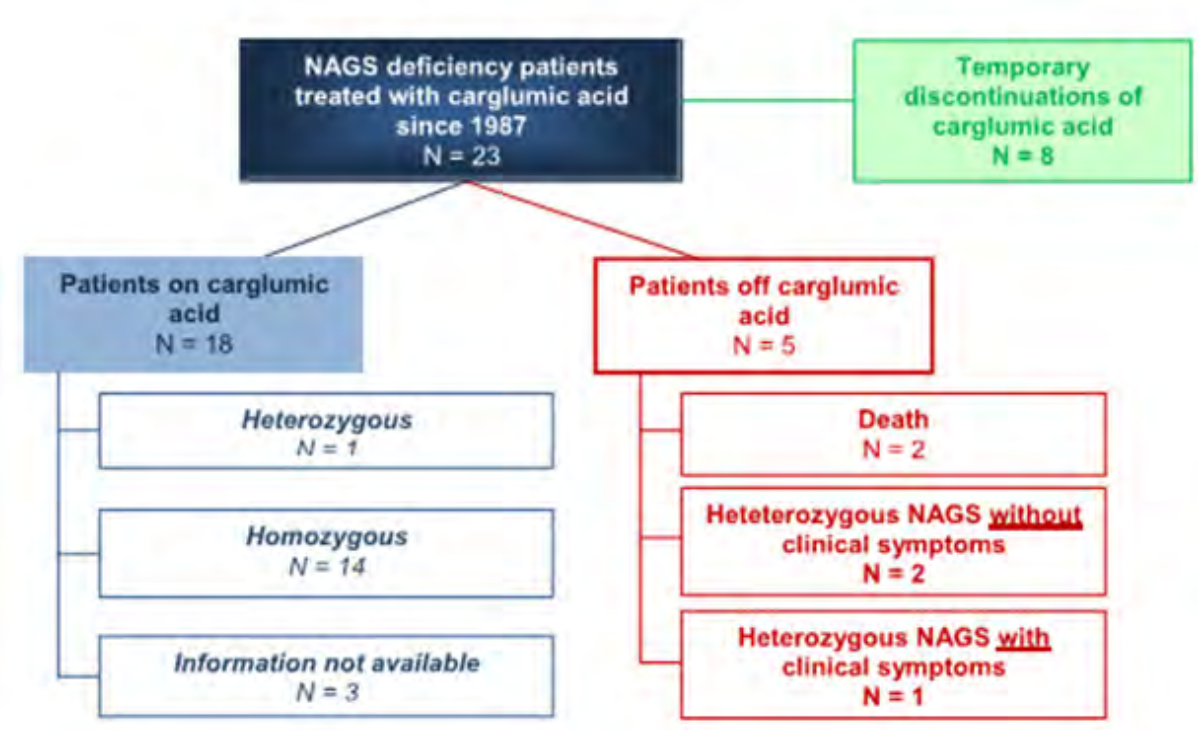
The rules for statistical analysis were:

- The long-term value is the last available value while on treatment, excluding Day 0 (D0). If several values were recorded the same day, the maximum value was kept.
- The short term values were any values available on D0 after first carglumic acid dose to D7 while on treatment. The maximum value was kept for each day giving a possible maximum of 7 values per patient, one for each day.

7.1.1.3. Participant flow

Participant flow is described in Figure 7.

Figure 7. Study flowchart.



7.1.1.3.1. *Major protocol violations/deviations*

Not applicable.

7.1.1.3.2. *Baseline data*

Baseline data were to be collected on all participants. As can be seen from Table 13 and Table 14, there are multiple missing data points. The 23 patients were all children aged from less than 1 month to 13 years at the initiation of treatment.

Table 13. Baseline Data; Abnormalities in Laboratory Parameters Prior to first dose of carglumic acid.

	Female (N=8)	Male (N=13)	Total (N=21)
Ammonia (umol/L)			
n	8	12	20
Normal	2 (25.0%)	1 (8.3%)	3 (15.0%)
Above normal	6 (75.0%)	11 (91.7%)	17 (85.0%)
Missing data	0	1	1
Glutamine (umol/L)			
n	7	9	16
Below normal	1 (14.3%)	0 (0.0%)	1 (6.3%)
Normal	1 (14.3%)	3 (33.3%)	4 (25.0%)
Above normal	5 (71.4%)	6 (66.7%)	11 (68.8%)
Missing data	1	4	5
Citrulline (umol/L)			
n	4	9	13
Below normal	1 (25.0%)	2 (22.2%)	3 (23.1%)
Normal	3 (75.0%)	5 (55.6%)	8 (61.5%)
Above normal	0 (0.0%)	2 (22.2%)	2 (15.4%)
Missing data	4	4	8

Table 14. Baseline Neurological, Psychomotor and Hepatic Clinical Status prior to first dose.

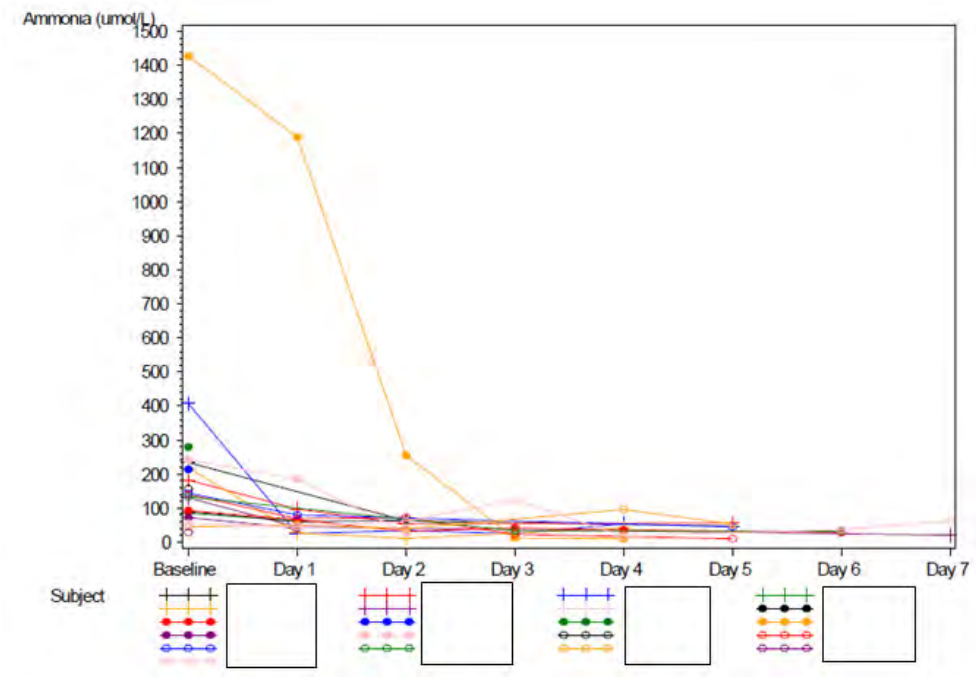
	Total (N=21)
Neurological development	
n	10
Affected	7 (70.0%)
Normal	3 (30.0%)
Missing data	11
Psychomotor development	
n	7
Normal	3 (42.9%)
Retardation	4 (57.1%)
Missing data	14
Hepatic development	
n	11
Affected	3 (27.3%)
Normal	8 (72.7%)
Missing data	10

7.1.1.4. Results for the primary efficacy outcome

7.1.1.4.1. *Ammonaemia*

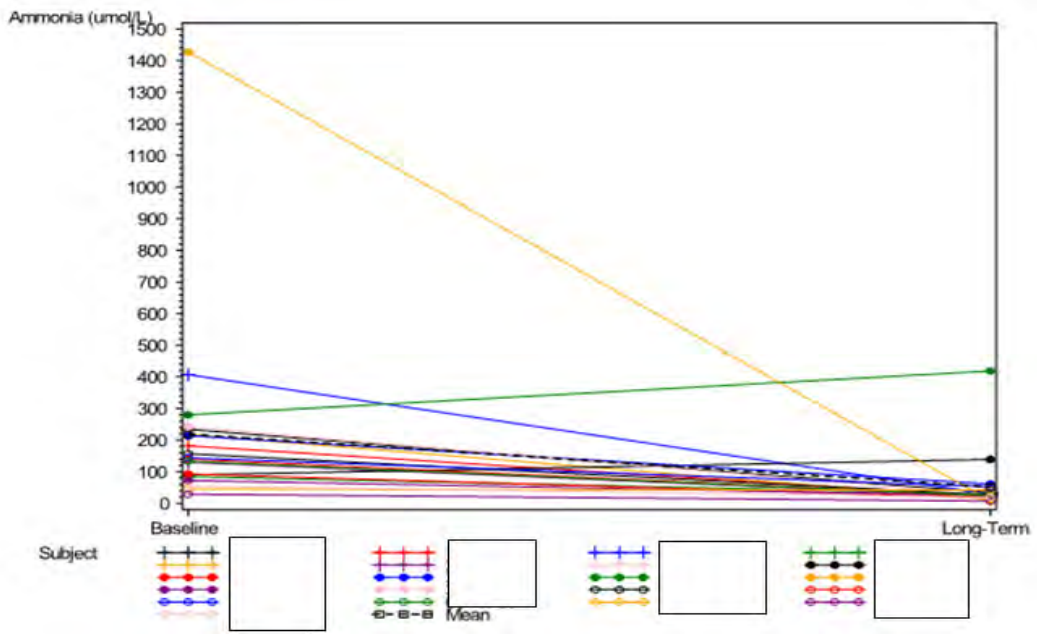
Among the 20 patients with a baseline ammonia measured, ammonia levels decreased over the first 7 days of treatment (Figure 8) in 21 patients. The levels remained low at the end of treatment (21 patients); however, there was a large variation in individual concentrations at the end of treatment (see Figure 9 and Figure 10 below). As can be seen from Figure 8, a low ammonia level is achieved by day 3 of treatment and in most patients; this low level is maintained long term. It should be noted that there were missing data in one patient at baseline (Table 13).

Figure 8. Changes in ammonia plasma levels from pre to ≤ 7 days after initiation of carglumic acid treatment.



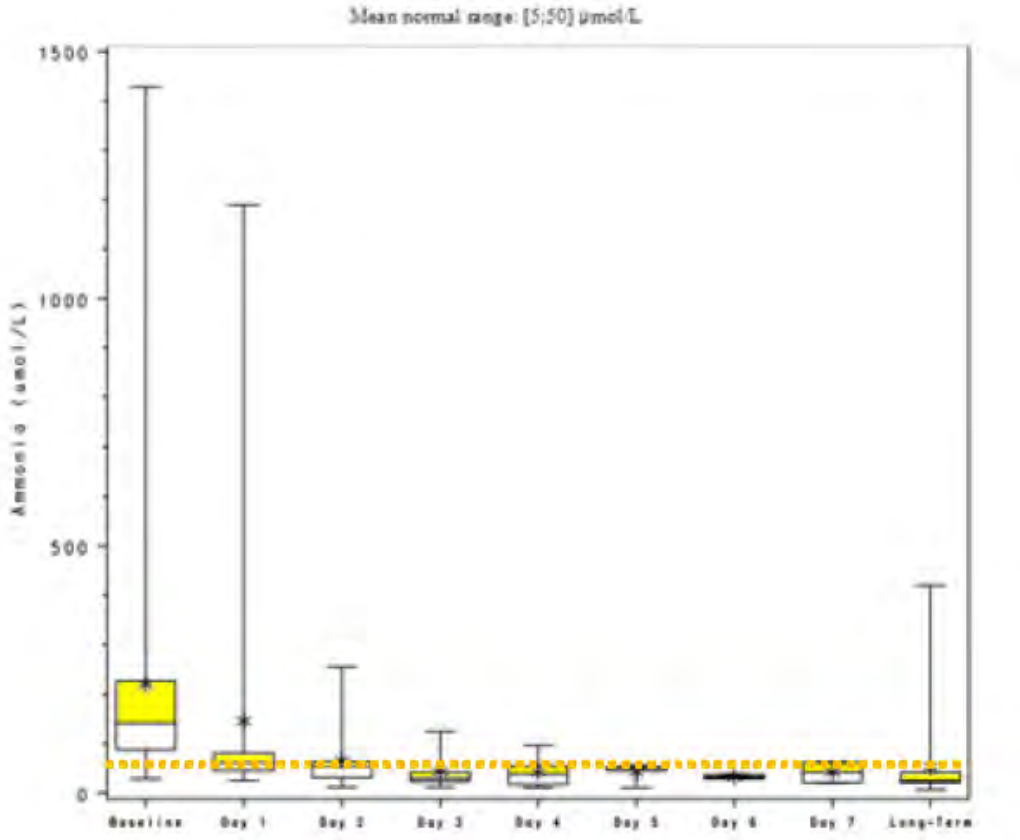
Patient identifiers have been redacted from this figure.

Figure 9. Changes in ammonia plasma levels from pre to last follow-up after initiation of carglumic acid treatment.



Patient identifiers have been redacted from this figure.

Figure 10. Ammonaemia prior to first dose of carglumic acid, ≤ 7 days and at last follow-up after initiation of carglumic acid treatment.



7.1.1.4.2. *Glutaminaemia*

Initially after the treatment with carglumic acid treatment there was a decrease in glutamine concentrations in 21 patients (Figure 11). On Day 1 of treatment the mean glutaminaemia decreased to a mean (95%CI) 544.8 µmol/L (437.9, 651.8). On Day 2 the mean (95%CI) glutamine value was 479.7 µmol/L (71.7, 887.7). On Day 4 of carglumic acid treatment, the mean (95%CI) was 422.0 µmol/L (139.0, 705.0). On Day 7 of carglumic acid treatment the mean was 470.0 µmol/L. The long term analysis the plasma levels of glutamine had a mean (95%CI) of 561.0 µmol/L (464.0, 658.0) (see Figure 12 and Figure 13 below). It should be noted that there were missing data in five patients at baseline Table 13).

Figure 11. Glutaminaemia Prior to First Dose of Carglumic Acid, ≤ 7 Days and at Last Follow-Up After Initiation of Carglumic Acid Treatment.

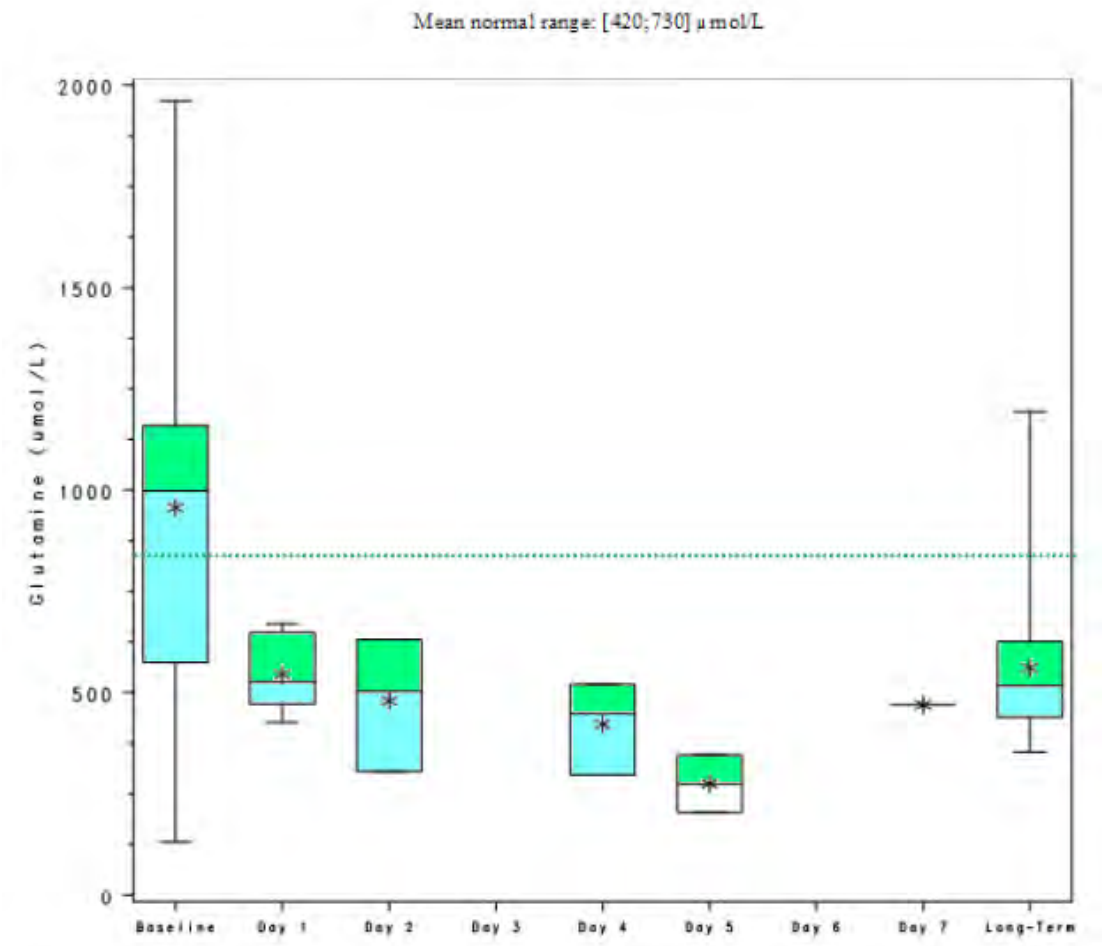
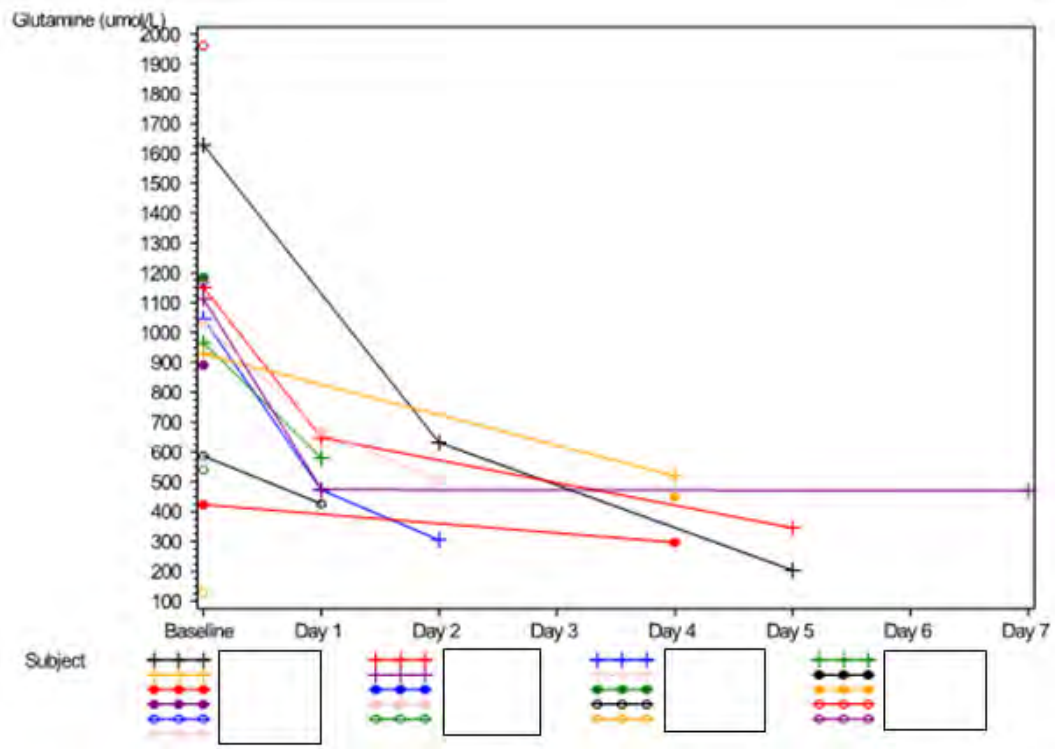
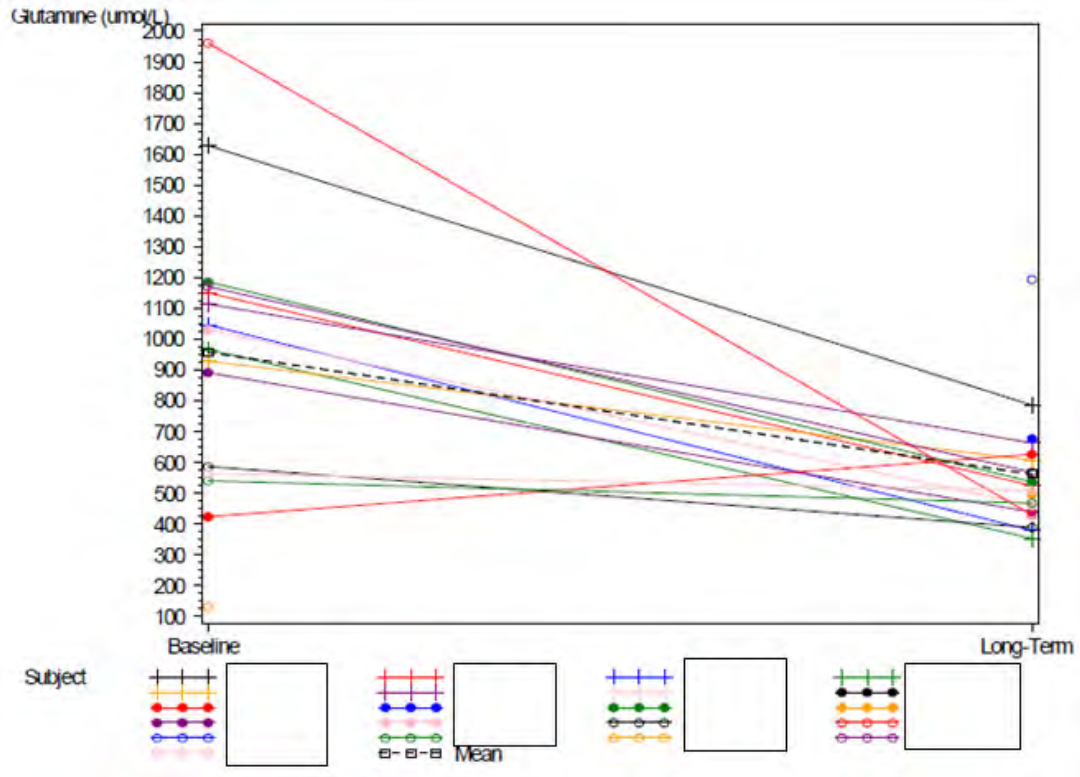


Figure 12. Changes in Glutamine Plasma Levels from Pre to ≤ 7 Days after Initiation of Carglumic Acid Treatment.



Patient identifiers have been redacted from this figure.

Figure 13. Changes in Glutamine Plasma Levels from Pre to Last Follow-up after Initiation of Carglumic Acid Treatment.



Patient identifiers have been redacted from this figure.

7.1.1.4.3. *Citrullinaemia*

Initially after the treatment with carglumic acid treatment there were changes in citrulline concentrations) in 6 patients (Figure 14). On Day 1 of treatment initiation, there was a mean decrease from baseline of - 6.2 µmol/L and a median decrease from baseline of - 10.0 µmol/L.

On Day 2 citrullinaemia showed a decrease from baseline to a mean of - 31.0 µmol/L and a median decrease from baseline of - 31.0 µmol/L. On Day 4 there was a mean increase from baseline of + 1.0 µmol/L, and a median increase from baseline of + 1.0 µmol/L. On Day 7, there was a mean increase from baseline of + 3.0 µmol/L, and a median increase from baseline of + 3.0 µmol/L (Figure 14 and Figure 15). However, these data are limited by the limited number of patients who had more than one sample available for analysis (Figure 15).

The long term measurement in 13 patients showed a mean increase from baseline of + 5.7 µmol/L and a median increase from baseline of + 4.0 µmol/L (Figure 16). It should be noted that there were missing data in eight patients at baseline (Table 13).

Figure 14. Citrullinaemia Prior to First Dose of Carglumic Acid, ≤ 7 Days and at Last Follow-Up after Initiation of Carglumic Acid Treatment – Mean normal range: 16 to 32 µmol/L.

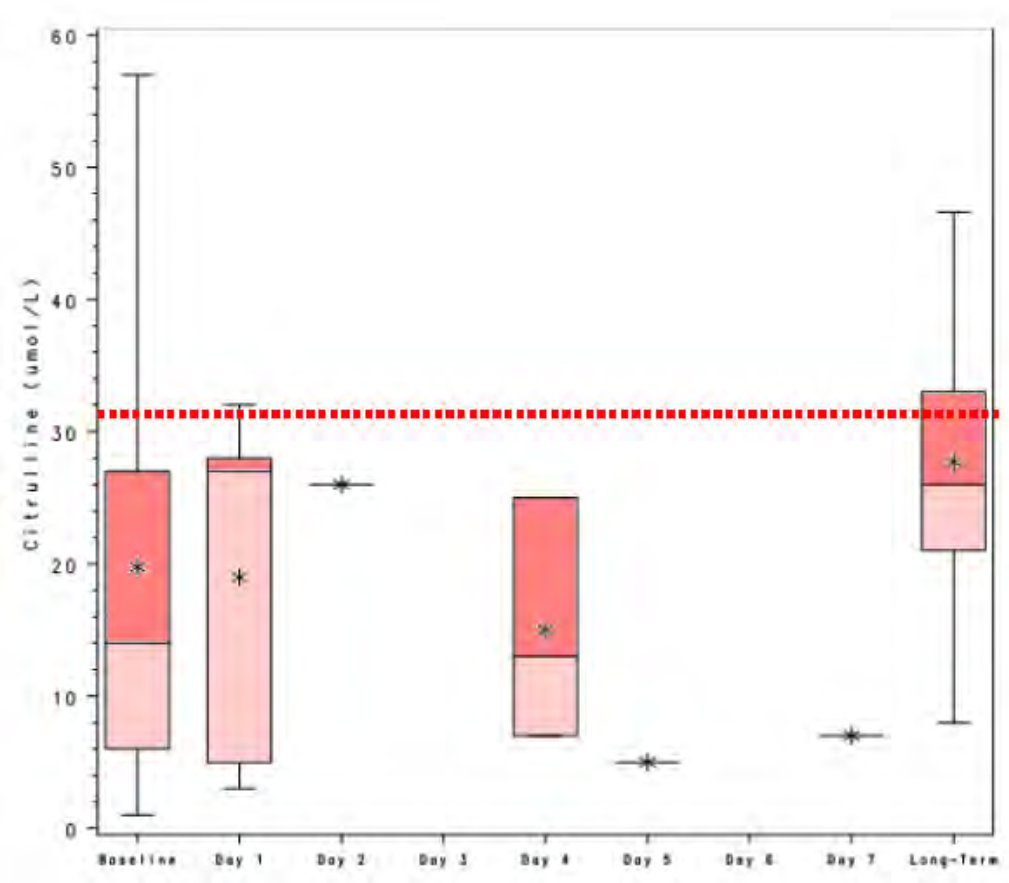
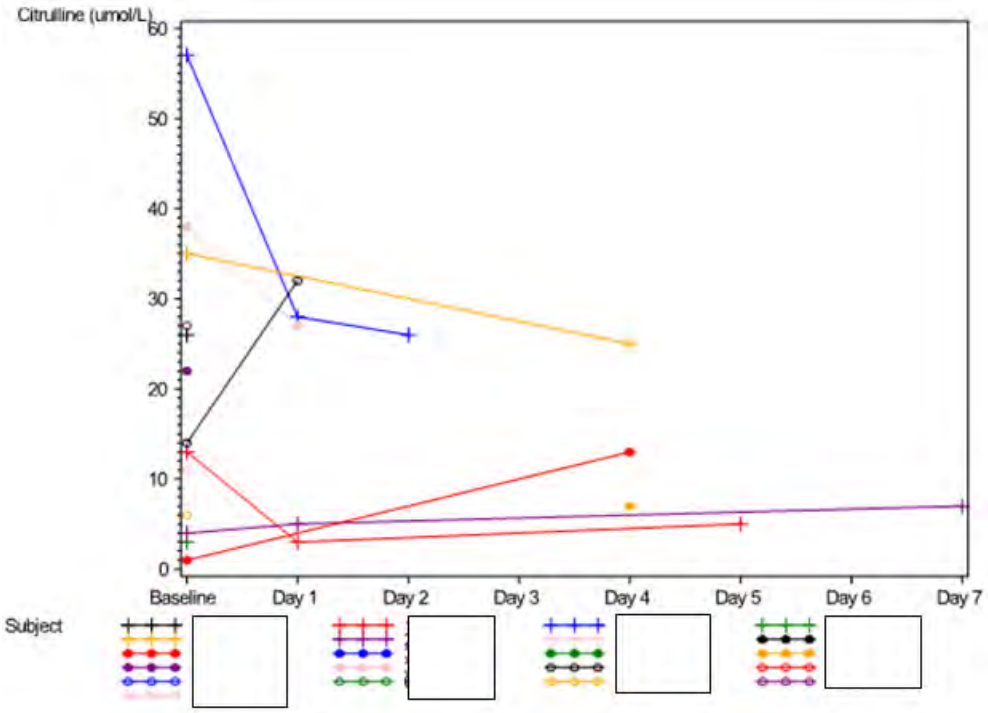
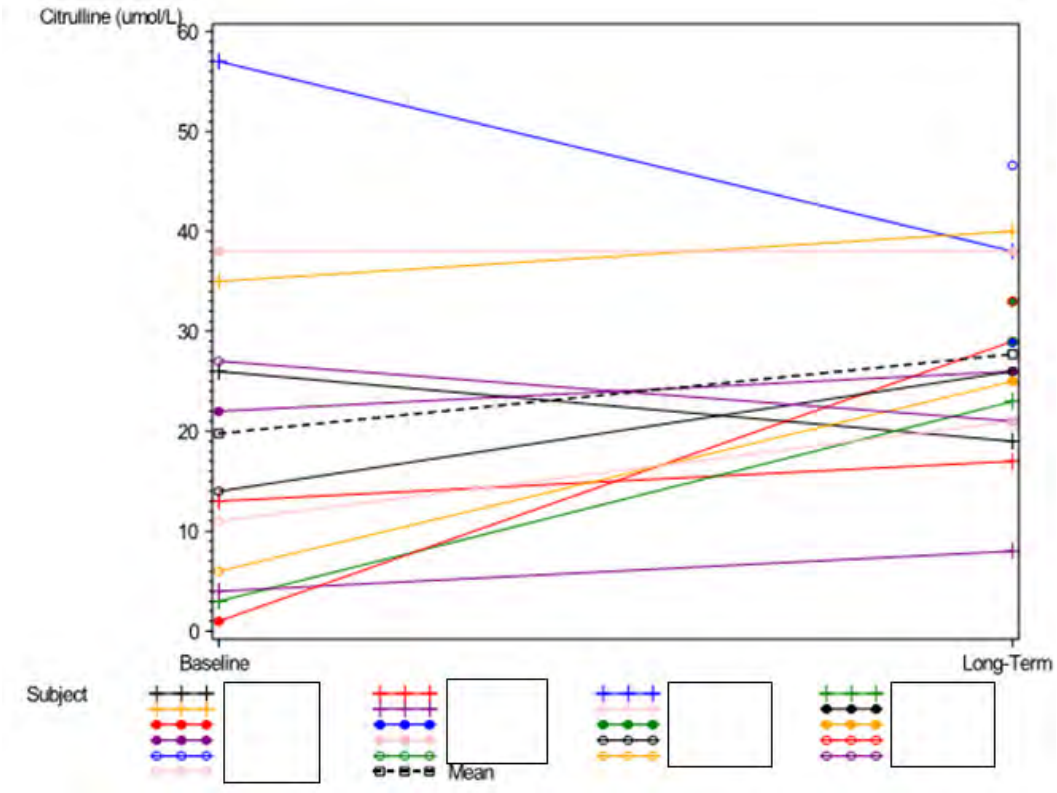


Figure 15. Changes in Citrulline Plasma Levels from Pre to ≤ 7 Days after Initiation of Carglumic Acid Treatment.



Patient identifiers have been redacted from this figure.

Figure 16. Changes in Citrulline Plasma Levels from Pre to Last Follow up after Initiation of Carglumic Acid Treatment.



Patient identifiers have been redacted from this figure.

7.1.1.5. Results for other efficacy outcomes

7.1.1.5.1. *Impact of diet on anthropometric status*

Because prolonged dietary protein restriction could affect normal growth, the impact of diet on the anthropometric status of all patients was investigated. The sponsor hypothesized that long term treatment with carglumic acid would allow a greater dietary protein intake and this would improve the anthropometric development in NAGS deficiency patients. The data is suggestive that this may have been the case in some patients in height (Figure 17) and weight (Figure 18) although other factors other than diet may account for these effects.

Figure 17. Height z-score (difference from baseline) as a Function of Diet and Time.

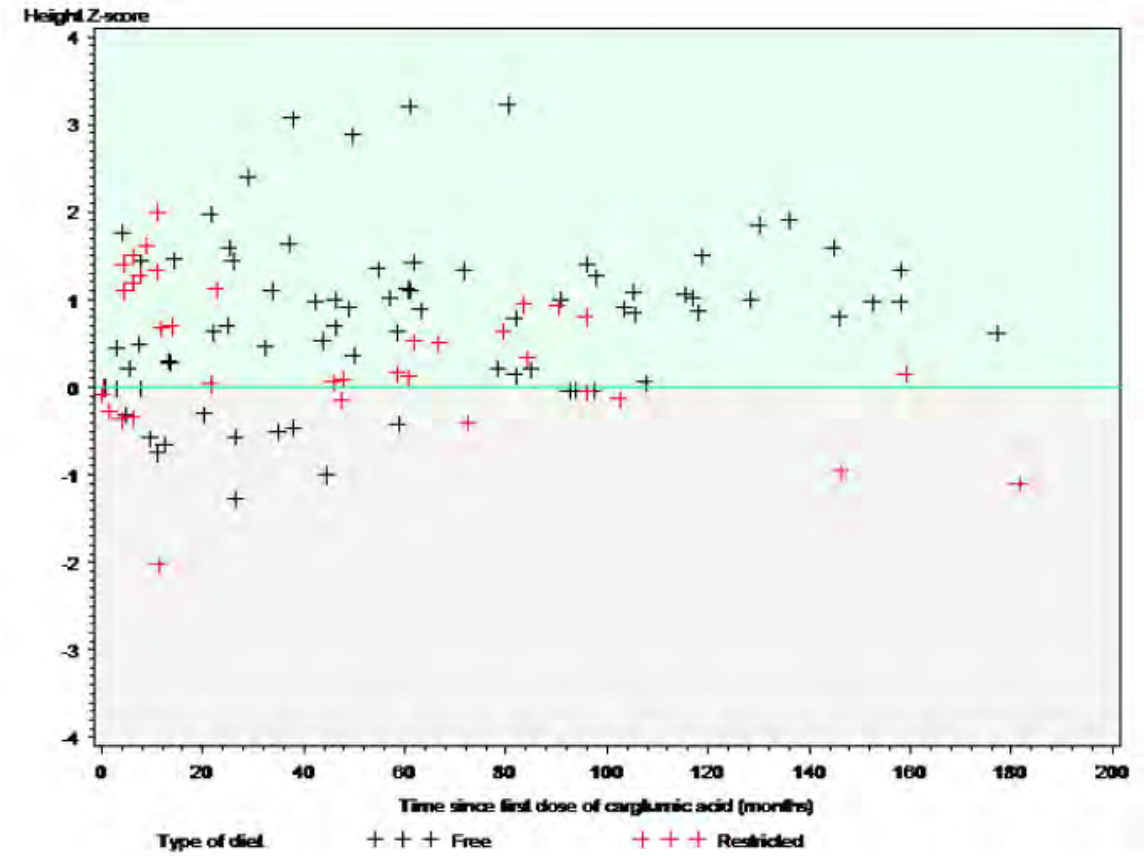
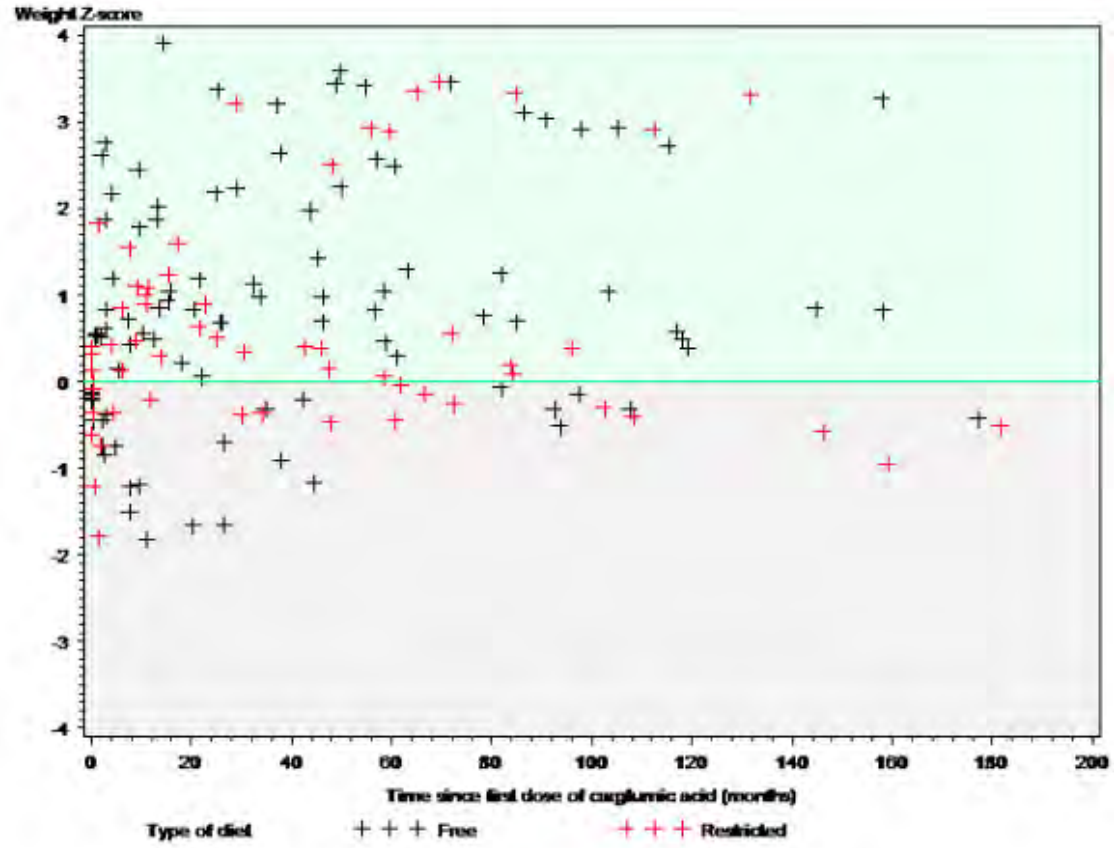


Figure 18. Weight z-score (difference from baseline) as a Function of Diet and Time.



7.1.1.5.2. *Analysis of the neurologic and psychomotor status*

At baseline, 7/10 patients (70%) presented with affected neurological status. Among the same corresponding group of patients, only 2/10 patients (20%) presented with affected neurological status at the long term evaluation. Five patients who presented with affected neurological development at baseline had normal neurological development at the last follow up. None of those non-affected (30%) at the baseline developed affected neurological status at the long term evaluation.

Psychomotor status was evaluated in 7 patients at baseline. The long term data showed that of the 4 patients (57.1%) that presented signs of retardation before carglumic acid treatment only 2 of them (28.6%) presented retardation at the last report. There was a recovery of the psychomotor status in 50% of the patients (2 patients) with retardation prior to the carglumic acid treatment.

None of the patients with normal psychomotor status at baseline worsened after the initiation of carglumic acid treatment.

7.1.1.5.3. *Analysis of the hepatic status*

The hepatic status was evaluated in 10 patients who presented baseline and long term data for hepatic status. Only 2 patients' livers were affected prior to carglumic acid treatment. At the long term evaluation, no patient had disrupted hepatic status.

7.2. Treatment of NAGS deficiency - Other efficacy studies

7.2.1. Study - Experience with N-carbamylglutamic acid (Carbaglu) in the US study

This study was performed following a 2004 FDA grant - IND (# 68,185) to study Carbaglu treatment for NAGS deficiency. Permission was extended to the study of CPSI deficiency, PA, MMA and hyperinsulinism and hyperammonaemia syndrome (HHS).

At the date of the report 7 patients have been enrolled in the study to assess the effect of carglumic acid on ureagenesis and hyperammonaemia:

- 2 with NAGS deficiency;
- 4 with propionic acidaemia; and
- 1 NAGS heterozygote.

The report covered the period from January 2004 to November 2008.

7.2.1.1. Study objectives

7.2.1.1.1. *Primary*

To determine whether a 3 day treatment with carglumic acid improves or restores ureagenesis in patients with NAGS deficiency, CPSI deficiency, PA, MMA and HHS as evidenced by $^{13}C/^{15}N$ incorporation into urea, concentrations of plasma ammonia, urea and amino acids.

7.2.1.1.2. *Secondary*

To evaluate the safety of short term (3-day) treatment with carglumic acid in patients. Clinical and laboratory safety parameters were evaluated in participants including idiosyncratic symptoms and changes in blood counts and liver and kidney functions.

7.2.1.2. Study design

Subjects were studied twice:

1. once before the very first administration of carglumic acid; and
2. the second time following 72 hours of oral or gastrostomy administration of carglumic acid at a dose of 100 mg/kg/day for subjects < 25 kg body weight or 2.2 g/m2/day for subjects 25 kg body weight.

Subjects were required to fast for 8 hours prior to the study. At the beginning of each study day, subjects were required to ingest a tracer which would be incorporated in vivo into urea:

- Subjects 1 and 2 received 15NH4C1.
- In subjects 3 to 7, the tracer was changed to [13C] sodium acetate.

7.2.1.3. Results

Subjects 1 and 3 both had NAGS deficiency and demonstrated a response to NCG, with a decrease in ammonia and glutamine, and an elevation of urea production.

Subject 2, a NAGS mutation heterozygote, showed no significant changes in any parameter.

Subjects 4 to 7 had propionic acidaemia and demonstrated pre-treatment ureagenesis that was much less compromised than NAGS deficiency subjects. They had some increases in urea production and decreases in glutamine. Decreases in ammonia were seen in subject 5 and 7, whereas no such change was seen in subject 4 and 6.

7.2.2. Analyses performed across trials (pooled analyses and meta analyses)

No pooled analysis was provided.

7.3. Evaluator's conclusions on clinical efficacy for the treatment of NAGS deficiency

The available retrospective data were limited and of poor quality. There were missing data in patients with follow up levels on Days 1 to 7 for each of the efficacy outcomes (missing data in 2 to 14 out of 21 patients for ammonia, 1 to 6 out of 21 patients for glutamine, and 1 to 5 out of 21 patients for citrulline). The regimen including dosing was determined by the individual treating physicians. Also the data were not collected prospectively. The data set would have been more rigorous if the enrolled subjects were subject to a single protocol and data were collected prospectively. Finally, the report was only up until 2007 and further efficacy data may be available after that time. However, NAGS deficiency is a rare disorder and the evaluator accepts that a randomised controlled study was not feasible. Despite the limitations in the data, there is evidence that the administration of carglumic acid results in a dramatic and relatively sustained improvement on the biochemical changes and the clinical symptoms of acute hyperammonaemia associated with NAGS deficiency. The limited long term data indicate that there may be ongoing benefit in administration of carglumic acid to these patients. While there is no control group, there is expected to be a very poor prognosis in individuals severely affected with NAGS deficiency. The limited data presented in the dossier supports that carglumic acid may improve the outcome in some of these patients.

In summary, the efficacy data are sufficient to support the registration of Carbaglu for use in the treatment of NAGS deficiency.

7.4. The acute treatment of hyperammonaemia in organic acidaemia decompensation episode – Pivotal efficacy studies

7.4.1. Study - Carbaglu retrospective observational study of hyperammonaemia in organic acidaemia decompensation episode

7.4.1.1. Study design

This is a Phase IIIb, multi centre, observational study, based on retrospective data collection and analysis of response to the treatment with Carbaglu (carglumic acid) in patients of all ages and of both gender with hyperammonaemia during organic acidaemia (OA) decompensation episodes.

Patients received carglumic acid for the treatment of hyperammonaemia during any OA decompensation episode. The dose was different in each patient at the discretion of the respective treating physician. The recommended initial dose of carglumic acid is 100 to 250 mg/kg/day, given twice or thrice daily. Each dispersible tablet of Carbaglu contains 200 mg of carglumic acid and was administered orally.

7.4.1.2. Primary objectives

To examine plasma ammonia (NH_3) levels as the main biological response to carglumic acid treatment during hyperammonaemia in every OA decompensation episode.

7.4.1.3. Secondary objectives

- To describe a demographic profile of the population.
- To evaluate the clinical and biological responses during the treatment with carglumic acid.
- To assess the safety of carglumic acid.

7.4.1.4. Locations

Different centres from 7 countries participated in this observational study protocol. Initially, 24 centres were screened to participate and 22 centres were proposed to participate in the study. Administrative matters related to the time frame of the data collection were forced to exclude 4

of these centres. The effectively participating centres were 21 active centres in Italy (2), France (4), Germany (1), Netherlands (1), Spain (10), Turkey (2) and the United Kingdom (1).

Two centres were excluded: centre 101 in Spain was excluded due to no post treatment data being available; and centre 501 in United Kingdom cancelled its participation. The study collected data from January 1995 until November 2009.

7.4.1.5. Inclusion and exclusion criteria

7.4.1.5.1. *Inclusion criteria*

To be eligible for inclusion into this data collection and analysis, each patient must fulfil the following inclusion criteria:

- Confirmed OA diagnosis: propionic acidaemia (PA), methyl-malonic acidaemia (MMA) or isovaleric acidaemia (IVA);
- Reported hyperammonaemia in at least one full OA decompensation episode treated with carglumic acid;
- Hyperammonaemia before carglumic acid treatment above 60 µmol/L.
- Patients of any age and racial/ethnic group can be included, as can patients of either sex.
- From the 41 patients included in the efficacy analysis, 4 (9.8%) were confirmed as isovaleric acidaemia (IVA), 21 patients (51.2%) were confirmed as methyl-malonic acidaemia (MMA), and 16 patients (39.0%) as confirmed propionic acidaemia (PA).

7.4.1.5.2. *Exclusion criteria*

- Severe hepatic insufficiency at the time of the treatment with carglumic acid;
- Inherited hepatic malformation (including vascular disorders like hepatic A-V shunt);
- Any inter current disease (other than OAs) which may generate hyperammonaemia per se;
- Different diagnosis, confirmed or suspected, than reported.

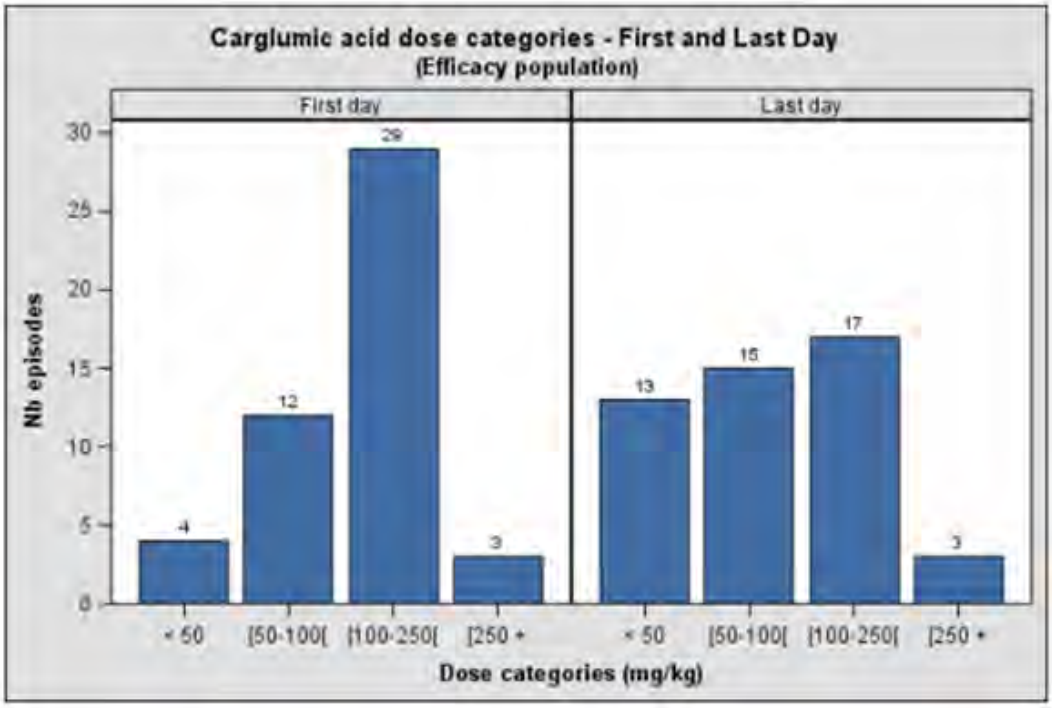
7.4.1.6. Study treatments

No dose has been pre-defined. In Europe, the recommended initial dose of Carbaglu is 100 to 250 mg/kg/day, typically given twice or thrice daily. The doses given to patients whose data was collected may differ at the discretion of the treating physicians. Route of administration was oral. At the discretion of the treating physicians; a window evaluation was defined up to a maximum of 15 days since the first administration of carglumic acid. No batch number assigned as not applicable. The administered first dose is shown in Table 15. Subsequent doses were, on average lower than the initial dose.

Table 15. Efficacy population: Carglumic acid dosing - First dose in 48 episodes in 41 patients.

Reference unit: Episode	All N=48
First dose	
Weight (kg)	
N	48
Mean (SD)	8.6 (14.8)
Median	3.1
Q1 - Q3	2.6 - 8.3
Range	1.9 - 75.3
Dose (mg/kg)	
N	48
Mean (SD)	96.3 (73.8)
Median	75.5
Q1 - Q3	40.7 - 135.9
Range	13.3 - 303.0
Dose (mg/kg)	
< 50	14 (29.2%)
[50-100[	12 (25.0%)
[100-250[	20 (41.7%)
[250 +	2 (4.2%)

Figure 19. First and last day carglumic acid dose in the general efficacy population - 48 episodes in 41 patients.



7.4.1.7. Efficacy variables and outcomes

7.4.1.7.1. *Primary efficacy outcome*

Change in plasma NH_3 level from baseline to endpoint for every OA decompensation episode treated with carglumic acid. The endpoint was determined by the treating physician (up to 15 days treatment). Changes in plasma NH_3 level were determined from baseline to endpoint for every OA decompensation episode treated with carglumic acid. Although the ammonaemia considered as abnormal in neonates is approximately 100 µmol/L, depending on different authors and different laboratory standard values, the average ammonaemia at the protocol

proposed end point of 60 µmol/L was selected because the standard range defines this threshold in non-neonatal population.

7.4.1.7.2. *Secondary efficacy outcomes*

Other biological markers

- plasma amino acids (AA chromatography);
- plasma and urinary organic acids;
- bicarbonate (HCO3);
- plasma and urinary ketone bodies.

Clinical symptoms

- Clinical markers neurological, psychiatric, psychomotor, respiratory and hepatic status.

7.4.1.8. Analysis populations

Among the 57 patients (67 episodes) with hyperammonaemia during decompensation episode/s enrolled in this study, 41 patients (48 episodes) were included for final efficacy data evaluation after the medical and data review for protocol deviations as shown in Table 16. In 23 patients minor deviations (for 26 episodes) were reported and in 17 patients had major deviations (for 19 episodes). In 3 patients (4 episodes) there were major deviations related to the protocol inclusion/exclusion criteria. In 16 patients (18 episodes), there were other major deviations. The evaluation led to the exclusion of (19 episodes for) 16 patients for efficacy evaluation. (In total 48 episodes were included in the efficacy population (67 recruited – 19 with major deviations). All the 57 patients (67 episodes), were entered to the safety evaluation. (All episodes with major deviations (19 episodes; 17 patients) were excluded from efficacy population corresponding to exclusion of 16 patients.)[1]

Comment: The sponsor should explain why 16 patients were excluded from the efficacy evaluation when there were 17 patients with major deviations.

Table16. Patient disposition.

Population	Total Number of patients	Total Number of episodes
Recruited	57	67
Safety Population	57	67
Efficacy Population	41	48
Deviations	32	37
Minor Deviations	23	26
Major Deviations	17	19
Major Deviations relating to I/E criteria	3	4
Other Major Deviations	16	18

7.4.1.9. Sample size

No formal sample size was predetermined. Approximately 35 patients were initially expected to be enrolled. The final number of patients enrolled was 57.

7.4.1.10. Statistical methods

The retrospective review was performed according to the statistical analysis plan. The database was structured with the CDISC Study Data Tabulation Model (SDTM) format. The primary analysis calculated the variation of plasma NH3 levels between the baseline and the endpoint. In

[1] Information in parentheses in this paragraph has been included (subsequently) for clarification.

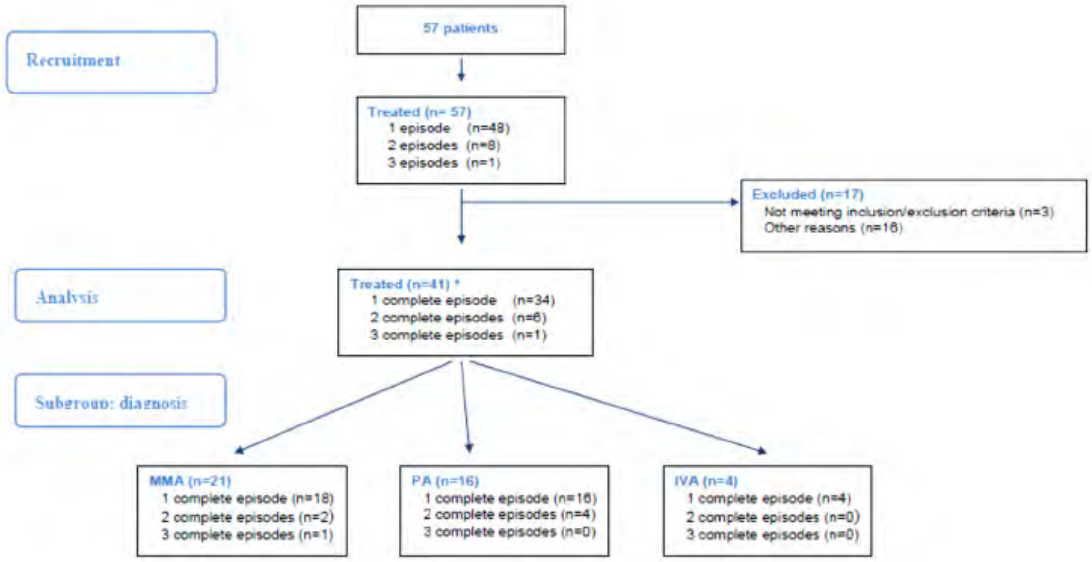
addition a paired t-test of change from baseline was performed with summary statistics for continuous data.

Secondary analyses used similar methods for continuous data; for binary categorical data a McNemar test was applied.

7.4.1.11. Participant flow

Participant flow is shown in Figure 20.

Figure 20. Participant flow.



7.4.1.12. Major protocol violations/deviations

Protocol deviations are listed in Table 17.

Table 17. Protocol deviations.

Category of Deviation	Deviations Criteria	Deviations Details	Patient Number	Episode
relating to I/E criteria	Medical History	Concomitant Medical history (Choledocus cyst)	¶	Episode 1
				Episode 2
	NH_3 level below 60 µmol/L	NH_3 level below 60 µmol/L (21 µmol/L)		Episode 1
	Wrong Diagnosis	Wrong Diagnosis (MMA + other)		Episode 1
other	Diagnosis not confirmed	Neither DNA nor lab test to confirm the OA diagnosis		Episode 1
				Episode 1
				Episode 1
				Episode 1
				Episode 1
				Episode 2
				Episode 1
				Episode 2
	NH_3 Baseline	No NH_3 data at Baseline		Episode 1
				Episode 1
				Episode 1
				Episode 1
	NH_3 End point	No NH_3 data at End point		Episode 1
				Episode 1
				Episode 2
				Episode 1
				Episode 1
				Episode 1
				Episode 1
				Episode 1

Patient identifiers have been redacted from this table.

7.4.1.13. Baseline data

From the 41 patients included in the efficacy analysis, 4 (9.8%) were confirmed as isovaleric acidaemia, 21 patients (51.2%) were confirmed as methyl-malonic acidaemia, and 16 patients (39.0%) as confirmed propionic acidaemia.

7.4.1.14. Gender distribution

The gender distributions of the patients included in the efficacy analysis showed that 19 patients (46.3%) were female and 22 (53.7%) were male.

7.4.1.15. Age at first decompensation episode

The evaluation of the age at the first episode showed that 28 patients (68.3%) were neonates and 13 were beyond the 4 weeks after birth at the time of the first decompensation episode. Only 1 patient suffered a second decompensation episode within the neonatal period. All the non-neonate patients were children except for 1 adult. The ages in the non-neonate group were from 1 month up to 22 year old; therefore there was only one adult patient in the efficacy evaluation group. The baseline age of the patients with episodes in the efficacy population was a median of 9.0 days. The presence of an adult within the efficacy population increased the mean age to 19.8 months. At the initiation of the treatment with carglumic acid, 29 episodes occurred during the first 4 weeks after birth (neonates) and 19 episodes occurred beyond the neonatal period (non-neonates).

7.4.1.16. Demographics

The average weight at the initiation of the episodes in the efficacy population was 7.4 kg (range: 1.9 to 75.3 kg); but the average weight at the initiation of the treatment with carglumic acid was 8.6 kg (Range: 1.9 to 75.3 kg). The highest weight corresponds to an adult with a PA decompensation episode (Table 18).

Comment: The sponsor should clarify the differences in weight at the initiation of the episodes and the initiation of the treatment.

Table 18. Baseline demographics.

Reference unit: Episode	All N=48
Age (days)	
N	48
Mean (SD)	600.9 (1592.7)
Median	9.0
Q1 - Q3	5.0 - 220.0
Range	2 - 8067
Age (months)	
N	48
Mean (SD)	19.8 (52.4)
Median	0.3
Q1 - Q3	0.2 - 7.2
Range	0 - 265
Neonate status at treatment Day 1	
Neonate	29 (60.4%)
Non Neonate	19 (39.6%)
Weight at start of episode (kg)	
N	46
Mean (SD)	7.4 (12.3)
Median	3.1
Q1 - Q3	2.6 – 5.9
Range	1.9 – 75.3
Height at start of episode (cm)	
N	31
Mean (SD)	60.8 (27.6)
Median	50.0
Q1 - Q3	48.5 - 53.0
Range	44.0 – 170.9
Weight at treatment Day 1 (kg)	
N	48
Mean (SD)	8.6 (14.8)
Median	3.1
Q1 - Q3	2.6 - 8.3
Range	1.9 - 75.3

7.4.1.16.1. *Ammonia scavenger*

Some cases were initially treated with ammonia scavenger medication before the initiation of the treatment with carglumic acid. A total of 43.8% of the episodes in the efficacy population were treated with ammonia scavenger medication before the initiation of the treatment with carglumic acid or during the treatment. The ammonia scavengers medications registered include Na-benzoate and Na-Phenylbutyrate.

7.4.1.16.2. *Clinical status at baseline*

The population had the range of symptoms consistent with OA decompensation, including significant neurological and gastrointestinal symptoms (Table 19).

Table 19. Clinical status at baseline.

Reference unit: Episode	All
	N=48
CLINICAL SYMPTOMS	
Symptoms	
None	0 (0.0%)
Poor sucking	26 (11.7%)
Vomiting	24 (10.8%)
Muscle hypotonia	28 (12.6%)
Abnormal movements	10 (4.5%)
Hypothermia	10 (4.5%)
Lethargy	27 (12.1%)
Hyperventilation	17 (7.6%)
Coma	8 (3.6%)
Apnoea	4 (1.8%)
Cerebral oedema	3 (1.3%)
Seizures	6 (2.7%)
Recurrent ketoacidosis	11 (4.9%)
Psychiatric symptoms	1 (0.4%)
Other	21 (21.5%)
NEUROLOGICAL STATUS	
Symptoms	
Normal	6 (8.5%)
Migraine-like headache	1 (1.4%)
Somnolence	31 (43.7%)
Ataxia	1 (1.4%)
Visual impairment	4 (5.6%)
Speech problems	2 (2.8%)
Confusion, disorientation	4 (5.6%)
Other	14 (31.0%)

7.4.1.17. Results for the primary efficacy outcome

The mean ammonaemia at end point was 58.5 µmol/L with a median of 52.0 µmol/L. This corresponded to a change of the ammonaemia from baseline to end point of a mean -292.2 µmol/L with a reduction range of - 24.0 to - 540.0 µmol/L (Table 20). There was a rapid reduction in ammonia concentrations upon commencement of treatment (Figure 21) and this was not significantly different in those previously treated with scavengers (Table 21) although those treated with NH_3 scavenger treatment were more likely to achieve an NH_3 level in the normal range.

Table 20. Change in ammonia from baseline.

Reference unit: Episode	All N=48
Baseline	
NH_3 Level (µmol/L)	
N	48
Mean (SD)	350.7 (321.3)
Median	215.0
Q1 - Q3	162.0 - 407.0
Range	76.0 - 1633.0
Normal Range Indicator	
HIGH	48 (100.0%)
NH_3 Category	
60 + µmol/L	48 (100.0%)
End Point	
NH_3 Level (µmol/L)	
N	48
Mean (SD)	58.5 (31.3)
Median	52.0
Q1 - Q3	33.5 - 74.5
Range	15.0 - 158.0
Normal Range Indicator	
HIGH	25 (52.1%)
LOW	2 (4.2%)
NORMAL	21 (43.8%)
NH_3 Category	
≤ 60 µmol/L	30 (62.5%)
+ 60 µmol/L	18 (37.5%)
Change from baseline to endpoint	
N	48
Mean (SD)	-292.2 (321.1)
Median	-169.0
Q1 - Q3	-335.0 - -108.0
Range	-1540.0 - 24.0
Change (%) from baseline to endpoint	
N	48
Mean (SD)	-70.8 (26.8)
Median	-80.6
Q1 - Q3	-88.8 - -65.2
Range	-98.3 - 27.9

Figure 21. NH_3 Response to carglumic acid dose categories at day 1.

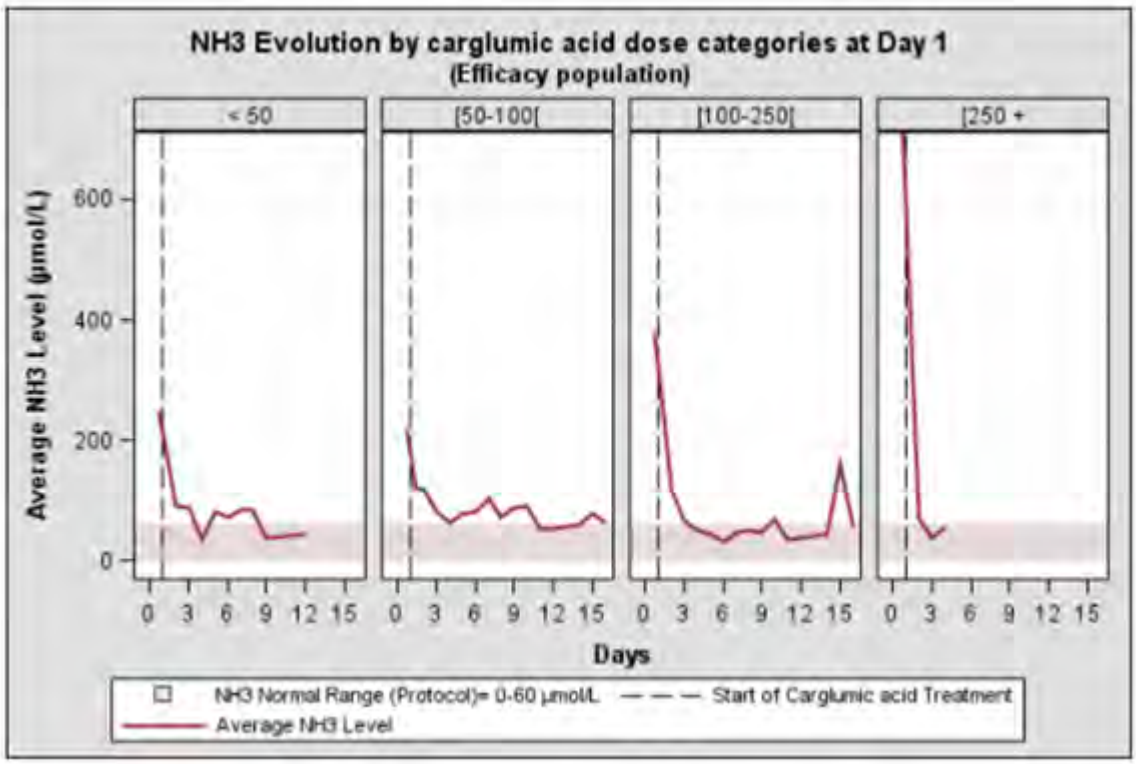


Table 21. Analysis of change in NH_3 by NH_3 scavenger treatments.

Reference unit: Episode	NH_3 Scavenger Treatments		All
	No	Yes	
	N=27	N=21	N=48
Baseline			
NH_3 Level (µmol/L)			
N	27	21	48
Mean (SD)	261.0 (302.3)	466.1 (314.6)	350.7 (321.3)
Median	184.0	383.0	215.0
Q1 - Q3	140.0 - 292.0	198.0 - 570.0	162.0 - 407.0
Range	76.0 - 1633.0	131.0 - 1200.0	76.0 - 1633.0
Normal Range Indicator			
HIGH	27 (100.0%)	21 (100.0%)	48 (100.0%)
NH_3 Category			
60 + µmol/L	27 (100.0%)	21 (100.0%)	48 (100.0%)
End Point			
NH_3 Level (µmol/L)			
N	27	21	48
Mean (SD)	60.8 (26.4)	55.6 (37.2)	58.5 (31.3)
Median	56.0	38.0	52.0
Q1 - Q3	42.0 - 74.0	30.0 - 75.0	33.5 - 74.5
Range	24.0 - 120.0	15.0 - 158.0	15.0 - 158.0
Normal Range Indicator			
HIGH	17 (63.0%)	8 (38.1%)	25 (52.1%)
LOW	0 (0.0%)	2 (9.5%)	2 (4.2%)
NORMAL	10 (37.0%)	11 (52.4%)	21 (43.8%)
NH_3 Category			
≤ 60 µmol/L	15 (55.6%)	15 (71.4%)	30 (62.5%)
+ 60 µmol/L	12 (44.4%)	6 (28.6%)	18 (37.5%)
Change from baseline to endpoint			
N	27	21	48
Mean (SD)	-200.2 (299.5)	-410.5 (315.4)	-292.2 (321.1)
Median	-123.0	-290.0	-169.0
Q1 - Q3	-175.0 - -84.0	-536.0 - -147.0	-335.0 - -108.0
Range	-1540.0 - 24.0	-1145.0 - -17.0	-1540.0 - 24.0
Change (%) from baseline to endpoint			
N	27	21	48
Mean (SD)	-62.5 (28.5)	-81.4 (20.6)	-70.8 (26.8)
Median	-70.7	-88.4	-80.6
Q1 - Q3	-81.3 - -49.8	-93.5 - -81.0	-88.8 - -65.2
Range	-96.2 - 27.9	-98.3 - -12.3	-98.3 - 27.9

7.4.1.18. Results for other efficacy outcomes

It should be noted that not all patients had baseline and/or endpoint values for the secondary efficacy outcomes. This is due to the retrospective nature of the study, in that not all outcomes were measured in all patients.

7.4.1.18.1. *Plasma amino acids (AA chromatography)*

Glutamine levels were significantly reduced from high to normal and from normal to low, consistent with treatment with carglumic acid. Other amino acids levels showed a trend towards lower concentrations, consistent slow resolution of the decompensation episode.

7.4.1.18.2. *Plasma and urinary organic acids*

Plasma and urinary organic acids are shown in Table 22.

Table 22. Urinary Organic Acids by Confirmed Diagnosis.

Normal Range Indicator	IVA		MMA		PA		All	
	Baseline	End Point	Baseline	End Point	Baseline	End Point	Baseline	End Point
Isovaleric acid								
ABNORMAL	2 (100.0%)	1 (100.0%)	5 (50.0%)	0 (0.0%)	3 (42.9%)	0 -	10 (52.6%)	1 (33.3%)
NORMAL	0 (0.0%)	0 (0.0%)	5 (50.0%)	2 (100.0%)	4 (57.1%)	0 -	9 (47.4%)	2 (66.7%)
Methylmalonic acid								
ABNORMAL	0 -	0 -	20 (95.2%)	7 (100.0%)	2 (33.3%)	0 -	22 (81.5%)	7 (100.0%)
NORMAL	0 -	0 -	1 (4.8%)	0 (0.0%)	4 (66.7%)	0 -	5 (18.5%)	0 (0.0%)
Propionic acid								
ABNORMAL	0 -	0 -	7 (63.6%)	0 (0.0%)	9 (100.0%)	2 (100.0%)	16 (80.0%)	2 (66.7%)
NORMAL	0 -	0 -	4 (36.4%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	4 (20.0%)	1 (33.3%)

7.4.1.18.3. *Bicarbonate (HCO_3)*

Plasma bicarbonate concentrations are shown in Table 23.

Table 23. Bicarbonate by Neonate Status.

	Neonate		Non Neonate		All	
	Baseline	End Point	Baseline	End Point	Baseline	End Point
Bicarbonate						
Result						
N	20	11	15	9	35	20
Mean (SD)	12.1 (6.29)	16.2 (4.98)	18.2 (7.01)	21.1 (7.39)	14.7 (7.2)	18.4 (6.5)
Median	11.5	16.0	20.1	23.3	14.0	20.4
Q1 - Q3	7.4 - 18.0	13.7 - 20.9	12.0 - 24.0	21.7 - 25.0	7.9 - 20.6	14.1 - 23.2
Range	3.0 - 23.2	5.0 - 21.4	5.0 - 27.4	2.7 - 26.7	3.0 - 27.4	2.7 - 26.7
Normal Range Indicator						
LOW	16 (80.0%)	8 (72.7%)	7 (46.7%)	3 (33.3%)	23 (65.7%)	11 (55.0%)
NORMAL	4 (20.0%)	3 (27.3%)	8 (53.3%)	6 (66.7%)	12 (34.3%)	9 (45.0%)

7.4.1.18.4. *Plasma and urinary ketone bodies*

There were insufficient data recorded from patients to perform an analysis for this marker.

7.4.1.19. Clinical symptoms

The clinical outcome for the efficacy population is shown in Table 24. Clinical markers showed an improvement in symptomatology from baseline status. The gastrointestinal and neurological markers were reduced after the initiation of the treatment with carglumic acid. Ketoacidosis and hyperventilation were reduced from baseline to the end point.

Table 24. Clinical Symptoms.

Reference unit: Episode	Period	
	Baseline	End Point
CLINICAL SYMPTOMS	N=48	N=30
None	0	8
Poor sucking	26	9
Vomiting	24	7
Muscle hypotonia	28	13
Abnormal movements	10	4
Hypothermia	10	1
Lethargy	27	7
Hyperventilation	17	4
Coma	8	1
Apnoea	4	2
Cerebral oedema	3	0
Seizures	6	1
Recurrent ketoacidosis	11	0
Psychiatric symptoms	1	0
Other	21	10
NEUROLOGICAL STATUS	N=46	N=25
Symptoms		
Normal	6	13
Migraine-like headache	1	0
Somnolence	31	7
Ataxia	1	1
Visual impairment	4	1
Speech problems	2	2
Confusion, disorientation	4	2
Other	14	5
PSYCHIATRIC STATUS	N=41	N=29
Symptoms		
Normal	27	25
Hyperactivity	1	0
Irritability	8	2
Nocturnal restlessness	2	0
Other	4	2
PSYCHOMOTOR STATUS	N=40	N=27
Symptoms		
Normal	27	17
Affected	13	8
HEPATIC STATUS	N=48	N=32
Symptoms		
Normal	36	27
Abnormal	12	5
RESPIRATORY STATUS	N=48	N=31
Symptoms		
Normal	28	26
Abnormal	20	5

7.5. Analyses performed across trials (pooled analyses and meta analyses)

No pooled analysis was provided.

7.6. Evaluator's conclusions on clinical efficacy for the acute treatment of hyperammonaemia in organic acidaemia decompensation episodes

The available retrospective data are limited and of poor quality. The regimen including dosing was determined by the individual treating physicians. Again the data were not collected prospectively. The data set would have been more rigorous if the enrolled subjects were subject to a single protocol and data were collected prospectively. Finally, the report was only up until 2009 and further efficacy data may be available after that time. The evaluator accepts that a randomised controlled study was not feasible given the rarity of organic acidaemia decompensation episodes. Despite the limitations in the data, there is evidence that the administration of carglumic acid results in a dramatic and relatively sustained improvement on the biochemical changes and the clinical symptoms of acute hyperammonaemia associated with

the types of organic acidaemia studied. While there is no control group, there is expected to be a very poor outcome with severe hyperammonaemia associated with organic acidaemia. Because of the retrospective nature of the study, not all outcomes were measured in all patients. Also only one adult patient was included in the dossier; explained by the fact that few patients survive into adulthood. The limited data presented in the dossier supports that carglumic acid may improve the outcome in some of these patients.

In summary, the efficacy data, although limited, are sufficient to support the registration of Carbaglu for use in the treatment of hyperammonaemia in organic acidaemia decompensation episodes.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Study of NAG deficient patients

In the pivotal efficacy studies, the following safety data were collected retrospectively. Data was retrieved from the clinical record retrospectively. The data were analysed by indication and considered NAG deficient patients and organic acidaemia patients separately.

General adverse events (AEs) were assessed by the sponsor as part of their study analysis.

8.1.2. Other studies evaluable for safety only

8.1.2.1. Exposure in healthy volunteers

Two sponsored clinical trials in healthy volunteers were performed, with 15 healthy volunteers exposed to carglumic acid in total.

8.1.3. Pivotal studies that assessed safety as a primary outcome

None were reported.

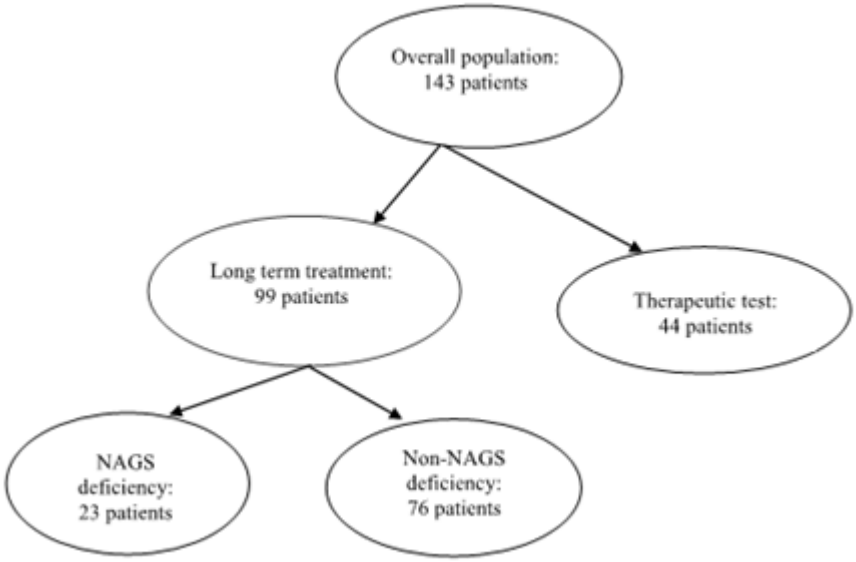
8.2. Patient exposure

8.2.1. Patient studies

According to the NAGS safety report, including patients who received carglumic acid only as therapeutic test of individual clinical/biochemical response before initiating any long-term treatment (n = 44 patients), 143 patients have been exposed to carglumic acid irrespective of the indication (23 patients for confirmed NAGS and 76 for other non-approved indications) from 1 January 1991 up to 31 December 2008 (Figure 22).

Comment: The report does not state from which reports the Non-NAGS patients are derived from and this should be clarified.

Figure 22. Patient exposure.



8.2.1.1. Study of NAG deficient patients

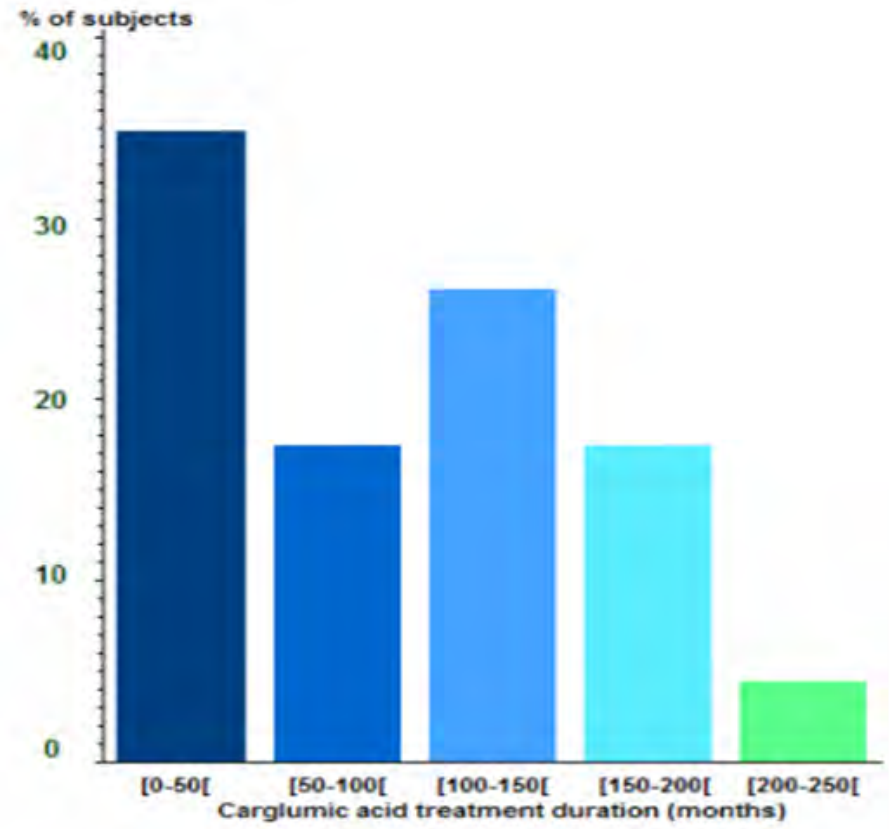
For the safety analysis, 23 patients were exposed at least to one dose of the study drug and were considered as the 'safety population'. At the report cut-off date (31/12/2007), the cumulative treatment duration for NAGS deficiency patients was 187.4 patient years taking into account the reported discontinuations (Table 25). Table25 summarises the details for each patient while Figure 23 shows the total duration of carglumic acid dosing.

Table 25. NAG deficient patient exposure.

Patient	Durations (years)
1	16.2
2	15.5
3	14.7
5	11.9
6	6.7
7	10.5
13	8.7
15	3.6
16	7.9
18	2.5
26	5.8
27	5.7
28	15.4
29	9.3
30	20.8
33	11.2
35	4.1
36	8.6
39	2.8
43	2.4
60	1.4
61	1.1
74	0.6
N = 23	187.4

Patient identifiers have been redacted from this table.

Figure 23. Total duration of Carglumic Acid Dosing.



8.2.1.2. Study of patients treated for hyperammonaemia due to organic acidaemia

A total of 57 patients were exposed at least to one dose of the study drug and were considered as the 'safety population'. The duration of the treatment with carglumic acid was between 1 and 16 days, with a mean of 5.3 days (median = 4.0 days). In regards to daily dose, the first dose of carglumic acid in the safety population ranged between 10 to 303 mg/kg, with a mean dose of 86.5 mg/kg (median = 62.9) of treatment. In 32.8% of the patients, the first dose was < 50 mg/kg, 26.9% between 50 and 100 mg/kg, 37.3% between 100 and 250 mg/kg, and 3.0% above 250 mg/kg. The duration of therapy ranged from 1 to 16 days (Table 26).

Table 26. Duration of carglumic acid treatment– Note inconsistency in number of patients.

Reference unit: Episode	All N=67
Duration of carglumic acid treatment (days)	
N	67
Mean (SD)	5.3 (4.5)
Median	4.0
Q1 - Q3	2.0 - 6.0
Range	1.0 – 16.0
Duration of carglumic acid treatment (days)	
1	8 (11.9%)
2	15 (22.4%)
3	6 (9.0%)
4	9 (13.4%)
5	12 (17.9%)
6	4 (6.0%)
10	1 (1.5%)
11	2 (3.0%)
12	2 (3.0%)
15	7 (10.4%)
16	1 (1.5%)
Missing	0

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Study of NAG deficient patients

According to the safety report, as of 31 December 2008, 18 of the 23 patients suffering from NAGS deficiency have experienced one or more AEs. In total, 120 AEs were reported including 37 serious adverse events (SAEs) and 83 non-serious AEs. These AEs are mainly related to 3 system organ classes (SOCs): 21% in gastrointestinal disorders, 19% in infections and infestations and 14% in nervous system disorders.

However, in the study report, a total of 17 patients experienced an AE, with a total of 118 AEs (see Table 27) with the type of events reported in Table 28. This may be due to differences in the reporting periods.

Comment: The sponsor should explain the discrepancy in the number of AEs between the study report and the safety report.

Table 27. Adverse Events Summary

	Total (N=23)
Number of AEs	
n	23
0	6 (26.1%)
1	2 (8.7%)
2	2 (8.7%)
3	1 (4.3%)
4	3 (13.0%)
5	1 (4.3%)
6	1 (4.3%)
7	2 (8.7%)
8	1 (4.3%)
9	1 (4.3%)
10	1 (4.3%)
14	1 (4.3%)
31	1 (4.3%)
Missing data	0
Number of AEs	
n	23
Mean (SD)	5.1 (6.8)
Median	4.0
Range	0.0 - 31.0
Missing data	0

Table 28. Distribution of Adverse Events by System Organ Class

System organ class	Number of adverse events	Percentage of the total number of adverse events
Blood and lymphatic system disorders	5	4 %
Ear and labyrinth disorders	7	6 %
Eye disorders	1	1 %
Gastrointestinal disorders	25	21 %
General disorders and administration site conditions	13	11 %
Hepatobiliary disorders	2	2 %
Infections and infestations	23	19 %
Injury, poisoning and procedural complications	1	1 %
Investigations	5	4 %
Metabolism and nutrition disorders	5	4 %
Musculoskeletal and connective tissue disorders	1	1 %
Nervous system disorders	17	14 %
Psychiatric disorders	5	4 %
Renal and urinary disorders	1	1 %
Reproductive system and breast disorders	1	1 %
Respiratory, thoracic and mediastinal disorders	2	2 %
Skin and subcutaneous tissue disorders	3	3 %
Social circumstances	1	1 %
TOTAL	**118**	**100 %**

8.3.1.2. Study of patients treated for hyperammonaemia due to organic acidaemia

According to the safety report, a total, 74 adverse events (AE) were reported during this retrospective observational study (Table 29). 25 out of the 57 patients (that is 43.9%) experienced at least one AE. Among these 74 AE, 23 were considered as severe. In total, 22

serious adverse events (SAE) were recorded for 13 patients (that is 22.8% of the total number of patients for the safety analysis). Among these 74 AE, 11 were associated with the patient's death; 7 patients (that is 12.3%) died due to an AE. In total, 24 drug related (with an investigator's causality assessment either 'related' or 'unknown') AEs were recorded for 9 patients (15.8% of the total number of patients).

Table 29. Adverse Events for Patients treated for hyperammonaemia due to organic acidaemia.

Events	Total (n=57)	
	Number of events	Number of patients (%)
All adverse events	74	25 (43.9%)
All severe adverse events	23	13 (22.8%)
Al serious adverse events	22	13 (22.8%)
All deaths	11	7 (12.3%)
All drugs related adverse events*	24	9 (15.8%)
Al serious drugs related adverse events	6	5 (8.8%)

*: AE with an investigator's causality assessment either "related" or "unknown"

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Study of NAG deficient patients

Among the 83 non serious AEs, only 1 was considered as 'related' to carglumic acid by both the reporter and the sponsor. This AE concerned a patient who experienced 'poor acceptance' (due to product acidity) a few days after the initiation of treatment. Following temporary discontinuation, the AE abated. After reintroduction, no similar event occurred.

8.3.2.2. Study of patients treated for hyperammonaemia due to organic acidaemia

The Study Report stated that the AE relationship to carglumic acid was 'related' for 1 event, 'unknown' for 23 events and 'unrelated' for 50 events (See Table 29 above). The related event is described below:

Patient A: this patient was treated with carglumic acid for 2 different episodes (on 18 September 2008, and from 13 to 16 March 2009 for PA. On these 2 occasions, the patient experienced non serious diarrhoea (from 20 to 22 September 2008, and on 15 March 2009). The investigator's causality assessment to study drug was 'unknown' for the first event of diarrhoea and 'unrelated' for the second event. Due to the positive re-challenge, sponsor's causality assessment to study drug is 'related'.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths - Study of NAG deficient patients

Among these 23 patients treated, 2 died due to an AE (patients B and C) (Table 30). Individual narratives for these 2 patients are presented below:

- Patient B:
  - On 30 May 2002, the patient started CGA. In October 2003, the patient's parents reduced the TDD of carglumic acid treatment to 100 mg because they wished to stop it completely; at that time, the patient was hospitalized to perform treatment discontinuation. On 20 October 2003, carglumic acid treatment was discontinued while plasma ammonia level was 35 µmol/L. On 21 October 2003, plasma ammonia level increased to 112 µmol/L. In October 2003 (during hospitalization), that is 15 months after first intake of CGA, the patient experienced pneumonia with fever up to 39°C; tests showed: no pathogen has been identified, liver function tests were normal. On 22 October 2003, the patient (weighing 52 kg, confirmed twice) received oral carglumic acid 250 mg divided in 2 administrations daily and intravenous phenylbutyrate (600

mg/kg). On 23 October 2003, the patient received intravenous sodium benzoate (500 mg/kg) and phenylbutyrate and unspecified antibiotics; on this day, plasma ammonia was 164 µmol/L. On 24 October 2003, plasma ammonia was 191 µmol/L. On 25 October 2003, the patient experienced hallucinations (was screaming), extension movements of the limbs and bradypnea. On the same day, tests showed: plasma ammonia = 233 µmol/L, brain CT scan ruled out cerebral oedema. On 27 October 2003, plasma ammonia was 141 µmol/L. On 28 October 2003, the patient underwent mechanical ventilation as corrective treatment. On 29 October 2003, the patient experienced multi organ failure with collapse and oliguria for which she was transferred to a pediatric intensive care unit. On 29 October 2003, plasma ammonia levels were 62 and 139 µmol/L. On 30 October 2003, brain MRI showed signs of encephalopathy (with meningeal enhancement) without brain oedema. On 31 October 2003, the patient died; no autopsy was performed. The overall patient outcome was fatal. Reporter's causality assessment to carglumic acid has been 'not mentioned ' for pneumonia, and modified from 'not mentioned' to 'unrelated' for the other events; according to him, it was difficult to explain the relationship with encephalopathy.

For this patient, the causality assessment to carglumic acid was 'probably unrelated'. The rationale for this assessment was firstly, it seemed that the patient's compliance appeared to be poor. Secondly, 1 month before patient's death, the dose of carglumic acid was decreased to 250 mg daily that is 5 mg/kg; this maintenance dose is not in accordance with the recommended maintenance dose. Thirdly, this patient experienced a severe pneumonia (possibly from nosocomial origin), complicated by a multi organ failure leading to death a few days later.

- Patient C:
  - On 18 July 1996, the patient started carglumic acid 250 mg 3 times daily. On an unspecified date, but after first intake of CGA, the patient experienced otitis media precipitated hyperammonaemia (282 µmol/L). On an unspecified date, after first intake of CGA, the patient experienced unspecified infections. On an unspecified date, after first intake of CGA, the patient experienced pneumonia which required hospitalization. On an unspecified date, after first intake of CGA, the patient experienced a severe episode of hyperammonaemia which was impossible to rescue. On 15 December 2007, the patient died; it was unknown whether an autopsy has been performed or not. The overall patient outcome was fatal. The reporter's causality assessment for carglumic acid has been modified from 'not mentioned' to 'unrelated' for the 'severe episode of hyperammonaemia'. The reporter's causality assessment has been not mentioned for 'otitis media', 'hyperammonaemia', infections' and 'pneumonia'. (This case has been published as: 'Morris AAM et al. N-Acetylglutamate synthetase deficiency: Favourable experience with carbamylglutamate. J Inher Metab Dis. 1998;21: 867-868).

The sponsor found that for this patient, causality assessment to carglumic acid was 'probably unrelated'. Firstly, before the patient's death, the dose of carglumic acid was very low at 6 mg/kg; this maintenance dose is not in accordance with the recommended maintenance dose. Secondly, this 11 year-old patient died following spontaneous worsening of her underlying disease.

8.3.3.2. Deaths - Study of patients treated for hyperammonaemia due to organic acidaemia

According to the Safety Report and the Study Report, 7 patients died due to an AE. These fatal SAE included: cardiogenic shock (1 event), condition aggravated (2), death (1), multi organ failure (1), hyperglycaemia (1), hyperlactacidaemia (1), methylmalonic acid aciduria (1), nervous system disorder (1), respiratory arrest (1) and respiratory tract infection (1) (Table 30).

The Reports stated that, except for 1 event, investigator's causality assessment to study drug was 'unrelated for all the above mentioned events. For this one only event ('nervous system disorder'), investigator's causality assessment to study drug was 'related' but classified as unrelated by the sponsor and is described below.

This female patient was born[2] (Day 1). Her patient's medical history included propionic acidaemia. Concomitant medications included L-carnitine, sodium benzoate, piperacillin sodium with tazobactam, gentamicin and vancomycin.

At Day 58[2] the patient (weight = 3.8 kg) started oral carglumic acid (Carbaglu) 75 mg/kg daily for propionic acidaemia. At Day 59, the patient received oral carglumic acid (Carbaglu) 100 mg/kg in 4 intakes. On Day 69, the patient discontinued carglumic acid (Carbaglu) as ammonaemia level was normalized. On Day 75, the patient experienced neurological damage (due to hyperammonaemia and epileptic seizures) and respiratory arrest for which she received unspecified corrective treatment; on Day 75, the patient died due to respiratory arrest. No autopsy was performed. Investigator's causality assessment to carglumic acid (Carbaglu) has been modified from 'unknown' to: 'related' for 'neurological damage' and 'unrelated' for 'respiratory arrest.

Sponsor's comments: the death occurred 6 days after discontinuation of carglumic acid (given for 9 days). This patient, with neurological symptoms prior to study drug administration (poor sucking, muscle hypotonia, lethargy, and somnolence) died due to neurological damage and respiratory arrest. According to the investigator's, causality assessment to study drug was 'unrelated' for the respiratory arrest and 'related' for neurological damage. Nevertheless, due to pre-existing neurological disorders, sponsor's causality assessment to study drug for 'neurological damage' is 'unrelated'.

[2] Identifying information redacted.

Table 30. Deaths in patients treated for hyperammonaemia due to organic acidaemia.

Trial / source	Centre	Patient ID	Age	Sex	Dose (mg)	Duration of exposure (days)	Diagnosis	Cause of death	Other medications
OE-CGA001-OA2009			2 months	M	600	12	MMA	Death due to sepsis	Phenobarbital, arginine, carnitine, biotin, phenylbutyrate, ranitidine, ampicillin, cefotaxime, metronidazole
OE-CGA001-OA2009			3 days	F	200	1	MMA	Methylmalonic acidemia Hyperlactacidaemia	-
OE-CGA001-OA2009			5.5 years	M	1600	8	PA	Worsening of underlying disease	Cefotaxime, amikacin
OE-CGA001-OA2009			24 days	M	360	6	MMA	Airway infection Worsening of underlying disease	Levocarnitine, biotin, sodium benzoate, imipenem/cislatin, vancomycin, amikacin, fluconazole
OE-CGA001-OA2009			1.5 month	F	100 mg/kg	11	PA	Death from neurological damage and respiratory arrest Respiratory arrest	Carnitin, sodium benzoate, piperacillin sodium/tazobactam, gentamycin, vancomycin
OE-CGA001-OA2009			4 days	M	200	3	MMA	Multi-organ failure	Levocarnitine, hydroxocobalamine, vitamin K, metronidazole, midazolam, insulin, amikacin, domperidone, esomeprazole, cefotaxime, bicarbonate, omeprazole, vitamins
OE-CGA001-OA2009			4 days	M	100	4	MMA	Cardiogenic shock Hyperglycemia drug unresponsive	Insulin, sodium benzoate, arginine, vitamin B12, carnitin, teicoplanine, furosemide

Patient identifiers have been redacted from this table.

8.3.3.3. SAEs - Study of NAG deficient patients

Excluding the two deaths, 9 patients experienced at least one SAE. None of these SAEs were assessed as related to CGA. The majority of SAEs were related to two body systems:

- 11 SAEs came from the gastrointestinal disorders (the most frequent AE is 'vomiting', reported 6 times);
- 9 SAEs came from the nervous system disorders.

8.3.3.4. SAEs - Study of patients treated for hyperammonaemia due to organic acidaemia

Including the patients who experienced an adverse event leading to death, 13 patients experienced a total of 22 SAEs. Excluding the 11 adverse events leading to death, these SAE included:

- Disseminated intravascular coagulation (1 event),

- Cardiac arrest (1),
- Cardio-respiratory arrest (1),
- Diarrhoea (1),
- Hepatic function abnormal (1),
- Infection (1),
- Drug toxicity (2),
- Hepatic enzyme increased (1),
- Encephalopathy (1),
- Anuria (1),
- Respiratory failure (1).

For 5 of these events ('cardiac arrest', 'diarrhoea', 'hepatic enzyme increased', 'encephalopathy' and 'respiratory failure'), investigator's causality assessment to study drug was 'unknown'.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Study of NAG deficient patients

For only one AE, the treatment with carglumic acid was transiently discontinued.

The breakdown of the management of treatment with carglumic acid due to an AE was:

- Dose increased for 3 AEs,
- Dose not changed for 73 AEs,
- Drug withdrawn for one AE,
- Not applicable for 20 AEs,
- Unknown for 21 AEs.

8.3.4.2. Study of patients treated for hyperammonaemia due to organic acidaemia

The Study Report stated that none of the AEs led to discontinuation of carglumic acid or to a dose being decreased or increased.

8.4. Laboratory tests

8.4.1. Laboratory tests - Study of NAG deficient patients

The Study Report stated that 'the baseline haematology and biochemistry parameters were recorded for differential diagnosis purposes and taken into account for safety reasons.' The report included a listing of all abnormal laboratory values. No analyses of these data were included in the report.

Comment: This is a deficiency in the data analysis.

8.4.2. Laboratory tests - Study of patients treated for hyperammonaemia due to organic acidaemia

The report included a listing of all abnormal laboratory values. The sponsor made no attempt to analyse these data. They stated that this was because of the retrospective nature of the study and the severity of the underlying illnesses.

Comment: This is a deficiency in the data analysis.

8.4.3. Electrocardiograph

Electrocardiogram data was not presented in the original patient reports. However, the sponsor did present a separate report titled 'QT Report - Overall Data Review, The Risk of QT Prolongation' dated 20-April-2009. The report included both preclinical and some limited clinical data.

The preclinical data included the following studies:

- Cardiovascular effect in conscious dogs.
- Evaluation of effect on cardiac action potential in isolated canine Purkinje fibres.

It was stated in the report that the preclinical data did not show any signal to suspect a risk of QT/QTc prolongation.

The electrocardiogram (ECG) data were retrospectively retrieved and reviewed for:

- All 15 healthy volunteers who were included in the 2 clinical studies;
- A total of 6 patients who are currently treated on a long term basis with carglumic acid.

Centralized review of these ECGs and measurement of ECG intervals was performed by a single expert.

In healthy volunteers, two 12 lead ECG were performed in each of the 15 subjects; the first one within 2 weeks preceding administration of carglumic acid and the second one 24 hours after the last administration. There was no QT/QTc prolongation and all ECGs were within normal limits. ECGs were not performed around peak plasma concentrations of carglumic acid.

In 6 of 19 (32 %) patients suffering from NAGS deficiency, an ECG was obtained during treatment with carglumic acid. The timing of ECG relative to last carglumic acid intake was known for 6 of the 10 ECGs (2h38 and 2h28 after 2 different intakes for patient No X1, 3h43 for patient No X2; 1h46 for patient No X3; 4h for patient No X4 and 3h for patient No X5)[3]. The report stated that there was no QT/QTc prolongation found and all ECGs were reported as within normal limits.

Comment: These data are inadequate to assess the risk of QT/QTc prolongation with carglumic acid.

8.4.4. Vital signs

Study of patients treated for hyperammonaemia due to organic acidaemia

The report did not include a listing or analysis of vital signs.

Comment: This is a deficiency in the data and analysis.

8.5. Post-marketing experience

The sponsor submitted the following safety updates:

- Clinical safety report on carglumic acid covering the period of 1 January 1991 to 31 December 2008. Orphan Europe Report (16 March 2009) Periodic Safety Update Report for Cabarglu (carglumic acid) Period covered by this report: Feb 1, 2003 to July 31, 2003. This report covers the studies included in the dossier and has been reviewed as part of the safety data analysis.
- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Aug 1, 2003 to Jan 31, 2004.

[3] Specific patient identifiers have been redacted.

- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2004 to July 31, 2004. One death reported (thought unrelated).
- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Aug 1, 2004 to Jan 31, 2005.
- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2005 to Jan 31, 2006.
- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2006 to Jan 31, 2007.
- Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2007 to Jan 31, 2010.

  Comment: This report covers a large number of AEs and some deaths (Table 31). It is unclear how many of these overlap with those already reported in the retrospective studies and whether they were included in the safety report. This report does include two severe cardiac events; a cardiac arrest and a cardio-respiratory arrest. Given the paucity of QT/QTc data in the dossier, an effect of carglumic acid cannot be excluded. The sponsor should clarify how many of the AEs overlap with the safety report.

Table 31. Comparison of ADR frequency per system organ class between the previous and current reporting period, reported or confirmed by a health care professional.

System Organ Class	Number / % of total number of ADR			
	Previous reporting period 1-Feb-2006 to 31-Jan-2007		Current reporting period 1-Feb-2007 / 31-Jan-2010	
	N	%	N	%
Blood and lymphatic system disorders	-	-	4	4%
Cardiac disorders	1	8%	2	2%
Ear and labyrinth disorders	-	-	6	5%
Endocrine disorders	-	-	1	1%
Eye disorders	-	-	1	1%
Gastrointestinal disorders	2	17%	15	14%
General disorders and administration site disorders	3	25%	10	9%
Hepatobiliary disorders	-	-	2	2%
Infections and infestations	-	-	18	17%
Injury, poisoning and procedural conditions	-	-	2	2%
Investigations	-	-	7	7%
Metabolism and nutrition disorders	1	8%	6	5%
Musculoskeletal and connective tissue disorders	-	-	1	1%
Nervous system disorders	3	25%	15	14%
Psychiatric disorders	-	-	3	3%
Renal and urinary disorders	1	8%	1	1%
Respiratory, thoracic and mediastinal disorders	-	-	4	4%
Skin and subcutaneous tissue disorder	1	8%	5	5%
Social circumstances	-	-	1	1%
Vascular disorder	-	-	2	2%
Total number of ADR	12	100%	106	100%
Total number of reports	7		38	

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

As far as the evaluator could assess from the listings, there were no signals indicating a risk of liver toxicity.

Comment: The sponsor should provide an analysis confirming that there is no indication of a risk of liver toxicity.

8.6.2. Haematological toxicity

As far as the evaluator could assess from the listings, there were no signals indicating a risk of haematological toxicity.

Comment: The sponsor should provide an analysis confirming that there is no indication of a risk of haematological toxicity.

8.6.3. Serious skin reactions

As far as the evaluator could assess from the listings, there were no signals indicating a risk of serious skin reactions.

8.6.4. Cardiovascular safety

As far as the evaluator could assess from the data, there were no signals indicating a risk of cardiovascular toxicity. However, the information around the risk of QT prolongation is inadequate to fully assess this risk.

Comment: The two cardiac deaths suggest that further investigation of the potential cardiotoxicity should be undertaken.

8.6.5. Unwanted immunological events

As far as the evaluator could assess from the listings, there were no signals indicating a risk of unwanted immunological toxicity.

8.7. Other safety issues

8.7.1. Safety in special populations

Most of the presented data was in neonates and children. There were no data related to pregnancy or the elderly.

8.7.2. Safety related to drug-drug interactions and other interactions

No data were presented in relation to drug-drug interactions.

8.8. Evaluator's overall conclusions on clinical safety

Overall, the safety profile is consistent across the studies and the reported adverse events do not indicate any major safety concerns.

However, the safety section has several inconsistencies that require further explanation as detailed below.

- According to the NAGS safety report, including patients who received carglumic acid only as therapeutic test of individual clinical/biochemical response before initiating any long-term treatment (n = 44 patients), 143 patients have been exposed to carglumic acid irrespective of the indication (23 patients for confirmed NAGS and 76 for other non-approved indications) from 1 January 1991 up to 31 December 2008 (Figure 22).

Comment: The report does not state from which reports the Non-NAGS patients are derived from and this should be clarified.

- According to the safety report, as of 31 December 2008, 18 of the 23 patients suffering from NAGS deficiency have experienced one or more AEs. In total, 120 AEs were reported including 37 serious adverse events (SAEs) and 83 non-serious AEs. However, in the study report, a total of 17 patients experienced an AE, with a total of 118 AEs (see Table 27) with the type of events reported in Table 28.

Comment: The inconsistencies in the number of AEs between reports should be clarified.

In the report titled 'Carbaglu Retrospective Observational Study of Hyperammonaemia in Organic Acidaemia Decompensation Episodes': Table 15 states that N = 67 while the study itself states that N = 57.

Comment: The inconsistencies in the number of patients should be clarified.

Additonal Comments: The sponsor should provide an analysis confirming that there is no indication of a risk of liver toxicity.

The sponsor should provide an analysis confirming that there is no indication of a risk of haematological toxicity.

A further investigation of the potential cardiotoxicity should be undertaken.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Carbaglu in the proposed usage are:

- Improvement in the biochemical and clinical derangements associated with acute hyperammonaemia caused by NAGS deficiency and in some organic acidaemias.
- While the numbers of patients with each particular type of organic acidaemias are small, the evaluator appreciates that these are extremely rare diseases and that the proposed treatment is for the hyperammonaemia rather than the underlying biochemical defect. The endpoints of improvement in the clinical biochemical markers of hyperammonaemia are appropriate and the primary endpoint of plasma ammonia concentrations is what would be used clinically. The evaluator does not think it is necessary to divide up the organic acidaemias for the purpose of treatment of the main complication; that being hyperammonaemia.
- Potential long term improved outcomes in patients, with NAGS deficiency, who receives ongoing therapy. The evaluator does acknowledge the lack of long term data on effects of treatment on growth and development. This is due lack of long-term data in enough patients in a sufficient number of patients.
- There are adequate data, albeit limited, in older neonates and children to support the efficacy of Carbaglu in these populations. There are almost no data in young adults and no data in older adults presented in the dossier. This is due to the extreme rarity of the disorder in adulthood. This may change in the future as more patients survive into adulthood with ongoing improvements in the therapy in childhood.

9.2. First round assessment of risks

Overall, the safety profile of Carbaglu is acceptable given the severity of the disease which it is treating. No concerning adverse events were identified, although it must be acknowledged that the dataset is necessarily small.

The risks of Carbaglu in the proposed usage are related to the inadequacy of the presented data. Specifically these are:

- Poorly defined dosing regimen due to inadequate pharmacokinetic data in the target population. There are almost no data in adult patients and the data in children is not presented in a way that supports the proposed weight based dosing.
- Some deficiencies in the safety data, specifically concerning:
  - Uncertainty about the sources of patient safety data in the summary reports.
  - Inconsistencies in the number of AEs between reports.
  - Incomplete data on the risk of liver toxicity.

- Incomplete data on the risk of haematological toxicity.
- Incomplete data on the risk of cardiotoxicity.

9.3. First round assessment of benefit-risk balance

The proposed indications are rare and the consequences of non-treatment are disabling and, in some cases, life threatening. There are few other potential therapies for the treatment of hyperammonaemia and none of these are particularly effective. Carbaglu currently offers the best acute therapy for hyperammonaemia associated with NAGS deficiency and the organic acidaemias as well as a potential long-term therapy for patients with NAGS deficiency.

Despite this, the benefit-risk balance of Carbaglu is currently unfavourable given the proposed usage, but would become favourable if the changes recommended in Section 10 are adopted. Specifically these are that the dosing be better supported and the outstanding issues around the safety data addressed satisfactorily.

10. First round recommendation regarding authorisation

The evaluator recommends that the application for Carbaglu currently be rejected. The application could be approved if the sponsor provides the following:

- A report estimating the PK parameters and the likely concentration profile of in the treated patients; defining differences between infants, children and adults if possible.
- The sources of patient safety data in the summary reports should be clarified.
- The inconsistencies in the number of AEs between reports should be addressed.
- An analysis confirming that there is no indication of a risk of liver toxicity.
- An analysis confirming that there is no indication of a risk of haematological toxicity.
- A further discussion, and potentially analysis, investigating cardiotoxicity.

11. Clinical questions

11.1. Pharmacokinetics

There is no PK analysis of the patient data. PK parameters for a single dose of carglumic acid in 12 healthy adults were submitted. However, the PK data in treated patients were sparse and difficult to interpret. Only raw data was produced and no analysis of these data was presented.

Please provide a population PK analysis based on these data to allow estimation of PK parameters in infants, children and adults.

11.2. Pharmacodynamics

No further questions.

11.3. Efficacy

1. From the report (Study – 'Carbaglu Retrospective observational study of Hyperammonaemia in Organic Acidaemia Decompensation Episodes' – Analysis Populations), the sponsor should explain why 16 patients were excluded from the efficacy evaluation when there were 17 patients with major deviations.

2. From the report, (Study – 'Carbaglu Retrospective observational study of Hyperammonaemia in Organic Acidaemia Decompensation Episodes'- Baseline data; demographics) the sponsor should clarify the differences in weight at the initiation of the episodes and the initiation of the treatment.

11.4. Safety

3. According to the NAGS safety report, including patients who received carglumic acid only as therapeutic test of individual clinical/biochemical response before initiating any long-term treatment (n = 44 patients), 143 patients have been exposed to carglumic acid irrespective of the indication (23 patients for confirmed NAGS and 76 for other non-approved indications) from 1 January 1991 up to 31 December 2008 (Figure 22).

   The report does not state from which reports the Non-NAGS patients are derived from and this should be clarified.

4. According to the safety report, as of 31 December 2008, 18 of the 23 patients suffering from NAGS deficiency have experienced one or more AEs. In total, 120 AEs were reported including 37 serious adverse events (SAEs) and 83 non-serious AEs. However, in the study report, a total of 17 patients experienced an AE, with a total of 118 AEs (see Table 27) with the type of events reported in Table 28.

   The inconsistencies in the number of AEs between reports should be clarified.

5. The sponsor should provide an analysis confirming their assertion that there is no indication of a risk of liver toxicity.

6. The sponsor should provide an analysis confirming their assertion that there is no indication of a risk of haematological toxicity.

7. A further investigation of the potential for cardiotoxicity should be undertaken.

8. The sponsor should supply a listing or analysis of vital signs in the clinical studies.

9. The sponsor should clarify how many of the AEs in the Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2007 to Jan 31, 2010 overlap with the safety report.

12. Second round evaluation of clinical data submitted in response to questions

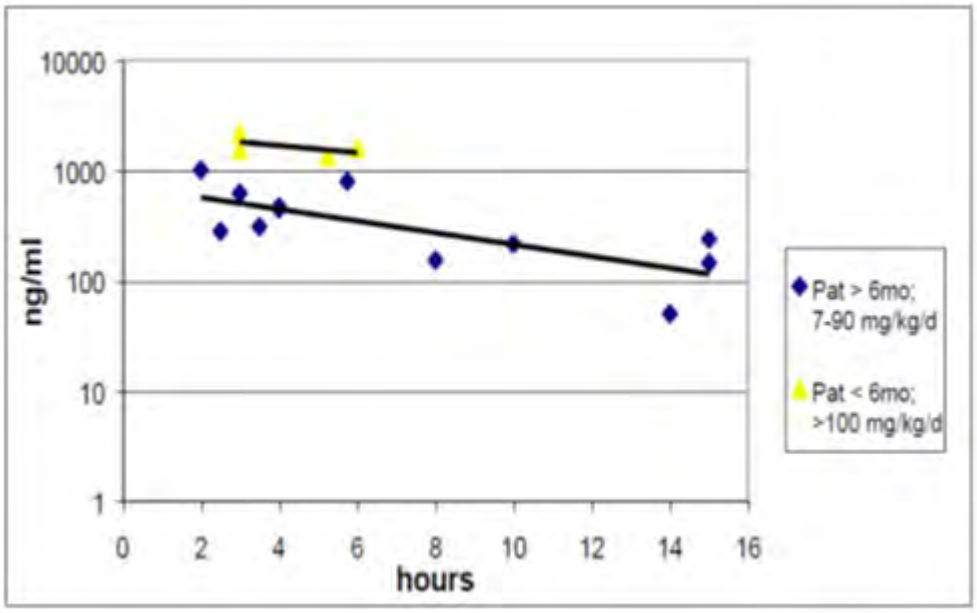
12.1. Clinical questions

12.1.1. Pharmacokinetics

The sponsor did not provide any further analysis. However, they did provide a copy of their response to the EMEA list of questions in relation to pharmacokinetics.

This was an expert opinion. This response did not include any new data. This report included a graph of carglumic acid plasma levels in patients which did show some consistency in concentrations between subjects (Figure 24). However, these data were not formally analysed and are few in number.

Figure 24. Carglumic acid plasma concentrations in patients.



The Evaluator is not satisfied with this response. The sponsor has failed to define the pharmacokinetics of carglumic acid in adults, children or infants.

12.1.2. Pharmacodynamics

No questions.

12.1.3. Efficacy

1. From the report, the sponsor should explain why 16 patients were excluded from the efficacy evaluation when there were 17 patients with major deviations.

The sponsor states that:

This discrepancy resides on the fact that one patient (information redacted) had 2 collected OA episodes treated with carglumic acid. The first episode was without any major deviation, whereas the second one presented with a major deviation (No NH_3 at endpoint – as described in the statistical tables in the study report. Consequently, this patient remained in the efficacy population only for the first episode.

The Evaluator is satisfied with this response.

2. From the study report, the sponsor should clarify the differences in weight at the initiation of the episodes and the initiation of the treatment.

The sponsor hypothesises that:

With regards the differences noted, the body weight was collected in the study case report form at the beginning of the episode and at the initiation of the treatment. In this case, the difference between the starting date of the episode and the initiation of the treatment was generally short (mean 3 days; median 1 day) except for one patient with 41 days between the episode and the initiation. With the young age of patients, the weight could change substantially during these two time points and this may be the basis for the observations.

The Evaluator is satisfied with this response.

12.1.4. Safety

3. According to the NAGS safety report, including patients who received carglumic acid only as therapeutic test of individual clinical/biochemical response before initiating any long-term

treatment (n = 44 patients), 143 patients have been exposed to carglumic acid irrespective of the indication (23 patients for confirmed NAGS and 76 for other non-approved indications) from 1 January 1991 up to 31 December 2008 (Figure 22).

The report does not state from which reports the Non-NAGS patients are derived from and this should be clarified.

The sponsor states that:

Carbaglu is indicated in the treatment of hyperammonaemia due to N-acetylglutamate synthase (NAGS) primary deficiency. The non-NAGS exposure will include the treatment of hyperammonaemia due to other causes, including (but not limited to) isovaleric acidaemia, methymalonic acidaemia and propionic acidaemia.

The Evaluator is not satisfied with this response. The sponsor should clarify exactly what other conditions were included in this analysis of the Non-NAGS patients.

4. According to the safety report, as of 31 December 2008, 18 of the 23 patients suffering from NAGS deficiency have experienced one or more AEs. In total, 120 AEs were reported including 37 serious adverse events (SAEs) and 83 non-serious AEs. However, in the study report, a total of 17 patients experienced an AE, with a total of 118 AEs (see Table 27) with the type of events reported in Table 28. The inconsistencies in the number of AEs between reports should be clarified.

The sponsor included data that demonstrated that these differences in the number of events are attributed to the dating period covered by the respective reports, where the time specified in the Clinical Safety Report is longer, and therefore includes additional safety data.

The Evaluator is satisfied with this response.

5. The sponsor should provide an analysis confirming their assertion that there is no indication of a risk of liver toxicity.

The sponsor includes the following data in their response:

The Sponsors confirms that a review of all Carbaglu cases received until 30 May 2014 was performed by Orphan Europe. Nine cases with following PT were identified as events which can be considered as liver toxicity. For six cases these events were considered by the physician as not related to Carbaglu. The additional three cases were reviewed.

· Case FRA-SPN-XXXXXXX[2] (PT ASAT and ALAT increased):

The patient (20 year-old) started Carbaglu in December 2010. In March 2011, the patient was hospitalized for hyperammonaemia. For hyperammonaemia, the patient was also treated with sodium benzoate, arginine, and citrulline. The patient presented with transaminase levels increased ten times more than normal due to hepatic cytolysis on 21 March 2011 (three months after starting drug). The patient presented with intra cranial hypertension and in cardiac arrest.

On 24 March 2011 the patient had multi organ failure (renal and hepatic failure). Despite the withdrawal of all treatment, the patient died due to circulatory and respiratory failure on 04 April 2014. The reporter causality was not reported.

Orphan Europe considers that the hypertransaminaemia occurred in a context of multi organ failure with hepatic cytolysis, cardiac arrest and hyperammonaemia.

· Case DEU-CLT-XXXXXXX[2] (PT elevation of liver enzymes):

The patient was treated with Carbaglu for Organic Acidaemia (specifically Isovaleric acidaemia). The patient started Carbaglu on 19 April 2006; before the first administration of Carbaglu, the value of ALAT and LDH were upper normal values:

ASAT (156 UI/L: normal values: 11-53) and LDH (855 UI/L normal values: 134-524). On 20 April 2006, a diagnosis of sepsis was performed. Treatment with Carbaglu was withdrawn on 20 April 2006. On 20 April 2006 and 21 April 2006, values of ASAT continued to increase (583 on 20 April 2006 and 1,218 on 21 April 2006). The sepsis resolved on 03 May 2006. The patient recovered from elevated liver enzymes on 04 May 2006. The reporter considered the causality for increased liver enzymes as 'unknown'.

Orphan Europe considers that the increase hepatic enzymes is due to sepsis and is not related to Carbaglu. The increase commenced prior to the administration of Carbaglu and continued to increase despite Carbaglu withdrawal. The value of transaminase returned to normal value when the sepsis resolved.

· Case OTH-LIT-XXXXXXX[2] (PT increased transaminase):

The patient experienced increased transaminase on several occasions. Transaminase levels and dates when these events occurred were not reported. This event occurred in a patient treated for OTC deficiency (off label use). The reporter causality was not reported.

Conclusion: On the basis of this review, in particular the review of the cases above, Orphan Europe considers that there is no risk of liver toxicity.

The Evaluator is satisfied with this response.

6. The sponsor should provide an analysis confirming their assertion that there is no indication of a risk of haematological toxicity.

The sponsor included the following data in their response:

The Sponsors confirms that a review of all Carbaglu cases received until 30 May 2014 was performed by Orphan Europe. Two cases were identified as events which can be considered as haematological toxicity.

· Case FRA-CLT-XXXXXXX[2]: PT eosinophilia

A 14 year old patient was treated for Carbaglu due to hyperammonaemia (value = 424 µmol/L). The value of eosinophil was normal (value = 0.08). One day after the intake, the patient presented hypereosinophilia (value = 3.3). The patient died the same day. Death was not related to hypereosinophilia.

The patient was also treated in the same time with acyclovir, ambroxol and antibiotics (piperacillin, tazocillin, amikacin) and phenobarbital. The diagnosis of infection is not reported but these corrective treatments confirmed that an infection was suspected. According to Orphan Europe, the increase of hypereosinophia can be explained by the infection from undetermined germ (broad spectrum antibiotics). Moreover, the patient had high value of ammonia with neurological disorder (treated by phenobarbital) and decompensation episode often occurred during infection.

· Case GBR-CLT-XXXXXXX[2]: PT thrombocytopenia and Coagulopathy

This patient experienced hypotensive cardiac arrest, coagulopathy and thrombocytopenia in a context of metabolic decompensation in propionic acidaemia. The patient recovered the same day when decompensation episode resolved.

Orphan Europe considers that the thrombocytopenia and coagulopathy were due to the context of metabolic decompensation.

Conclusion: On the basis of this review, in particular the review of the cases above, Orphan Europe considers that there is no risk of haematological toxicity.

The Evaluator is satisfied with this response.

7. A further investigation of the potential for cardiotoxicity should be undertaken.

The Sponsors confirms that a review of all Carbaglu cases received until 30 May 2014 was performed by Orphan Europe. Three cases were identified as events which can be considered as cardiotoxicity.

· Case DEU-SPN-XXXXXXX[2]: PT restrictive cardiomyopathy

This case of cardiomyopathy occurred in a CPS patient. Cardiomyopathy (shortening fraction = 23 %) occurred about one month after Carbaglu administration. Carbaglu was discontinued but the patient didn't recover. With corrective treatments, cardiomyopathy improved. The physician specified that the causality was 'unknown'. This event was considered as a potential risk.

· Case GBR-CLT-XXXXXXX[2]: PT Cardiac arrest

This case was described in the question 4 (report of PT thrombocytopenia and Coagulopathy). This cardiac arrest occurred in a context of decompensation. This event resolved in one day when decompensation episode resolved.

Orphan Europe considers that this cardiac arrest was probably due to the patient status (decompensation episode) and was not related to Carbaglu toxicity.

· Case GBR-CLT-XXXXXXX[2]: PT bradycardia

This event of bradycardia occurred in a patient treated for methylmalonic acidaemia. The event was considered as 'not serious' by the reporter (no value of heart rate available). The patient recovered the same day.

Orphan Europe considers that this bradycardia was probably due to the patient status (decompensation episode associated with vomiting and pyrexia) and was not related to Carbaglu toxicity.

Conclusion: After review of these cases, Orphan Europe considers that bradycardia and cardiac arrest are not potential risk because these events occurred during a decompensation episode and were subsequently resolved. However, the event 'restrictive cardiomyopathy' was considered as a potential risk. From this review, no other case was found. The risk was not considered as identified because some cases of cardiomyopathy can occur without explanation. This event will continue to be monitored.

The Evaluator is satisfied with this response.

8. The sponsor should supply a listing or analysis of vital signs in the clinical studies.

The sponsor states that:

As part of the conduct of the two pivotal studies used to support the proposed indication for Carbaglu, data on vital signs were collected, including patient demographics such as weight and height. In addition, data on clinical symptoms and on neurological, psychiatric, psychomotor, hepatic and respiratory status were recorded. These data have been presented in listings from the original clinical study reports.

The Evaluator is not satisfied with this response. The sponsor has not provides vital signs such as Blood Pressure, Pulse Rate and Respiratory Rate. The sponsor should be asked to supply these data.

9. The sponsor should clarify how many of the AEs in the Periodic Safety Update Report for Carbaglu (carglumic acid) Period covered by this report: Feb 1, 2007 to Jan 31, 2010 overlap with the safety report.

The sponsor states that:

In review of the two documents referred to in this Evaluation Report, Orphan Europe can confirm a total of 12 cases are covered in both reports.

The Evaluator is satisfied with this response.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the risks of carglumic acid are unchanged from those identified in Section 9.1.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of carglumic acid in the proposed usage are:

- Poorly defined dosing regimen due to inadequate pharmacokinetic data in the target population. There are almost no data in adult patients and the data in children is not presented in a way that supports the proposed weight based dosing.

13.3. Second round assessment of benefit-risk balance

Despite this, the benefit-risk balance of Carbaglu is currently unfavourable given the proposed usage, but would have become favourable if the changes recommended in the first round recommendation (Section 10) had been adopted. Specifically these were that the dosing be better supported and the outstanding issues around the safety data addressed satisfactorily. The response from the sponsor did not address these concerns.

13.4. Second round recommendation regarding authorisation

As the sponsor failed to address the pharmacokinetic and safety concerns raised by the first round evaluation, the evaluator recommends that the application for Carbaglu currently be rejected.

14. References

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Rubio V, Grisolia S. Human carbamoylphosphate synthetase I. Enzyme. 1981;26(5):233-9

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