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RESEARCH**

APPLICATION NUMBER:
22-562

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Virginia Elgin, M.D. Helen Sile, M.D.
Review Completion Date	February 18, 2010
Established Name	carglumic acid
(Proposed) Trade Name	Carbaglu®
Therapeutic Class	not yet finalized
Applicant	Orphan Europe
Formulation(s)	oral tablet
Dosing Regimen	100 - 250 mg/kg/day
Indication(s)	treatment of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency
Intended Population(s)	pediatric and adult patients with NAGS deficiency

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, an approval action is recommended.

1.2 Risk Benefit Assessment

Carglumic acid 100 to 250 mg/kg/day oral formulation provides a favorable benefit/risk ratio. Carglumic acid provides a therapeutic option for patients with N-acetyl glutamate synthetase (NAGS) deficiency, the rarest form of urea cycle disorders. Currently approved treatments for urea cycle disorders reduce blood ammonia levels through their effect as nitrogen scavengers. However, carglumic acid effectively and rapidly reduces plasma ammonia levels within 24 hours of initiation of treatment and normalizes ammonia levels within 3 days of initiation of treatment in patients with NAGS deficiency. Patients with NAGS deficiency treated chronically with carglumic acid maintain normal plasma ammonia levels for the duration of treatment with carglumic acid. When treatment with carglumic acid has been instituted early, acute hyperammonemic episodes resolved and patients exhibited normal neurologic development. N-acetylglutamate is the essential allosteric co-factor for carbamyl phosphate synthetase (CPS), the enzyme that catalyzes the first step in the urea cycle. Thus, patients with NAGS deficiency are unable to synthesize urea from ammonia. Carglumic acid is structurally similar to N-acetylglutamate (NAG) and replaces the absent or deficient co-factor (NAG) and activates the enzyme carbamyl phosphate synthetase. Thus, carglumic acid by binding to CPS is thought to cause a conformational change rendering CPS catalytically active and restores the activity of the urea cycle in patients with NAGS deficiency.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical

An Endocrinologic and Metabolic Drugs Advisory Committee meeting was convened on January 13, 2010, to discuss carglumic acid. The advisory committee recommended that carglumic acid be approved for the treatment of hyperammonemia due to NAGS deficiency. Additionally, the advisory committee recommended that the Applicant implement a patient registry that will evaluate the long-term safety of carglumic acid treatment in patients with NAGS deficiency. Since long-term safety data are lacking in NAGS deficiency patients, this registry should be designed to collect and analyze long-

term outcome (e.g., survival and neurocognitive outcome) data in a consistent and organized manner.

Nonclinical

The sponsor should conduct a chronic (9-month) toxicity study in a nonrodent species to provide safety data that are currently lacking. The sponsor should conduct a two year carcinogenicity study in a single species.

Clinical Pharmacology

The sponsor should conduct in vitro studies to evaluate drug-drug interactions by identifying enzymes that mediate the metabolism of carglumic acid. The sponsor should conduct in vitro studies to evaluate the potential for carglumic acid to inhibit or induce CYP isoenzymes.

1.5 Summary of Clinical Findings

1.5.1 Brief Overview of Clinical Program

Carglumic acid, 100 to 250 mg/kg/day, administered orally for the treatment of hyperammonemia due to NAGS deficiency was evaluated in an open-label, uncontrolled retrospective review of the clinical courses of 23 NAGS deficiency patients who received carglumic acid. The Applicant did not provide any data from prospective, controlled trials to support the efficacy and safety of carglumic acid, and stated that prospective trials were not feasible due to the rarity of NAGS deficiency. Additionally, data from an on-going, 3-day, open label, uncontrolled Phase 2 trial (IND 68,185) was also referenced and submitted as part of the application. In the retrospective case series review, the clinical experiences with carglumic acid and data collection from the 23 patients spans from 1991 through December 2007.

1.5.2 Efficacy

Retrospective Case Series

Treatment with carglumic acid effectively lowers plasma ammonia level acutely and maintains normal ammonia level chronically in patients with hyperammonemia due to NAGS deficiency. The primary efficacy evaluation was based on carglumic acid treatment effect on short-term ammonia levels (within 7 days after first carglumic acid treatment). Persistence of efficacy was also examined by evaluating the plasma ammonia level response to long-term treatment with carglumic acid. Long-term response was evaluated by the last available blood ammonia level while on treatment with carglumic acid. Outlined below in Table 1 is the plasma ammonia level at baseline and days 1 to 7 post-initiation of the first carglumic acid treatment. The results in Table 1 demonstrate that a reduction in ammonia level is observed within 24 hours of the first dose of carglumic acid, and normal plasma ammonia levels are attained by day 3 of

carglumic acid treatment in those patients for whom data were available. Table 1 also demonstrates that for the patients that continued carglumic acid therapy, normal ammonia levels are maintained for the duration of treatment.

Table 1: Ammonia levels pre and post exposure to carglumic acid

Timepoint	Statistics (N = 21*)	Ammonia** (µmol/L)	
Baseline (prior to first treatment with carglumic acid)	N	20	Change from baseline
	Mean (SD)	218.9 (299.0)	
	Median	142.0	
	Range	29.0-1428.0	
	Missing Data	1	
Day 1	N	14	14
	Mean (SD)	145.9 (303.1)	-92.0 (107.8)
	Median	61.5	-60.5
	Range	25.0-1190.0	-382.0-6.0
	Missing Data	7	7
Day 2	N	11	11
	Mean (SD)	64.7 (65.9)	-220.2 (335.4)
	Median	54.0	-128.0
	Range	11.0-255.0	-1173.0-6.0
	Missing Data	10	10
Day 3	N	6	6
	Mean (SD)	43.3 (40.8)	-332.7 (551.0)
	Median	29.5	-108.0
	Range	12.0-124.0	-1416.0-69.0
	Missing Data	15	15
Day 4	N	6	6
	Mean (SD)	42.3 (30.8)	-332.0 (550.0)
	Median	38.5	-117.0
	Range	10.0-96.0	-1418.0-51.0
	Missing Data	15	15
Day 5	N	5	5
	Mean (SD)	42.2 (18.5)	-106.8 (71.7)
	Median	47.0	-126.0
	Range	10.0-56.0	-187.0-8.0
	Missing Data	16	16
Day 6	N	3	3
	Mean (SD)	32.3 (4.5)	-61.3 (41.6)
	Median	32.0	-65.0
	Range	28.0-37.0	-101.0 - -18.0
	Missing Data	18	18

*N = 23 total patients minus 2 patients (b) (6) excluded from efficacy analysis due to heterozygote NAGS mutation and asymptomatic status

**Mean ammonia normal range: 5 to 50 µmol/L

Reviewer's table modified from sponsor's tables 3, 7a, and 8a Carbaglu Final, pages 9, 74, and 86

Table 1 Continued: Ammonia levels pre and post exposure to carglumic acid

Timepoint	Statistics (N = 21*)	Ammonia** (µmol/L)	Change from baseline
Day 7	N	2	2
	Mean (SD)	41.5 (29.0)	-51.0 (82.0)
	Median	41.5	-51.0
	Range	21.0-62.0	-109.0-7.0
	Missing Data	19	19
Long-term (last available value on carglumic acid treatment)	N	21	20
	Mean (SD)	51.8 (88.6)	-167.0 (314.1)
	Median	25.0	-108.0
	Range	7.0-419.0	-1419.0-139.0
	Missing Data	0	1

*N = 23 total patients minus 2 patients (b) (6) excluded from efficacy analysis due to heterozygote NAGS mutation and asymptomatic status

**Mean ammonia normal range: 5 to 50 µmol/L

Reviewer's table modified from sponsor's tables 3, 7a, and 8a Carbaglu Final, pages 9, 74, and 86

Plasma ammonia levels have been used previously as an efficacy endpoint in clinical trials for products approved for the treatment of hyperammonemia due to urea cycle disorders. Although plasma glutamine levels have not previously been evaluated as a primary efficacy endpoint in clinical trials for products approved to treat hyperammonemia due to urea cycle disorders, plasma glutamine levels are abnormal in patients with NAGS deficiency. Treatment with carglumic acid would be expected to normalize plasma glutamine levels. Therefore, plasma glutamine levels were evaluated as a supportive efficacy measure. Plasma glutamine level appeared to decrease with short and long-term treatment with carglumic acid in NAGS deficiency patients for whom data were available. Again, as with long-term plasma ammonia levels, long-term response for plasma glutamine was based on the last available plasma glutamine value while on treatment with carglumic acid.

Although there were no standardized and validated tools used at all centers to assess neurologic changes and/or neurocognitive development, it appears that decreasing ammonia levels improves acute hyperammonemic encephalopathy and long-term neurologic outcome. Of the 17 patients with neurocognitive/neurologic data available, 9 patients (53%) presented with neurologic impairment that improved post-initiation of carglumic acid therapy. Three patients (18%) had normal neurologic function at presentation and remained neurologically unimpaired post-initiation of treatment with carglumic acid. However, 5 patients (29%) sustained permanent neurologic impairment despite treatment with carglumic acid. The Applicant attributed permanent neurologic impairment in these patients to hyperammonemic episodes that occurred prior to the initiation of carglumic acid because these patients maintained normal plasma ammonia levels during continuous treatment with carglumic acid. Thus, 12/17 or (71%) of patients with long-term neurologic outcome information had an absence of clear neurologic impairment.

Study IND 68, 185

The product, carglumic acid, effectively lowers plasma ammonia levels acutely in patients with NAGS deficiency. In study IND 68,185, plasma ammonia levels decreased in 2 of the 3 NAGS deficient patients (66.7%) after a 3-day treatment period with carglumic acid. However, only one patient had an abnormal ammonia level at baseline.

Table 2: Ammonia levels pre and post 3 day treatment with carglumic acid

Ammonia Levels (µmol/L) Pre and Post carglumic acid exposure			
Patient	Baseline Average	Post-Baseline Average	Paired Difference (Post-baseline vs Baseline)
(b)	47	10	-37
(b)	12	16	3.9
(b)	105	46	-58.9

1.5.3 Safety

The retrospective case series and study IND 68,185 have established a favorable safety and tolerability profile for carglumic acid 100 to 250 mg/kg/day oral for the treatment of hyperammonemia associated with NAGS deficiency. Despite the small sample size that may limit the identification of potential safety signals, 91% of the patients studied in the retrospective case series had exposure to carglumic acid of at least one year, and the mean length of exposure in patients in the retrospective case series was 8.2 years. The safety profile of carglumic acid will be summarized individually for the 2 separate studies: “retrospective case series” and “Study IND 68,185”.

Retrospective Case Series

There were a total of 23 patients evaluated in the safety analysis for the uncontrolled, retrospective case series. All 23 patients received at least one dose of carglumic acid. Of the 23 patients, 2 patients (8.7%) received carglumic acid for less than one year, 7 patients (30%) received carglumic acid treatment between 1 and 5 years, 6 patients (26%) received carglumic acid treatment for at least 5 years but less than 10 years, and 8 patients (35%) received carglumic acid for at least 10 years. The total exposure to carglumic acid over the course of the case series is unknown.

Overall, there were 2 deaths (8.7%) during the 21 years of follow-up. Both of the patient deaths were assessed by the Applicant as unrelated to carglumic acid treatment. (b) (6) was a 9 year-old female admitted to the hospital for discontinuation of carglumic acid therapy under medical supervision. Her plasma ammonia levels had been erratic during treatment and were attributed to chronic non-compliance. Carglumic acid was discontinued upon parental request. As the patient was undergoing weaning from carglumic acid, her plasma ammonia level increased from 35 µmol/L to 233 µmol/L (normal plasma ammonia ≤ 50 µmol/L). During this same hospitalization, she became febrile and developed pneumonia. She required mechanical ventilation and

experienced multi-organ system failure with encephalopathy leading to her death. (b) (6) was an 11 year-old female who experienced an acute episode of hyperammonemia (419 $\mu\text{mol/L}$) in December 2007 as a consequence of pneumonia. Despite efforts to treat the hyperammonemia with multiple interventions, the patient worsened and died. The Reviewer agrees with the Applicant's assertion that the patient deaths appear to be unrelated to treatment with carglumic acid.

There were ten patients (43.5%) who reported non-fatal serious adverse events (SAEs). Most of the non-fatal SAEs were related to the system organ class (SOC) gastrointestinal and nervous system disorders. Vomiting (6 patients) and somnolence (2 patients) were the most frequently reported non-fatal SAE preferred terms. It is unclear whether these SAEs were related to treatment with carglumic acid or related to hyperammonemic episodes associated with the patients' underlying disease.

The most commonly reported adverse event (AE) preferred terms were anemia (6 patients), ear infection (4 patients), tonsillitis (4 patients), nasopharyngitis (4 patients), headache (3 patients), and diarrhea (3 patients). It is unclear whether these commonly reported AEs were related to treatment with carglumic acid, however, these AEs, with the exception of anemia, are also commonly occurring in the general population. Anemia was not expected as a commonly reported AE, however, the development of anemia in the patients evaluated in the retrospective case series might be related to the frequent blood sampling that was performed to obtain the various laboratory parameters, a result of protein intake restriction or their underlying chronic disease.

The Applicant reported treatment-related AEs in 3 patients. One patient experienced treatment non-compliance due to "product acidity" and another patient experienced "bitter taste". There was also a report of hyperhidrosis that was considered treatment-related.

There were 5 patients who discontinued treatment in the retrospective case series. Three of the patients were discontinued from carglumic acid treatment because of their heterozygote NAGS mutation and asymptomatic clinical course. As stated above, two patients died and, therefore, discontinued treatment.

In addition to anemia that was reported in 6 patients, there were 2 patients that developed clinically significant laboratory abnormalities. One patient developed jaundice with elevated total bilirubin that resolved spontaneously without any intervention or dose adjustment. Another patient developed an elevated AST without any other associated hepatic abnormalities or findings. This patient's AST was noted to be decreasing on his last documented follow-up.

Study IND 68,185

No deaths, non-fatal SAEs or discontinuations were reported in this 3-day trial. The only AE reported in this trial was an episode of rhinorrhea, cough and congestion

experienced by patient 4MT. Patient 4 MT who has propionic acidemia was diagnosed with "strep throat".

According to this Reviewer, carglumic acid is a novel therapy for the treatment of hyperammonemia due to NAGS deficiency, an inherited, serious, and life-threatening disorder. Other approved therapies decrease plasma ammonia levels through their effects as nitrogen scavengers. However, carglumic acid has the capacity to replace in vivo N-acetyl glutamate, a necessary co-factor for the enzyme (carbamyl phosphate synthase) that initiates the urea cycle. Patients with NAGS deficiency have a mutation in the gene that encodes the enzyme, N-acetylglutamate synthase, resulting in an absence or reduction in the amount of available NAG. Carglumic acid is a structural analog of NAG and replaces the deficient NAG cofactor and allows for normal ureagenesis to proceed. Thus, carglumic acid appears to provide a specific treatment for patients with NAGS deficiency and improves available treatment options for patients with this extremely rare disease.

2 Introduction and Regulatory Background

Urea Cycle and Urea Cycle Defects

The urea cycle consists of a series of enzymes that function interdependently to convert ammonia, a product of protein catabolism, into urea, a molecule that can be excreted into the urine. Urea cycle disorders result from a deficiency of any of the following enzymes: N-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase 1 (CPS 1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL), arginase (ARG). These disorders are autosomal recessive diseases with the exception of ornithine transcarbamylase deficiency, which is an X-linked disorder. Urea cycle disorders have an overall prevalence of approximately 1 in 30,000 live births. OTC deficiency is the most common urea cycle disorder, while NAGS deficiency is one of the rarest.

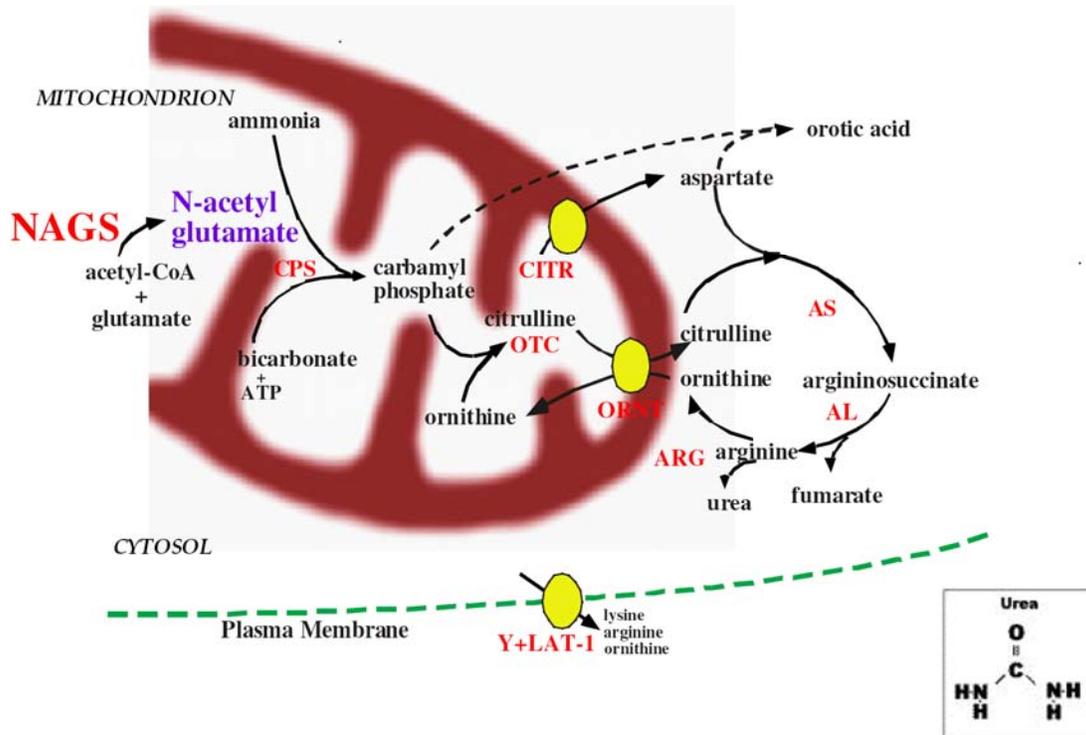
N-acetylglutamate synthase (NAGS) deficiency

N-acetylglutamate synthase is an enzyme that is essential for the function of the urea cycle. It is located in the liver and intestine.¹ The following figure illustrates NAGS in the mammalian urea cycle:²

1 Caldovic L, Tuchman M et al. Cloning and expression of the human N-acetylglutamate synthase gene. *Biochemical and Biophysical Research Communications* 2002; 299: 581-586

2 Caldovic L and Tuchman M. *N-acetylglutamate and its changing role through evolution. Biochem J* 2003; 372: 279-290

Figure 1: The Urea Cycle



The first step in the urea cycle is the formation of carbamyl phosphate (CP) from ammonia (NH₃), bicarbonate (HCO₃⁻) and 2 molecules of ATP in the following reaction:



The enzyme, carbamyl phosphate synthetase (CPS), in the mitochondrial matrix of hepatocytes, requires the co-factor N-acetylglutamate (NAG) to catalyze the above displayed reaction. NAG, the essential allosteric co-factor for the enzyme carbamyl phosphate synthetase (CPS), is made in the mitochondrial matrix when acetyl-CoA and L-glutamate combine in a reaction catalyzed by the enzyme, N-acetylglutamate synthetase. The concentration of NAG within the mitochondria controls the activity of CPS, and therefore, regulates ureagenesis.³

NAGS deficiency is a rare urea cycle disorder which results from a defect in N-acetylglutamate synthetase. Inherited NAGS deficiency results from one or more mutations in the NAGS gene, which causes an absence or a decrease in the enzyme activity. Without the co-factor NAG, CPS is catalytically inactive. The gene for NAGS is located on the long arm of chromosome 17 within band 17 q21.31, and the molecular diagnostic methods became available in 2003.

³ Meijer A, et al. Control of Ureagenesis. Eur J. Biochem 1985: 148: 189-196

The autosomal recessive disorder expresses phenotypes that range from acute neonatal onset to late-onset disease in adults. The neonatal-onset phenotype has a devastating clinical course, and usually reflects complete absence of NAGS activity. It is thought that the early-onset (neonatal-onset) presentation correlates with the presence of either 2 NAGS null alleles or 2 missense mutations, which lead to complete absence of NAGS activity. Symptoms result primarily from hyperammonemia. Newborns who have hyperammonemia may present with respiratory alkalosis, hypotonia, lethargy, and vomiting. Symptoms may progress to include cerebral edema, seizures, and death. If newborns survive the acute hyperammonemic episode, they usually tend to exhibit significant development delays, residual neurologic impairments and seizure disorders.

Late-onset NAGS deficiency has a variable age of onset, and the degree of residual enzyme activity is heterogeneous. Patients with partial NAGS deficiency may present with their initial symptoms anywhere from the first year of life to adulthood. In infants, they may become symptomatic following weaning from breast milk or a change from a lower protein infant formula to cow's milk. In children and adults, events such as acute infection, a high dietary protein load, or a combination of the two may lead to hyperammonemia. Symptoms result primarily from hyperammonemia, and the most common clinical findings include central nervous system symptoms such as lethargy, irritability, or somnolence. These symptoms may progress to agitation, disorientation, combativeness, ataxia, and amblyopia. Children with partial enzymatic defects tend to have better outcomes than the ones with complete absence of NAGS activity. Children with partial NAGS deficiency may exhibit cognitive dysfunction such as learning disabilities and attention deficit hyperactivity disorders.

Delay in diagnosis may occur since symptoms can be attributed to more common conditions such as gastroenteritis, cyclical vomiting, encephalitis, Reye's syndrome, epilepsy, and drug toxicity. Findings in patients with NAGS deficiency include elevated plasma ammonia level, elevated plasma glutamine, normal or low levels of plasma citrulline, normal urinary orotic acid and normal pH or respiratory alkalosis. Previously, diagnosis has relied on the results of enzyme activity assays. Due to the low abundance of NAGS, a large amount of liver tissue is required to perform enzyme activity assays. The invasive nature of a liver biopsy along with the need for an adequate liver sample size might have led to under-diagnosis of NAGS deficiency historically. Since the molecular diagnostic methods became available in 2003, DNA testing is now used to confirm the diagnosis.

The degree of neurologic impairment in urea cycle disorders has been shown to correlate with peak levels of ammonia⁴ and the duration of hyperammonemic coma.⁵

4 Uchino T, et al. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. *J. Inher. Metab. Dis.* 1998; 21 (Suppl 1): 151-159

5 Msall M, et al. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. *N Engl J Med* 1984; 310: 1500-1505

Hyperammonemia is the primary pathophysiologic consequence of NAGS deficiency and other urea cycle disorders. Hyperammonemia leads to multiple biochemical and structural changes in the brain, and is thought to cause swelling of astrocytes in the brain as well as pleomorphic changes in the mitochondria. The brain lacks a complete urea cycle and relies on the synthesis of glutamine to remove excess ammonia and to store temporary nitrogen. This process is primarily localized in the astrocytes, such that hyperammonemia leads to accumulation of glutamine from glutamate and ammonia via glutamine synthetase. Excess glutamine is released into the extracellular space, altering astrocyte-neuronal transmission. This creates an imbalance of excitatory versus inhibitory neurotransmission because of increased glutamate production combined with decreased synaptic uptake of glutamate. It is thought that acute hyperammonemia leads to changes in astrocyte protein expression, glutamine synthetase, glial fibrillary acidic protein, glutamate transporter, nitric oxide synthase, and peripheral benzodiazepine receptors. These changes alter the brain's ability to remove additional ammonia, to regulate cerebral blood flow, to maintain energy homeostasis and neurotransmission.⁶

Prior to the availability of nitrogen scavenging therapies, all patients with neonatal-onset urea cycle disorders died rapidly. There are no published outcome studies in NAGS deficiency patients due to the rarity of this type of urea cycle disorder. Therefore, available published clinical outcomes are reported for all urea cycle disorders in aggregate. Since ammonia scavenging therapies have become available, survival has improved for neonatal-onset urea cycle disorders. It has been reported that most patients with neonatal-onset urea cycle defects tend to survive until age 5 or more.⁷ However, patients who survive the neonatal hyperammonemic episodes are left with significant neurocognitive sequelae.

6 Tuchman M, Mew Ah N. Interim Report: Experience with carbamylglutamic acid (Carbaglu) in the US: Ureagenesis restoration in hyperammonemic patients. February 2009. pp 1-20

7 Summar M and Tuchman M. Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders. The Journal of Pediatrics. 2001; 138: S6-S10

2.1 Product Information

Figure 2: Chemical structure of carglumic acid



Sponsor's Figure from Module 2, 2.3 Quality Overall Summary, page 1

Proposed Trade Name (established name): Carbaglu® (carglumic acid)

Proposed Indication: For the treatment of hyperammonemia due to a liver mitochondrial enzyme deficiency of N-acetylglutamate synthase (NAGS)

Proposed Age Group: Adult and pediatric populations with NAGS deficiency

Pharmacologic Class: not yet finalized as of 2-18-2010

Chemical Class: New molecular entity (NME)

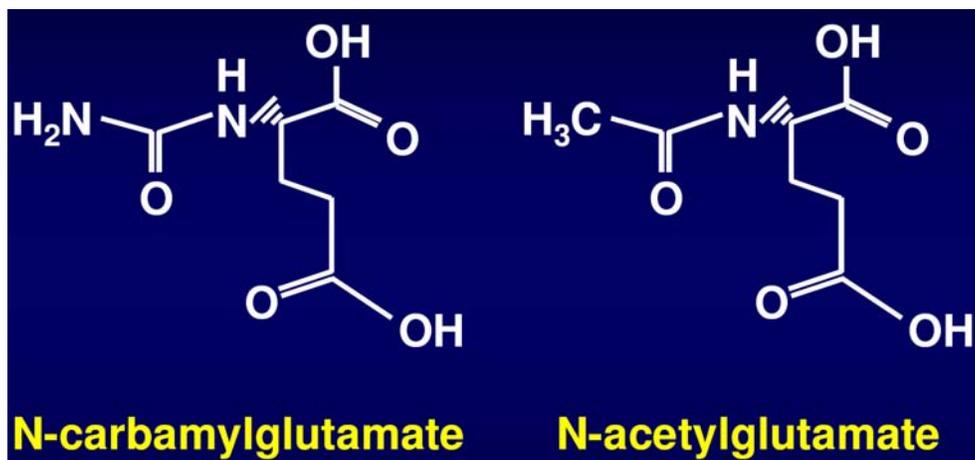
Molecular Formula: C₆H₁₀N₂O₅

Molecular Weight: 190.16

Chemical Name: N-carbamoyl-L-glutamic acid or (2S)-2(carbamoylamino)pentanedioic acid

Carbaglu® is an oral preparation of carglumic acid used to treat hyperammonemia associated with a liver mitochondrial enzyme deficiency of N-acetylglutamate synthase (NAGS). The active substance known as N-carbamoyl-L-glutamic acid or carglumic acid, is a structural analogue of the NAGS product, N-acetyl-glutamate (NAG). Figure 3 shows that carglumic acid differs from NAG by the substitution of a terminal ammonia group (NH₂) for the terminal methyl group (CH₃) normally found in NAG. NAG is a cofactor that activates carbamyl phosphate synthetase (CPS), the first enzyme of the urea cycle, which is essential to the normal functioning of the urea cycle.

Figure 3: Similarities between carglumic acid and N-acetylglutamate



Sponsor's Figure from Module 5, Volume 1.16 (Caldovic L and Tuchman M. N-acetylglutamate and its changing role through evolution. *Biochem J.* 2003; 372: 279-90)

Carglumic acid is a white crystalline powder, which is available as 200 mg tablets. The Applicant's proposed initial dose is between 100 to 250 mg/kg/day, divided into two to four doses a day to be given before meals.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no products that are currently approved in the U.S. for the specific treatment of hyperammonemia due to NAGS deficiency. There are 2 currently marketed nitrogen scavenging products. Table 3 below demonstrates the currently marketed formulations and dosages of products approved for treatment and management of hyperammonemia in urea cycle disorders in the U.S.

Table 3: Approved Products for Hyperammonemia in urea cycle disorders

Name of Drug	Formulations	Indications	Initial FDA approval	Dose
Ammonul (sodium phenylacetate and sodium benzoate)	Injectable, 10%/10%	adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle	February 17, 2005	Weight based dosing Loading dose over 90 to 120 min Maintenance dose over 24 hrs 0 to 20 kg 2.5 mL/kg = 250 mg/kg > 20 kg 55 mL/m ² = 5.5 g/m ²
Buphenyl (sodium phenylbutyrate)	Oral, tablet Oral, powder	adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)	May 13, 1996	Weight based dosing < 20 kg 450-600 mg/kg/day larger patients 9.9-13.0 g/m ² /day

Reviewer's table constructed from data obtained from individual approved product labels

In clinical practice, other interventions are used in conjunction with nitrogen scavenging therapies to treat hyperammonemia secondary to NAGS deficiency. Hemodialysis rapidly decreases plasma ammonia levels but its use is limited to acute life-threatening clinical settings. Liver transplantation is considered curative for all urea cycle disorders. Other standard therapies in clinical practice are as follows:

- Arginine: synthesis of arginine is usually decreased in NAGS deficiency; therefore, it becomes an essential amino acid
- Citrulline: by pulling aspartate into the pathway may increase nitrogen clearance

- Carnitine is added to the hyperammonemia treatment regimen even though expert opinions are divided as to its benefit. It is thought to conjugate with sodium benzoate.⁸
- Dietary protein restriction is implemented but with supplementation of essential amino acids

2.3 Availability of Proposed Active Ingredient in the United States

Carglumic acid has not been approved in the U.S.; however, it has been approved and marketed in Europe since January 24, 2003.

2.4 Important Safety Issues With Consideration to Related Drugs

Carglumic acid is a structural analogue of N-acetyl-glutamate. It is a new molecular entity and the first in its class.

Except for the pre-marketing and postmarketing experience in Europe, carglumic acid safety database is limited. This Reviewer is not aware of any other drugs that have similarities to or are in the same class as carglumic acid.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- **January 20, 1998:** Orphan drug designation granted (application 97-1099)
- **July 8, 2002:** Pre-IND file opened to provide guidance to the sponsor
- **September 24, 2002: Pre-IND Guidance meeting**
- **July 8, 2003:** Applicant submitted Original IND 61,265
- **August 12, 2003:** IND 61,265, first clinical review determined to be safe to proceed
- **April 28, 2004: Type B Pre-NDA meeting** held between the Agency and the Applicant, Orphan Europe
 - Requirement for a chronic toxicity study in non-rodent species and a 2 year carcinogenicity study in one species discussed
- **October 13, 2005:** Transfer of IND 68,185; 61,265, and 70,942 from Division of Metabolism and Endocrinology Products to Division of Gastroenterology Products

⁸ Summar M. Current Strategies for the Management of neonatal urea cycle disorders. The Journal of Pediatrics. 2001; 138: S30-S39

- **May 15, 2007:** Fast track designation granted

2.6 Other Relevant Background Information

September 23, 2003: IND 68,185

Mendel Tuchman, MD has researched carglumic acid under IND 68,185 (submitted September 23, 2003) for the treatment of NAGS deficiency. Studies under IND 68,185 were amended to include patients with carbamyl phosphate synthetase 1 (CPS 1 or CPS) deficiency, propionic academia (PA), methylmalonic academia (MMA), and hyperinsulinism and hyperammonemia syndrome (HHS). The Applicant obtained right of reference to the data in IND 68,185, and included data under this IND in the application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Reviewer believes that the quality of the NDA submission was adequate despite the limitations associated with the uncontrolled, retrospective case series. The Applicant organized data from patient medical records that spanned 20 years. Therefore, the quality of the data provided in this submission varied depending on the timing of the collection of data (i.e. data from 1987 versus 2007) and variable documentation exhibited by different treating physicians, centers and European countries. Translation of information obtained from clinic charts, hospital records, diagnostic tests and laboratory parameters was performed by the Applicant within the limits of the legibility of hand written documents. Case report forms (CRFs) were developed as part of the long-term follow-up program for patients treated with carglumic acid and to organize required reporting of safety data to the regulatory agencies.

The Division of Scientific Investigations (DSI) completed a review dated December 4, 2009, and the review notes that there were no concerning issues identified. Therefore, data provided by the Applicant in support of the efficacy and safety application for carglumic acid 100-250 mg/kg/day for the treatment of hyperammonemia due to NAGS deficiency is acceptable for review.

3.2 Compliance with Good Clinical Practices

Study IND 68,185

Study IND 68,185 is being conducted in accordance with U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312), and is being conducted in accordance with U.S. Title 21 CFR on Good Clinical Practices (GCPs)

which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

Retrospective Case Series

The data obtained for the retrospective case series review and analyses were not prospectively collected. However, a signed informed consent was obtained for each patient for whom data was collected. According to the Applicant, all of the patient treatment, data collection, and analyses were conducted in accordance with acceptable ethical standards. The Applicant certifies that they did not use, in any capacity, the services of any persons debarred under section 306 (k)(1)(a) or (b) of the Act [21 U.S.C. 335 (a)(k)(1)].

3.3 Financial Disclosures

The sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR (f), the sponsor certified that no clinical investigator was the receipt of any significant payments of any sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Table 4 below has the ingredients, including excipients for the carglumic acid 200 mg tablet. For viral safety reasons, excipients of non-animal origin were chosen.

Table 4: Composition of a 200 mg carglumic acid tablet

Name of ingredients	Unit formula	Function	Reference to standards
Active substance			
Carglumic acid	200.00 mg	active substance	In-house standards
N-carbamoyl-L-glutamic acid			
Excipients			
Cellulose, microcrystalline	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0316
Sodium lauryl sulfate	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0098
Hypromellose	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0348
Croscarmellose sodium	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0985
Silica, colloidal anhydrous	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0434
Sodium stearyl fumarate	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 1567
(b) (4)	(b) (4)	(b) (4)	USP, current Edition Ph. Eur. current Edition, 0008
Total	500.00 mg		
	(b) (4)		

Reviewer's table modified from sponsor's table, module 2, 2.3 Quality Overall Summary, page 1

During an inspection (date: October 30 to November 5, 2009) of the manufacturing process, the international compliance team noted several deficiencies and issued a form FDA 483 to the firm. Several deviations were cited: 1. written stability program for drug products did not include reliable test methods (i.e. for carbaglu 200 mg tablets (to-be-marketed (TBM) formulation) the impurities testing methods is not stability indicating and is found to be inadequate), 2. equipments used to manufacture the carbaglu 200 mg tablets were not routinely calibrated and did not meet specifications to ensure adequate performance. Final resolution of the deficiencies cited in FDA 483 is pending the sponsor's response and Offices of Compliance and New Drug Quality Assessment (ONDQA) reviews and decisions.

For additional information, please see Dr. Haber's chemistry, manufacturing and controls review, which is currently pending. An information request was issued to the sponsor on January 7, 2010, and a response has not yet been received. Thus, final recommendations from ONDQA and compliance cannot be provided at this time.

4.2 Clinical Microbiology

Microbiology review is not performed because carglumic acid is an oral formulation.

4.3 Nonclinical Pharmacology/Toxicology

Based on Dr. Ng's preliminary draft pharmacology/toxicology review dated 2-16-2010, below is a brief overview of the findings.

No significant effects on blood pressure, heart rate or ECG were observed in conscious dogs after administration of single oral doses of up to 1000 mg/kg carglumic acid. No significant effects were noted on CNS and respiratory functions in rats when oral doses of up to 1000 mg/kg of carglumic acid were administered.

Two oral toxicity studies were conducted in rats for a period of 2-weeks and 26-weeks. A two-week study conducted in neonatal rats on days 4 to 21 post-partum resulted in mortality at all doses of carglumic acid (250, 500, 1000, and 2000 mg/kg/day) compared to control. The rats in the high dose group (2000 mg/kg/day) exhibited signs of dehydration, swollen abdomen, hypokinesia prior to their deaths, which occurred 2-3 days after carglumic acid treatment. The deaths of the rats in the high dose group were considered drug related; whereas, the deaths of the rats in the 250 to 1000 mg/kg/day were attributed to gavage errors. At carglumic acid doses of 1000 mg/kg/day, the rats were noted to have a decrease in body weight gain, reduction in BUN, and a histopathologic finding of dilated kidneys in male rats. Interstitial mononuclear cell aggregation in kidneys was observed at carglumic acid doses of 500 and 1000 mg/kg/day in a twenty six-week study conducted in juvenile rats compared to control. At carglumic acid doses of 1000 mg/kg/day in the 26-week study, multicellular hepatic necrosis was observed. Chronic toxicity study in non-rodent species have not yet been conducted.

A 2-year carcinogenicity study has not yet been conducted. However, carglumic acid has tested negative in a battery of genotoxicity testing (Ames test, in vitro chromosome aberration test, and in vivo micronucleus assay in rats). In addition, no drug-related fetal malformations were observed in rats and rabbits that received oral carglumic acid doses of 2000 mg/kg/day and 1000 mg/kg/day, respectively in reproductive toxicology studies.

For complete details of nonclinical studies, please see Dr. Ng's pharmacology/toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Unlike the currently available therapies discussed in section 2.2, carglumic acid is designed to correct the actual metabolic error by being the alternate allosteric activator of the enzyme carbamyl phosphate synthetase. The activity of the urea cycle is

regulated by the rate of synthesis of N-acetylglutamate (NAG). The normal function of N-acetylglutamate synthase is to mediate the reaction of acetyl coenzyme A and glutamate to synthesize NAG. NAG acts as an activator of the first enzyme of the urea cycle, carbamyl phosphate synthetase (CPS). The activation process requires the binding of NAG to CPS. Hence, when NAGS deficiency occurs, there is an inability to form adequate NAG, which leads to a failure to activate the enzyme, CPS (see Figure 4). A failure to activate CPS then leads to inability to form carbamyl phosphate from ammonia, bicarbonate and 2 molecules of ATP, the entry step into the urea cycle.

Carglumic acid is a structural analogue of NAG; therefore, it is designed to treat the cause of the hyperammonemia rather than the hyperammonemia itself so that ammonia will not accumulate, and ureagenesis can occur. Carglumic acid is intended to pass into the mitochondria and activate CPS 1 (see Figure 5).

Figure 4: The Urea Cycle depicted in NAGS deficiency where N-acetylglutamate is unable to be synthesized from acetyl Co A and glutamate

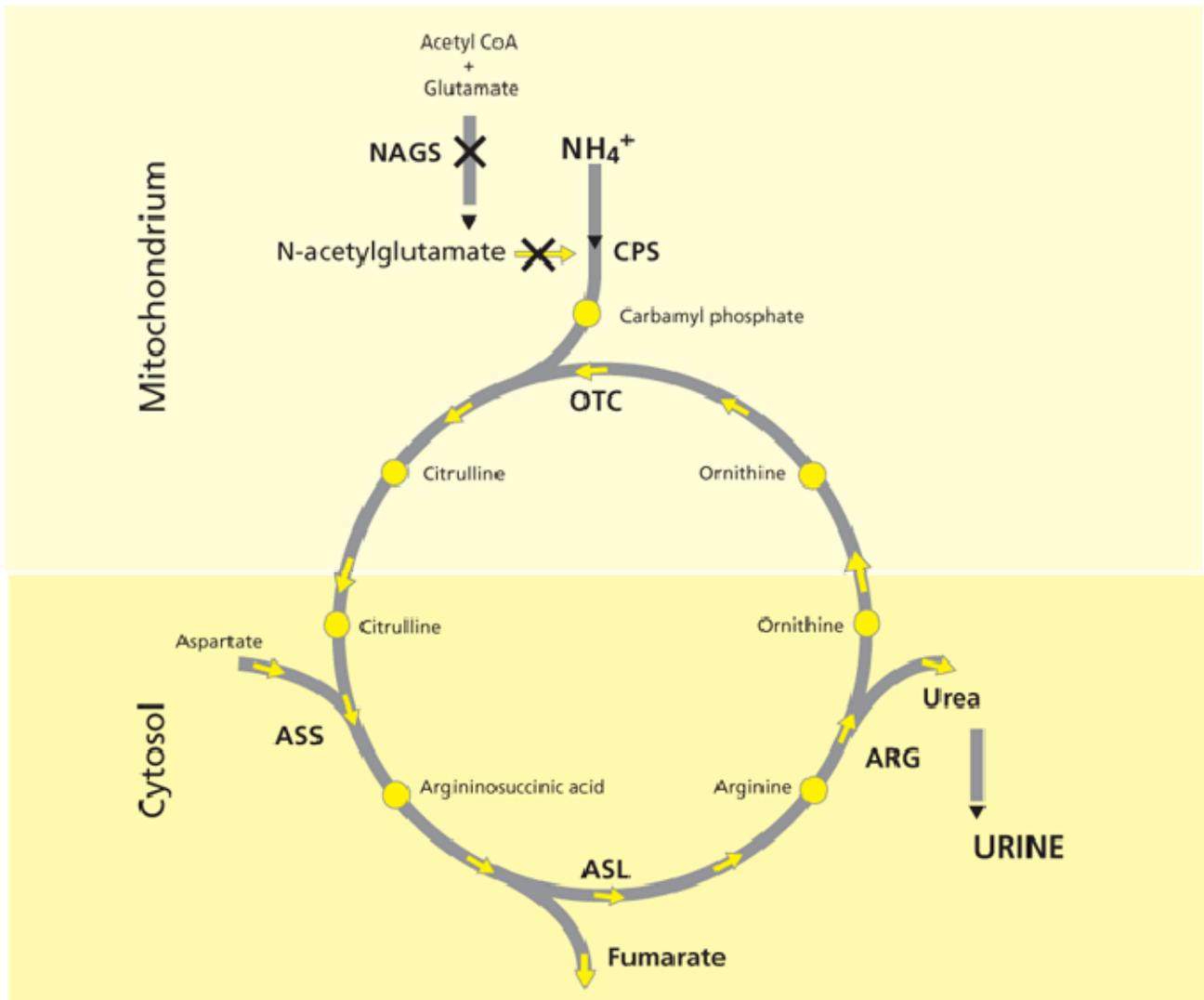


Figure adopted from Orphan Europe [<http://www.orphan-europe.com/Data/ModuleGestionDeContenu/03-Diseases/Hyperammonaemia/16.asp>] accessed December 3, 2009

Figure 5: Carglumic acid is designed to serve as the required cofactor to activate the enzyme carbamyl phosphate synthetase (CPS)

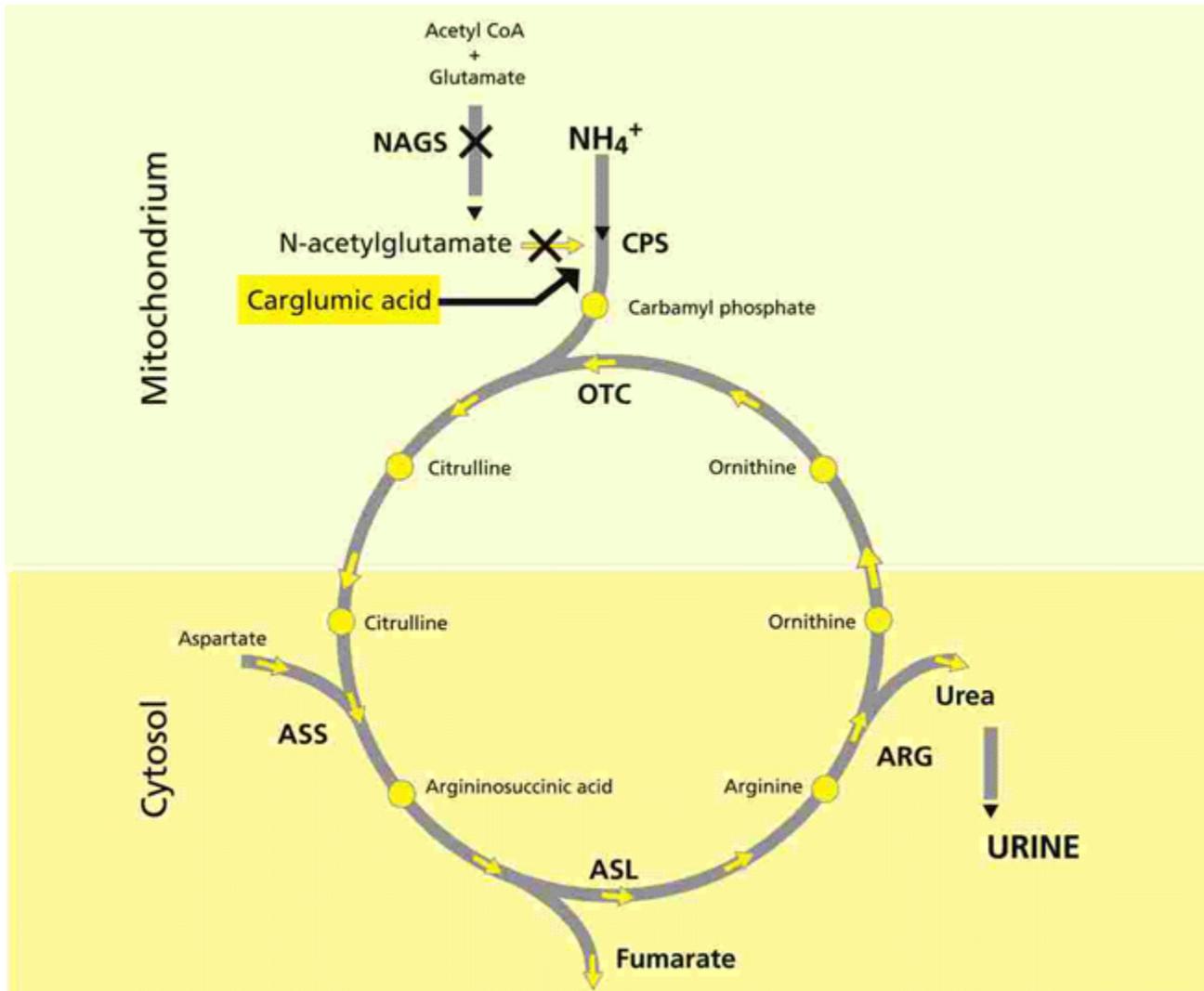


Figure adopted from Orphan Europe [<http://www.orphan-europe.com/Data/ModuleGestionDeContenu/03-Diseases/Hyperammonaemia/16.asp>] accessed December 3, 2009

4.4.2 Pharmacodynamics

No pharmacodynamic studies were conducted.

4.4.3 Pharmacokinetics

Carbaglumic Acid

- Mean $T_{max} \approx 1.5 - 4$ hrs after oral dosing
- Mean $T_{1/2} \approx 5.6$ hrs
- Total clearance ≈ 350 L/hr

- Apparent volume of distribution: 2600-3000L
- Plasma elimination: biphasic (0-12 hrs, 12-72 hrs)
- Fecal elimination: up to 72% excreted unchanged
- Renal elimination: 5 to 10% of dose excreted unchanged in the urine
- Metabolism: not by phase 1 or 2 enzymes in the liver but the carbon backbone maybe recycled into other biomaterials (i.e. amino acids)
- Might undergo enterohepatic re-circulation; intestinal transporters for carglumic acid have not been identified

For additional information, see Dr. Estes' clinical pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies

Table 5: Summary of 2 Studies which evaluate treatment of NAGS Deficiency with carglumic acid

Study ID Phase	Title	Objectives	Endpoints	N	Treatment Dose duration
IND 68-185 Phase 2	N-carbamylglutamate (Carbaglu) in the treatment of hyperammonemia	Determine short term efficacy and safety of carglumic acid for the treatment of hyperammonemia in patients with NAGS deficiency, carbamyl phosphate synthetase deficiency, propionic acidemia, and methylmalonic acidemia	Primary: urea, ammonia, and glutamine levels pre and post carglumic acid exposure Secondary: CBC, liver function tests, plasma amino acids, creatinine	7*	100 mg/kg/day if wt < 25 kg OR 2.2 g/m ² /d if wt ≥ 25 kg 3 days
NDA 22-562 Retrospective Case Series	Carbaglu Retrospective Data Review in NAGS Deficiency Patients	Review the clinical and biological response of NAGS deficient patients to carglumic acid within the first 7 days of treatment (short term) and long term	Ammonia, Glutamine and Citrulline levels Growth, neurological and psychomotor developmental outcomes	23	higher initial dose with lower maintenance dose variable dosing and duration of treatment

*Reflects the 7 patients that enrolled and completed the trial. The trial is currently on-going.
 Reviewer's table constructed from sponsor's module 2, 2.5 clinical overview and 2.7 clinical summary

5.2 Review Strategy

The review was conducted utilizing the following information sources:

- Electronic and paper submission of NDA 22-562
- Data from ongoing study IND 68,185 by Mendel Tuchman, MD
- Interactions with the applicant via e-mail for clarification and additional data
- Original NDA 20-645 Ammonul (sodium phenylacetate and sodium benzoate) injection clinical review dated February 10, 2005
- Current approved label for Buphenyl (sodium phenylbutyrate) tablets and powder
- Current approved label for Ammonul (sodium phenylacetate and sodium benzoate) injection
- Independent literature review
- Proposed labeling for carglumic acid
- Submitted electronic datasets
- Consultative meetings regarding data findings and clinical issues

The Applicant submitted a retrospective case series consisting of 23 patients with NAGS deficiency summarizing their clinical course during treatment with carglumic acid. The Applicant also obtained a right of reference to the ongoing study under IND 68,185. The Applicant did not provide any data from prospective, controlled trials to support the efficacy and safety of carglumic acid, and stated that prospective trials were not feasible due to the rarity of NAGS deficiency. Study IND 68,185 is an open-label, uncontrolled clinical trial evaluating the effect of carglumic acid on ureagenesis.

The most substantive data on the effect of carglumic acid in the treatment of hyperammonemia due to NAGS deficiency was provided from the retrospective clinical description of 23 patients with NAGS deficiency from 8 European countries. The Applicant translated and organized the information from the patients' medical records into individual patient narratives, subject profiles and datasets to evaluate the exposure of carglumic acid and its effect on various parameters such as plasma ammonia, glutamine, and citrulline levels, and overall growth and neurologic outcomes. Data from study IND 68,185 were considered supportive and were evaluated separately. This study included data from only 3 patients with NAGS deficiency.

There was no formal statistical analysis of efficacy; however, descriptive statistics were provided. Since plasma ammonia levels have been used historically as efficacy endpoints in applications for products that treat hyperammonemia due to urea cycle disorders, the Reviewer used this approach to assess the efficacy and safety of carglumic acid in hyperammonemia due to NAGS deficiency.

Safety data from the same two sources were also reviewed. Because the majority of patients in the retrospective case series were exposed to carglumic acid for at least 1 year, the safety review focused on this case series to identify potential safety signals.

The safety review from study IND 68,185 was not expected to be highly informative due to the small sample size and short duration (i.e., 3 days) of carglumic acid exposure.

5.3 Discussion of Individual Studies

A. Study IND 68-165

Title: "N-carbamylglutamate (Carbaglu) in the treatment of hyperammonemia"

The primary objective of this trial is to determine whether a 3 day treatment with Carbaglu improves or restores ureagenesis in patients with NAGS deficiency, CPS 1 deficiency, propionic acidemia (PA), and methylmalonic acidemia (MMA), and the secondary objective is to evaluate the safety of short-term treatment with Carbaglu in patients with the above mentioned enzymatic deficiencies. The trial began in January 2004 and is currently on-going. The 3 investigators involved in the trial are as follows: Mendel Tuchman, MD (Children's National Medical Center, Washington D.C), Marc Yudkoff, MD (Children's Hospital of Philadelphia), and Nicholas Mew, MD (Children's National Medical Center, Washington D.C).

Study Design (IND 68,185)

This is a two-center, open-label, Phase 2 trial of 3 days duration to assess the efficacy and safety of oral formulation of N-carbamylglutamate (carglumic acid) in the improvement or restoration of ureagenesis capacity in patients with NAGS deficiency, CPS 1 deficiency, Propionic academia (PA), and Methylmalonic academia (MMA). The trial includes a control group in addition to the aforementioned patients with the 4 disorders. The control group consists of 14 healthy adult volunteers who will undergo the identical procedures as the 4 study groups (patients with the 4 disorders). The study is not yet completed, and interim data were included in the application for review. The study is anticipated to take 3 years to complete, and it aims to enroll approximately 70 patients (approximately 14 in control and 56 in study group).

Medical officer comments

In the interim study reports submitted with the application, no information about the control group except inclusion and exclusion criteria were provided.

Study Endpoints

Primary (Efficacy)

¹³C/¹⁵N incorporation into plasma:

- Urea μmol/L
- Ammonia μmol/L
- Alanine

Secondary (Safety)

- CBC
- Serum BUN, creatinine

- Plasma amino acids

Control Group Inclusion and Exclusion Criteria

The inclusion criteria for the control group included the following:

- Patients \leq 50 years
- Patients generally healthy without chronic diseases (e.g. diabetes, heart disease, liver or kidney disease, or autoimmune disease)
- Patients willing to complete both phases of the trial

The exclusion criteria for the control group included the following:

- Patients should not be acutely ill on the day of the study
- Pregnant females (females must be menstruating, have a negative pregnancy test within a week of the study, or have circumstances that preclude pregnancy such as menopause)

Study Group Inclusion and Exclusion Criteria

The inclusion criteria for the study group included the following criteria:

- Patients 1 day to 70 years of age
- Female patients with hysterectomy, who are menopausal, or who are having menstruation at the time of beginning the study (documentation of a negative pregnancy test is required for females 12 years or older, unless conditions exist that preclude pregnancy)
- Patients should be diagnosed with one of the following four inborn errors of metabolism:
 - N-acetyl-glutamate synthetase (NAGS) deficiency (molecular diagnosis required)
 - Carbamyl phosphate synthetase 1 (CPS or CPS 1) deficiency (low enzyme activity in the liver with normal or greater activity of ornithine transcarbamylase (OTC), or molecular confirmation)
 - Propionic academia (PA); urine organic acid analysis and confirmation of absence of responsiveness to biotin and vitamin B₁₂
 - Methylmalonic academia (MMA)

The exclusion criteria for the study group consisted of the following:

- No acute illness on the part of the patient on the day of the study
- Patients who required a peripherally inserted catheter (PICC) line for blood draws may require moderate sedation. Patients who fail sedation would be excluded from the study.
- Patients with hyperammonemia caused by other urea cycle disorders:
 - Other urea cycle disorders
 - Lysinuric protein intolerance
 - Mitochondrial disorders
 - Congenital lactic acidemia

- Fatty acid oxidation defects
- Primary liver disease

Medical officer comments

During this study, all patients were clinically stable and none were acutely ill upon study entry.

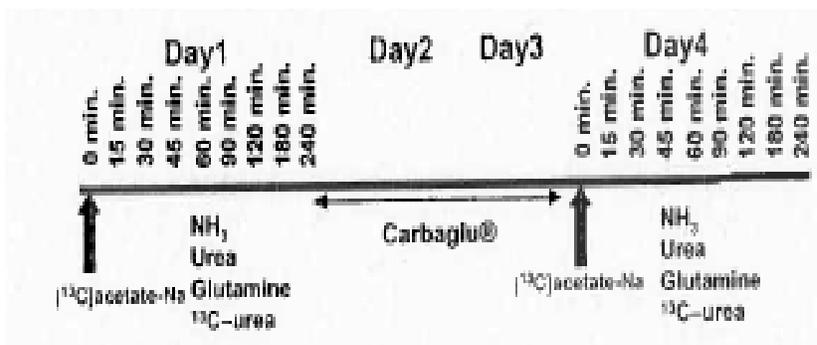
Study Procedures and Timelines

All patients were fasted eight hours prior to initiation of N-carbamylglutamate treatment. After baseline laboratory samples were obtained, patients ingested a tracer. After administration of the tracer, laboratory samples were obtained at varying intervals (i.e. 15 min, 30 min, 1 hr, and 2 hr). Patients were then given the first dose of N-carbamylglutamate at the study site. The tracer, ¹⁵NH₄Cl was used in patients 1 and 2; whereas, the tracer [1-¹³C] sodium acetate was used in patients 3-7.

As demonstrated in Figure 6 below, patients had laboratory assessments twice during the three day study period:

1. before the first administration of carglumic acid
2. 72 hours following the administration of oral or gastrostomy administration of carglumic acid at a dose of 100 mg/kg/day for patients weighing < 25 kg, or 2.2 g/m²/d for patients weighing ≥ 25 kg

Figure 6: Study Schedule



Best Possible Copy

Applicant's figure 8 from Appendix 2 protocol Tuchman, Mendel, page 12

During the course of the study, plasma was obtained and frozen to later analyze for ammonia, amino acids, total urea, [¹⁵N] urea, and [¹³C] urea. The ammonia, amino acids, and total urea were analyzed at Children's National Medical Center in Washington D.C. The [¹⁵N] urea was analyzed at Children's Hospital of Philadelphia at Dr. Marc Yudkoff's laboratory using gas chromatography-mass spectrometry. Patients who were able to cooperate, provided breath samples collected in tubes that were analyzed for ¹³CO₂. The breath ¹³CO₂ and [¹³C] urea samples were analyzed in Dr. Yudkoff's laboratory using isotope ratio mass spectrometry.

The following provides more information regarding study procedures:

- Patients may not have anything to eat or drink after midnight before the study except water.
- All medications will be continued to avoid a compromise of the current treatment.
- The morning dose of phenylbutyrate and/or phenylacetate and/or benzoate, and/or L-citrulline, and/or L-arginine if applicable for NAGS and CPS deficient patients will be taken as prescribed throughout the study.
- Patients with methylmalonic academia or propionic acidemia will continue to take any medication (e.g. sodium bicarbonate or sodium citrate) that in the opinion of the patients' physician could not reasonably be deferred until the stable isotope procedure is concluded. All patients would be studied under the same clinical conditions both before and after taking N-carbamylglutamate.
- An intravenous catheter for blood sampling will be inserted in the hand or arm. For a small number of patients with difficult vascular access, a PICC line will be inserted by an interventional radiologist or anesthesiologist and will be maintained for the duration of the three day study.
- Total blood volume drawn will not exceed 3 cc/kg per patient.
- Blood specimens: 5 ml in a green top (sodium heparin), placed on ice, centrifuged, and the plasma removed. The samples will be frozen and analyzed for ammonia, urea, glutamine, and a complete blood count.
- After obtaining the baseline samples of blood, the patient will receive 30 ml of water that contains [1-¹³C]sodium-acetate. This will be followed with an additional 30 ml of water to ensure complete administration of the isotope
- Blood samples will be subsequently obtained at 15, 30, 45, 60, 90, 120, 180 and 240 minutes. Plasma will be used for the determination of ammonia, total urea, glutamine, and for [¹³C]urea. An aliquot of the first blood sample will be analyzed to measure the carglumic acid level.
- Breath samples will be taken in breath tubes at each time point for ¹³CO₂ analysis. The study will be concluded between four and five hours.

Compliance with Drug Administration

The following mechanisms were in place to ensure compliance:

- The first and last dose will be given by the General Clinical Research Center (GCRC) staff.
- In each of the two days in which the patient is not present at the GCRC, a random urine sample will be analyzed for the presence of N-acetyl-L-glutamate (the unmetabolized portion of N-carbamylglutamate).
- A blood aliquot from the post-treatment sample will be analyzed for the presence of NCLG.
- A pill count will be performed at the second visit.
- Patients will undergo an explanation of the importance of taking all of the N-carbamylglutamate during the three day study.

- Each participant must have at least one parent/companion with him/her during the entire study period who will help promote and ensure compliance.
- The parents/companions will actively participate in the study, including keeping a diary that logs when the patient takes a dose and whether there were any aberrations such as incomplete dose, early or late timing of the dose. Dosing information will be used as a covariate to control for drug compliance and help complete accurate analyses of study outcomes.

Demographics and Baseline Characteristics

The three day trial, IND 68,185 has, thus far, enrolled 7 patients with the following disorders:

- Two patients with NAGS deficiency with compound heterozygote mutations
- One patient with a NAGS deficiency with a single heterozygote mutation
- Four patients with propionic acidemia; a condition that may lead to NAGS deficiency via accumulation of the metabolite propionyl-CoA which in theory can suppress NAGS activity

Efficacy Results

The results of the 7 patients described above will be discussed individually. A clinical history for each patient and their trial results on a case by case basis will be presented.

The differences in labeled urea concentration between the first 2 patients (1MT and 2MT) and patients 3MT to 7MT were due to the use of a tracer containing ^{15}N , while the other patients 3MT to 7MT used a ^{13}C tracer. Dr. Tuchman identified some shortcomings with the $^{15}\text{NH}_4\text{Cl}$ tracer, and therefore, chose to use the ^{13}C tracer for the following reasons:

- $^{15}\text{NH}_4\text{Cl}$ tracer required administering small amounts of urea to patients with an already compromised urea cycle
- The $^{15}\text{NH}_4\text{Cl}$ tracer in an individual with an expanded ammonia pool might dilute the tracer, thus confounding the results and making the comparison with control results difficult to interpret
- The nitrogen tracer requires the use of gas chromatography-mass spectrometry, which was found to be a less sensitive measure than isotope-ratio mass spectrometry for the detection of isotopic abundance

Patient 1MT Case History and Results

Clinical Presentation (Patient 1MT)

Patient 1 developed recurrent vomiting, irritability, and lethargy at nine years of age, with an ammonia level elevated at 256 $\mu\text{mol/L}$ (normal < 35 $\mu\text{mol/L}$). Plasma glutamine and alanine were also elevated; however, plasma citrulline, urinary orotic acid and liver transaminases were normal. She received an initial diagnosis of “unspecified urea cycle disorder”.

Treatment History and Diagnosis (Patient 1MT)

Patient 1 received treatment during frequent hospitalizations for acute decompensations associated with hyperammonemia. Treatment included a protein restricted diet, sodium benzoate, and L-citrulline. She continued to have symptoms with numerous hospital admissions for hyperammonemia and neuro-psychiatric signs, including hyperactivity, headaches, irritability, and hallucinations. At age 10, she had a liver biopsy showing CPS activity of 2.3 $\mu\text{mol}/\text{min}/\text{g}$ liver (control 4.1) and ornithine transcarbamylase (OTC) activity at 31.5 $\mu\text{mol}/\text{min}/\text{g}$ liver (control 78.6), ruling out a primary deficiency of either enzyme. Molecular genetic analysis revealed patient 1 to be a compound heterozygous for two mutations in the NAGS gene (R509Q and IVS4 nt-1 G>C).

She developed a debilitating spastic diplegia with some paralysis of both lower extremities. According to the physicians at Children’s National Medical Center, her spastic diplegia was attributed to treatment with large doses of citrulline. Citrulline, which metabolizes to arginine might have caused arginine toxicity, manifesting as spasticity. Her citrulline was discontinued, and both citrulline and arginine levels normalized.

During participation in the trial, this patient received 1340 mg of [15N]ammonium chloride dissolved in water and ingested over less than a minute. Blood sampling was performed 15, 30, 60, 90, and 120 minutes, after which the patient received oral administration of carglumic acid at a dose of 2.2 g/m²/d divided into four doses. The patient took carglumic acid for 72 hours after which the same blood tests were repeated.

Table 6 is a summary of ammonia, urea, glutamine and citrulline levels before and after a three day treatment with carglumic acid. Figure 7 demonstrates the serum concentrations of ¹⁵N-Urea over time.

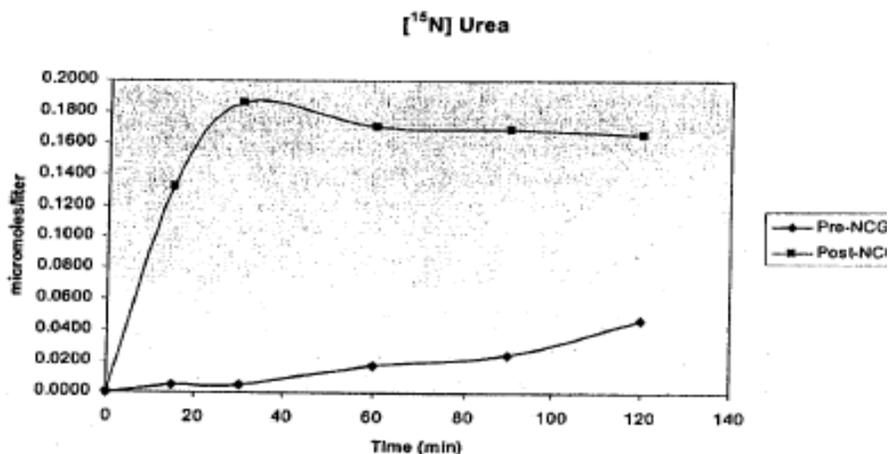
Table 6: Laboratory values for Patient 1MT before and after treatment with carglumic acid

Laboratory Value	Pre-NCG*	Post-NCG*	Reference Range	N blood samples
	Mean (range)	Mean (range)		
Ammonia ($\mu\text{mol}/\text{L}$)	47 (20-70)	10.0 (8-11)	17-60	3 pre; 3 post 6 total
Urea (mmol/L)	1.2 (1.1-1.4)	2.7 (2.5-2.9)	1.2-7	6 pre; 6 post 12 total
Glutamine ($\mu\text{mol}/\text{L}$)	485 (399-568)	334.7 (307-394)	428-747	4 pre; 6 post 10 total
Citrulline ($\mu\text{mol}/\text{L}$)	29 (21-40)	21 (12-29)	16-51	4 pre; 6 post 10 total

*NCG = carglumic acid

Reviewer’s table modified from sponsor’s table 1, module 5 Report 13 Carbaglu in the US, page 11

Figure 7: Patient 1MT's Blood Concentration of ¹⁵N-Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 11

Following completion of the trial, Patient 1MT and her affected sister began treatment with N-carbamylglutamate provided by Sigma-Aldrich under single patient INDs. Both received N-carbamylglutamate at a dose of 2.2 g/m²/day. The physician who follows Patient 1MT and her sister has reported to Dr. Tuchman that both sisters have normalized ammonia with no adverse effects.

Patient 2MT Case History and Results

Clinical Presentation (Patient 2MT)

Patient 2MT was the mother of Patient 1MT, and was noted to have a heterozygous mutation of NAGS. She was reported to be an otherwise healthy 51 year old woman who suffered from multiple episodes of headache and nausea with ammonia values > 100 μmol/L. The ammonia level was obtained following the diagnosis of hyperammonemia in her daughter.

Treatment History and Diagnosis (Patient 2MT)

She was found to have a heterozygous mutation (IVS4-1G>C). During participation in the study, Patient 2MT received 1400 mg of [¹⁵N]ammonium chloride dissolved in water and ingested over less than a minute. Blood sampling was performed 15, 30, 60, 90, and 120 minutes, after which the patient received oral administration of Carbaglu at a dose of 2.2 g/m²/d divided into four doses. The patient took carglumic acid for 72 hours after which the same blood tests were repeated.

Medical officer comments

The patient did not receive any other treatments for NAGS deficiency or hyperammonemia prior to participation in the three day carglumic acid clinical trial.

Table 7 below summarizes ammonia, urea, glutamine and citrulline levels before and after three day treatment with carglumic acid. Figure 8 demonstrates the serum concentrations of ¹⁵N-Urea over time.

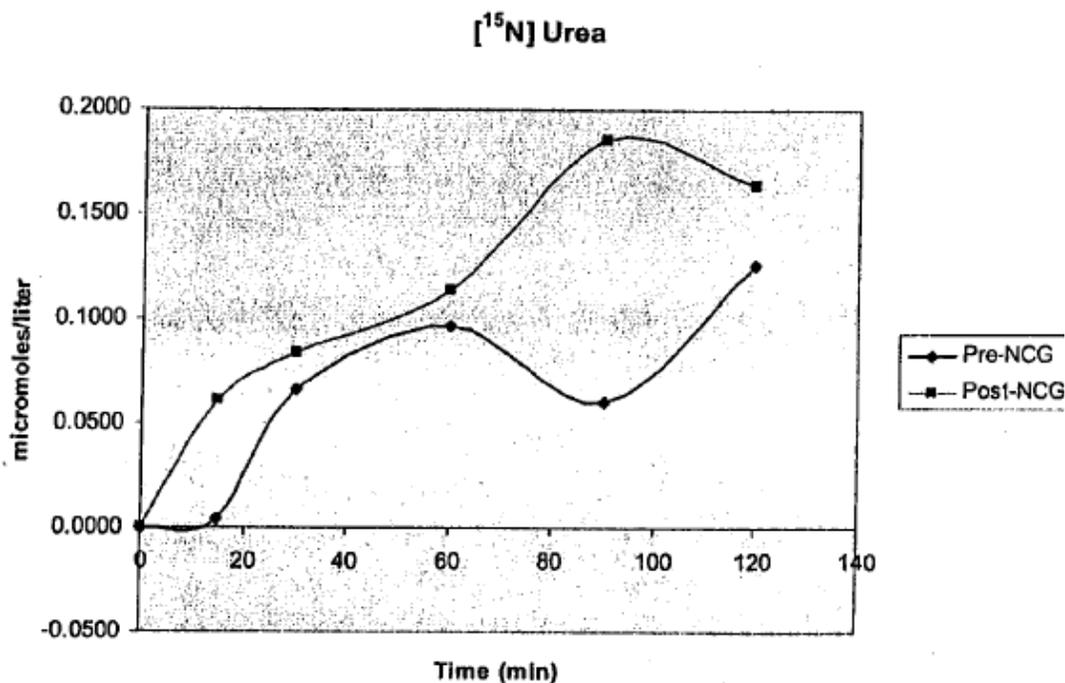
Table 7: Laboratory values for Patient 2MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG	Post-NCG	Reference Range	N blood samples
	Mean (range)	Mean (range)		
Ammonia (µmol/L)	12.3 (7-15)	16.3 (11-23)	17-60	3 pre; 4 post 7 total
Urea (mmol/L)	3.6 (3.6-3.6)	3.6 (3.2-3.6)	1.2-7	6 pre; 6 post 12 total
Glutamine (µmol/L)	471.5 (429-525)	452.7 (429-483)	428-747	6 pre; 6 post 12 total
Citrulline (µmol/L)	24 (20-26)	14 (10-22)	16-51	6 pre; 6 post 12 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 12

Figure 8: Patient 2MT's Blood Concentration of ¹⁵N-Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 12

Patient 3MT Case History and Results

Clinical Presentation (Patient 3MT)

Patient 3MT was a 58 year old woman who enjoyed good health until age 40 when she developed frequent migraine headaches, nausea, vomiting, lethargy, and intermittent staring spells, and ataxia followed by coma. She was noted to be a compound heterozygote for NAGS. At the age of 45, she developed a hyperammonemic coma with a peak ammonia level of 500 μM . She received an initial tentative diagnosis of partial ornithine transcarbamylase deficiency.

Treatment History and Diagnosis (Patient 3MT)

Her initial treatment included lactulose and dietary modification which consisted of a low protein diet. When she was started on L-citrulline and sodium phenylbutyrate, lactulose was discontinued but she remained protein-restricted. Her dose of citrulline was 1.5 g with meals, 0.5 g with evening snack (2.6 g/m²/day). Her total daily dose of Buphenyl was 10.2 g/m²/day. Ondansetron was also added to treat chronic nausea.

Despite taking citrulline and sodium phenylbutyrate, her hyperammonemia persisted. For 17 years, she experienced multiple attacks with associated elevated ammonia levels requiring hospitalization. She continued to have headaches, nausea, and episodic confusion. She developed type 2 diabetes following a significant weight gain on a combination of high carbohydrate and low protein diet (2300-2500 Kcal/d and 38 g of protein/d) and required insulin therapy.

Her ammonia level at the time of study entry was 105 $\mu\text{mol/L}$. She was diagnosed following testing in Dr. Mendel Tuchman's laboratory and found to be a compound heterozygote with two mutations on the NAGS gene: V350I and L442V. Nine consecutive ammonia levels prior to initiation of Carbaglu were elevated (79-159 $\mu\text{mol/L}$). Plasma ammonia levels decreased post 72 hours of treatment with Carbaglu to near normal range of 29 to 69 $\mu\text{mol/L}$. The [¹³C] tracer incorporation into urea was very low prior to treatment and was restored to normal following 3 days of Carbaglu therapy, consistent with normalization of ureagenesis in this patient. After participating in the study with three days exposure to Carbaglu, her headaches, nausea, and confusion all resolved.

Table 8 below summarizes ammonia, urea, glutamine and citrulline levels before and after three day treatment with carglumic acid. Figure 9 demonstrates the serum concentrations of ¹³C-Urea over time.

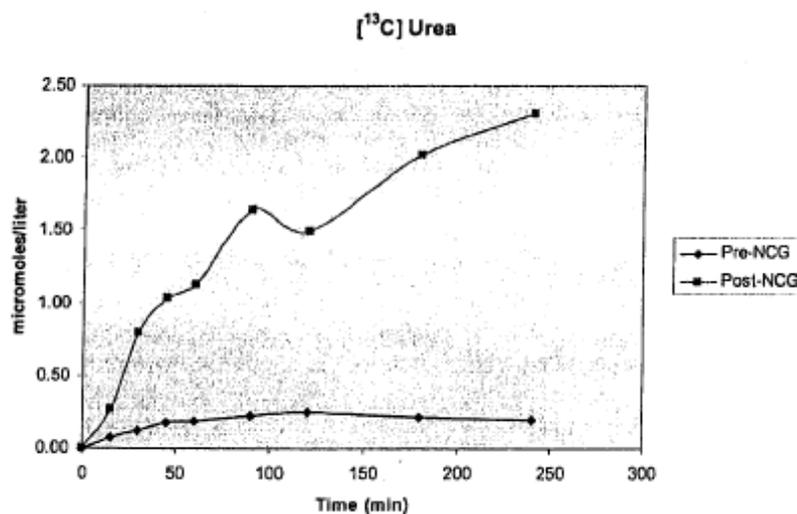
Table 8: Laboratory values for Patient 3MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG Mean (range)	Post-NCG Mean (range)	Reference Range	N blood samples
Ammonia ($\mu\text{mol/L}$)	105.2 (79-159)	46.3 (29-69)	17-60	9 pre; 9 post 18 total
Urea (mmol/L)	1.7 (1.4-1.8)	6.0 (5.4-6.8)	1.2-7	9 pre; 9 post 18 total
Glutamine ($\mu\text{mol/L}$)	597.3 (430-670)	405.4 (379-445)	428-747	9 pre; 9 post 18 total
Citrulline ($\mu\text{mol/L}$)	94.4 (37-151)	91.5 (32-174)	16-51	9 pre; 9 post 18 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 13

Figure 9: Patient 3MT's Blood Concentration of ^{13}C -Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 13

Following her participation in the trial, this patient continued to receive treatment with N-carbamylglutamate provided by Sigma-Aldrich under a single patient IND (70,942). Per Dr. Tuchman's report dated February 27, 2009, this patient had a two year history of daily treatment with N-carbamylglutamate at a dose of 2.2 g/m²/day divided tid (approximately 100 mg/kg/day). Her treating physician reported no adverse effects and resolution of both her hyperammonemia symptoms and her diabetes. She has transitioned over to a normal diet and sodium phenylbutyrate and citrulline were

discontinued. Ondansetron, used to treat nausea secondary to hyperammonemia was also discontinued.

Patient 4MT Case History and Results

Clinical Presentation (Patient 4MT)

Patient 4MT was a six year-old boy who was born at term and developed severe hyperammonemia at day of life (DOL) 4. He had a peak plasma ammonia level of 1200 μM with metabolic acidosis requiring hemodialysis.

Treatment History and Diagnosis (Patient 4MT)

Urine organic acid analysis revealed the diagnosis of propionic acidemia. Therapeutic interventions included special formula, L-carnitine, biotin and sodium phenylbutyrate. His ammonia normalized by DOL 8. He was continued on the aforementioned medications except for sodium phenylbutyrate, which was discontinued after 7 months. Following discontinuation of sodium phenylbutyrate, his ammonia level ranged from normal to twice normal. During the first three years of his life, he experienced acute exacerbations of propionic acidemia that resulted in multiple hospitalizations, with one exception that involved an episode of acute pancreatitis. During his decompensation episodes, his ammonia would range from three to six times the upper limit of normal. His developmental delay was significant. He was ambulatory but was non-verbal. He was fed through a gastrostomy tube. Genetic mutation analysis revealed a homozygous frame-shift mutation G216fs mutation in the alpha subunit of the Propionyl-CoA Carboxylase gene (PCCA).

Medications at the time of study entry include the following:

- Carnitine 10% solution 70 ml
- Coenzyme Q10 (200 mg soft gel)
- Aquasol E
- DHA 10 mg
- Biotin 10 mg
- Kenalog (prn stoma site)
- Polyvisol 1 ml
- Zofran 2.5 ml
- Special formula Contents
 - XMTVI Maximum 81.6 g (devoid of methionine, threonine, valine, and isoleucine)
 - Essential amino acid mix, 5.3 g
 - 300 ml milk
 - Canola or walnut oil to 35 ml
 - Valine 3 ml
 - Isoleucine 1 ml
 - Water, to a total volume of 1700 ml

On the first and the fourth day of the study, this patient experienced rhinorrhea, cough and congestion. It was later discovered that he had strep throat.

Table 9 summarizes ammonia, urea, glutamine, citrulline, glycine and alanine levels before and after three day treatment with carglumic acid. Figure 10 demonstrates the serum concentrations of ¹³C-Urea over time.

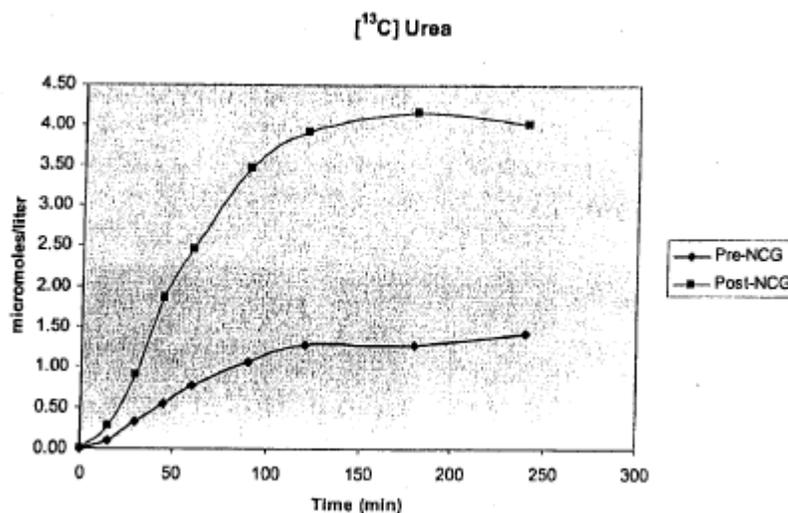
Table 9: Laboratory values for Patient 4 MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG	Post-NCG	Reference Range	N blood samples
	Mean (range)	Mean (range)		
Ammonia (µmol/L)	39.7 (32-47)	34.4 (24-40)	14-65	9 pre; 9 post 18 total
Urea (mmol/L)	4.7 (3.9-5.4)	4.3 (4.3-4.6)	1.2-7	9 pre; 9 post 18 total
Glutamine (µmol/L)	620.9 (548-651)	363.4 (319-398)	405-923	9 pre; 9 post 18 total
Citrulline (µmol/L)	29.4 (25-31)	20.3 (18-23)	9-52	9 pre; 9 post 18 total
Glycine (µmol/L)	1312.6 (1213-1373)	833.4 (782-883)	138-349	9 pre; 9 post 18 total
Alanine (µmol/L)	521.6 (414-560)	306.6 (256-366)	157-481	9 pre; 9 post 18 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 14

Figure 10: Patient 4MT's Blood Concentration of ¹³C-Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 14

Patient 5MT Case History and Results

Clinical Presentation (Patient 5MT)

Patient 5MT was an 11 year old girl with propionic acidemia. She was born at term following an uncomplicated pregnancy. She presented at DOL 2 with hyperammonemia and metabolic acidosis.

Treatment History and Diagnosis (Patient 5MT)

Physicians presumed a diagnosis of organic acidemia, and laboratory tests later confirmed a diagnosis of propionic acidemia. She developed seizures at two weeks of life and required seizure medication (Phenobarbital and lamotrigine) until the age of one year. She was exposed to various medications and dietary modifications. She required multiple hospitalizations for acute illnesses such as pneumonia that led to metabolic decompensation. At the time of clinical trial entry, she had a mild developmental delay and was fed by a gastrostomy tube. At her most recent clinic visit, prior to clinical trial entry she was on the following medications:

- Ampogel 5 ml po q d
- Maalox 200-200 (2 mg/5 ml) q d
- Pyridoxine 12.5 mg po q d
- Zyrtec syrup 10 mg po q hs
- **Sodium benzoate 14 mg po qid (to chelate ammonia)**
- Metronidazole 250 mg po q d X 7 days q monthly (to clear the gut of propionate-generating bacteria)
- Thiamine HCl 50 mg po q d except Saturday and Sunday
- Coenzyme q10 150 mg po q d
- Carnitor 10% liquid, 1050 mg po qid
- Biotin 10 mg po q d

Table 10 summarizes ammonia, urea, glutamine, citrulline, glycine, and alanine levels before and after three day treatment with carglumic acid. Figure 11 demonstrates the serum concentrations of ¹³C-Urea over time.

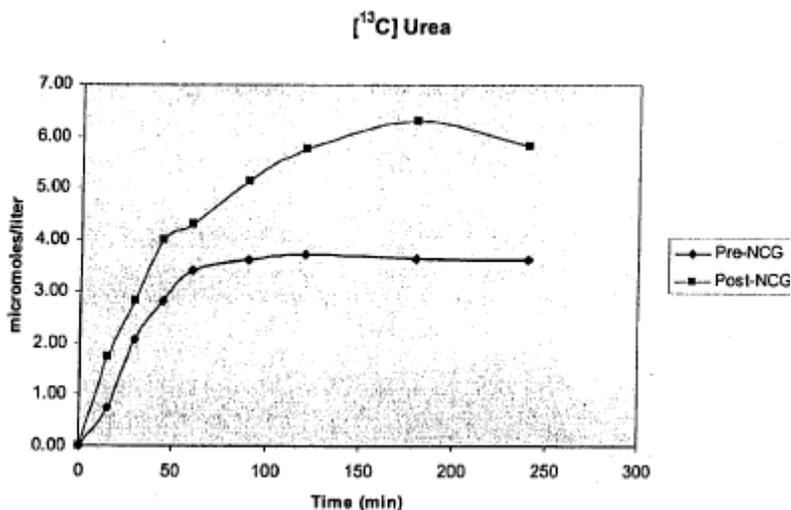
Table 10: Laboratory values for Patient 5MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG	Post-NCG	Reference Range	N blood samples
	Mean (range)	Mean (range)		
Ammonia (µmol/L)	58.0 (50-68)	48.3 (37-52)	14-65	9 pre; 9 post 18 total
Urea (mmol/L)	5.2 (4.6-5.7)	5.8 (5.4-6.1)	1.2-7	9 pre; 9 post 18 total
Glutamine (µmol/L)	573.1 (524-634)	339.0 (309-365)	405-923	9 pre; 9 post 18 total
Citrulline (µmol/L)	21.4 (17-24)	14.7 (13-16)	9-52	9 pre; 9 post 18 total
Glycine (µmol/L)	1032 (970-1108)	935.9 (877-969)	138-349	9 pre; 9 post 18 total
Alanine (µmol/L)	272.6 (231-300)	242.2 (201-299)	157-481	9 pre; 9 post 18 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 15

Figure 11: Patient 5MT's Blood Concentration of ¹³C-Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 15

Patient 6MT Case History and Results

Clinical Presentation (Patient 6MT)

Patient 6MT, an eight year old girl born at term via normal spontaneous vaginal delivery to a 22 year old G1 mother. She was discharged home on DOL 2 but presented to the emergency room DOL 3 with hypothermia, metabolic acidosis and a plasma ammonia level of 808 μM .

Treatment History and Diagnosis (Patient 6MT)

The patient received her diagnosis of propionic acidemia with the results from urine organic acids and plasma acylcarnitine. She was hemodialyzed and required ventilatory as well as vasopressor support. In the newborn period, she developed a dilated cardiomyopathy which resolved with treatment. Her treatment regimen included dietary modification, medical management with L-carnitine and biotin. Her ammonia levels chronically ranged from 55 to 122 μM . Acute exacerbations of her condition led to more than 30 hospitalizations or emergency room visits. She presented to this clinical trial with moderate developmental delay, little speech, and she was fed with a gastrostomy tube. Medications listed in her most recent clinic visit prior to clinical trial entry include:

- IV carnitine infusion 1 g once per week
- L-valine 1% solution, 77 ml/day added to the formula
- Carnitor 10% solution, 15 ml po q d
- Biotin 10 mg po q d
- Pantothenic acid 50 mg po qod
- L-Alanine powder 1 g po q d
- Polycitra 9 ml po bid
- Phenobarbital 6.5 ml po bid

Table 11 summarizes ammonia, urea, glutamine, glycine, and alanine levels before and after three day treatment with carglumic acid. Figure 12 demonstrates the serum concentrations of ^{13}C -Urea over time.

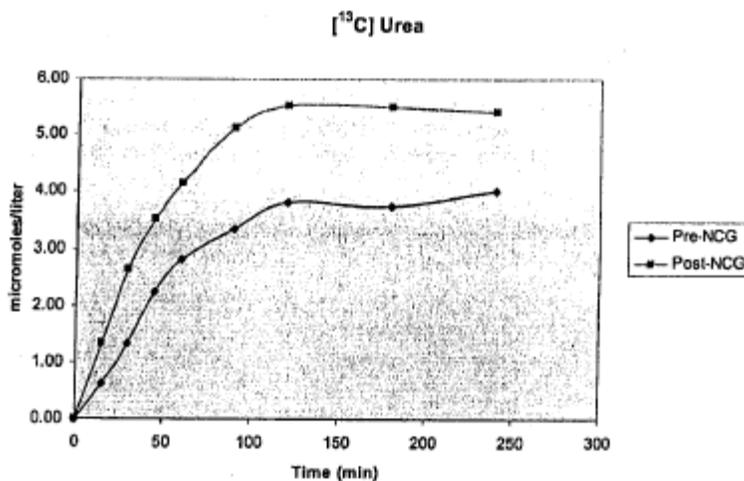
Table 11: Laboratory values for Patient 6MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG Mean (range)	Post-NCG Mean (range)	Reference Range	N blood samples
Ammonia ($\mu\text{mol/L}$)	61.4 (53-71)	61.9 (52-73)	14-65	9 pre; 9 post 18 total
Urea (mmol/L)	5.3 (4.6-6.1)	6.4 (5.7-7.1)	1.2-7	9 pre; 9 post 18 total
Glutamine ($\mu\text{mol/L}$)	534.2 (482-574)	307.9 (289-332)	405-923	9 pre; 9 post 18 total
Citrulline ($\mu\text{mol/L}$)	18.7 (17-22)	18.1 (16-20)	9-52	9 pre; 9 post 18 total
Glycine ($\mu\text{mol/L}$)	911.1 (853-955)	810.9 (773-840)	138-349	9 pre; 9 post 18 total
Alanine ($\mu\text{mol/L}$)	282.3 (236-331)	182.9 (174-193)	157-481	9 pre; 9 post 18 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 16

Figure 12: Patient 6MT's Blood Concentration of ^{13}C -Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 16

Patient 7MT Case History and Results

Clinical Presentation (Patient 7MT)

Patient 7MT was a five year old boy born at term via a spontaneous vaginal delivery. At the age of two weeks, he presented with vomiting and lethargy. He had a mild metabolic acidosis and a plasma ammonia level of 382 μ M.

Treatment History and Diagnosis (Patient 7MT)

Analyses of urine organic acids and plasma acylcarnitine led to the diagnosis of propionic acidemia. He was started on a special formula diet that included a high rate of IV glucose infusion along with intralipid and L-carnitine treatment. With this treatment intervention, his ammonia decreased to 68 μ M by 24-36 hours. He was admitted to the hospital 14 more times for decompensations associated with acute illnesses, five of which were for pancreatitis. He exhibited mild developmental delay, predominantly in the language area. He required feeding through a gastrostomy tube. Subsequent genetic testing revealed him to be heterozygous for a c.183+3 G>C mutation in the beta-subunit of Propionyl-CoA Carboxylase (PCCB). He also had two heterozygous sequence variants, both potentially pathogenic (c.734G>A and c.967-14 A>G). His medications listed by his physician prior to clinical trial entry included the following:

- Carnitine 15 ml (1500 mg) via g-tube (260 mg/kg/d)
- Sodium benzoate: 5 g/d with formula (216 mg/kg/d)
- Flagyl 100 mg bid via g-tube (9 mg/kg/d)
- Viokase 1/3 of a tablespoon (22,400 units of lipase) qid with feedings
- Prevacid 15 mg (1 tablet) via g-tube bid

Medical officer comments

There is a reported association between PA and pancreatitis although the exact etiology remains unclear.⁹ The episodes of pancreatitis were probably related to his underlying propionic acidemia.

Table 12 summarizes ammonia, urea, glutamine, citrulline, glycine, and alanine levels before and after three day treatment with carglumic acid. Figure 13 demonstrates the serum concentrations of ¹³C-Urea over time.

9 Bultron G, et al. Recurrent Acute Pancreatitis Associated with Propionic Acidemia. Journal of Pediatric Gastroenterology and Nutrition. 2008: 47: 370-371

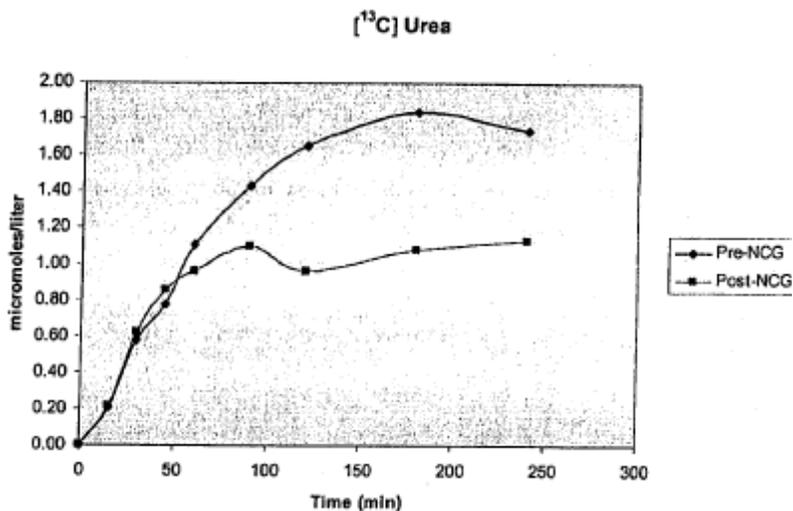
Table 12: Laboratory values for Patient 7MT before and after treatment with carglumic acid

Laboratory value	Pre-NCG	Post-NCG	Reference Range	N blood samples
	Mean (range)	Mean (range)		
Ammonia (μmol/L)	78.8 (63-95)	40.1 (36-46)	14-65	9 pre; 9 post 18 total
Urea (mmol/L)	2.9 (2.9-3.2)	3.5 (3.2-3.9)	1.2-7	9 pre; 9 post 18 total
Glutamine (μmol/L)	685.9 (650-731)	472.3 (373-519)	405-923	9 pre; 9 post 18 total
Citrulline (μmol/L)	23.2 (21-26)	20.6 (19-23)	9-52	9 pre; 9 post 18 total
Glycine (μmol/L)	594.9 (570-616)	691.0 (647-726)	138-349	9 pre; 9 post 18 total
Alanine (μmol/L)	528.7 (400-614)	510.1 (381-578)	157-481	9 pre; 9 post 18 total

NCG = carglumic acid

Reviewer's table modified from sponsor's table 2, module 5 Report 13 Carbaglu in the US, page 17

Figure 13: Patient 7MT's Blood Concentration of ¹³C-Urea over time



Sponsor's figure from module 5, Report 13 Carbaglu in the US, page 17

B. Individual patient narrative review from Applicant's retrospective case series

The Applicant provided individual patient narratives and subject profiles collected on 23 patients with NAGS deficiency, who received treatment with carglumic acid. The 23 patients were treated with carglumic acid at 14 sites that were either hospitals or outpatient clinics located in the Netherlands, Germany, France, United Kingdom, Sweden, Italy, Spain, and Austria over a period of approximately 21 years (1987 to 2008). The majority of patients were treated in France. Six patients were treated at the Hospital for Mothers and Children in Lyon, France, and 3 patients were treated in other cities (Paris, Colmar, and Grenoble) in France. Five patients were treated in Germany, four patients were treated in the United Kingdom, and one patient each was treated in Italy, Spain, Sweden, Austria, and the Netherlands.

Narratives for each patient will be reviewed below, and the data is obtained from the individual patient narratives, subject profiles, and modules 2 and 5 in paper format provided by the sponsor. Each narrative contains a brief description of birth history, first clinical presentation of hyperammonemia along with suspected or probable diagnosis and interventions used to decrease ammonia levels. For patients in whom data are available, liver biopsy and DNA results are presented. Concomitant medications, protein diet information and timing of initiation of carglumic acid are also described. Relevant and available information on growth, neurologic and psychomotor assessments are included. The 3 plasma biomarkers, ammonia, glutamine and citrulline are discussed separately and graphic presentation of plasma ammonia levels are provided for all patients except patient (b) (6), which was not made available by the sponsor. Additionally, the sponsor generated the graphic illustrations of the glutamine and citrulline levels based on the NIH normal reference range for plasma amino acids in children published in 2006. However, patients were treated at various facilities in different European countries with different methodologies for amino acid analyses, and each laboratory reference range was specific to that particular laboratory result. Therefore, the graphic representations of the glutamine and citrulline data submitted by the sponsor do not necessarily accurately represent true low or high glutamine and citrulline values.

Narrative for Patient 1

Patient 1 was born (b) (6). He presented at day of life (DOL) 3 with vomiting and failure to thrive. He was hospitalized at the age of three weeks with vomiting, hypotonia, inattentiveness, and hepatomegaly. He was re-hospitalized at one month of age and found to have an ammonia (NH₃) level of 512 µmol/L with a normal urine orotic acid level. The diagnosis at that time was an unspecified urea cycle disorder. He began treatment with intravenous (IV) sodium benzoate (1800 mg/d), arginine 800 mg/d, carnitine 300 mg/d, and a high caloric enteral feeding with absolute protein restriction (0.0 g/kg/d). His ammonia level decreased to 145 µmol/L on February 1, 1991 and continued to decrease to 40 µmol/L by February 25, 1991. After one month of

hospitalization, the patient was discharged on a treatment regimen that included sodium benzoate (800 mg/d) and a partially protein-restricted diet (2.2 g/k/d).

In March (b) (6), the patient was again hospitalized due to hyperammonemic episodes (160-207 µmol/L). His protein intake was decreased, and he underwent a liver biopsy that showed normal ornithine transcarbamylase (OTC) activity, and slightly low activity for carbamyl phosphate synthetase 1 (CPS 1 or CPS). Testing did not include evaluation for NAGS deficiency. The biopsy results shown below in Table 13 revealed low activity for CPS 1 and normal activity for OTC.

Table 13: Results of first liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	1.09	µmol/h/mg prot	1.34-2.34
(b) (6)	Liver biopsy	OTC	48.70	µmol/h/mg prot	25.9-45.1

Reviewer's table modified from Individual Patient Narrative, sponsor's table page 2

His sodium benzoate was discontinued without any deleterious effect, and he remained protein restricted at 1.6 g/kg/d. His ammonia levels fluctuated between 124 and 148 µmol/L. In June of 1991, he underwent a second liver biopsy to evaluate for NAGS deficiency. The second biopsy results illustrated below in Table 14 revealed poor arginine stimulated activity for NAGS.

Table 14: Results of second liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	29.30	nmol/min/mg prot	34-203
(b) (6)	Liver biopsy	NAGS + Arg	39.70	nmol/min/mg prot	144-320

Reviewer's table modified from Individual Patient Narrative, sponsor's table page 2

He was subsequently started on carglumic acid at a dose of 325 mg/kg/d (900 mg tid) on (b) (6). Twenty-four hours (b) (6) before beginning therapy with carglumic acid, his highest ammonia level was 234 µmol/L, and two days (b) (6) following initiation of treatment with carglumic acid, his lowest ammonia level recorded was 27 µmol/L. Despite the patient's good response to carglumic acid treatment, there were non-compliance issues. He continued a protein-restricted diet (1.5 g/kg/d).

Medical officer comments

The sponsor notes that "treatment was interrupted due to poor acceptance by the child", and the event of poor tolerance is described as "product acidity".

He was re-hospitalized in October (b) (6) with vomiting, asthenia, and hyperammonemia (274-500 µmol/L). Carglumic acid was re-initiated at a dose of 140 mg/kg/d (400 mg tid), and plasma ammonia levels decreased within 24 hours to 52 µmol/L and subsequently remained within normal limits. His dose was further decreased on (b) (6) to 22 mg/kg/d (100 mg bid). At his last follow-up visit in November

2007, his dose was 6 mg/kg/d (150 mg bid). He progressively increased his protein intake to normal levels.

Subsequent DNA testing performed in February 2005 confirmed the presence of two heterozygous NAGS mutations as shown in Table 15.

Table 15: Results of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
(b) (6)	Het NAGS def	c.278delC (110X)	exon 1	heterozygous
(b) (6)	Het NAGS def	c.499A>G (M167V)	exon 2	heterozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table page 2 and Subject Profile, page 1

Previous or Concomitant Therapy

In (b) (6), the patient's dose of sodium benzoate was reduced from 1800 mg/d IV to 800 mg/d po and later increased in (b) (6) to as high as 1200 mg/d po. Treatment with sodium benzoate was discontinued at the end of (b) (6).

When treatment with carglumic acid began, carnitine remained as a concomitant therapy until (b) (6) at a dose of 1000 mg/d po.

Growth and Development

Patient 1 experienced normal growth and development. He has normal intellectual development, completed college, and retains no significant neurologic impairment.

Patient 1's Plasma Ammonia Levels

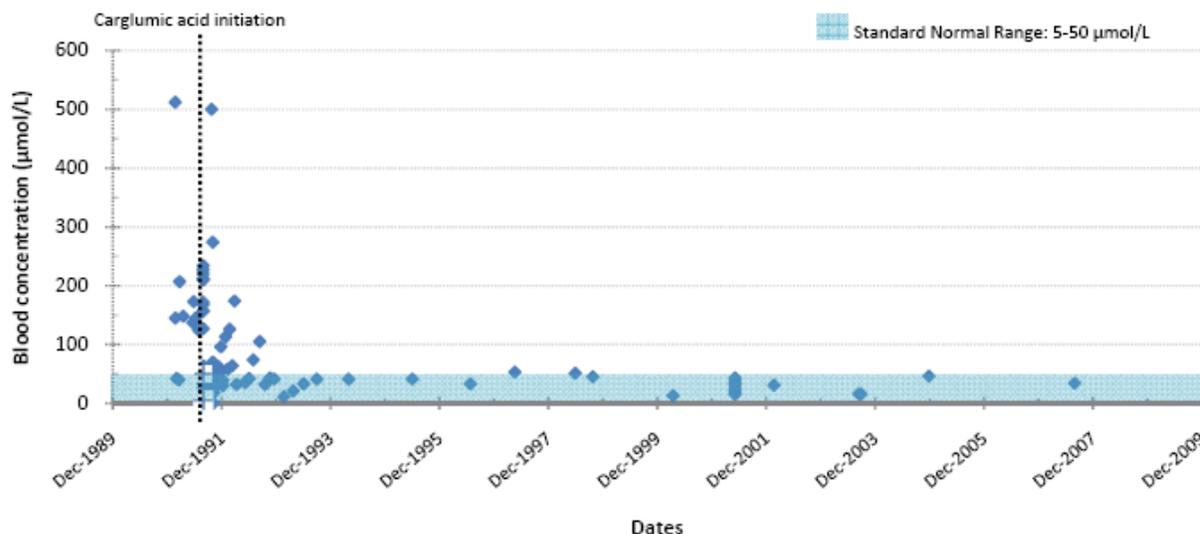
Patient 1's plasma ammonia level was 512 µmol/L before any therapy was initiated. Twenty-four hours post standard antihyperammonemic therapy was started, it decreased to 145 µmol/L. The ammonia levels decreased further to between 40 and 42 µmol/L with continuation of antihyperammonemic therapy with sodium benzoate, arginine, carnitine, and protein restriction.

From March to July 1991, ammonia levels were again above normal in the range of 207-234 µmol/L, before starting carglumic acid therapy August 7, 1991. Figure 14 below depicts his ammonia levels before and subsequent to treatment with carglumic acid. The following list includes additional information about his ammonia levels:

- Day 3 following initiation of carglumic acid ((b) (6)), the patient's ammonia ranged from 27-63 µmol/L over a 24 hour period
- Prior to re-initiation of carglumic acid ((b) (6)), ammonia levels were elevated between 274 and 500 µmol/L
- When carglumic acid was re-introduced ((b) (6)), the ammonia levels decreased to a range of 52-70 µmol/L.
- Throughout 1992, increases in ammonia levels one hour following meals were noted in the range of 105-174 µmol/L. At that time, the carglumic acid dose was 22 mg/kg/d.

- As the dose was lowered over time to as low as 6 mg/kg/d, ammonia levels remained within the normal range (16 to 34 $\mu\text{mol/L}$).

Figure 14: Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

Patient was on 6 mg/kg/day of carglumic acid therapy without any protein intake restriction and had maintained a normal ammonia level of 34 $\mu\text{mol/L}$ at the last available ammonia level recorded on August 4, 2007.

Patient 1's Plasma Glutamine Levels

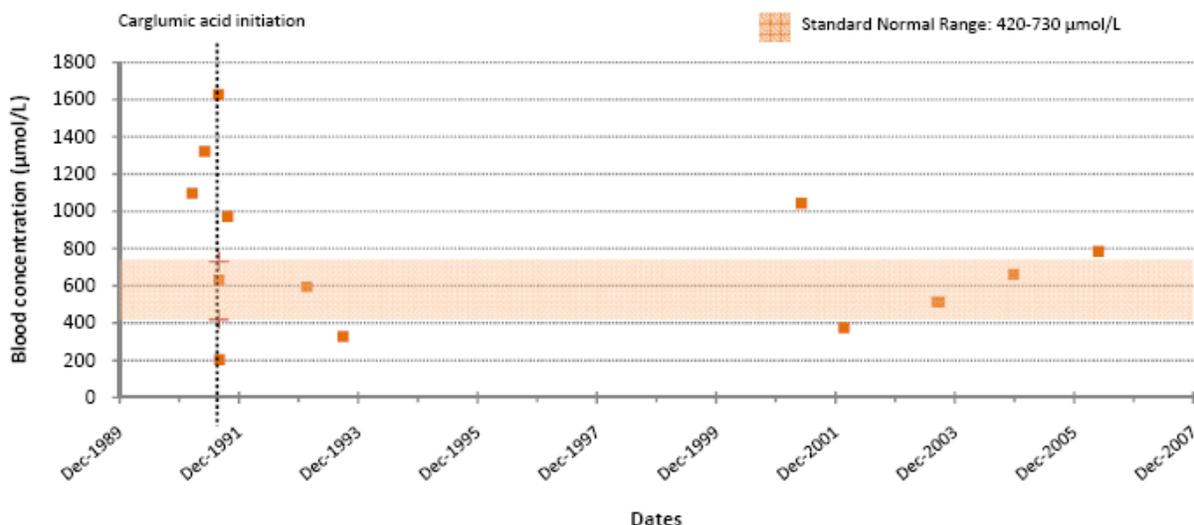
Patient 1's plasma glutamine level from February 25, 1991 to August 6, 1991 (before treatment with carglumic acid) ranged from 1097 to 1628 $\mu\text{mol/L}$ (normal range 400-685 $\mu\text{mol/L}$) despite treatment with standard therapy (sodium benzoate, arginine, carnitine, and protein restriction). Standard therapy was initiated on (b) (6). The notable glutamine level changes include the following:

- 3 days following treatment with carglumic acid (b) (6), the glutamine level was 631 $\mu\text{mol/L}$
- 6 days following treatment with carglumic acid (b) (6), the glutamine level was 204 $\mu\text{mol/L}$
- An interruption of therapy with carglumic acid led to an increase of glutamine level to 972 $\mu\text{mol/L}$ recorded on (b) (6)
- After the patient was re-started on carglumic acid therapy on (b) (6), his glutamine levels remained within normal range except during a control visit on (b) (6), when the glutamine level was elevated at 1043 $\mu\text{mol/L}$ (normal range 432-706 $\mu\text{mol/L}$). There was no symptomatology associated with this increased glutamine level.

- Glutamine levels from January 26, 2002 to September 2, 2003 remained within slightly low to normal levels between 374 to 513 $\mu\text{mol/L}$ (normal range 432-706 $\mu\text{mol/L}$) while on carglumic acid therapy ranging from 6 to 8 mg/kg/d

Figure 15 below summarizes Patient 1's glutamine levels both before and after initiation of treatment with carglumic acid on August 7, 1991.

Figure 15: Patient 1 glutamine levels pre and post exposure to carglumic acid



standard normal range is obtained from the NIH normal range table of plasma amino acids for children dated 2006 Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

It should be noted that a "control visit" is the date an evaluation was performed by the treating physician as part of a follow-up. During these "control visits", increase in ammonia and glutamine levels were sometimes observed due to temporary discontinuations of carglumic acid treatment. According to the sponsor, the reasons for these discontinuations may have included patient non-compliance, interruption before enzymatic test, or lack of product availability in the pharmacy.

The elevated glutamine level of 1043 $\mu\text{mol/L}$ that occurred on May 10, 2001 may be due to temporary discontinuation of carglumic acid for unclear reasons. However, the patient did not appear to be symptomatic from this laboratory abnormality.

Patient 1's Plasma Citrulline Levels

In patient 1, citrulline levels were normal (26 $\mu\text{mol/L}$) before the initiation of carglumic acid treatment and remained within normal range for the majority of the recorded timepoints (August 6, 1991 to May 2, 2006) except for the 3 following timepoints when they were low.

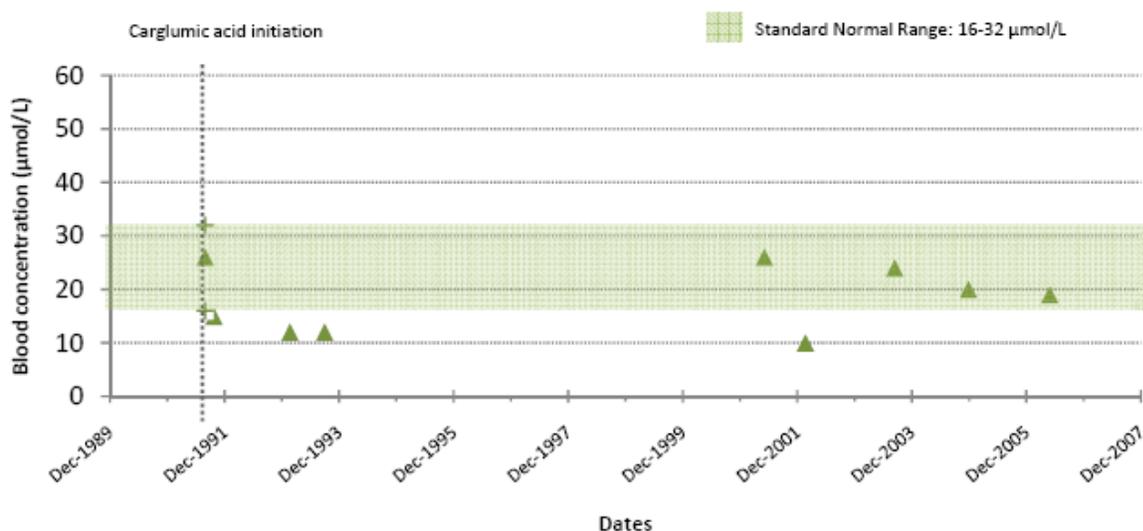
January 28, 1993: 12 $\mu\text{mol/L}$ (normal range 14-31 $\mu\text{mol/L}$)

September 6, 1993: 12 $\mu\text{mol/L}$ (normal range 14-31 $\mu\text{mol/L}$)

January 26, 2002: 10 $\mu\text{mol/L}$ (normal range 19-33 $\mu\text{mol/L}$)

Figure 16 below illustrates citrulline levels before and after treatment with carglumic acid.

Figure 16: Patient 1 citrulline levels pre and post exposure to carglumic acid



standard normal range is obtained from the NIH normal range table of plasma amino acids for children dated 2006
Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

Citrulline levels are expected to increase with carglumic acid therapy. However, in this particular patient, it is difficult to interpret his citrulline results as he was receiving citrulline supplementation for an undocumented period of time.

It should be noted that the laboratory specific normal ranges used in the narratives generally differ from the standard normal range used in the graphic representation of citrulline levels.

Narrative for Patient 2

Patient 2 was born (b) (6). In (b) (6), at the age of three months, he presented with axial hypotonia and developmental delay. At the age of five months, hyperammonemia was detected at a level of 146 $\mu\text{mol/L}$. Starting September 27, 1991, Patient 2 received the following treatments:

- Sodium benzoate (250 mg/kg/d IV)
- Arginine (2280 mg/d) IV
- Carnitine (1000 mg/d) IV
- Protein restriction (0.0 g/kg/d)

When he improved clinically, he was switched to oral versions of the above medications and his protein intake was gradually increased. CPS 1 deficiency was the suspected

diagnosis. The ammonia level continued to fluctuate above normal. Due to “lack of biochemical control”, sodium benzoate, arginine, and carnitine were all discontinued October 15, 1991.

Medical officer comments

The sponsor did not provide any further information to clarify the reasoning behind the discontinuation of all interventions. However, the patient did have an ammonia level of 1026 µmol/L on October 24, 1991.

In June 1992, prior to initiation of treatment with carglumic acid, Patient 2 had already suffered severe neurologic damage and psychomotor retardation. Two days (b) (6) (b) (6) prior to the initiation of carglumic acid on (b) (6), ammonia levels ranged from 64-260 µmol/L. The initial dose of carglumic acid was 396 mg/kg/d or 1000 mg qid. Within 24 hours, plasma ammonia levels fell to a range of 55-85 µmol/L following the onset of treatment. Nine days (b) (6) following the start of therapy with carglumic acid, the dose was decreased in half to 198 mg/kg/d or 500 mg qid. Three weeks following the start of therapy, the dose was again decreased to 79 mg/kg/d or 200 mg qid. As of the last recorded visit on August 10, 2007, the patient was still receiving the same dose of 200 mg qid, which at that time amounted to 16.3 mg/kg/d. Since taking carglumic acid, the patient has had only a moderate protein intake. It was increased from 1.5 g/kg/d to ≤ 2.5 g/kg/d. As of August 10, 2007, he had received treatment with carglumic acid for more than 15 years. Once carglumic acid was initiated and maintained, Patient 2 did not experience any further episodes of hyperammonemia.

As mentioned above, Patient 2 was originally thought to have a CPS 1 deficiency. The results of the liver biopsy from June 1993 as shown in Table 16 revealed what appeared to be a normal NAGS level of activity although the arginine stimulation test was not performed.

Table 16: Patient 2's result of first liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
June 30, 1993	Liver biopsy	NAGS	79.80	nmol/min/g prot	34-203

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

In November of 1993, a second liver biopsy was performed, which appeared to confirm a deficiency of CPS 1 as previously suspected (Table 17).

Table 17: Patient 2's results of second liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
November 1993	Liver biopsy	CPS 1	0.29	µmol/h/mg prot	1.34-2.34
November 1993	Liver biopsy	OTC	38.50	µmol/h/mg prot	23.9-43.10

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

In May of 2007, a DNA test was performed to confirm a genetic mutation in either CPS 1 or NAGS. Results in Table 18 revealed that Patient 2 had a homozygous form of NAGS deficiency.

Table 18: Patient 2's results of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
May 18, 2007	NAGS deficiency	c.598T>C (C200R)	exon 2	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 2 and Subject Profile sponsor's table, page 1

Previous or Concomitant Therapy

Patient 2 received other neurologic medications reportedly to control what was described as neurologic episodes and prevent further brain damage. These medications included the following:

- Carbamazepine
- Risperidone
- Topiramate

Medical officer comments

The dosage or sequential use of the above medications is not known. Both carbamazepine and topiramate have numerous indications, so their exact use in the case of Patient 2 is unknown. It is not clear whether carbamazepine, topiramate, or some combination of the two were being used to control his epilepsy.

Growth and Development

Patient 2's overall growth has been -0.5 to 1.0 standard deviations below normal for height and weight.

He suffered severe neurologic damage and developed significant psychomotor retardation before starting therapy with carglumic acid. As of August 2007, he is ambulatory but does not speak and has intermittent incontinence. He experiences frequent tonic clonic seizures that require anticonvulsant therapy.

Patient 2's Plasma Ammonia Levels

Prior to treatment with carglumic acid, plasma ammonia levels ranged between 34-1026 µmol/L. On the day therapy with carglumic acid was initiated (June 19, 1992), the lowest ammonia level attained was 55 µmol/L and the highest was 85 µmol/L. Within 24 hours of therapy (b) (6) with carglumic acid, the lowest ammonia level attained was 27 µmol/L and highest level was 63 µmol/L. Approximately 1 month (b) (6) (b) (6) post initiation of therapy with carglumic acid, patient had ammonia levels in the range of 52 to 84 µmol/L.

During the first 6 months of therapy, the plasma ammonia levels fluctuated above the normal range. After that time period, the ammonia levels remained within normal limits over the following years. Ammonia levels over the duration of treatment with carglumic acid were as follows:

November 3, 1992: 35-103 $\mu\text{mol/L}$

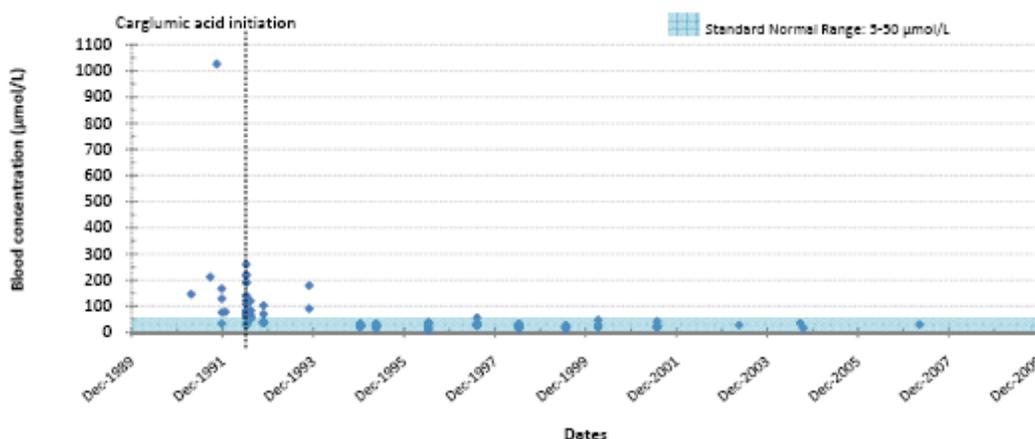
November 5, 1993; 2 samples obtained: 91 (fasting) to 179 (after a meal)

It should be noted that carglumic acid was discontinued 1 week (b) (6) prior to liver biopsy being performed on (b) (6).

December 21, 1994 to April 13, 2007: 9-56 $\mu\text{mol/L}$

Figure 17 illustrates ammonia levels before and after treatment with carglumic acid.

Figure 17: Patient 2's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 9

Medical officer comments

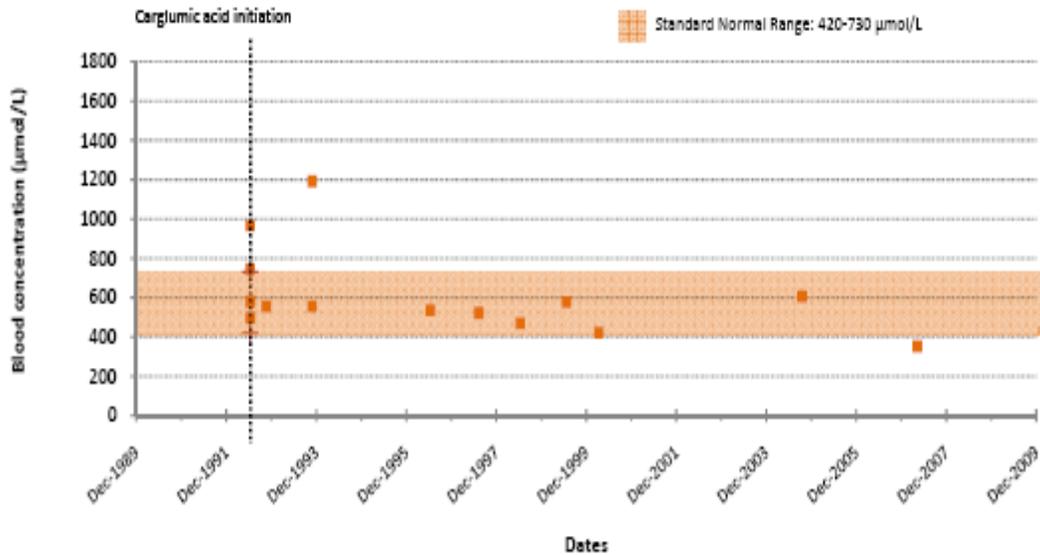
The ammonia levels remained above normal in the first 6 months after treatment with carglumic acid was initiated. No ammonia levels were available between November 4, 1992 and November 4, 1993. Despite not achieving normal ammonia levels within the first 6 months of treatment with carglumic acid, there was a definite decrease in the maximal ammonia levels relative to ammonia levels prior to carglumic acid therapy.

Patient 2's Plasma Glutamine Levels

Before receiving treatment with carglumic acid, the plasma glutamine level was increased at 966 $\mu\text{mol/L}$ (normal range 250-820 $\mu\text{mol/L}$). Several hours post initiation of treatment with carglumic acid, the glutamine level normalized to 745 $\mu\text{mol/L}$.

Glutamine levels remained within normal limits for the duration of treatment with carglumic acid except at 2 time points. It was elevated at 1192 $\mu\text{mol/L}$ at the "control visit", November 4, 1993. The day after the control visit (November 5, 1993) the level decreased to 557 $\mu\text{mol/L}$. In addition, glutamine had decreased to 353 $\mu\text{mol/L}$ (normal range 432-705 $\mu\text{mol/L}$) at the last recorded visit on April 13, 2007. Figure 18 illustrates glutamine levels before and after treatment with carglumic acid.

Figure 18: Patient 2 glutamine levels pre and post exposure to carglumic acid



Sponsor's figure, Individual Patient Narrative, page 8

Patient 2's Plasma Citrulline Levels

Before the initiation of treatment with carglumic acid, citrulline levels were low at 2 time points (normal range 10-30 µmol/L).

April 24, 1991: 9 µmol/L

December 11, 1991: 3 µmol/L

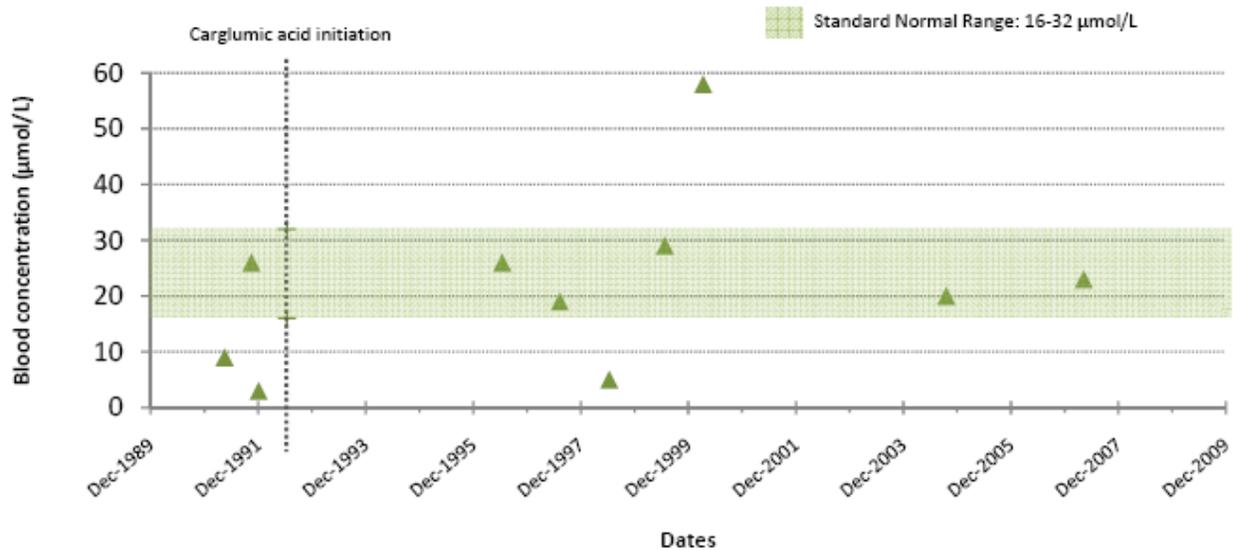
Since beginning therapy with carglumic acid, citrulline has remained within normal limits the majority of the sampling periods except for 2 time points where it was low once and high another time.

June 18, 1998: 5 µmol/L (normal range 18-34 µmol/L)

March 16, 2000: 58 µmol/L (normal range 10-30 µmol/L)

Figure 19 illustrates citrulline levels in Patient 2 before and after treatment with carglumic acid.

Figure 19: Patient 2 citrulline levels pre and post exposure to carglumic acid



Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

Although Patient 2 did not have documentation that he received citrulline supplementation, he remained on moderate protein intake restriction for the duration of carglumic acid therapy. It is unclear whether the changes in protein intake might have contributed to the variable citrulline levels.

Narrative for Patient 3

Patient 3 was a male born (b) (6) at 37 weeks via c-section secondary to preeclampsia. At DOL 5, the patient presented with the following symptoms:

- Poor feeding
- Oliguria
- Hyporeactivity with lethargy and hypotonia
- Tremor
- Abnormal movements
- Alkalosis
- Ammonia level of 557 µmol/L

His symptoms progressed to the point where he developed cerebral edema identified by ultrasound. Clinically, he had axial hypotonia with distal hypertonia. Hepatomegaly and oliguria were also present. He received peritoneal dialysis for three days (b) (6), (b) (6) and was started on standard therapy starting April 13, 1993, which consisted of intravenous sodium benzoate (500 mg/kg/d), arginine (500 mg/d) and carnitine (800 mg/d). He also received high caloric enteral feeding with no protein. The medications were switched to oral formulations on April 19, 1993 and the sodium benzoate dose was increased on April 26, 1993 to 625 mg/kg/d. On April 15, 1993, the carnitine dose was reduced to 400 mg/d.

Initiation of treatment with carglumic acid began on April 29, 1993. The ammonia levels ranged from 40-157 $\mu\text{mol/L}$ seven days before the initiation of carglumic acid therapy. The starting dose of carglumic acid was 231 mg/kg/d (200 mg tid). The plasma ammonia decreased to 66 $\mu\text{mol/L}$ within 24 hours and then to 31 $\mu\text{mol/L}$ within 48 hours (May 1, 1993). The sodium benzoate dose was decreased to 375 mg/kg/d on May 2, 1993, and then discontinued on May 6, 1993. Carnitine and Arginine were discontinued on May 8 and July 20, 1993, respectively. Ammonia levels remained within normal limits 48 hours after initiating carglumic acid therapy with one exception, July 12, 1994 (ammonia level 175 $\mu\text{mol/L}$), where it was attributed to an increase in the patient's protein intake and unexplained laboratory procedure issue.

Medical officer comments

The sponsor does not provide an explanation as to the laboratory procedure that caused the elevated ammonia level on July 12, 1994. Although there is a report of increased protein intake of 3.5 g/kg/d on July 12, it does not appear to be the only factor contributing to the elevated ammonia level. The patient has had protein intakes as high as 3.80 g/kg/d on December 20, 1994 and June 6, 1995 with normal corresponding ammonia levels (30 $\mu\text{mol/L}$ and 14 $\mu\text{mol/L}$, respectively).

As previously mentioned, the initial dose of carglumic acid was 231 mg/kg/d (200 mg tid). After 5 days, the dose of carglumic acid was reduced to 100 mg/kg/d (100 mg tid). After three months of age, the only therapy the patient received was carglumic acid. Up until the age of 7 months the dose ranged between 70 and 90 mg/kg/d (divided qid). After 7 months of age, the patient remained on a total daily dose of 800 mg a day, until 3 years of age.

Around the age of 2.5 years, the patient began refusing therapy with carglumic acid and the mother tried administering it twice a day in milk. On June 4, 1996, his dose was increased to 1200 mg a day (divided tid). This amounted to a dosing range of 57-86 mg/kg/d. This total daily dosing regimen remained the same through the age of 8 years, at which point the patient was receiving 50 mg/kg/d. As of the last recorded visit on July 16, 2007, the patient had received treatment with carglumic acid for more than 14 years. The last recorded dose was 25 mg/kg/d, for a total daily dose of 1200 mg (600 mg bid). As for his diet, he slowly increased protein intake over a 2 week period from April 16 to April 29, 1993 so that when the patient began receiving carglumic acid (April 29, 1993), he was on 2.5 g/kg/d. Protein intake was unrestricted from July 12, 1994 until the last recorded visit in 2007.

Initially, the patient was thought to have hyperammonemia secondary to either NAGS or CPS 1 deficiency. The diagnosis of NAGS deficiency gained support given the rapid response to therapy with carglumic acid. In June and April of 1993, liver biopsy results in Table 19 revealed low NAGS and low arginine stimulated NAGS activity, as well as low OTC and CPS 1 activities.

Table 19: Patient 3's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	19.50	nmol/min/g prot	34-203
(b) (6)	Liver biopsy	NAGS + Arg	22.00	nmol/min/g prot	>144
(b) (6)	Liver biopsy	CPS 1	0.66	µmol/h/mg prot	1.34-2.34
(b) (6)	Liver biopsy	OTC	14.80	µmol/h/mg prot	25.9-45.1

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

In February 2003, the patient underwent DNA testing to evaluate for either CPS 1 or NAGS gene mutation. Results shown in Table 20 below confirmed a homozygous mutation for NAGS deficiency.

Table 20: Patient 3's results of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
February 25, 2003	NAGS deficiency	1228T>C (S410P)	exon 5	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 2

Previous or Concomitant Therapy

Patient 3 received rectal diazepam (2mg) April 12, 1993.

Growth and Development

Patient 3 experienced "catch up growth" within four months of starting treatment with carglumic acid, and since then, he remained on an average growth curve for height and weight. Hepatomegaly and hypotonia disappeared a few months following the initiation of carglumic acid. All neurologic impairments resolved within three months of the initiation of therapy with carglumic acid. No neurologic problems have been recorded as of the last control in 2007. Despite a prior history at DOL 5 of being comatose with cerebral edema (according to ultrasound), the patient developed normally with normal developmental milestones, and had normal to above average school attendance and performance.

Clinical Course

Patient 3 experienced problems with recurrent ENT febrile infections, chicken pox, and a surgical procedure that required general anesthesia. He received an additional dose of carglumic acid when febrile at 40°C. During a 3 month period, the patient had increased vomiting and decreased appetite associated with infectious illnesses. This was between 2.5 and 3 years of age, and the symptoms resolved with an increase in the dose of carglumic acid to 1200 mg/d.

Patient 3's Plasma Ammonia Levels

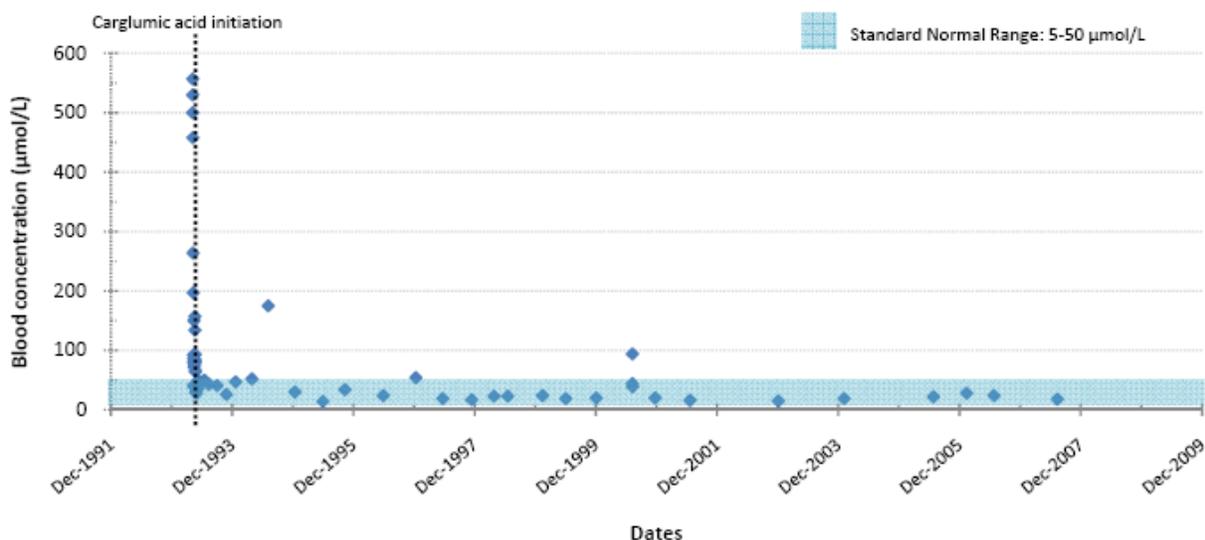
Despite peritoneal dialysis and standard therapy (sodium benzoate, arginine, and carnitine), ammonia levels continued to peak in the range of 124 to 264 µmol/L. Twelve hours after 3 doses of carglumic acid the level decreased from 93 to 66 µmol/L, and decreased further to 31 µmol/L the next morning (b) (6). The ammonia level remained below the upper limit of normal during the treatment period with carglumic

acid with the exception of a peak at 175 $\mu\text{mol/L}$ (b) (6) during a period of increased protein intake. There were no reported symptoms associated with this higher level.

Due to a lack of drug supply, treatment with carglumic acid was interrupted for 4 days and this led to the following symptoms in the patient: dizziness, somnolence, headache, problems concentrating, and a plasma ammonia level of 94 $\mu\text{mol/L}$ (July 13, 2000). The patient received a total dose of 2200 mg (101 mg/kg/d) with the first 2 doses administered within a 6 hour timeframe (1000 mg, 600 mg), and the plasma ammonia level normalized to 44 $\mu\text{mol/L}$.

Figure 20 below illustrates ammonia levels before and after treatment with carglumic acid in Patient 3.

Figure 20: Patient 3's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

Patient 3's Plasma Glutamine Levels

Patient 3's plasma glutamine levels were within normal limits during the majority of the sampling periods pre and post initiation of carglumic acid therapy with the exceptions discussed below.

Prior to initiation of treatment with carglumic acid, patient exhibited normal glutamine levels except at 2 timepoints:

April 14, 1993: 1054 $\mu\text{mol/L}$ (normal range 548-1096 $\mu\text{mol/L}$)

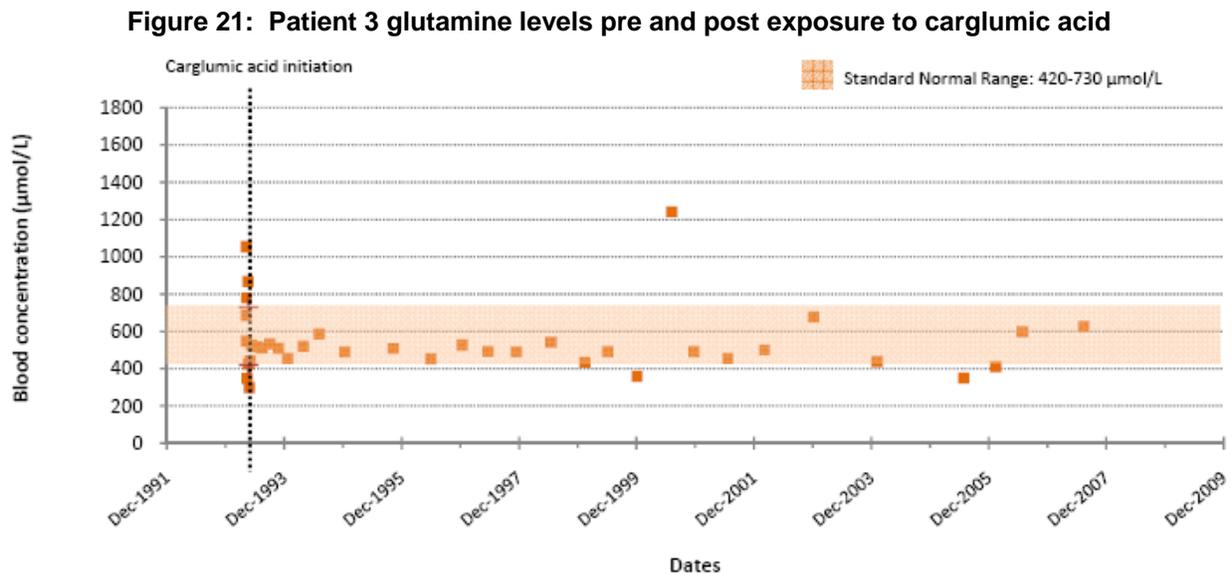
higher than all the other values but within the normal range

April 19, 1993: low at 347 $\mu\text{mol/L}$

Post initiation of carglumic acid therapy, the majority of glutamine levels remained within normal limits except for 4 timepoints

May 3, 1993: low at 297 $\mu\text{mol/L}$ (normal range 400-760 $\mu\text{mol/L}$)
December 9, 1999: low at 358 $\mu\text{mol/L}$
July 13, 2000: high at 1242 $\mu\text{mol/L}$
July 1, 2005: low at 350 $\mu\text{mol/L}$ (normal range 432-705 $\mu\text{mol/L}$)
January 16, 2006: low at 410 $\mu\text{mol/L}$

Figure 21 below illustrates glutamine levels before and after treatment with carglumic acid.



Sponsor's figure, Individual Patient Narrative, page 9

Medical officer comments

The clinical decompensation that the patient experienced during the 4 day carglumic acid shortage in July of 2000 may be attributed to elevated ammonia and glutamine levels of 94 $\mu\text{mol/L}$ and 1242 $\mu\text{mol/L}$, respectively.

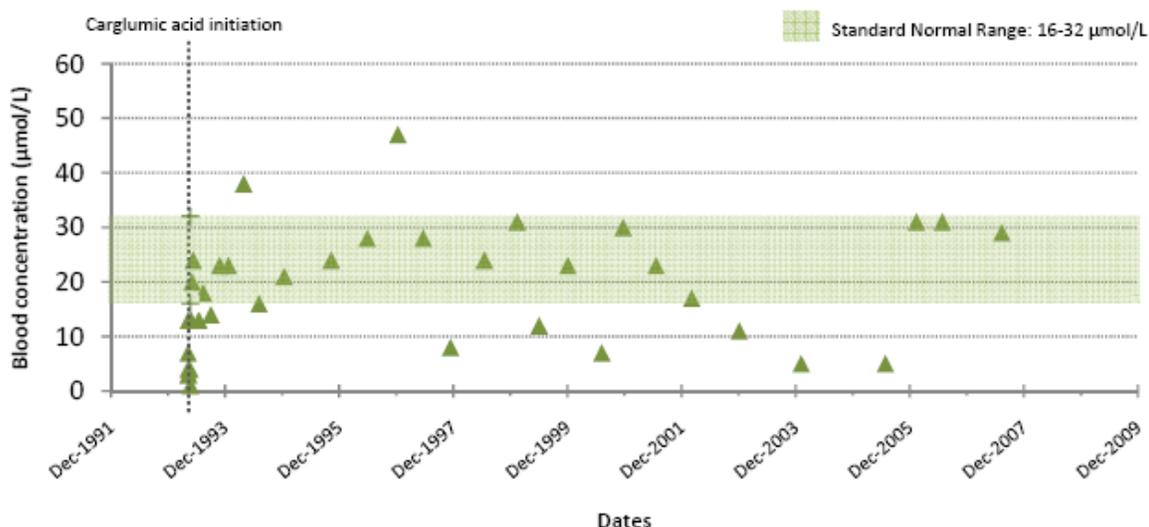
Patient 3's Plasma Citrulline Levels

Patient 3's citrulline levels were as low as 1 $\mu\text{mol/L}$ (normal 11-21 $\mu\text{mol/L}$) prior to initiation of carglumic acid therapy. Citrulline levels normalized within 4 days (May 3, 1993, 13 $\mu\text{mol/L}$) and remained within normal limits with four exceptions:

- November 18, 1997: 8 $\mu\text{mol/L}$ (reason unknown)
- July 13, 2000: 7 $\mu\text{mol/L}$ (interruption of treatment for 4 days for drug shortage)
- January 9, 2004 and July 1, 2005: 5 $\mu\text{mol/L}$ (normal range 19-39 $\mu\text{mol/L}$); reasons unknown

Figure 22 below illustrates citrulline levels before and after treatment with carglumic acid.

Figure 22: Patient 3 citrulline levels pre and post exposure to carglumic acid



Sponsor's figure, Individual Patient Narrative, page 9

Narrative for Patient 5

Patient 5 is a female born at term (b) (6). She has one sister who died at DOL 22 from hyperammonemia with a suspected diagnosis of CPS deficiency. The second sister was born healthy. Patient 5 was restricted to breast feeding DOL 1. DOL 2 her ammonia level was 149 µmol/L. She was placed on a high caloric parenteral diet and an unknown dose of IV arginine was initiated. After nine days of this treatment, oral carnitine (67 mg/kg/d) and sodium benzoate (267 mg/kg/d) were added to the regimen. After one month, arginine was increased to 158 mg/kg/d and sodium benzoate increased to 395 mg/kg/d. Due to clinical decompensation, her dose of sodium benzoate was adjusted on multiple occasions.

Carglumic acid therapy was initiated on January 23, 1996 at a dose of 254 mg/kg/day (300 mg qid). Sodium benzoate was discontinued on January 29, 1996. Arginine was given to the patient up until the last "recorded control" in 2007. Arginine was switched from IV to oral therapy approximately on October 31, 1995. From December 1996 to January 2001, the total daily dose was 2000 mg. After January 2001, the mother initiated a decrease in the carglumic acid to a total daily dose of 800 mg, or approximately 40 mg/kg/d (200 mg qid). From January 16, 2002 to November 28, 2006, the total daily dose was somewhat higher at 1000 mg/d. On May 31, 2007, the registered dose was 10 mg/kg/d (TDD: 600 mg/d). Protein intake was restricted from birth by an unknown amount until treatment with carglumic acid began. Following a rapid response to therapy with carglumic acid, protein became unrestricted and remained unrestricted as of the last follow-up visit in 2007.

Medical officer comments

There are no further details provided regarding the symptoms associated with the clinical decompensation. It is difficult to determine the maximum dose of sodium benzoate that the patient received since some of the doses were provided in mg only and others were provided in mg/kg/d.

Initially, Patient 5 was thought to have hyperammonemia secondary to either CPS 1 or OTC deficiency. A liver biopsy performed in December 1995 with results as shown in Table 21 below did not reveal any CPS 1 or OTC deficiency.

Table 21: Patient 5's results of first liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	22.20	nmol/min/mg prot	> 12
(b) (6)	Liver biopsy	OTC	537.00	nmol/min/mg prot	> 160

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1 and Subject Profile, sponsor's table, page 27

A second liver biopsy was performed in (b) (6), which checked for both basal and arginine-stimulated NAGS deficiency in addition to CPS 1 activity. The arginine-stimulated NAGS activity results shown in Table 22 revealed a decrease in NAGS enzyme activity.

Table 22: Patient 5's results of second liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	26.20	nmol/min/mg prot	> 12
(b) (6)	Liver biopsy	NAGS	98.00	nmol/min/g prot	> 34
(b) (6)	Liver biopsy	NAGS + Arg	64.00	nmol/min/g prot	>144

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

DNA test (Table 23) was performed years later which confirmed a homozygous gene mutation for NAGS deficiency.

Table 23: Patient 3's results of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
N/A	NAGS deficiency	W324X/W324X	N/A	homozygous

N/A = not available

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 2

Previous or Concomitant Therapy

Arginine therapy was maintained at a dose range of 500 to 2200 mg/d (January 28, 1996 to May 31, 2007) throughout treatment with carglumic acid.

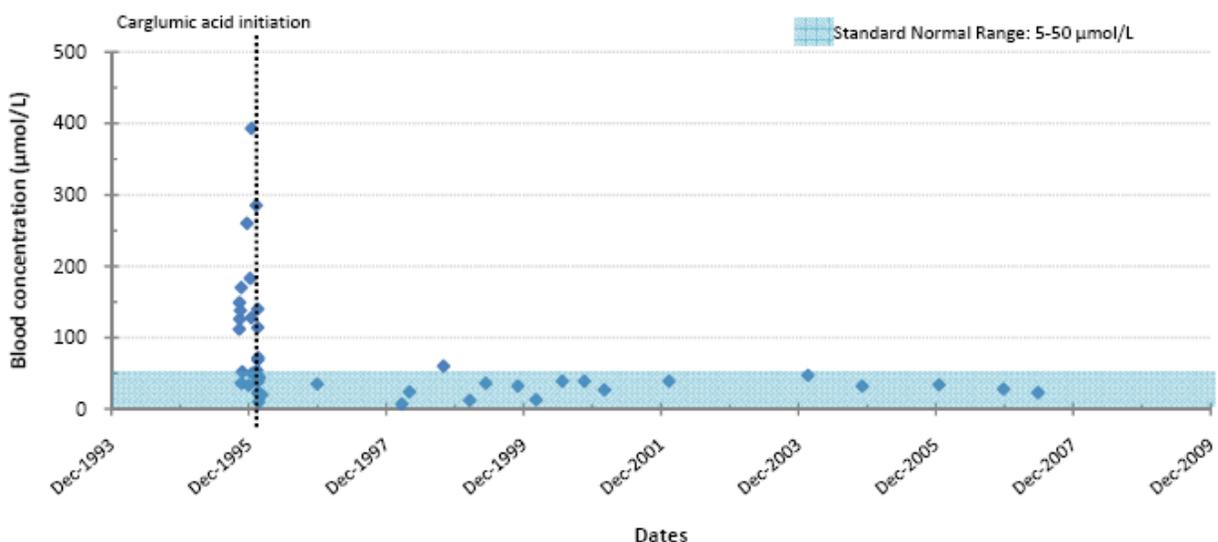
Growth and Development

Patient 5 suffered no identified neurologic damage, and as of 2007, she was performing well in school.

Patient 5's Plasma Ammonia Levels

Prior to the first dose of carglumic acid, Patient 5's ammonia level was 140 $\mu\text{mol/L}$ (January 23, 1996). Nine hours after the first dose of carglumic acid, the ammonia level decreased to 69 $\mu\text{mol/L}$. Approximately 24 hours post initiation of carglumic acid therapy, it has remained within normal limits (46 $\mu\text{mol/L}$ at 1600 on January 24, 1996), with one exception where the level increased to 72 $\mu\text{mol/L}$ at 8 am on January 25, 1996, 48 hours after initiating therapy. Figure 23 below illustrates ammonia levels before and after treatment with carglumic acid in Patient 5.

Figure 23: Patient 5's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

Once ammonia levels normalized at 23 $\mu\text{mol/L}$ on January 26, 1996 (day 3 of carglumic acid treatment), they remained within normal limits in the range of 7 to 47 $\mu\text{mol/L}$.

Patient 5's Plasma Glutamine Levels

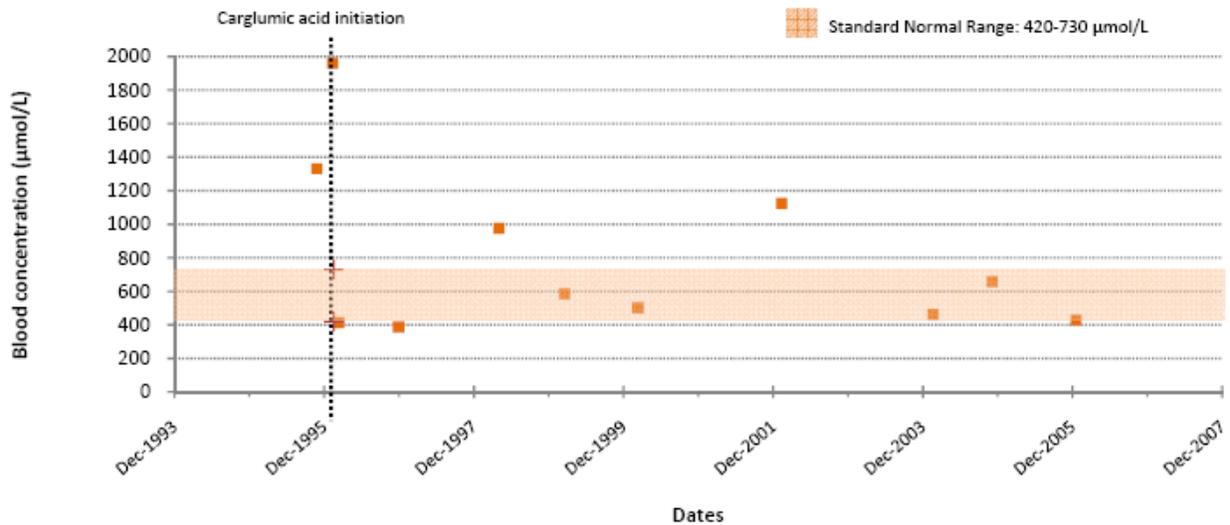
Patient 5's glutamine levels remained high following treatment with sodium benzoate, arginine, and carnitine. The highest level was 1961 $\mu\text{mol/L}$ (normal range 254 - 823 $\mu\text{mol/L}$). Once carglumic acid therapy began, glutamine levels remained within normal limits until the last recorded visit on May 31, 2007 with two exceptions listed below:

April 8, 1998: high at 977 $\mu\text{mol/L}$

January 16, 2002: high at 1123 $\mu\text{mol/L}$

Figure 24 below depicts glutamine levels before and after initiation of carglumic acid.

Figure 24: Patient 5 glutamine levels pre and post exposure to carglumic acid



Sponsor's figure, Individual Patient Narrative, page 9

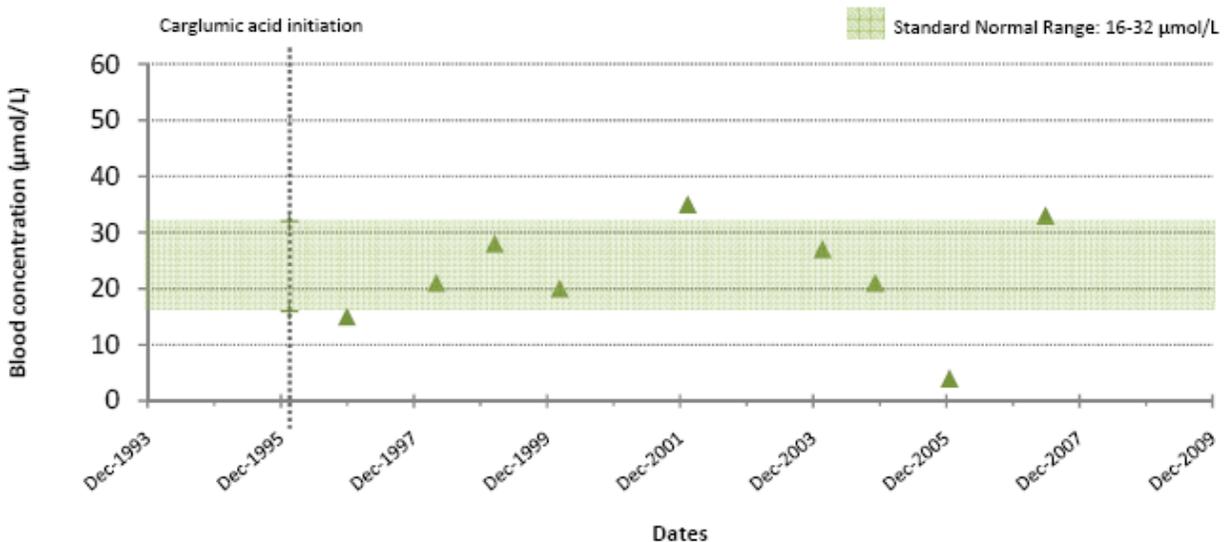
Medical officer comments

As expected, glutamine levels normalized with carglumic acid therapy; however, the etiology of the 2 elevated glutamine levels while on treatment with carglumic acid is unclear.

Patient 5's Plasma Citrulline Levels

Citrulline levels were within normal limits in Patient 5 during treatment with carglumic acid. As Figure 25 depicts below there were no citrulline levels obtained before the initiation of carglumic acid therapy.

Figure 25: Patient 5 citrulline levels post exposure to carglumic acid



Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

The 4 citrulline levels that appear to be outside the standard normal range in Figure 25 above actually fall within the specific laboratory's normal range. Below are the citrulline values with their reference ranges:

- December 4, 1996: 15 µmol/L (normal range 10-46 µmol/L)*
- January 16, 2002: 34.8 µmol/L (normal range 10-46 µmol/L)*
- December 21, 2005: 4.4 µmol/L (normal range 1-46 µmol/L)*
- May 31, 2007: 33 µmol/L (normal range 1-46 µmol/L)*

Narrative for Patient 6

Patient 6 was a male born at term (b) (6). His first sister died at DOL 22 from a severe decompensation secondary to hyperammonemia. The second sister was healthy. Patient 5 is his third sister.

On DOL 1, Patient 6 was treated with a hypercaloric infusion of IV glucose, and oral feeding was started on DOL 2. By DOL 3, plasma ammonia levels had increased from 85 to 144 µmol/L. Given the prior history of his siblings, Patient 6 was started on carglumic acid treatment on (b) (6) at a dose of 211 mg/kg/d (100 mg 6 times a day) as well as an unknown dose of IV arginine. Despite the hyperammonemia, he remained asymptomatic. On (b) (6), he was switched to oral arginine at a dose of 211 mg/kg/d (600 mg/d). He was discharged from the hospital DOL 8 and remained on treatment with carglumic acid for 6.7 years. Arginine was gradually reduced and eventually discontinued based upon DNA results from August 2003. Patient 6's initial diagnosis was hyperammonemia. Results of liver biopsy performed April 15, 1997 shown below in Table 24 revealed low NAGS activity at baseline and following arginine stimulation.

Table 24: Patient 6's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	12.00	nmol/min/g prot	> 34
(b) (6)	Liver biopsy	NAGS + Arg	62.00	nmol/min/g prot	>144

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

In August of 2003, a DNA test was performed, which confirmed a heterozygous genetic mutation for NAGS deficiency (Table 25).

Table 25: Patient 6's results of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
August 2003	Het NAGS deficiency	W324X	N/A	heterozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Throughout his treatment with carglumic acid, the patient did not have a protein-restricted diet. After it was confirmed he had a heterozygous mutation and remained asymptomatic, the decision was made to discontinue treatment with carglumic acid in September 2003.

Previous or Concomitant Therapy

See above. The only concomitant therapy was arginine and this was discontinued on August 2003.

Growth and Development

Patient 6 experienced normal growth and development. In this patient, there was no neurological or psychomotor deficit recorded on any visits. He did not experience any hyperammonemia after starting therapy with carglumic acid. His carglumic acid was discontinued in September 2003.

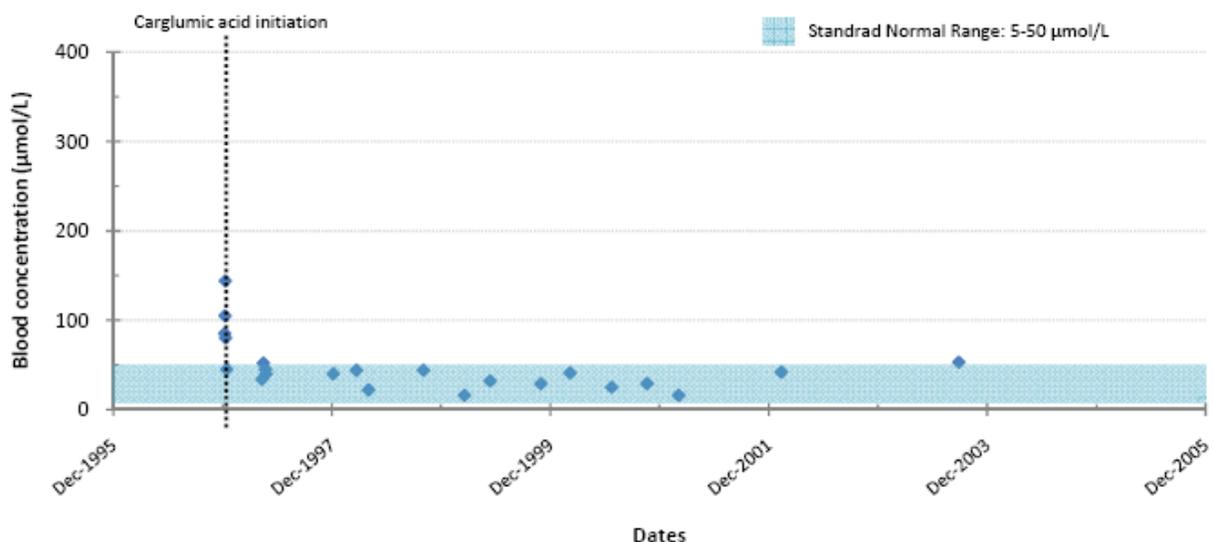
Medical officer comments

It is not known whether he remained asymptomatic after 2003, when carglumic acid therapy was stopped.

Patient 6's Plasma Ammonia Levels

Patient 6's ammonia level decreased to 80 $\mu\text{mol/L}$ from 144 $\mu\text{mol/L}$, 24 hours post initiation of carglumic acid therapy. Five days post initiation of carglumic acid, on December 20, 1996, his ammonia level normalized at 45 $\mu\text{mol/L}$. Ammonia levels remained normal throughout the duration of treatment. One week after discontinuation of carglumic acid in 2003, he had a borderline ammonia value of 52 $\mu\text{mol/L}$. Figure 26 below shows ammonia levels before and after beginning therapy with carglumic acid.

Figure 26: Patient 6's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

Patient's treatment with carglumic acid was discontinued due to his heterozygote NAGS mutation and his asymptomatic clinical course.

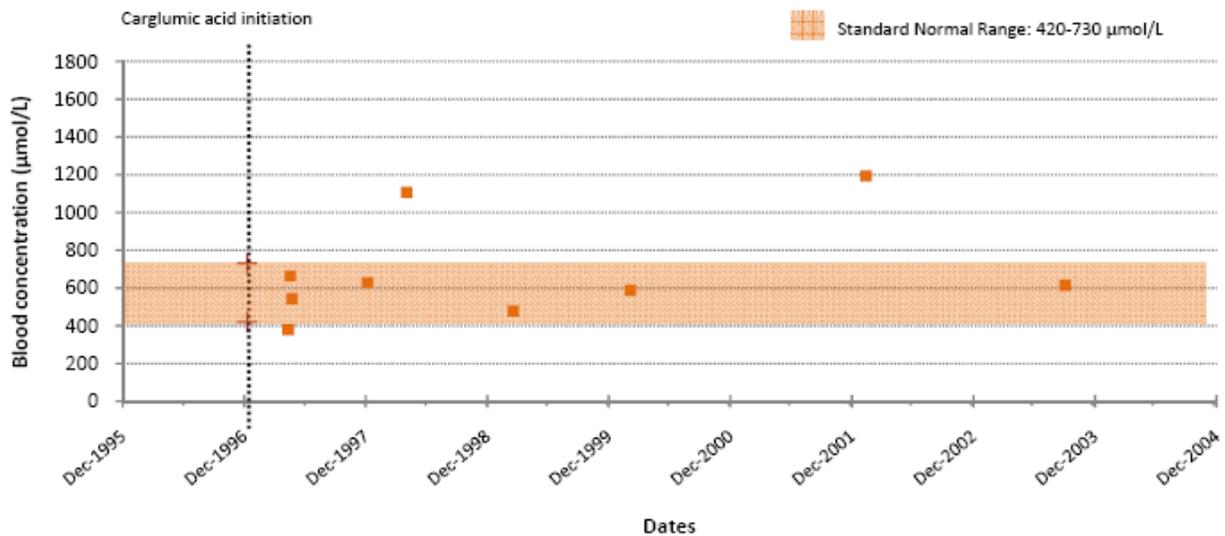
Patient 6's Plasma Glutamine Levels

Plasma glutamine levels in patient 6 were normal during the 6.7 years of therapy with carglumic acid with two exceptions:

- April 8, 1998: 1108 $\mu\text{mol/L}$ (normal range: 254-823 $\mu\text{mol/L}$)
- January 16, 2002: 1193 $\mu\text{mol/L}$

Figure 27 below depicts the glutamine levels obtained only after initiation of therapy with carglumic acid.

Figure 27: Patient 6's glutamine levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

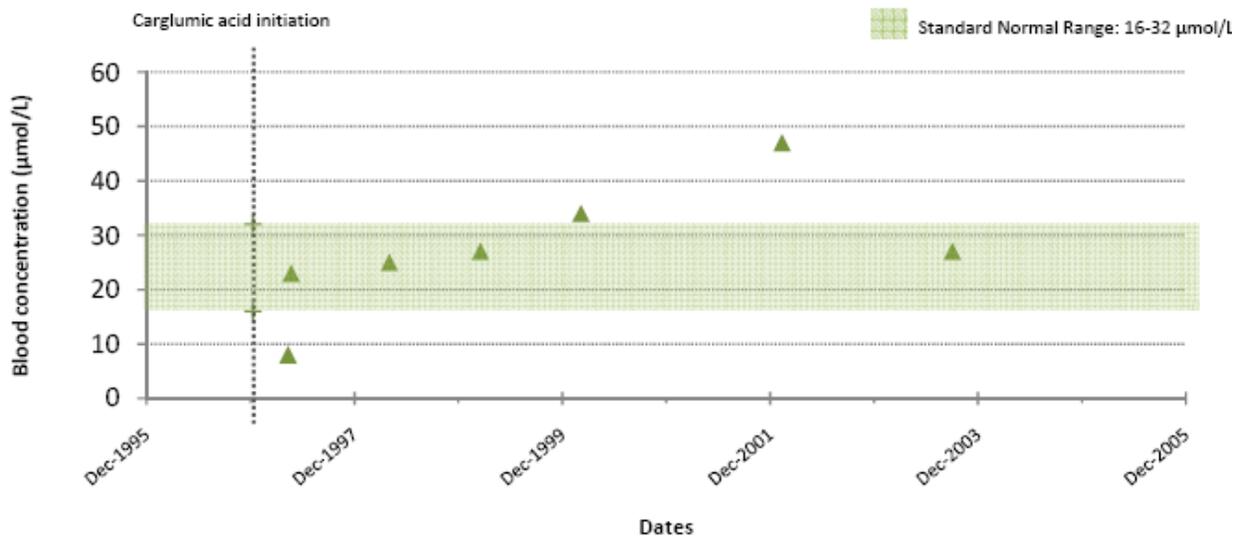
Medical officer comments

The etiology for these two elevations in glutamine levels is not clear.

Patient 6's Plasma Citrulline Levels

The patient's citrulline levels were normal during the 6.9 years of treatment with carglumic acid. Figure 28 below shows citrulline levels only after carglumic acid therapy was started.

Figure 28: Patient 6's citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

The 2 citrulline levels that appear to be outside the standard normal range in

Figure 28 above actually fall within the specific laboratory's normal range. Below are the citrulline values with their reference ranges:

February 10, 2000: 34 µmol/L (normal range 10-46 µmol/L)

January 16, 2002: 46.6 µmol/L (normal range 10-46 µmol/L)

Patient 6 had one abnormal citrulline level while on carglumic acid therapy at 8 µmol/L on April 17, 1997. The etiology of this abnormality is unclear.

Narrative for Patient 7

Patient 7 was a female born (b) (6). At 6 months of age, she sat upright and walked without support at 12 months. At 13 months, the patient had an episode of vomiting associated with hypotonia, somnolence, and mild ketosis. She recovered completely within 24 hours and physicians suspected some unidentified form of drug intoxication. She developed an aversion to protein.

From 11 years and 8 months of age to 12 years and 11 months of age, the patient had 4 episodes of somnolence, confusion, motor agitation, disorientation, restlessness, aggressiveness, and vomiting. These episodes coincided with infections or the intake of protein-rich foods. During the fourth episode, she was found to have a plasma ammonia level of 221 µmol/L with a normal urine orotic acid. These two findings were consistent with NAGS or CPS deficiency.

Starting (b) (6), the patient received IV sodium benzoate, arginine, citrulline, and a high-caloric protein-free parenteral feeding. Dosing information on the above treatments is not clear except for the addition of phenylbutyrate at 250 mg/kg/d IV that same day. By (b) (6), Patient 7 was receiving an oral version of sodium phenylbutyrate at 340-350 mg/kg/d. That same day, arginine's dose was lowered to 175 mg/kg/d and was given orally instead of IV. The hyperammonemia was not under adequate control and in light of the liver biopsy results shown in Table 26, treatment with carglumic acid was initiated on (b) (6) at a starting dose of 103 mg/kg/day (total daily dose of 3600 mg).

Table 26: Patient 7's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	19.90	mIU/mg prot	>12
(b) (6)	Liver biopsy	OTC	325.00	mIU/mg prot	> 160
(b) (6)	Liver biopsy	NAGS	22.00	nmol/min/g prot	34-203
(b) (6)	Liver biopsy	NAGS + Arg	22.00	nmol/min/g prot	144-320

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

At an unspecified date, DNA test was performed, which confirmed a homozygous genetic mutation for NAGS deficiency (Table 27).

Table 27: Patient 7's result of DNA test performed to confirm NAGS DNA mutation

Date of result	Diagnosis	Mutation	Location	Type
N/A	NAGS deficiency	A279P/A279P	N/A	homozygous

N/A = not available

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 2

Protein in the diet was restricted to 0.8 g/k/d and concomitant medications were continued, but there were dosing and route of administration changes (see below). Sodium phenylbutyrate was discontinued after the first four months of therapy with carglumic acid. Both arginine and citrulline were maintained with decreasing doses. Carglumic acid dose was increased to 4000 mg a day administered as 1000 mg qid to maintain a 100 mg/kg/d dosing. Four months after starting carglumic acid therapy, protein intake was increased. After eight months of carglumic acid therapy, the dose was decreased to 66 mg/kg/d (3000 mg total daily dose administered as 750 mg qid). At the age of 17, the dose had been reduced to 54 mg/kg/d of carglumic acid (600 mg qid).

Previous or Concomitant Therapy

The listing below shows that there were a number of medications given concomitantly with carglumic acid. The dosing and route of administration appear to have been changed multiple times. These medications include:

- IV glucose
- IV/PO arginine
- IV citrulline

- IV sodium benzoate
- IV phenylbutyrate
- PO sodium phenylbutyrate
- PO Aktiferritin
- PO L-Carnitine
- Erythrocyte concentrate
- Seravit

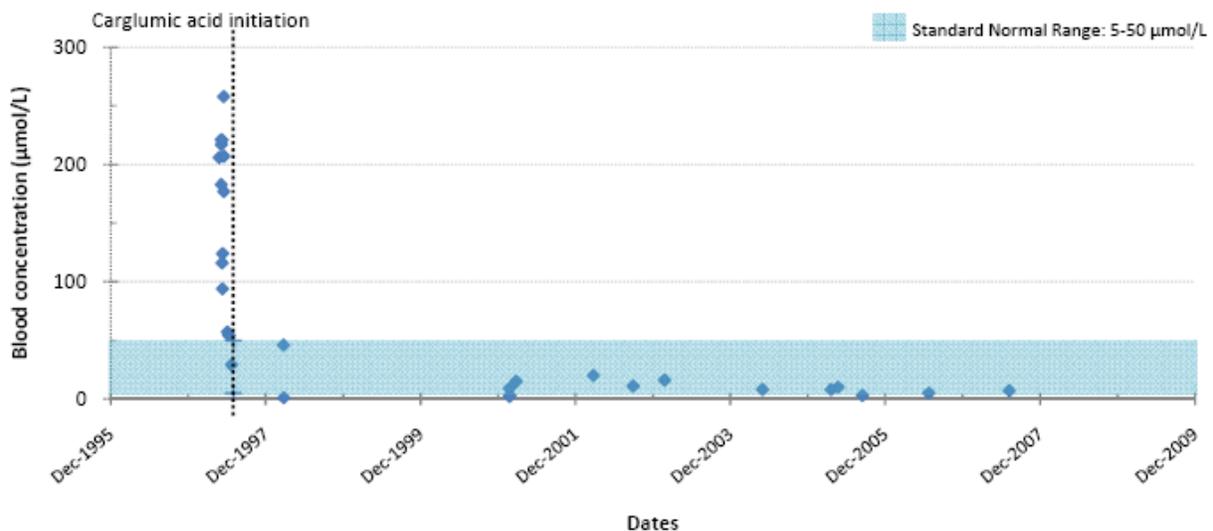
Growth and Development

The patient was noted on May 15, 1997 visit, at the age of 12 years and 11 months, to have a total IQ of 78 with what was described as normal neurologic development although she did not recognize people in her family. She was reported to have psychomotor retardation at that time. As described above, recurrent episodes of confusion were noted to have occurred in June of 1997. After the start of therapy with carglumic acid, patient's neurological and psychomotor developmental findings were reported as normal. In May of 2001, she was attending high school, doing well, and was described as intellectually, physically, and neurologically without any abnormalities.

Patient 7's Plasma Ammonia Levels

Patient 7's ammonia levels normalized and remained normal within 24 hours after initiation of carglumic acid. Prior to initiation of carglumic acid therapy, patient's ammonia levels were in the range of 54 to 258 $\mu\text{mol/L}$. Starting (b) (6) (24 hours post first carglumic acid therapy), her ammonia levels were in the range of 1 to 46 $\mu\text{mol/L}$ for the duration of carglumic acid treatment. Figure 29 below depicts ammonia levels pre and post initiation of carglumic acid therapy.

Figure 29: Patient 7's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

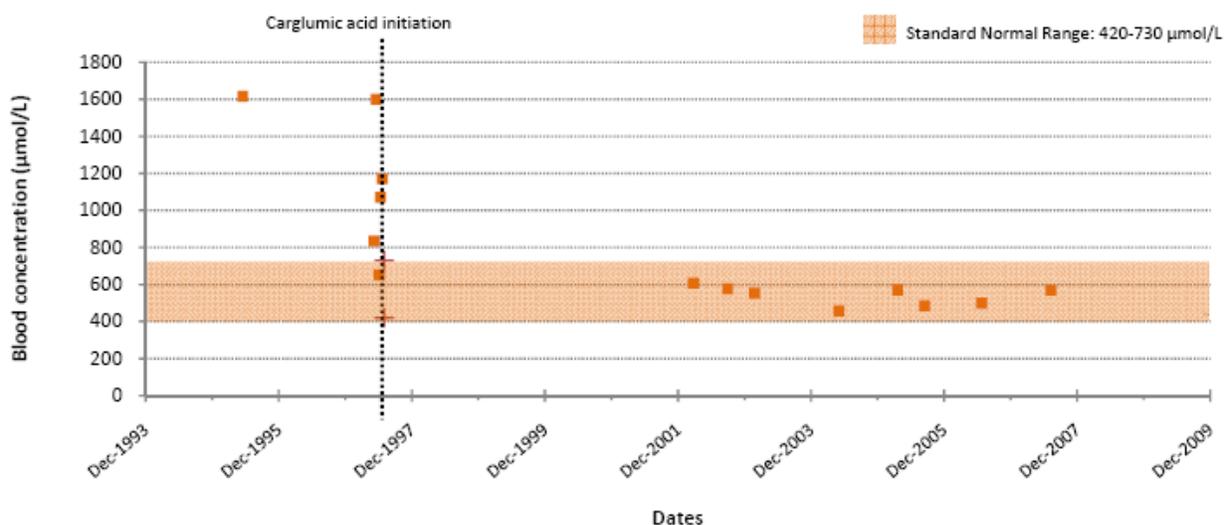
Medical officer comments

This particular patient could not achieve normal ammonia levels despite receiving multiple doses of the standard anti-hyperammonemic therapies. However, once carglumic acid was initiated, her ammonia levels normalized.

Patient 7's Plasma Glutamine Levels

Patient 7's glutamine levels were elevated to as high as 1600 µmol/L but normalized after initiation of carglumic acid in the range of 457 to 608 µmol/L. All of the glutamine levels obtained prior to carglumic acid therapy were elevated in the range of 835 to 1616 µmol/L, except for a result of 652 µmol/L at one timepoint (normal range 254-823 µmol/L). The only abnormal glutamine level obtained post initiation of carglumic acid was on June 27, 1997 (24 hours post initiation of carglumic acid) at 1170 µmol/L. Figure 30 below depicts glutamine levels pre and post initiation of carglumic acid therapy.

Figure 30: Patient 7's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

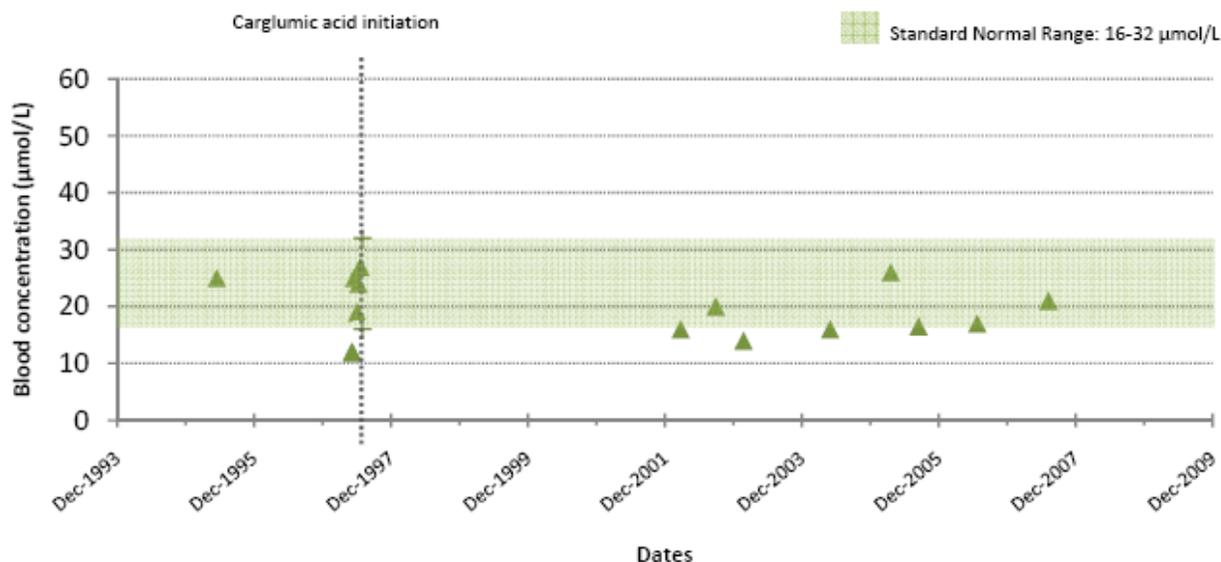
Medical officer comments

As expected, the majority of glutamine levels decreased after initiation of carglumic acid therapy and then remained normal with continuation of carglumic acid treatment.

Patient 7's Plasma Citrulline Levels

Patient 7's citrulline levels were normal prior to and following initiation of carglumic acid. Figure 31 below depicts citrulline levels pre and post initiation of carglumic acid therapy.

Figure 31: Patient 7's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

Despite some citrulline levels appearing slightly below the standard normal range in the figure, they were within the specific laboratory normal reference ranges (normal ranges 10-46 µmol/L; and 12-58 µmol/L depending on age). Patient also received supplementation with citrulline for an unspecified time period.

Narrative for Patient 13

Patient 13 was a female born (b) (6) at term. On DOL 2, the patient developed agitation, anorexia, nausea and difficulties breast feeding. In the days that followed, she developed both axial and distal hypotonia, overall decreased reactivity, intermittent polypnea, episodic agitation, trembling in the upper extremities, jaundice, poor feeding and dehydration. In addition to the above findings, on DOL 5, the patient developed an incomplete Moro sign but hepatomegaly was absent. Plasma ammonia levels on April 14, 1999 ranged from 163-182 µmol/L. On April 15, the ammonia level was 184 µmol/L and three treatments were initiated that day:

- Hypercaloric diet
- Protein-restricted diet (0.0 g/kg/d for 2 days)
- Carglumic acid at a dose of 200 mg/kg/d

Her dose of carglumic acid was continued at 720 mg/d administered as 180 mg qid. During the year, the dose was slowly reduced to 96 mg/kg/d. At the last recorded visit December 18, 2007, the dose was 20 mg/kg/d. Her protein intake was slowly increased, and there was no restriction in dietary protein starting in 2000 until 2007 (last recorded visit).

Diagnostic Tests

Hyperammonemia due to unspecified urea cycle defect (either NAGS or CPS 1 deficiency) was the suspected diagnosis. Liver biopsy results shown in Table 28 revealed normal activities for NAGS and OTC but low activities for CPS 1 and NAGS with arginine stimulation.

Table 28: Patient 13's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	53.00	µIU/mg prot	> 34
(b) (6)	Liver biopsy	NAGS + Arg	49.00	µIU/mg prot	> 144
(b) (6)	Liver biopsy	CPS 1	0.53	µmol/hr/mg prot	1.34-2.34
(b) (6)	Liver biopsy	OTC	35.23	µmol/hr/mg prot	25.9-45.1

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

In February 2003, DNA test was performed, which confirmed a homozygous genetic mutation for NAGS deficiency (Table 29).

Table 29: Patient 13's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
February 25, 2003	NAGS deficiency	1552 G>A (A518T)	exon 7	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Previous or Concomitant Therapy

See above. The only other concomitant therapy was domperidone (4 mg po) given the first week of therapy with carglumic acid for unspecified reasons.

Growth and Development

Patient 13's neurologic status normalized within 10 days following initiation of carglumic acid. The neonatal jaundice resolved, and there were no further symptoms of hyperammonemia with two exceptions:

- At the age of 18 months, the patient had what was reported as mild symptoms with a plasma ammonia of 75 µmol/L, and with no associated glutaminemia. At the time, the patient was on an unrestricted protein diet. Her dose of carglumic acid was increased to 98 mg/kg/d, and the mild symptoms resolved.
- In November of 2001, the patient did not take carglumic acid over a 48 hour period. The plasma ammonia increased to 175 µmol/L without an increase in glutamine levels. Reportedly, there were no significant symptoms, and the patient responded well to a re-initiation of carglumic acid treatment.

She went on to develop normally from a neurologic standpoint. She sat at 6 months on her own, crawled at 8 months, walked at 12 months, and began to say her first words at 14 months. She performed normally in school.

Medical officer comments

No details were provided of the "mild symptoms" that the patient experienced during these 2 exacerbations.

Patient 13's Plasma Ammonia Levels

The sponsor uses the neonatal ammonia reference range of 0-90 $\mu\text{mol/L}$ from (b) (6), (b) (6) in the subject profile and then changes the reference range for ammonia to 0-50 $\mu\text{mol/L}$ from (b) (6) until the last recorded visit in 2007.

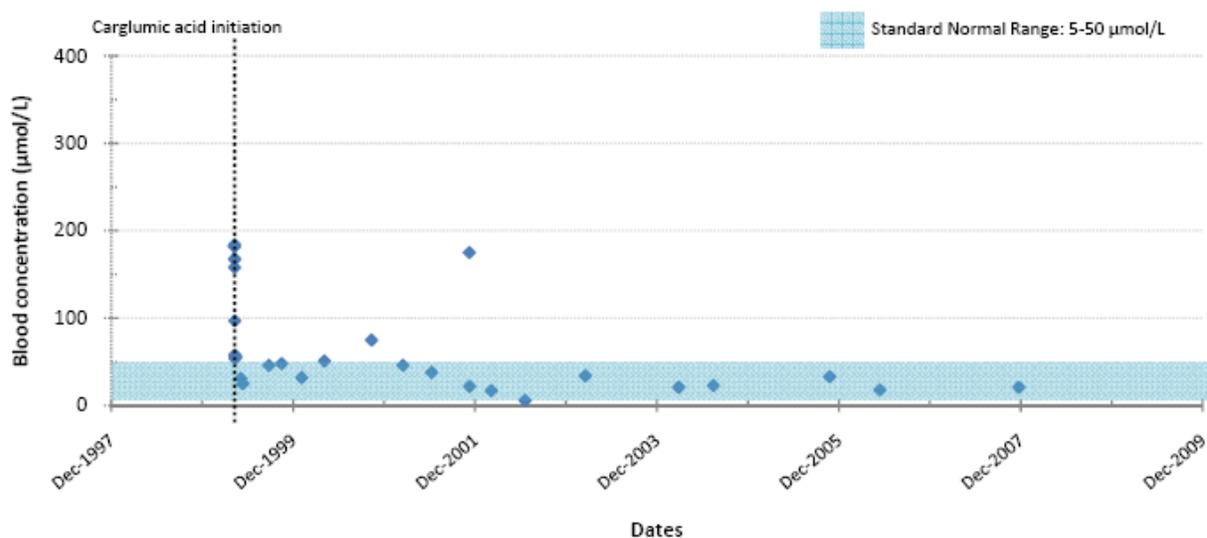
Twenty four hours prior to the initiation of carglumic acid, the ammonia level ranged from 182 to 184 $\mu\text{mol/L}$. Two hours post first carglumic acid therapy, patient's ammonia level decreased to 158 $\mu\text{mol/L}$ and then slightly increased in the 3rd and 4th hour post first dose of carglumic acid to 167 $\mu\text{mol/L}$ and 168 $\mu\text{mol/L}$, respectively. Eight hours post initiation of carglumic acid therapy, the ammonia level had decreased to 97 $\mu\text{mol/L}$.

Patient 13's plasma ammonia levels decreased from 184 to 58 $\mu\text{mol/L}$ approximately 13 hours post initiation of carglumic acid treatment (normal range for neonate 0 to 90 $\mu\text{mol/L}$). At 2 and 5 days post initiation of therapy, ammonia levels had normalized at 54 $\mu\text{mol/L}$ and 56 $\mu\text{mol/L}$, respectively.

Starting May 11, 1999 approximately 3 weeks post initiation of treatment with carglumic acid, patient's ammonia level remained normal at 31 $\mu\text{mol/L}$ (normal range 0-50 $\mu\text{mol/L}$). Ammonia levels remained within normal limits for the duration of treatment except for 2 episodes (see growth and development section). The first episode was due to a "relatively low dose of carglumic acid", and the second episode occurred after not receiving carglumic acid treatment for 48 hours.

Figure 32 shows ammonia levels before and after initiation of therapy with carglumic acid.

Figure 32: Patient 13's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

A clear explanation is lacking ("relatively low dose of carglumic acid") for the trigger of the first episode of hyperammonemia. There was an increase in the total daily dose of carglumic acid from 800 mg to 1200 mg around the time that the patient was reported to have had her first hyperammonemic exacerbation.

Based on the frequent ammonia samples that this patient had performed, it demonstrates that an initial decrease in ammonia level can be observed within 2 hours post the first dose of carglumic acid.

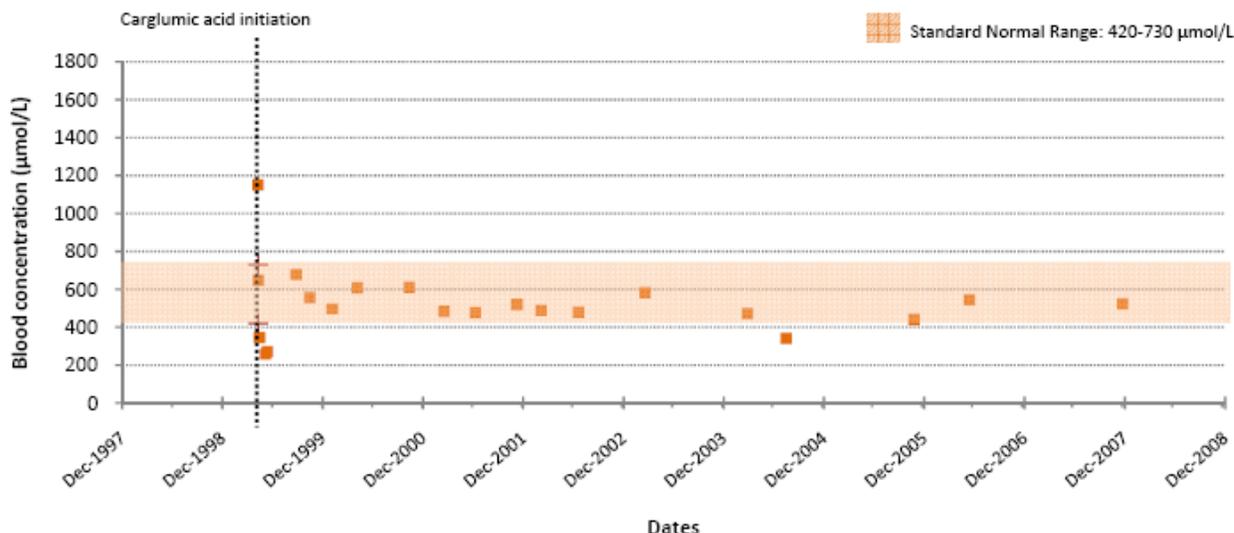
Patient 13's Plasma Glutamine Levels

Patient 13's glutamine levels normalized within 24 hours following initiation of treatment with carglumic acid. It decreased from a high of 1150 $\mu\text{mol/L}$ to 648 $\mu\text{mol/L}$ within 24 hours post the start of carglumic acid therapy (normal range 400 to 760 $\mu\text{mol/L}$). The majority of the glutamine levels remained within normal limits during treatment with carglumic acid except for 4 timepoints:

- April 20, 1999: low at 346 $\mu\text{mol/L}$
- May 11, 1999: low at 257 $\mu\text{mol/L}$
- May 18, 1999: low at 271 $\mu\text{mol/L}$
- July 19, 2004: low at 342 $\mu\text{mol/L}$ (normal range 432-705 $\mu\text{mol/L}$)

Figure 33 below illustrates glutamine levels before and after exposure to carglumic acid.

Figure 33: Patient 13's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

The etiology of the 4 below normal glutamine levels is unclear.

Patient 13's Plasma Citrulline Levels

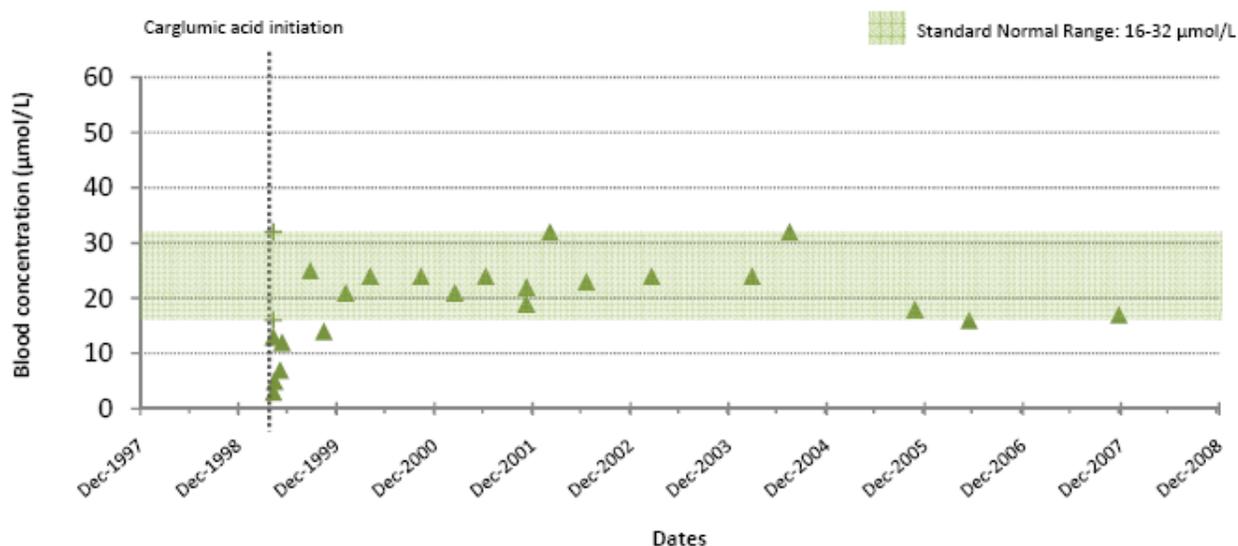
Patient 13 had a normal citrulline level at 13 $\mu\text{mol/L}$ on the day that carglumic acid therapy was started (normal range 11-21 $\mu\text{mol/L}$); however, the majority of her citrulline levels fluctuated in between abnormal high and low values.

Citrulline levels were abnormal at the following timepoints:

- April 16, 1999: low at 3 $\mu\text{mol/L}$
- April 20, 1999: low at 5 $\mu\text{mol/L}$
- May 11, 1999: low at 7 $\mu\text{mol/L}$
- August 31, 1999: high at 25 $\mu\text{mol/L}$
- April 10, 2000: high at 24 $\mu\text{mol/L}$
- October 16, 2000: high at 24 $\mu\text{mol/L}$
- June 14, 2001: high at 24 $\mu\text{mol/L}$
- November 13, 2001: high at 22 $\mu\text{mol/L}$
- February 8, 2002: high at 32 $\mu\text{mol/L}$
- June 24, 2002: high at 23 $\mu\text{mol/L}$
- February 21, 2003: high at 24 $\mu\text{mol/L}$
- March 1, 2004: high at 24 $\mu\text{mol/L}$ (normal range 11-19 $\mu\text{mol/L}$)
- October 28, 2005: low at 18 $\mu\text{mol/L}$ (normal range 19-39 $\mu\text{mol/L}$)
- May 18, 2006: low at 16 $\mu\text{mol/L}$
- November 26, 2007: low at 17 $\mu\text{mol/L}$

Figure 34 below illustrates citrulline levels before and after exposure to carglumic acid therapy.

Figure 34: Patient 13's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

There was no documentation of citrulline supplementation; therefore, the etiology of the high citrulline levels is unclear. In addition, the clinical significance of an elevated citrulline level while a patient is receiving carglumic acid treatment is unknown.

Narrative for Patient 15

Patient 15 was a male born term (b) (6), the third child. His first sister died at six months of age from complications secondary to hyperammonemia, and his second sister, (b) (6) was being treated at the time of his birth with carglumic acid for NAGS deficiency. Because of the known family history, Patient 15 was started on DOL 1 with the following treatment:

- IV arginine (308 mg/kg/d)
- IV sodium benzoate (487 mg/kg/d; reduced in 24 hours to 258 mg/kg/d)

DOL 2, Na benzoate was discontinued, and Na phenylbutyrate replaced it at a dose of 464 mg/kg/d po. DOL 2, following a meal during the first week of therapy, the patient's ammonia level was 93 µmol/L (neonate normal range 0-90 µmol/L). After a week on treatment, his ammonia level following a meal was 53 µmol/L. Protein was introduced to the diet gradually, and sodium phenylbutyrate and arginine were switched to oral therapy.

The results of a liver biopsy performed at DOL 6 is shown below in Table 30. These results revealed low basal enzyme activity and no response to arginine stimulation.

Table 30: Patient 15's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	12.00	pmol/min/g prot	> 34
(b) (6)	Liver biopsy	NAGS + Arg		pmol/min/g prot	> 144

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1 and Subject Profile, sponsor's table, page 20

In March 2003, a DNA test was performed that confirmed a heterozygous genetic mutation for NAGS deficiency (Table 31).

Table 31: Patient 15's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
March 2003	Het NAGS deficiency	W484R	N/A	heterozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Treatment with carglumic acid was initiated on August 20, 1999 after the result of the biopsy was known at a dose of 126 mg/kg/d (150 mg tid). The dose was later reduced on March 8, 2003 to 12 mg/kg/d (200 mg q d) and then discontinued during the same month when the DNA test results were made available. Protein intake was restricted until February 26, 2003 when there were no further restrictions.

Previous or Concomitant Therapy

Patient 15's family history led him to begin receiving therapy DOL 1 with IV sodium benzoate and arginine. Sodium phenylbutyrate was slowly reduced to a dose of 113 mg/kg/d at the age of one year in August of 2000. In March of 2003, when carglumic acid was discontinued, phenylbutyrate was re-initiated at a dose of 1200 mg/d and later reduced to 300 mg/d. Arginine was decreased to 3 mmol and discontinued after August 2003 when the DNA test results became available. The patient began treatment with carnitine in July of 2000 at a dose of 19 mg/kg/d.

Medical officer comments

It is not clear whether phenylbutyrate was ever discontinued as of the last recorded visit on March 11, 2003.

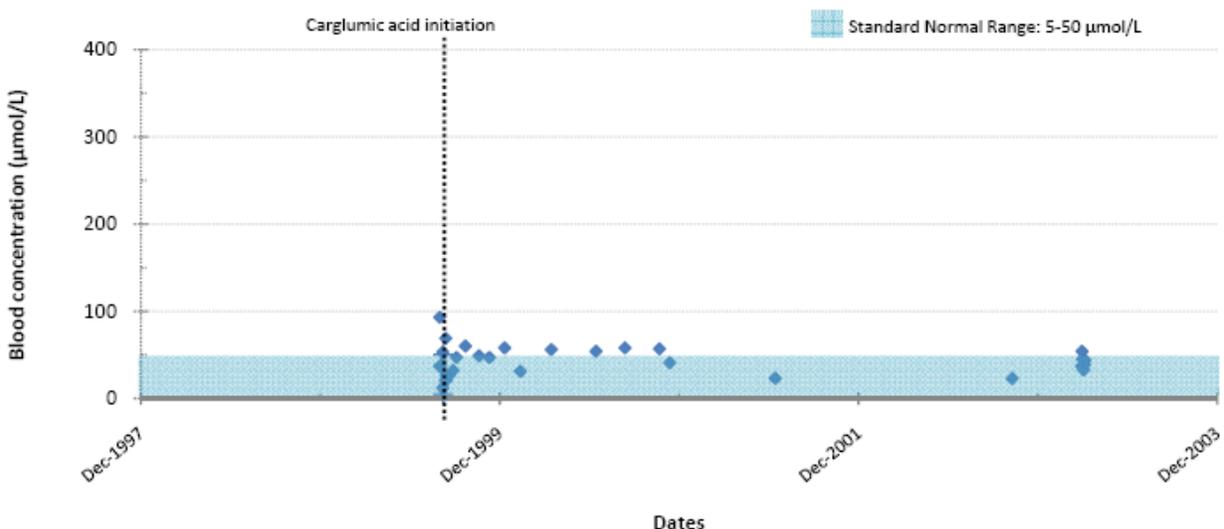
Growth and Development

This patient developed normally and never experienced any symptoms associated with hyperammonemia. He started walking and speaking at 12 months. Developmental tests performed at 22 months of age showed age equivalence in his development.

Patient 15's Plasma Ammonia Levels

Patient 15's plasma ammonia levels were reported to be within normal limits prior to initiation of carglumic acid therapy except for a level of 93 $\mu\text{mol/L}$, which occurred on August 6, 1999 (neonate normal range 0-90 $\mu\text{mol/L}$). Two days prior to initiation of carglumic acid treatment August 18, 1999), patient's ammonia level was noted to be 69 $\mu\text{mol/L}$ one hour following a meal. While on carglumic acid therapy, patient's ammonia levels ranged from 23 to 60 $\mu\text{mol/L}$ prior to the discontinuation of carglumic acid treatment in March 2003. Figure 35 depicts Patient 15's ammonia levels before and after treatment with carglumic acid.

Figure 35: Patient 15's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

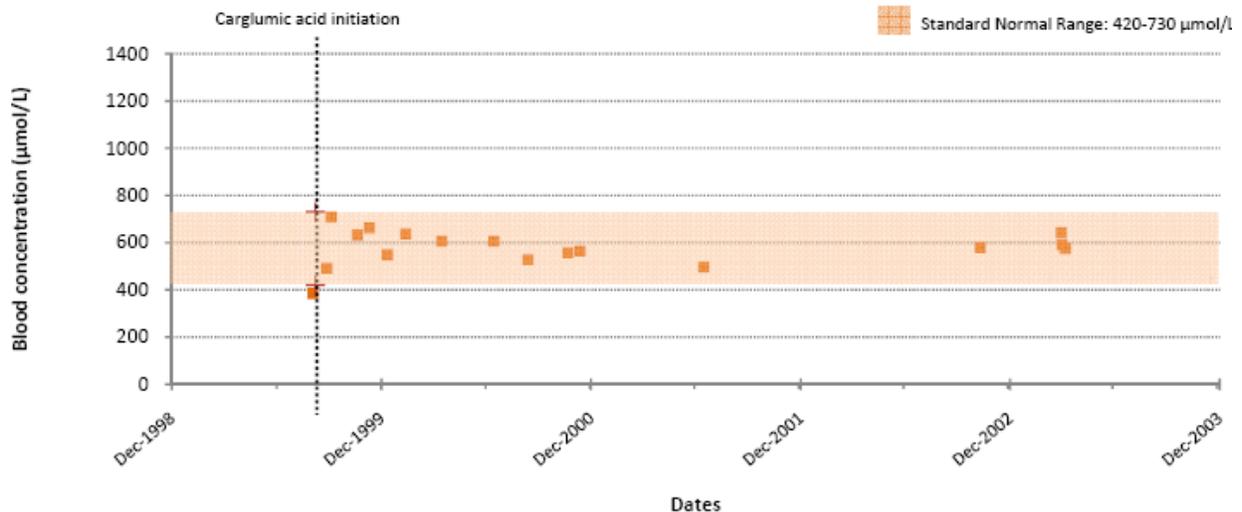
Medical officer comments

Although the patient has had slight elevations of ammonia between 54-60 µmol/L in the years from September 27, 1999 to March 5, 2003 while receiving carglumic acid therapy, he remained asymptomatic and had normal neurological development documented. Patient's treatment with carglumic acid was discontinued after 3.6 years of exposure due to the DNA test results and his clinically asymptomatic condition.

Patient 15's Plasma Glutamine Levels

Patient 15's glutamine levels were within normal range except for one pre-carglumic acid treatment level of 385 µmol/L (normal range 400-1000 µmol/L). Post initiation of treatment with carglumic acid, patient had normal glutamine levels until the last recorded value on (b) (6). Figure 36 depicts Patient 15's glutamine levels before and after treatment with carglumic acid.

Figure 36: Patient 15's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

Patient 15's Plasma Citrulline Levels

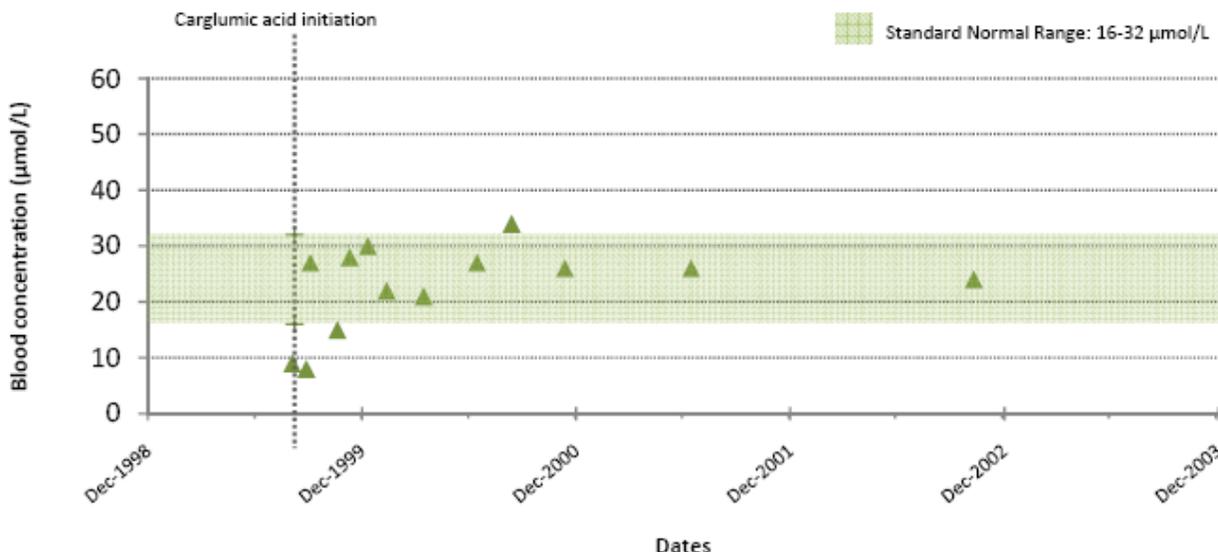
The majority of patient 15's citrulline levels were within the normal range post initiation of treatment with carglumic acid except for 2 citrulline levels obtained at the following time points:

September 2, 1999: low at 8 µmol/L (normal range 15-30 µmol/L)

August 17, 2000: high at 34 µmol/L

There was one citrulline level obtained on August 9, 1999, prior to initiation of treatment with carglumic acid, and it was documented to be low at 9 µmol/L. Figure 37 depicts Patient 15's citrulline levels before and after treatment with carglumic acid.

Figure 37: Patient 15's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

Through the years (September 9, 1999 to October 14, 2002), the patient's citrulline levels have been between 15-34 µmol/L while on carglumic acid therapy. No data is available on citrulline levels after the patient discontinued carglumic acid therapy.

Narrative for Patient 16

Patient 16 was born a male child at term on (b) (6). He was asymptomatic until 1996 when behavioral changes occurred. He became oppositional. He began to have learning difficulties in school and developed an aversion to protein-containing foods. On (b) (6), the patient presented with confusion, memory problems, focal cerebral edema and hyperactivity in the bilateral temporal region seen in an electroencephalogram (EEG). He had no seizures and no hepatomegaly, and his CSF was described as normal. He was subsequently hospitalized with hypothermia, impaired consciousness, and a focal EEG abnormality. Patient 16 was then treated for herpes encephalitis.

On (b) (6), the patient had an episode of confusion, vomiting, and headache 3 hours following a meal. He had a plasma ammonia level of 356 µmol/L. He received a high caloric, low protein diet. He was then transferred to a metabolic unit where a urea cycle defect was suspected, either NAGS deficiency or CPS deficiency, because of the presence of normal orotic aciduria. Over a five week period, the patient received a combination of protein restriction, sodium benzoate, sodium phenylbutyrate, and arginine. Despite these interventions he continued to have episodes of hyperammonemia between 181-290 µmol/L. He exhibited multiple symptoms such as mydriasis, fever, vomiting, cough, tracheal pain, headache and myosis.

On (b) (6), the patient presented with a combination of hyperammonemia (407 $\mu\text{mol/L}$), hyperglutaminemia, and hyperargininemia. He underwent a duodenal biopsy. Table 32 displays the duodenal biopsy results, which showed normal activity levels of the CPS and OTC enzymes.

Table 32: Patient 16's results of duodenal biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	duodenal biopsy	CPS 1	0.14	mmol/h/mg prot	0.1-0.17
(b) (6)	duodenal biopsy	OTC	9.10	mmol/h/mg prot	5.90-14.30

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

Medical officer comments

The description of the EEG findings ("bilateral temporal hyperactivity") and the clinical significance of these findings is difficult to interpret. The focal EEG abnormality that led to treatment of herpes encephalitis was not well characterized in the narrative or the subject profile provided.

At that point, physicians suspected he had NAGS deficiency and he started therapy with carglumic acid on (b) (6) at a dose of 100 mg/kg/d (1500 mg tid). As his metabolic markers began to quickly normalize, his dose of carglumic acid was lowered to 1000 mg tid one day later. On the third day of treatment, his dose was again lowered to a total daily dose of 1500 mg (500 mg tid). As of 2008, his treating physician has confirmed that he is treating Patient 16 at a total daily dose of 1000 mg. Protein intake was unrestricted following the initiation of carglumic acid. In (b) (6), few months after starting treatment with carglumic acid, the patient underwent a liver biopsy which showed both low basal NAGS activity and low arginine stimulated NAGS activity (see Table 33).

Table 33: Patient 16's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS	24.00	mIU/mg prot	>12
(b) (6)	Liver biopsy	NAGS	30.00	nmol/min/g prot	34 -203.0
(b) (6)	Liver biopsy	NAGS + Arg	46.00	nmol/min/g prot	144 - 320.0

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 2

No DNA testing has been reported. The sponsor was able to obtain information from Patient 16's physician that the patient had a homozygous mutation of the NAGS gene. However, the sponsor never received a written report from the treating physician to confirm the DNA test results.

Previous or Concomitant Therapy

Since the diagnosis of a urea cycle disorder in December of 1999, the patient was treated with standard therapies, which included arginine (700 mg), sodium benzoate (250 mg), carnitine (150 mg), and sodium phenylbutyrate (250 mg). Standard treatment was stopped on (b) (6) prior to the initiation of carglumic acid on January 28,

2000. While the patient received standard therapy, his ammonia level ranged from 16-495 $\mu\text{mol/L}$.

Growth and Development

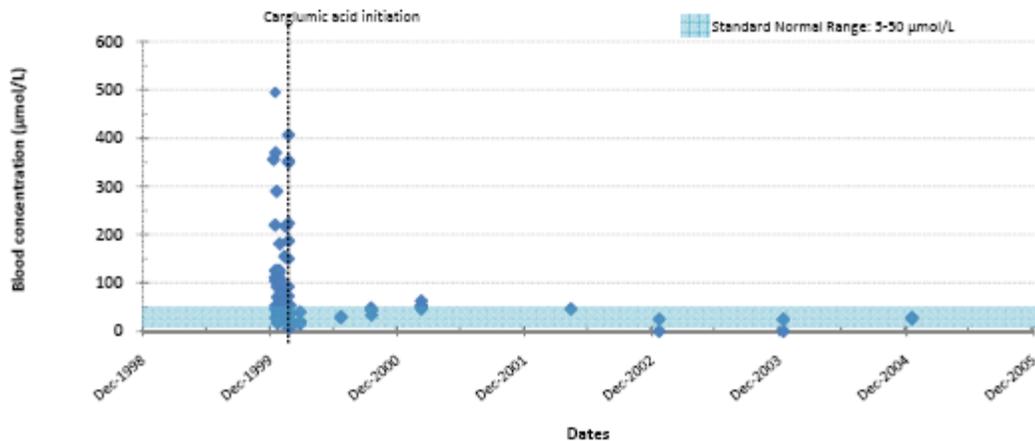
Patient 16 did not have any more episodes of hyperammonemic decompensation following the initiation of carglumic acid. He developed normally, and did not experience any neurologic or psychiatric sequelae.

Patient 16's Plasma Ammonia Levels

Patient 16's plasma ammonia levels did not respond well to standard therapy. However, following the initiation of carglumic acid on (b) (6), the patient did not have any further episodes of hyperammonemia. Ammonia levels decreased from a high of 407 $\mu\text{mol/L}$ to 353 $\mu\text{mol/L}$, 2 hours post initiation of carglumic acid. Eight hours after initiation of carglumic acid, ammonia levels normalized at 23 $\mu\text{mol/L}$. Patient 16 continued to exhibit normal ammonia levels (4 to 48 $\mu\text{mol/L}$) throughout the duration of treatment with carglumic acid except on (b) (6) when his levels had slightly increased above normal (51-63 $\mu\text{mol/L}$).

Figure 38 depicts the patient's ammonia levels before and after treatment with carglumic acid.

Figure 38: Patient 16's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

Because the patient had multiple ammonia samples drawn on the day treatment was initiated, there was a clear documented trend of decreasing ammonia levels over an 8 hour window. His ammonia level was at 407 $\mu\text{mol/L}$ prior to initiation of treatment and decreased at 2 hours to 353 $\mu\text{mol/L}$, then to 350 $\mu\text{mol/L}$ at 3 hours, then to 187 $\mu\text{mol/L}$ at 4.5 hours, then to 22 $\mu\text{mol/L}$ at 6 hours and remained normal at 23 $\mu\text{mol/L}$ 8 hours after initiation of carglumic acid treatment.

Patient 16's Plasma Glutamine Levels

Patient 16's glutamine levels were elevated in the range of 800 to 1806 $\mu\text{mol/L}$ prior to initiation of carglumic acid therapy. Glutamine levels normalized 24 hours post initiation of treatment with carglumic acid except at the following 3 timepoints:

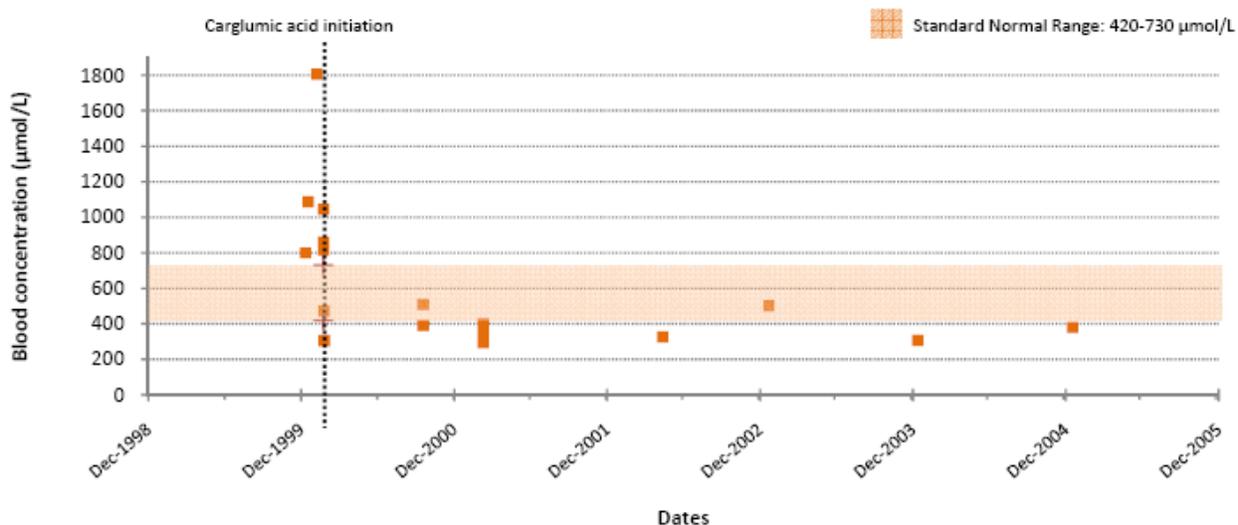
January 29, 2000: high at 472 $\mu\text{mol/L}$ (normal range 332-366 $\mu\text{mol/L}$)

September 22, 2000: high at 508 $\mu\text{mol/L}$ and 391 $\mu\text{mol/L}$

December 26, 2002: slightly high at 502 $\mu\text{mol/L}$ (normal range 170-500 $\mu\text{mol/L}$)

Figure 39 depicts Patient 16's glutamine levels before and after treatment with carglumic acid.

Figure 39: Patient 16's glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

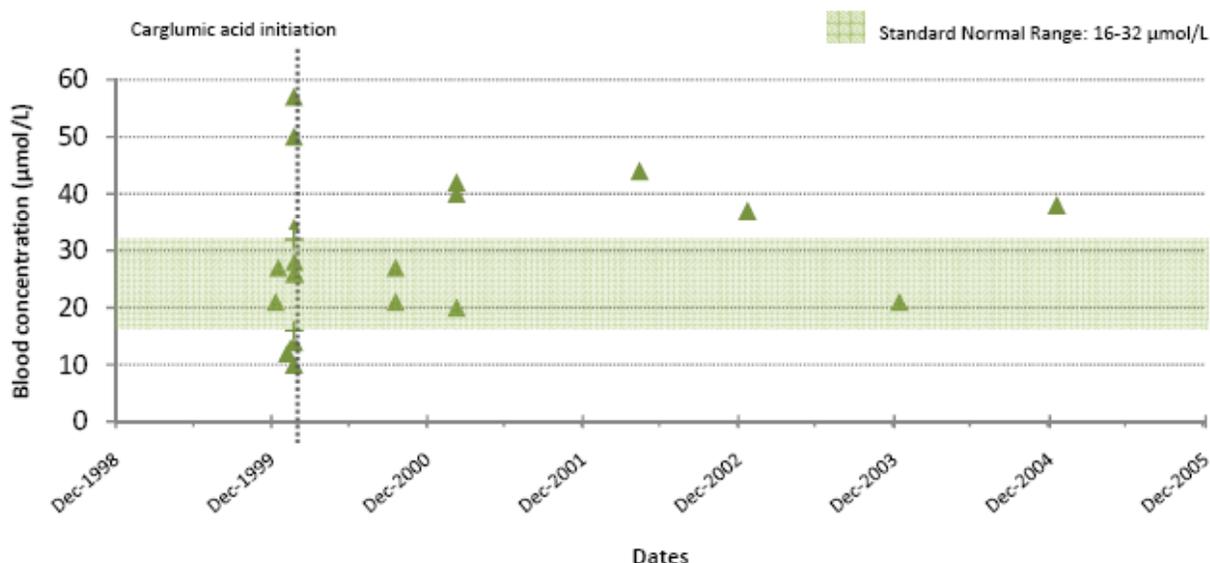
Glutamine levels decreased with initiation of carglumic acid therapy; however, the etiology of the abnormal glutamine levels at the 3 timepoints is unclear.

Patient 16's Plasma Citrulline Levels

Patient 16's citrulline levels were low in the range of 10 to 27 $\mu\text{mol/L}$ (normal range 28-50 $\mu\text{mol/L}$) prior to initiation of therapy with carglumic acid. With carglumic acid treatment, the majority of citrulline levels normalized, but his levels continued to fluctuate in the slightly low range of 20 to 27 $\mu\text{mol/L}$. He did have one documented elevated citrulline level at 57 $\mu\text{mol/L}$ 8 hours post initiation of carglumic acid treatment.

Figure 40 depicts the citrulline levels measured before and after starting treatment with carglumic acid.

Figure 40: Patient 16's citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

There was no clear trend identified for the citrulline levels for the duration of treatment with carglumic acid; however, patient's citrulline levels increased towards the normal range 24 hours after treatment with carglumic acid was started.

Narrative for Patient 18

Patient 18 was born a female at term, (b) (6), the fourth child. Her first sister died at the age of six months from complications secondary to hyperammonemia, and her second sister (b) (6) and her brother, (b) (6) were receiving treatment with carglumic acid for NAGS deficiency at the time of her birth. As a result of patient 18's family history, carglumic acid therapy began on DOL 4 at a dose of 100 mg/kg/d (100 mg tid) prior to the development of symptoms of hyperammonemia.

A liver biopsy performed on (b) (6), DOL 3, showed both low basal NAGS activity and low arginine stimulated NAGS activity. In the biopsy results shown below in Table 34, there was no testing of enzymatic activity for CPS 1 and OTC.

Table 34: Patient 18's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	8.00	pmol/min/mg prot	>34
(b) (6)	Liver biopsy	NAGS + Arg	32.00	pmol/min/mg prot	>144

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

Results of DNA testing shown below in Table 35 revealed a heterozygous mutation for the NAGS gene.

Table 35: Patient 18's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
March 2003	Het NAGS deficiency	W484R	N/A	heterozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

The DNA test results combined with a lack of symptoms in Patient 18, led to a decrease, then a discontinuation of carglumic acid over a period of one week in March 2003. Her last recorded dose on March 8, 2003 was 16 mg/kg/d.

Previous or Concomitant Therapy

At birth, arginine and sodium phenylbutyrate were initiated. The dose of arginine was variable, however, the sodium phenylbutyrate dose was maintained at 1200 mg/d. In March 2003, sodium phenylbutyrate was decreased and then discontinued over a one week period.

Medical officer comments

No details were provided regarding the variable dosing of arginine.

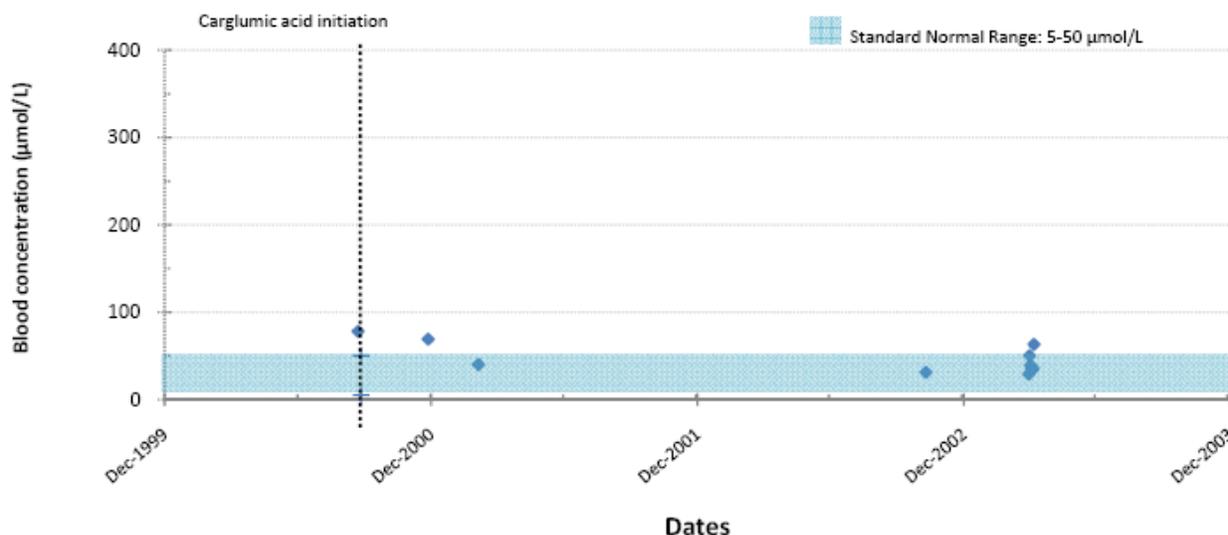
Growth and Development

This patient developed normally and without any neurologic or psychomotor problems.

Patient 18's Plasma Ammonia Levels

Patient 18's ammonia levels remained in the range of 29 to 69 µmol/L post initiation of treatment with carglumic acid but was not higher than 78 µmol/L, which was the pre-treatment ammonia level. Figure 41 depicts the patient's ammonia levels before and after treatment with carglumic acid.

Figure 41: Patient 18's Ammonia levels Pre and Post exposure to carglumic acid treatment

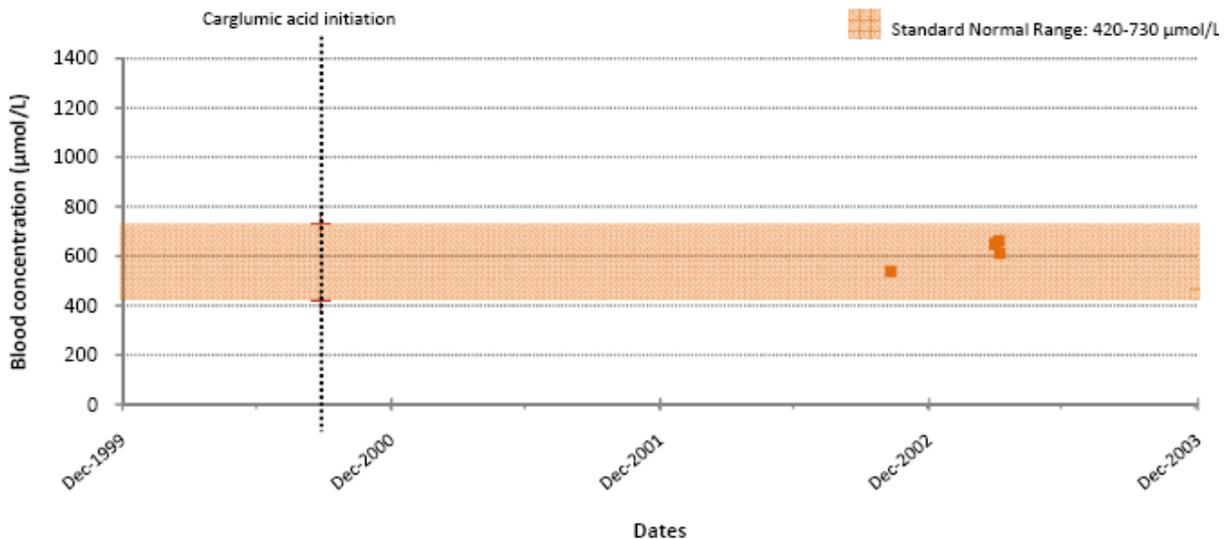


Sponsor's figure, Individual Patient Narrative, page 6

Patient 18's Plasma Glutamine Levels

Patient 18's five glutamine samples, which were obtained post initiation of treatment with carglumic acid demonstrated levels within the normal range. Figure 42 depicts the patient's glutamine levels after treatment with carglumic acid was initiated.

Figure 42: Patient 18's Glutamine levels Post exposure to carglumic acid treatment

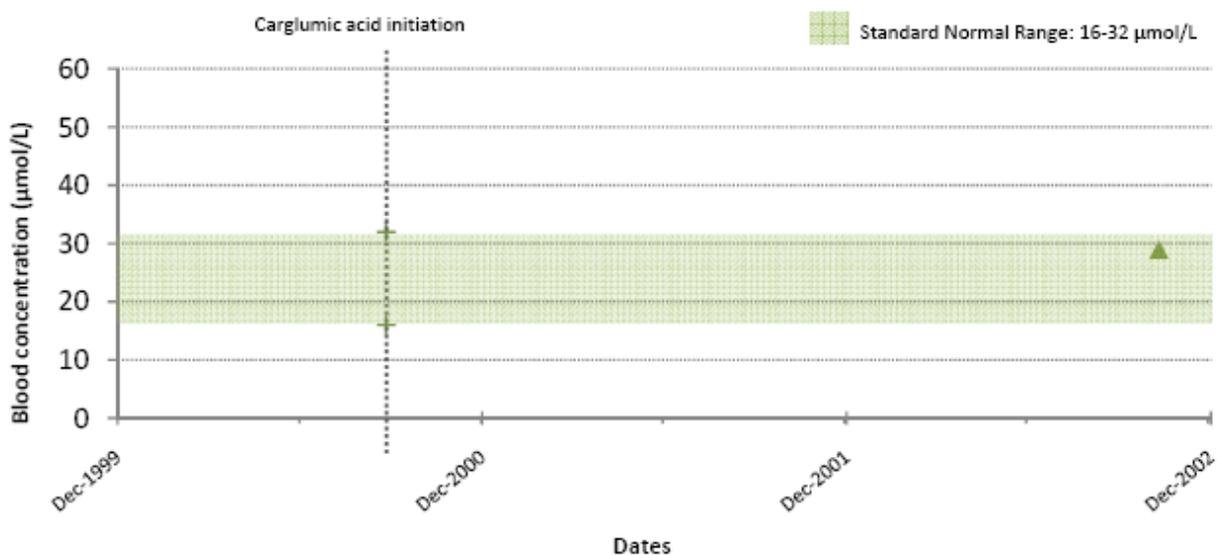


Sponsor's figure, Individual Patient Narrative, page 7

Patient 18's Plasma Citrulline Levels

Patient 18 had only one recorded value for citrulline, which was within normal limits. Figure 43 below demonstrates a citrulline level of 29 µmol/L obtained on October 14, 2002.

Figure 43: Patient 18's Citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Narrative for Patient 26

Patient 26 is a male born (b) (6) at term. No family history was provided. At approximately 2.5 months of life on (b) (6), the patient presented with hyperthermia, vomiting, gastroenteritis without dehydration, hypotonia, hyporeactivity, and general fatigue. The next day (b) (6), he developed moderate hypertonia. On (b) (6), he developed slight axial hypotonia. On (b) (6), (b) (6), the patient's presentation included hepatomegaly (2 cm below the costal margin). Two days later the patient presented with hypotonia, hyporeactivity but reactive to painful stimulation, and a normal abdominal examination. The plasma ammonia was 96 µmol/L on (b) (6). On (b) (6), the patient responded to smile and eye contact, but was noted to be very quiet and lacked a normal cry. Because infection was suspected, he was started on broad spectrum antibiotics (amikacin, ceftriaxone, and augmentin) for six days along with fluids to control dehydration. It was initially believed that sepsis might have caused the hyperammonemia.

On (b) (6), he appeared to have normal eye contact and a smile response, but he also had axial with moderate segmental hypotonia, decreased reactivity, and hepatomegaly (4 cm below the costal margin). At that time, the ammonia level was elevated at 158 µmol/L, and glutamine was also elevated at 911 µmol/L (normal range for glutamine 400-760 µmol/L). The patient was placed on a protein-restricted diet.

The hyperammonemia persisted and peaked at 367 µmol/L. On (b) (6), with an ammonia level of 218 µmol/L and a glutamine level of 841 µmol/L, the patient started therapy with carglumic acid at a dose of 182 mg/kg/d (total daily dose of 1000 mg). At this point, physicians suspected NAGS deficiency based on the combination of hepatomegaly and hyperammonemia. Within 8 hours of beginning therapy with carglumic acid, the ammonia level had decreased to normal (41 µmol/L). The total daily dose (TDD) was 600 mg from March 30, 2004. The last recorded dose on November 30, 2007 was 30 mg/kg/d (TDD of 600 mg). Protein intake restriction was eliminated after the initiation of carglumic acid therapy.

Patient 26 never had any biopsies to test for liver enzyme activities for NAGS, CPS or OTC. A DNA test result shown in Table 36 revealed a homozygous mutation of the NAGS gene.

Table 36: Patient 26's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
March 25, 2002	NAGS deficiency	598T>C (C200R)	Exon 2	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Previous or Concomitant Therapy

In January 2002, for a period of one week, the patient received the following antibiotic therapies, amikacin, ceftriaxone, and augmentin, since infection was the suspected etiology for his elevated ammonia level and associated symptoms. Doses of the antibiotics were not provided.

Growth and Development

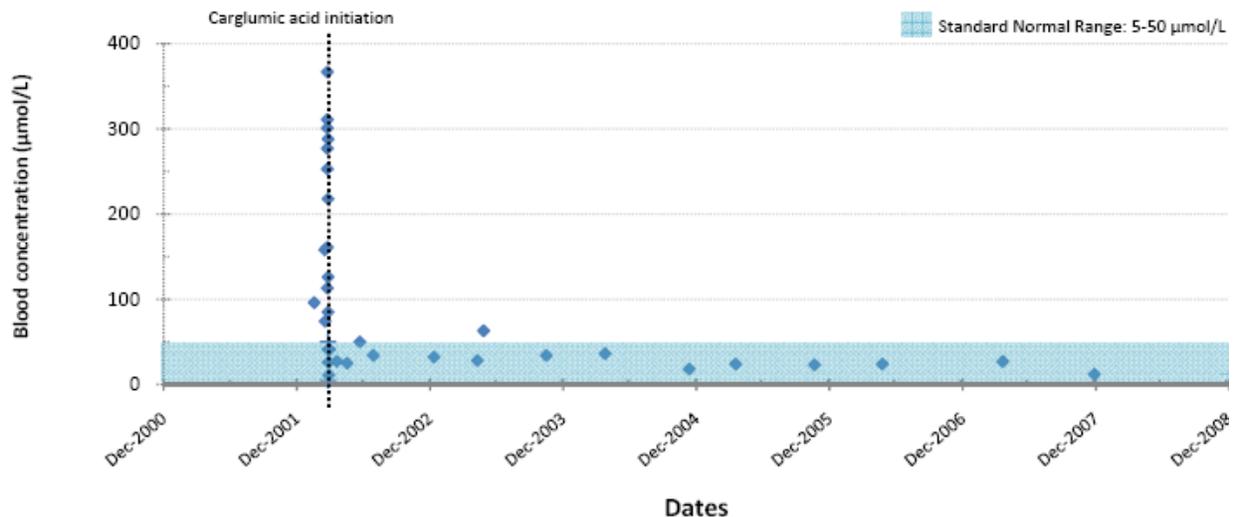
The patient remained small for his age, but his height and weight remained proportionate. He did not experience any further episodes of decompensation secondary to hyperammonemia. He did not suffer any hepatic, neurologic, or psychomotor sequelae. At seven months, he sat upright and had well-controlled hand movements. In July 2002, he was examined and found to be developmentally normal for age. On March 29, 2004, the patient had a normal neurologic exam with “skillful psychomotor performance and speech”. At the last recorded visit (November 30, 2007), the patient was doing well in school without any known neurologic impairments.

Patient 26’s Plasma Ammonia Levels

Patient 26’s ammonia levels decreased from a high of 288 $\mu\text{mol/L}$ to normal at 41 $\mu\text{mol/L}$ within 8 hours of initiation of carglumic acid and remained within normal limits (11-50 $\mu\text{mol/L}$) through the last recorded visit on November 30, 2007.

Figure 44 depicts the patient's ammonia levels before and after treatment with carglumic acid.

Figure 44: Patient 26's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor’s figure, Individual Patient Narrative, page 6

Medical officer comments

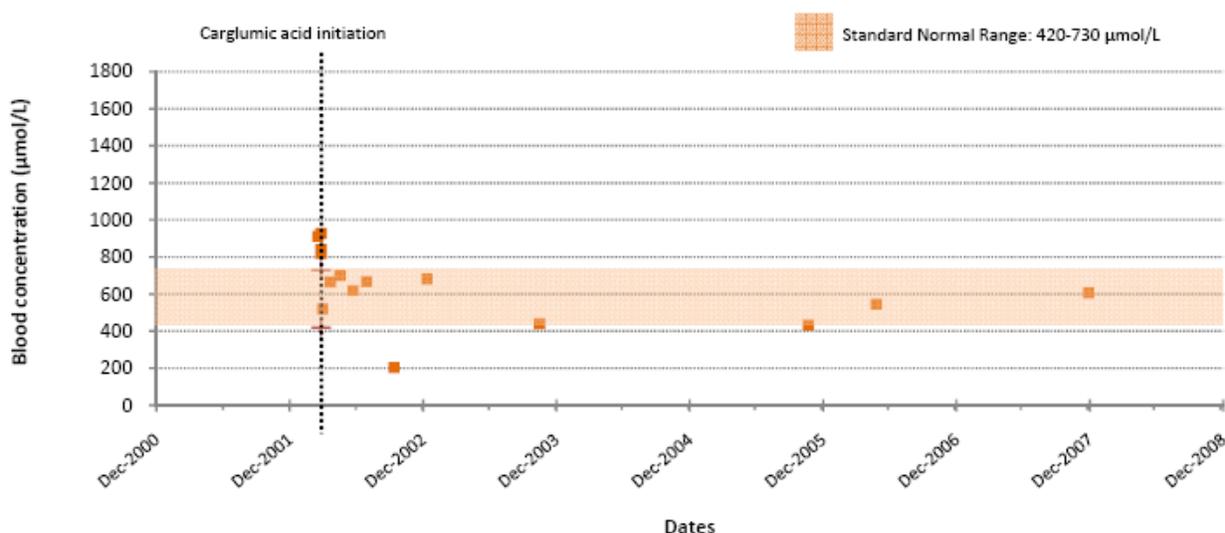
Due to frequent ammonia samples obtained on the day that treatment was initiated with carglumic acid, decreasing ammonia levels are observed starting at the second hour: 288 $\mu\text{mol/L}$ first hour post initiation of carglumic acid therapy, then 126 $\mu\text{mol/L}$ 2 hours post initiation of therapy, 85 $\mu\text{mol/L}$ approximately 4 hours post initiation of carglumic acid therapy.

Patient 26's Plasma Glutamine Levels

Patient 26 had high glutamine levels in the range of 820 to 928 $\mu\text{mol/L}$ (normal range 400-760 $\mu\text{mol/L}$) prior to and on the day treatment was initiated with carglumic acid therapy. Four days (March 5, 2002) post initiation of carglumic acid therapy, glutamine levels normalized except for one low level at 205 $\mu\text{mol/L}$, which occurred on September 16, 2002. No glutamine levels were obtained between March 2 and March 4, 2002.

Figure 45 depicts the patient's glutamine levels before and after treatment with carglumic acid.

Figure 45: Patient 26's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Patient 26's Plasma Citrulline Levels

Patient 26 had citrulline values that were in the normal range at 19 to 21 $\mu\text{mol/L}$ pre treatment with carglumic acid. On the day treatment was initiated, he had 2 high values at 33 $\mu\text{mol/L}$ and 35 $\mu\text{mol/L}$ (normal range 11-21 $\mu\text{mol/L}$).

Post carglumic acid therapy, citrulline levels remained elevated in the range of 23 to 33 except for 3 timepoints where they were noted to be normal

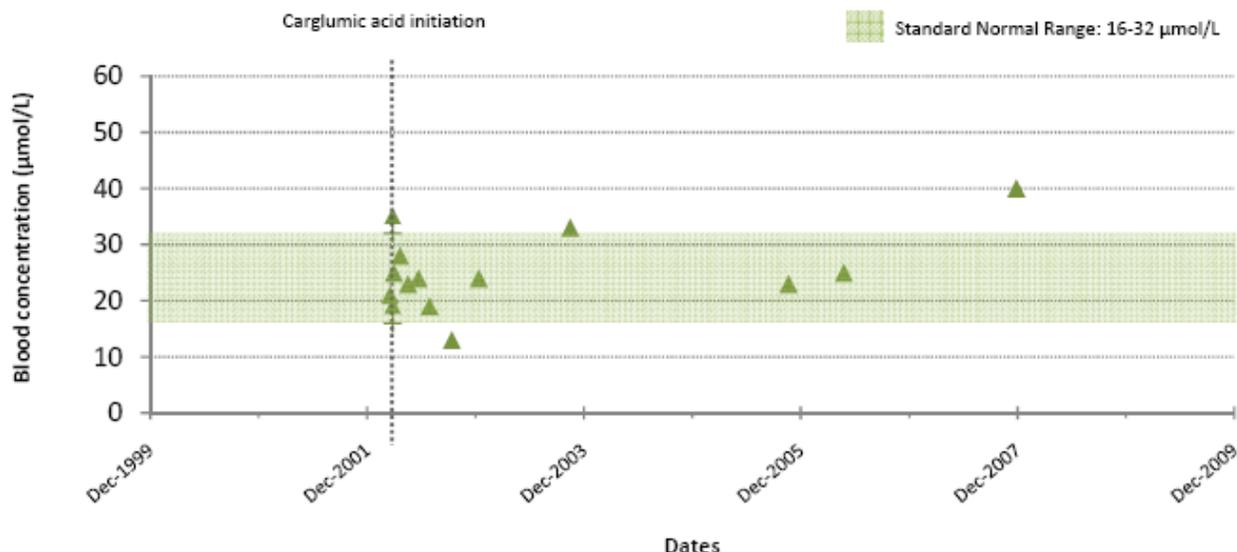
July 3, 2002: 19 $\mu\text{mol/L}$ (normal range 11-21 $\mu\text{mol/L}$)

September 16, 2002: 13 $\mu\text{mol/L}$

November 30, 2007: 40 $\mu\text{mol/L}$ (normal range 23-42 $\mu\text{mol/L}$)

Figure 46 depicts Patient 26's citrulline levels before and after treatment with carglumic acid.

Figure 46: Patient 26's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Narrative for Patient 27

Patient 27 was born at term on (b) (6), a female with a sibling who had a confirmed diagnosis of NAGS deficiency (b) (6). Because of the known family history, and the fact that (b) (6) responded successfully to treatment with carglumic acid, this patient was hospitalized for 2.5 hours after birth to be observed for any signs of hyperammonemia.

On DOL 1, the patient's plasma ammonia level was elevated at 113 µmol/L and 130 µmol/L following breast feeding. Despite elevated ammonia levels, the patient did not exhibit any symptoms of hyperammonemia. NAGS deficiency was the suspected diagnosis based on the family history. No biopsy was performed to test enzyme activity.

On DOL 2 (b) (6), the patient received therapy with carglumic acid at a dose of 244 mg/kg/d (total daily dose 800 mg). Prior to initiation of carglumic acid, the ammonia level was 117 µmol/L, then 132 µmol/L one hour after the first dose, and then 126 µmol/L two hours after the first dose. Six hours after the first dose of carglumic acid, the ammonia level decreased to 55 µmol/L.

Starting (b) (6), the ammonia levels stabilized to within normal limits (3-45 µmol/L). The carglumic acid dose was decreased on April 30, 2002, to 122 mg/kg/d (total daily dose of 400 mg; 100 mg qid). The dose was decreased over the period of approximately one year to 50 mg/kg/d. At the last recorded visit, July 17, 2007, the dose was 48 mg/kg/d (400 mg bid). The glutamine level was elevated on the first day of treatment with carglumic acid (1114 µmol/L) but normalized from April 30,

2002 onwards. At (b) (6) the patient developed hyperbilirubinemia which resolved spontaneously.

DNA test results shown in Table 37 revealed a homozygous mutation for NAGS deficiency.

Table 37: Patient 27's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
February 25, 2003	NAGS deficiency	1228T>C (S410P)	Exon 5	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Previous or Concomitant Therapy

No previous or concomitant therapy for hyperammonemia was initiated.

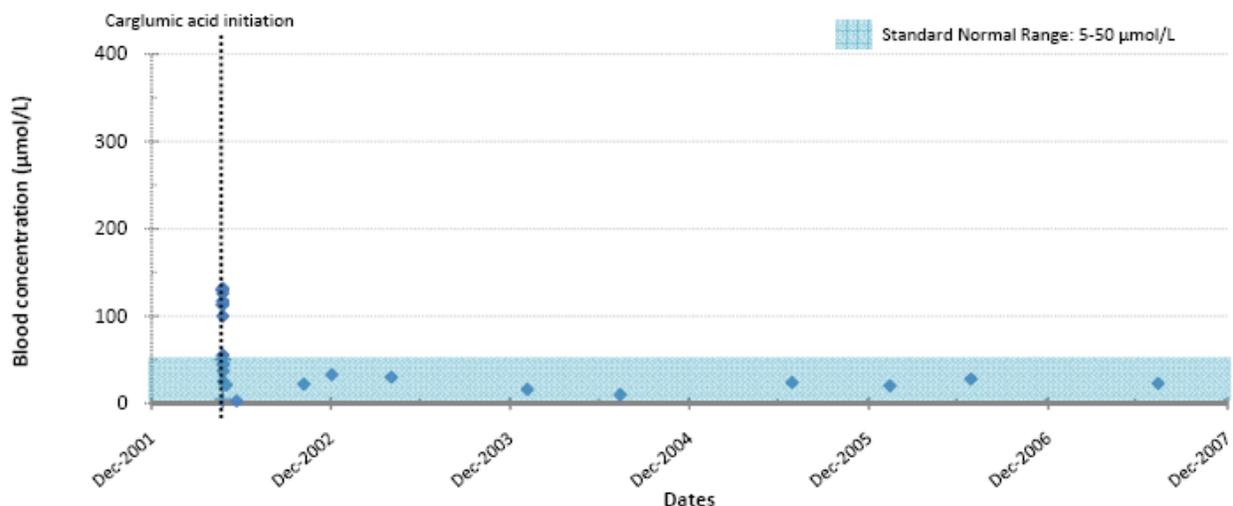
Growth and Development

The patient had a completely normal developmental history except for the fact that the patient's overall growth was below average, although the height/weight ratio remained proportionate.

Patient 27's Plasma Ammonia Levels

Patient 27's elevated ammonia levels decreased to 55 µmol/L within six hours of therapy with carglumic acid but increased to a high of 117 µmol/L fifteen hours post initiation of carglumic acid treatment. Twenty four hours (April 30, 2002) post initiation of carglumic acid therapy, ammonia levels had stabilized to within normal range between 25 to 45 µmol/L. After the April 30, 2002 timepoint, the ammonia levels remained within normal limits for the duration of treatment with carglumic acid. Figure 47 depicts the patient's ammonia levels before and after treatment with carglumic acid.

Figure 47: Patient 27's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 5

Medical officer comments

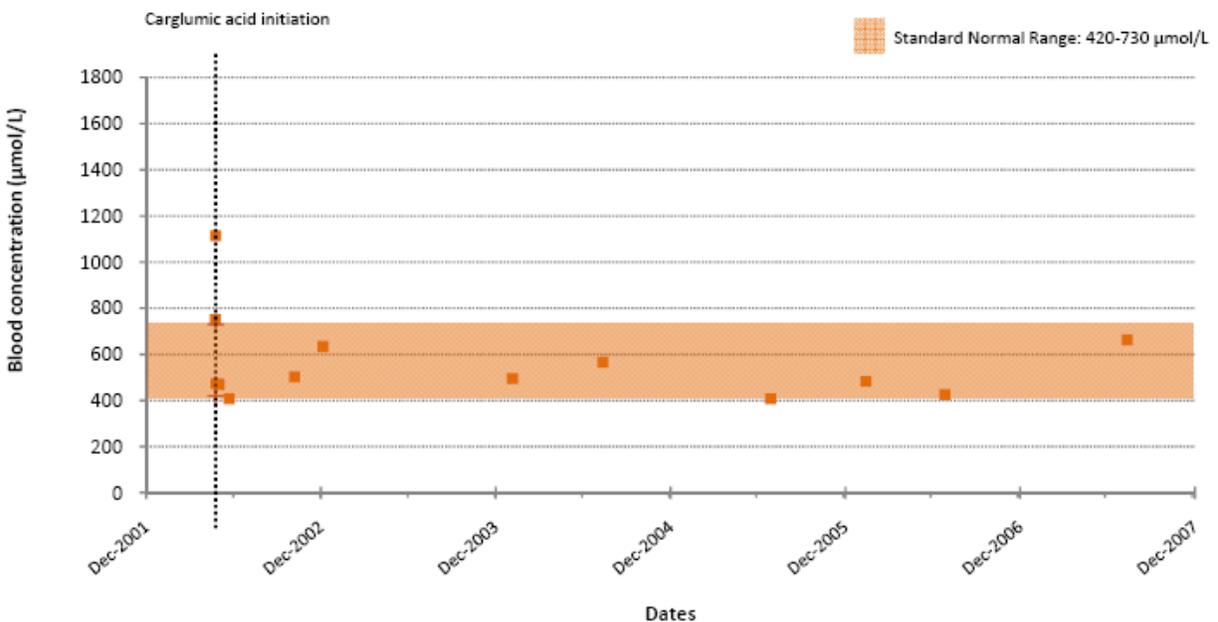
The significance of the fluctuating ammonia levels < 24 hours post initiation of treatment with carglumic acid is difficult to interpret. However, approximately 24 hours post initiation of treatment with carglumic acid therapy without any concomitant medications or protein restriction, the patient's ammonia levels stabilized in the range of 25-45 µmol/L and remained within the normal range for 5 years thereafter.

Patient 27's Plasma Glutamine Levels

Patient 27 had an elevated glutamine level at 1114 µmol/L on April 28, 2002, 24 hours prior to initiation of treatment with carglumic acid. Glutamine levels remained normal post initiation of carglumic acid treatment until the last visit in July of 2007.

Figure 48 depicts the patient's glutamine levels before and after treatment with carglumic acid.

Figure 48: Patient 27's Glutamine levels Pre and Post exposure to carglumic acid treatment

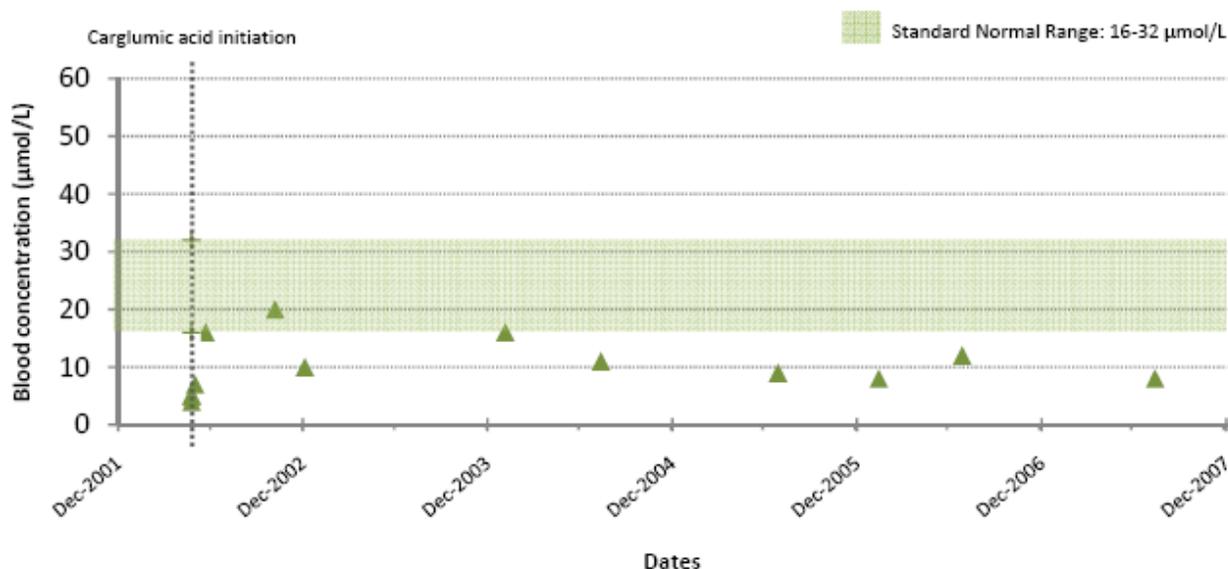


Sponsor's figure, Individual Patient Narrative, page 6

Patient 27's Plasma Citrulline Levels

Patient 27 had one citrulline level that was low at 5 µmol/L prior to initiation of treatment with carglumic acid (normal range 11-21 µmol/L). Post initiation of carglumic acid treatment, the majority of her citrulline levels remained low in the range of 4 to 10 µmol/L. At her last reported visit on July 16, 2007, her citrulline level was low at 8 µmol/L (normal range 19-39 µmol/L) although the patient remained asymptomatic. Figure 49 depicts the patient's citrulline levels before and after treatment with carglumic acid.

Figure 49: Patient 27's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 5

Narrative for Patient 28

Patient 28 was a male born on (b) (6). Thirty six hours after birth, the patient became encephalopathic. The patient received treatment with carglumic acid (chemical grade) as well as an unknown dose of sodium benzoate beginning during his first year of life (1993), after a liver biopsy confirmed the diagnosis of NAGS deficiency. Table 38 reveals the result of a liver biopsy in which NAGS basal activity is reported.

Table 38: Patient 28's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	49.6	nmol/g/wt/hr	N/A

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

Medical officer comments

Relevant family history, type of delivery, birth weight and height was not provided. However, this patient's case was confounded by non-compliance.

Based on the provided biopsy results, it cannot be determined whether a NAGS deficiency existed. Moreover, no DNA test report was provided in this patient's narrative or subject profile.

The patient also had a diagnosis of asthma and McLeod syndrome. When carglumic acid (chemical grade) was initiated in 1993, the patient was placed on protein restriction. However, the amount of protein restriction was not provided. Beginning (b) (6), carglumic acid therapy (pharmaceutical grade) was begun at a dose of 11 mg/kg/d (200 mg bid). When the pharmaceutical grade version of carglumic acid was introduced, the patient was taken off any protein restriction. In (b) (6), the

dose of carglumic acid was reduced to 6 mg/kg/d (200 mg once a day) based on the parents' decision. The last recorded daily dose was 500 mg (250 mg bid) on December 31, 2007. Despite several episodes of decompensation, the parents requested carglumic acid treatment to be discontinued.

Previous or Concomitant Therapy

The patient was treated with chemical grade carglumic acid in 1993 and did not start the pharmaceutical grade carglumic acid until May 2002. An unknown dose of sodium benzoate was introduced in 1993.

Growth and Development

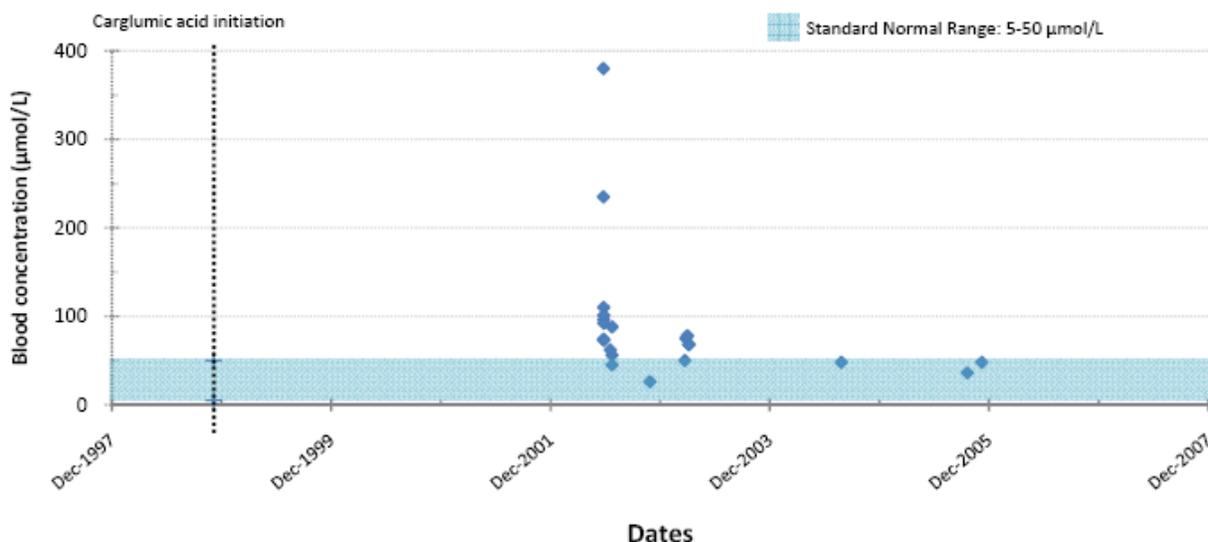
The patient developed normally. According to the treating physician, the patient suffered some episodes of decompensation due to lack of treatment compliance.

Patient 28's Plasma Ammonia Levels

Patient 28's ammonia level took one month to normalize due to a low dose of carglumic acid (TDD: 400 mg to 500 mg administered as either 200 mg bid or 250 mg bid). Prior to initiation of carglumic acid, ammonia levels were in the range of 235 to 380 $\mu\text{mol/L}$. Twenty four hours (b) (6) after initiation of carglumic acid therapy, the ammonia level had decreased to 92 $\mu\text{mol/L}$. Approximately 1 month (b) (6) post initiation of treatment, ammonia levels were in the range of 45 to 88 $\mu\text{mol/L}$.

Figure 50 depicts the patient's ammonia levels before and after treatment with carglumic acid.

Figure 50: Patient 28's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 5

Medical officer comments

Although chemical grade carglumic acid was reportedly started in 1993, Figure 50 provided by the sponsor does not reflect an accurate start date (1998 according to Figure 50). There were no ammonia levels provided prior to the start of therapy with chemical grade carglumic acid. Similarly, the initiation date of pharmaceutical grade carglumic acid is not accurately reflected in Figure 50.

The majority of the patient's ammonia levels remained above the normal range (56 to 110 µmol/L from May 31, 2002 to November 10, 2005) attributed to reported issues of parental non-compliance with carglumic acid therapy

Patient 28's Plasma Glutamine and Citrulline Levels

There was no amino acid chromatography results reported for this patient. Therefore, no graphic summary or other information was provided regarding glutamine or citrulline levels.

Narrative for Patient 29

Patient 29 was a female born (b) (6) with a birth weight of 3.4 kg. Her older brother is Patient 28. Patient 29, given the family history, was prospectively treated with chemical grade carglumic acid from the time of birth. A liver biopsy performed in September 1994 shown in Table 39 demonstrated unclear results. There was no DNA test reported.

Table 39: Patient 29's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	86.1	nmol/g/wt/Wt/hr	N/A

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

Medical officer comments

This patient's case was confounded by reported issues of non-compliance with medical treatment.

Chemical grade carglumic acid was started on (b) (6) due to the known family history; however, compliance was erratic. The initial dose of chemical grade carglumic acid was 250 mg qid along with protein restriction. The carglumic acid dose was later reduced to 250 mg tid. Patient's ammonia levels fluctuated between 23 and 117 µmol/L from June 1994 to April 1998.

In October of 2000, before re-initiating treatment with chemical grade carglumic acid, her plasma ammonia levels ranged from 174-278 µmol/L. Unknown dose of chemical grade carglumic acid along with protein restriction was prescribed. In February 2002, the patient was tired and had vomiting. Chemical grade carglumic acid was prescribed at an unknown dose.

Because of a severe metabolic decompensation and an ammonia level of 254 µmol/L, the patient was hospitalized and placed on pharmaceutical grade carglumic acid

beginning (b) (6) at a low dose of 9 mg/kg/d (200 mg bid). Protein intake was not restricted at this time.

On (b) (6), the dose was further reduced to 4 mg/kg/d at the parents' request to a once a day dose of 250 mg. In September 2002, the patient did not have any clinical symptoms.

On (b) (6), the patient was on a low daily dose of carglumic acid at 100 mg and was admitted to the hospital to discontinue treatment under supervision. When pharmaceutical grade carglumic acid was stopped, her ammonia increased from 35 µmol/L to a maximum level of 233 µmol/L. Intravenous sodium benzoate and phenylbutyrate were introduced first, and later pharmaceutical grade carglumic acid at an unspecified very low dose. The last recorded dose was 5 mg/kg/d for a total daily dose of 250 mg (125 mg bid) on October 22, 2003.

During her hospitalization, the patient developed a fever (up to 39°C) with pneumonia, however the infectious pathogen was not identified. On (b) (6) the patient was screaming and appeared to be hallucinating. She also exhibited extension movements of the arms and bradypnea. The patient was intubated on (b) (6), (b) (6), the patient developed multiorgan failure and oliguria. The patient was then transferred to a pediatric intensive care unit (PICU). A brain MRI performed on (b) (6), revealed signs of encephalopathy without cerebral edema. The patient died early on (b) (6) and no autopsy was performed.

Medical officer comments

The description of the patient exhibiting "extension movements of the limbs" combined with bradypnea might be an attempt to describe the patient's presentation of decerebrate posturing. However, a CT scan and MRI did not confirm cerebral edema.

Previous or Concomitant Therapy

Protein restriction was discontinued in May 2002 when the patient received pharmaceutical grade carglumic acid. The patient also received treatment with unknown doses of sodium benzoate and sodium phenylbutyrate while being treated with chemical grade carglumic acid.

Growth and Development

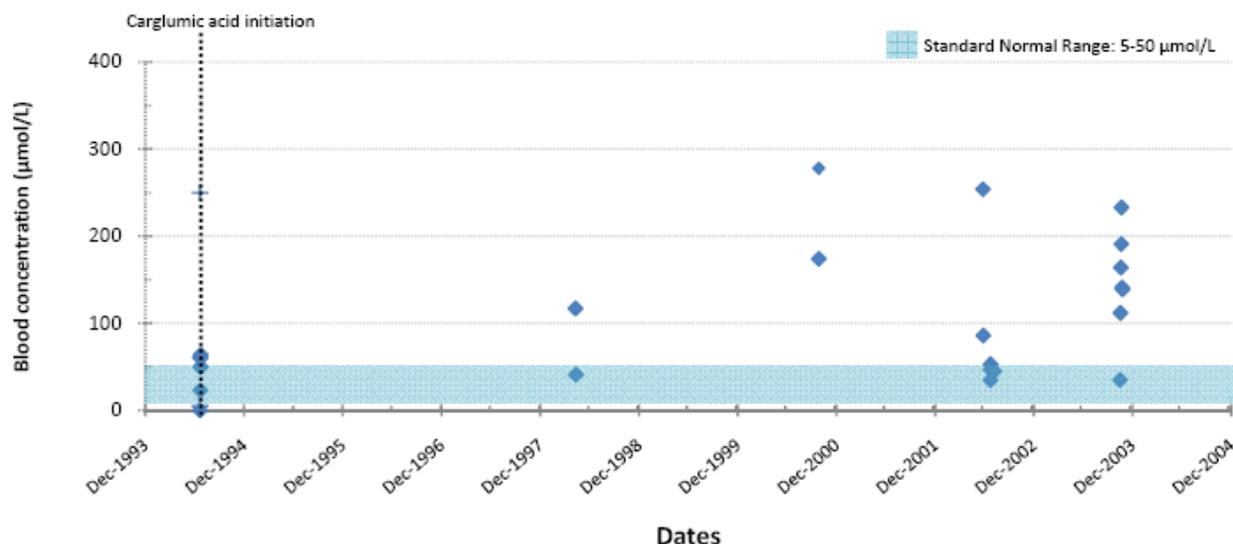
Limited anthropometric data were reported. The patient had multiple episodes of hyperammonemic exacerbations, which were attributed to non-compliance with treatment.

Patient 29's Plasma Ammonia Levels

Patient 29's plasma ammonia levels were erratic, and as Figure 51 indicates, often abnormally high. Non-compliance reportedly contributed to the lack of normalization of

ammonia levels. Figure 51 depicts Patient 29's ammonia levels before and after treatment with carglumic acid.

Figure 51: Patient 29's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

Pre initiation of pharmaceutical grade carglumic acid on May 31, 2002, this patient's ammonia levels were in the range of 23 to 278 µmol/L. Post initiation of pharmaceutical grade carglumic acid, the patient's ammonia levels were in the range of 35 to 233 µmol/L. Non-compliance may have contributed to the abnormal ammonia levels post initiation of pharmaceutical grade carglumic acid therapy.

Patient 29's Plasma Glutamine and Citrulline Levels

There was no amino acid chromatography results reported for this patient. Therefore, no graphic summary or other information was provided regarding glutamine or citrulline levels.

Narrative for Patient 30

Patient 30 was a male born (b) (6). There is no other birth history or family history provided. The first reported plasma ammonia in 1976 was 78 µmol/L. In 1986, he had a plasma ammonia level of 214 µmol/L, and in 1988, his ammonia level was 400 µmol/L. He received treatment with chemical grade carglumic acid since April 1, 1987. Dosing information of the chemical grade carbamyl glutamate was not provided.

In 1995, the patient presented with severe encephalopathy and sepsis. His ammonia level was 525 µmol/L, and after undergoing hemodialysis, his ammonia level was reduced to 100 µmol/L, and eventually to normal levels. He was treated several times with unknown doses of sodium benzoate and arginine. He was placed on a protein restricted diet that is still in effect as of his last recorded visit in April of 2007. After the decompensation in 1995, he was left with severe cerebral dysfunction and paraplegia

with incontinence. Due to frequent episodes of hyperammonemia, NAGS deficiency was suspected and a liver biopsy was performed. Table 40 shows results of liver biopsy that is consistent with NAGS deficiency.

Table 40: Patient 30's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	14.3	nmol/min/g prot	34-103
(b) (6)	Liver biopsy	NAGS + Arg	21.4	nmol/min/g prot	144-320

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

No DNA testing was reported as of the data cutoff date of December 31, 2007.

Medical officer comments

Information regarding his history and clinical presentation that led to initiation of chemical grade carglumic acid in 1987 were not provided, other than the aforementioned ammonia levels.

The patient started treatment with pharmaceutical grade carglumic acid on June 18, 2002 at a dose of 40 mg/kg/d (total daily dose of 2400 mg). This dose was progressively reduced to as low as 10 mg/kg/d (total daily dose of 600 mg) as of his last recorded visit in 2007. Plasma ammonia remained mildly elevated at 61 $\mu\text{mol/L}$ as of his last recorded test on April 17, 2007.

Previous or Concomitant Therapy

The patient received chemical grade carglumic acid, sodium benzoate, and arginine before he began treatment with the pharmaceutical grade carglumic acid.

Growth and Development

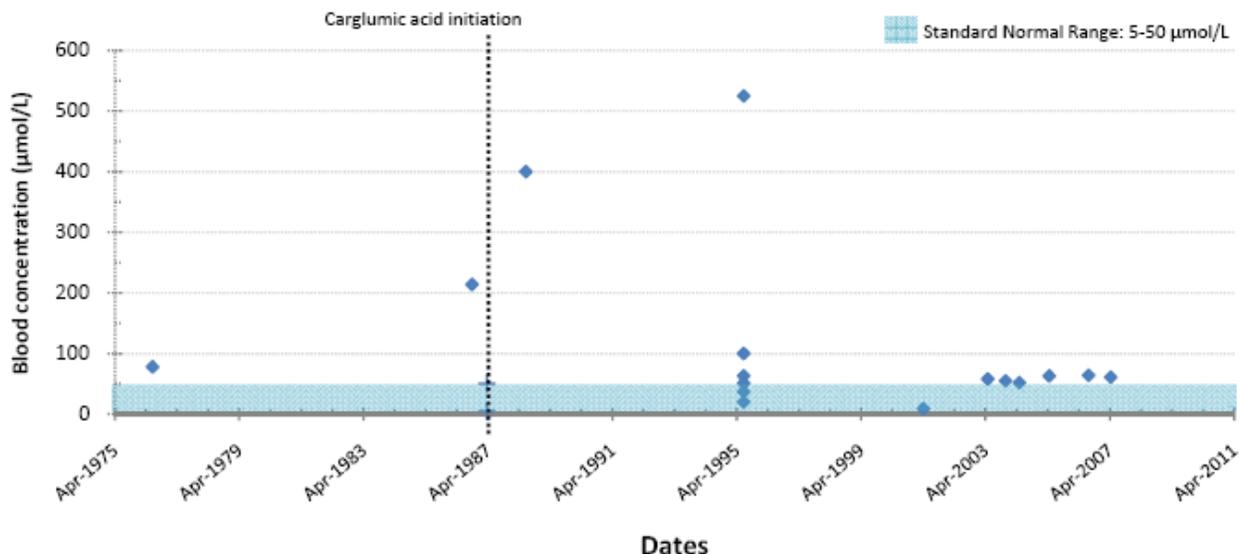
At the time, he began therapy with pharmaceutical grade carglumic acid, he exhibited normal growth parameters but had already developed severe neurological and psychomotor impairment. He had severe intellectual impairment with limited communication skills, incontinence, and paraplegia of the lower extremities. These impairments did not change following the introduction of pharmaceutical grade carglumic acid in 2002.

Patient 30's Plasma Ammonia Levels

While on therapy with the chemical grade carglumic acid, which was started in (b) (6), the patient's ammonia levels were not consistently within normal limits. The treatment in (b) (6) (chemical grade carglumic acid, sodium benzoate, hemodialysis, and arginine) decreased his ammonia level from 525 to 20 $\mu\text{mol/L}$. Starting (b) (6), plasma ammonia levels on pharmaceutical grade carglumic acid were in the 52-64 $\mu\text{mol/L}$ range.

Figure 52 depicts Patient 30's ammonia levels before and after treatment with carglumic acid.

Figure 52: Patient 30's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 3

Medical officer comments

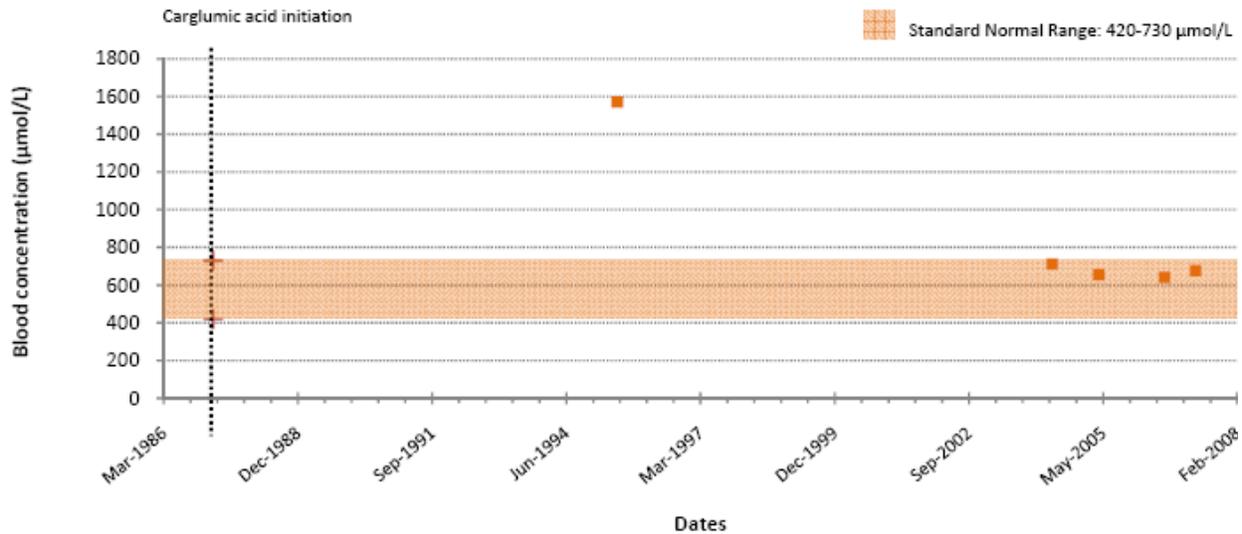
The patient's ammonia level of 78 µmol/L prior to any therapy was obtained in 1976, and he received his first treatment with chemical grade carglumic acid 11 years later in 1987. He had 2 ammonia levels of 214 µmol/L and 400 µmol/L in 1986 and 1988, respectively. However, there was no information provided regarding his symptoms, neurologic and psychomotor developments from 1976 to 1988. The patient presented in 1995 with severe encephalopathy and an ammonia level of 525 µmol/L. Despite being treated with pharmaceutical grade carglumic acid in (b) (6) and lowering of his ammonia levels, he had already sustained irreversible neurologic and psychomotor impairment.

Patient 30's Plasma Glutamine Levels

Patient 30 had one high recorded glutamine level of 1571 µmol/L on (b) (6), which occurred prior to his treatment interventions with sodium benzoate, hemodialysis, arginine, and protein restriction but on-going treatment with chemical grade carglumic acid. All subsequent recorded glutamine levels post initiation of treatment with pharmaceutical grade carglumic acid were within normal limits between 641 and 712 µmol/L (normal range 0-718 µmol/L).

Figure 53 depicts Patient 30's glutamine levels after treatment with carglumic acid (chemical and pharmaceutical grades).

Figure 53: Patient 30's Glutamine levels Post exposure to carglumic acid treatment



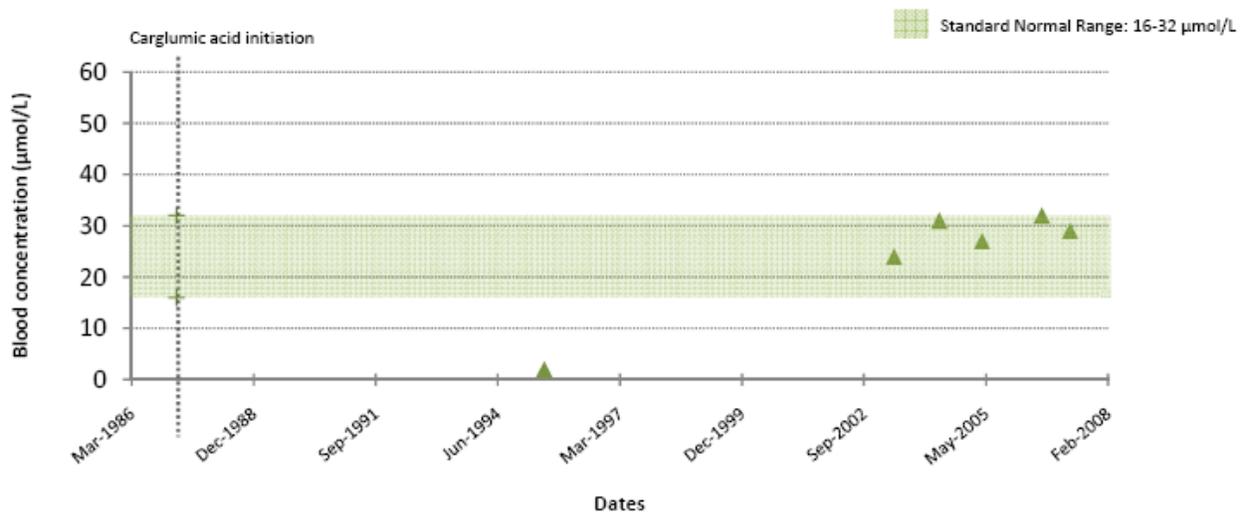
Sponsor's figure, Individual Patient Narrative, page 4

Patient 30's Plasma Citrulline Levels

Patient 30 had one low recorded citrulline level of 2.2 µmol/L on January 1, 1995, which occurred prior to his treatment interventions with sodium benzoate, hemodialysis, arginine, and protein restriction but on-going treatment with chemical grade carglumic acid. Post initiation of pharmaceutical grade carglumic acid, his citrulline levels normalized in the range of 24 to 31.9 µmol/L

Figure 54 below illustrates all citrulline levels obtained post treatment with chemical and pharmaceutical grades carglumic acid.

Figure 54: Patient 30's Citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 3

Narrative for Patient 33

Patient 33 was a female born (b) (6). Family history and information about her height or weight at birth was not provided. On DOL 3 ((b) (6)), after breast feedings, the patient developed vomiting, tachypnea with stridor and sudden uncoordinated movements. Her plasma ammonia level was 316 µmol/L, and her glutamine level was 1186 µmol/L. At that point, physicians suspected a urea cycle defect. Initially, she was treated with phenobarbitone, L-carnitine, and sodium benzoate. Subsequently in (b) (6), her plasma ammonia levels ranged from 150 to 280 µmol/L. The patient underwent a liver biopsy in (b) (6), and the biopsy results shown in Table 41 revealed NAGS deficiency.

Table 41: Patient 33's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	NAGS	2.1	nmol/min/g prot	n/a
(b) (6)	Liver biopsy	NAGS + Arg	2.5	nmol/min/g prot	n/a
(b) (6)	Liver biopsy	CPS 1	1.6	µmol/h/mg prot	0.6-5.5
(b) (6)	Liver biopsy	OTC	72.0	µmol/h/mg prot	13.0-43.0

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

Following the biopsy, Patient 33 was treated with sodium benzoate (at variable doses in the range of 300 to 1000 mg), carglumic acid (initially chemical grade and then later pharmaceutical grade), along with a protein restricted diet. Carglumic acid was started on (b) (6) at a dose of 250 mg tid. No DNA tests have been reported to date.

Previous or Concomitant Therapy

The patient was treated initially with phenobarbitone, L-carnitine, and sodium benzoate beginning on (b) (6). The initial dose of sodium benzoate was 300 mg/d and this dose was reduced to 30 mg/kg/d as of July 2007. The patient had a protein restricted diet, and at last report on July 12, 2007, she was on a 2 g/kg/d diet of protein.

Growth and Development

During the first 5 years of life, the patient was normal for weight and below a z score of -2 for height. There was some improvement in height parameters after the age of four. Information regarding her neurologic and psychomotor development and liver function test results were not provided. There were several hyperammonemic exacerbations but few details were provided. In December 2007, there was a hyperammonemic decompensation that occurred in association with pneumonia, which led to the patient's death.

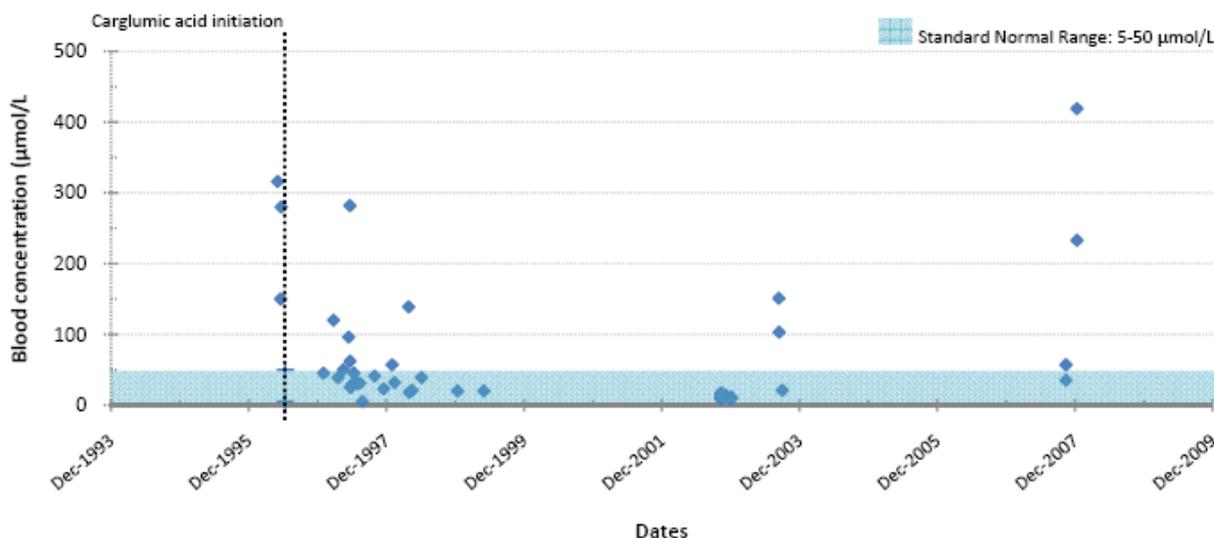
Patient 33's Plasma Ammonia Levels

Patient 33's ammonia level was initially 316 µmol/L on May 8, 1996. Following standard therapy with sodium benzoate, protein restriction, L-carnitine, and phenobarbitone, her plasma ammonia levels ranged from 150-280 µmol/L during May 24 to 27, 1996. She experienced the following hyperammonemic episodes while on treatment with carglumic acid (carglumic acid started on July 18, 1996):

- February 28, 1997 (120 $\mu\text{mol/L}$)
- May 20 to 26, 1997 (96-282 $\mu\text{mol/L}$)
- April 3, 1998 (139 $\mu\text{mol/L}$)
- August 17 to 18, 2003 (103-151 $\mu\text{mol/L}$)
- December 14, 2007 (233-419 $\mu\text{mol/L}$)

Figure 55 depicts Patient 33's ammonia levels before and after treatment with carglumic acid.

Figure 55: Patient 33's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

The date the patient was changed from chemical to pharmaceutical grade carglumic acid was not provided in the individual patient narrative or subject profile.

Patient 33's Plasma Glutamine Levels

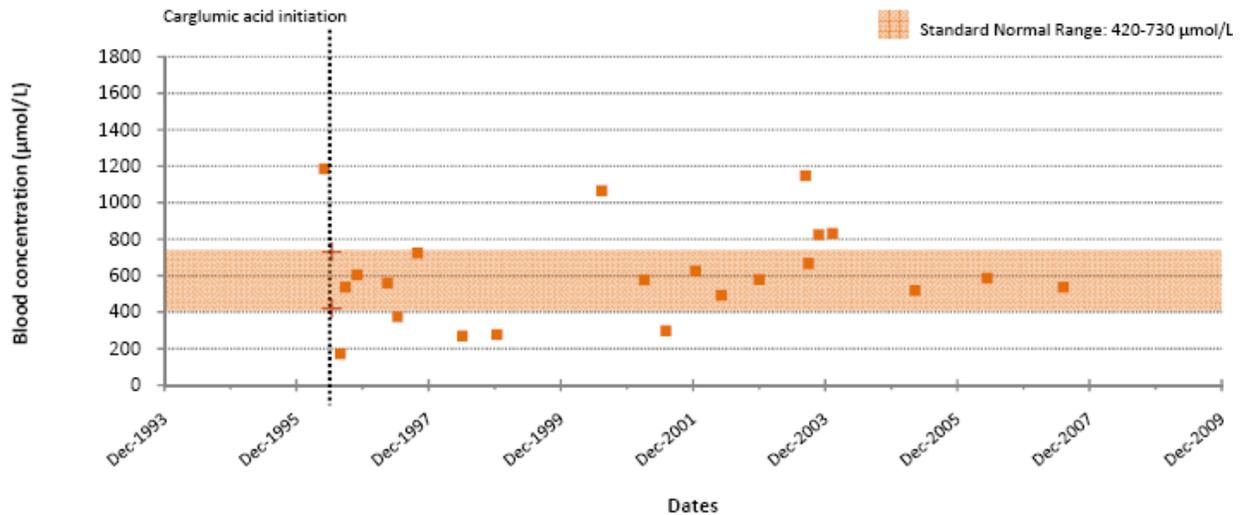
Prior to initiation of treatment with pharmaceutical grade carglumic acid, glutamine level was high at 1186 $\mu\text{mol/L}$ on May 8, 1996. Following initiation of carglumic acid treatment, the glutamine levels for the most part were within the normal range. Fluctuations outside the range of normal (normal range 250-1100 $\mu\text{mol/L}$) included the following:

- August 5, 1996 (171 $\mu\text{mol/L}$)
- August 17, 2003 (1148 $\mu\text{mol/L}$)

The glutamine levels during the severe hyperammonemic decompensation in December of 2007 were not recorded.

Figure 56 depicts Patient 33's glutamine levels before and after treatment with carglumic acid.

Figure 56: Patient 33's Glutamine levels Pre and Post exposure to carglumic acid treatment

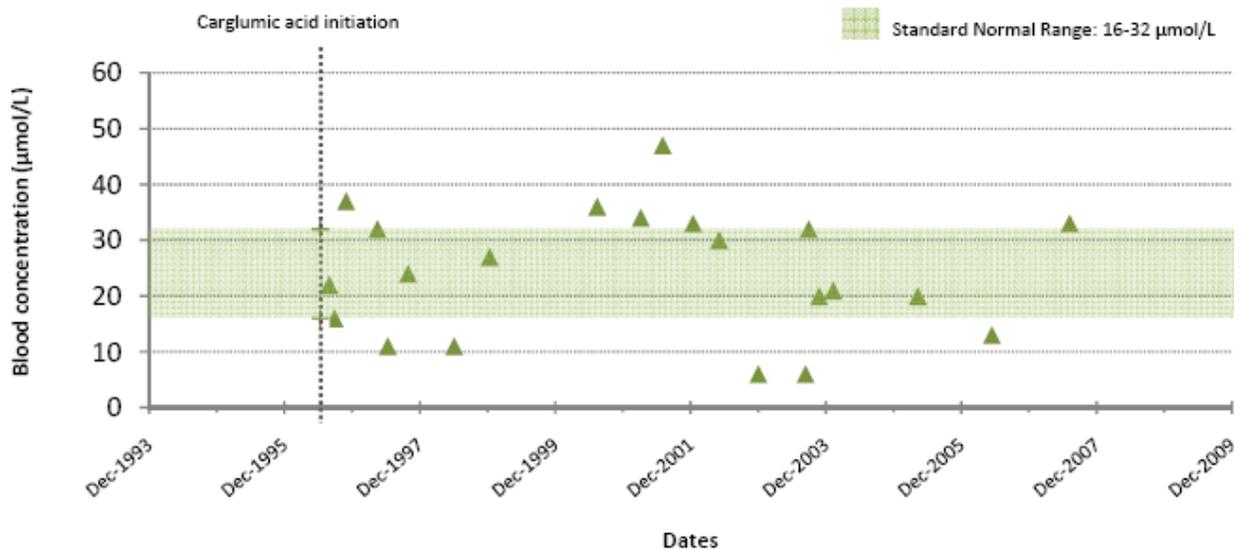


Sponsor's figure, Individual Patient Narrative, page 7

Patient 33's Plasma Citrulline Levels

Patient 33's citrulline levels were within the specific laboratory's normal range between 6 and 47 µmol/L (normal range 0-54 µmol/L) post initiation of carglumic acid therapy. No citrulline levels were obtained prior to treatment with carglumic acid. Figure 57 depicts Patient 33's citrulline levels after treatment with carglumic acid.

Figure 57: Patient 33's citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Narrative for Patient 35

Patient 35 was a male born [redacted] (b) (6). His weight at birth was approximately 3 kg. No further birth or family history was provided. Within the first three days of life,

he developed poor feeding, tachypnea (70/min), hypotonia, lethargy, and seizures. His plasma ammonia levels were in the range of 926-1428 $\mu\text{mol/L}$. He underwent hemodialysis from (b) (6). Concomitantly, he received IV sodium benzoate at a dose of 500 mg/kg/d and arginine (350 mg/kg/d). Carbamazepine was given, but the dose was not provided. Sodium benzoate was decreased and then discontinued on November 20, 2003. Arginine was stopped on November 22, 2003. Carbamazepine was stopped on November 25, 2003.

Beginning November 15, 2003, he received oral carglumic acid at a starting dose of 134 mg/kg/d (100 mg qid). The patient received breast milk and IV glucose from November 17 (DOL 5), and the plasma ammonia level normalized to 12 $\mu\text{mol/L}$ on November 18, 2003. Physicians at the time suspected a diagnosis of transient hyperammonemia of the newborn.

The dose of carglumic acid was reduced from November 22 (70 mg/kg/d) to November 24 (34 mg/kg/d) and then discontinued on November 25, 2003. The patient was re-hospitalized (b) (6) with a plasma ammonia level of 220 $\mu\text{mol/L}$, and the dose of carglumic acid was re-initialized at a dose of 122 mg/kg/d (100 mg qid). At the time of his hospitalization, (b) (6), he also received IV glucose, IV sodium benzoate, and arginine, as well as IV antibiotic therapy. The patient's ammonia level normalized within 24 hours to < 30 $\mu\text{mol/L}$. The dose of carglumic acid was then progressively reduced and concomitant medications were stopped. Since (b) (6) (b) (6) until the last reported visit (b) (6), the dose of carglumic acid was in the range of 42 to 62 mg/kg/d (total daily dose of 250-800 mg a day, divided in two or three daily doses).

No liver biopsy was performed in this patient. In December of 2003, the patient had a DNA test, which showed a homozygous mutation for NAGS deficiency (see Table 42).

Table 42: Patient 35's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
December 2003	NAGS deficiency	R414P/R414P	Exon 7	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Previous or Concomitant Therapy

Protein intake was initially restricted at 0.5 g/kg/d in November 2003; however, it was adjusted to slightly restricted or free levels at 2-3 g/kg/d until the last report in May 2007.

Growth and Development

The patient's initial symptoms resolved after treatment. In January of 2004, he was noted as having hypotonia. Both his hypotonia and hepatomegaly resolved within a few months of initiating treatment. The patient developed normally within the first year of life. A brain MRI done in May 2004 was reported as normal. In July 2004, an exam by the pediatric neurologist was reported as normal without any residual neurologic sequela. In November 2004, he began to walk at 12 months. In January 2005, he

presented with an episode of tremor and slight ataxia. In February 2005, he had another episode of ataxia. No ammonia levels were reported during these 2 episodes; therefore, it was not possible to correlate ammonia levels with the symptoms the patient experienced. In October 2005, he was reported to have normal neurologic and psychomotor development, with appropriate motor skills for his age. As of the last report in May 30, 2007, the patient was developing normally.

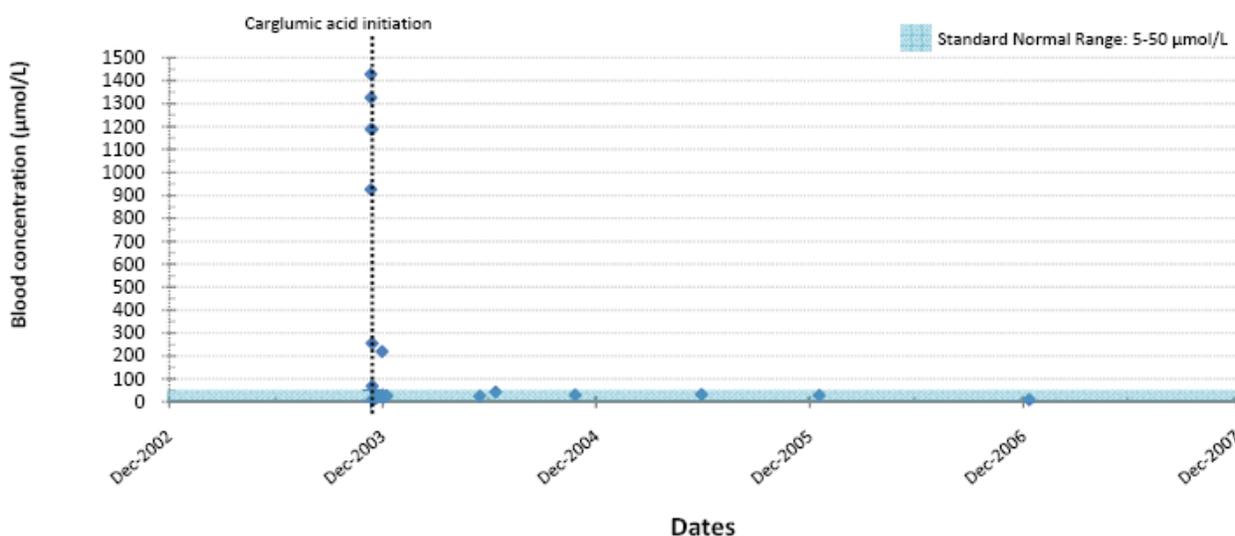
Patient 35's Plasma Ammonia Levels

Patient 35's ammonia levels were as high as 1428 $\mu\text{mol/L}$ prior to therapeutic interventions. A combination of carglumic acid along with other interventions normalized his ammonia levels. In December 2003, when the patient was re-hospitalized with an ammonia level of 220 $\mu\text{mol/L}$, a combined approach, using carglumic acid and other therapies, was utilized to normalize his ammonia.

Twenty four hours (December 5, 2003) post re-initiation of carglumic acid therapy, patient's ammonia levels normalized at 30 $\mu\text{mol/L}$ and remained normal in the range of 9 to 43 $\mu\text{mol/L}$ for the duration of therapy.

Figure 58 depicts Patient 35's ammonia levels before and after treatment with carglumic acid.

Figure 58: Patient 35's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

Despite an extremely elevated ammonia level at 1428 $\mu\text{mol/L}$ prior to carglumic acid therapy, on day 3 (November 18, 2003) of carglumic acid treatment, his ammonia level normalized at 12 $\mu\text{mol/L}$. Twenty four hours (November 16, 2003) post initiation of treatment with carglumic acid, there was a decreasing trend in ammonia levels at 1190

$\mu\text{mol/L}$. At 48 hours (November 17, 2003), the ammonia level had decreased further to 255 $\mu\text{mol/L}$.

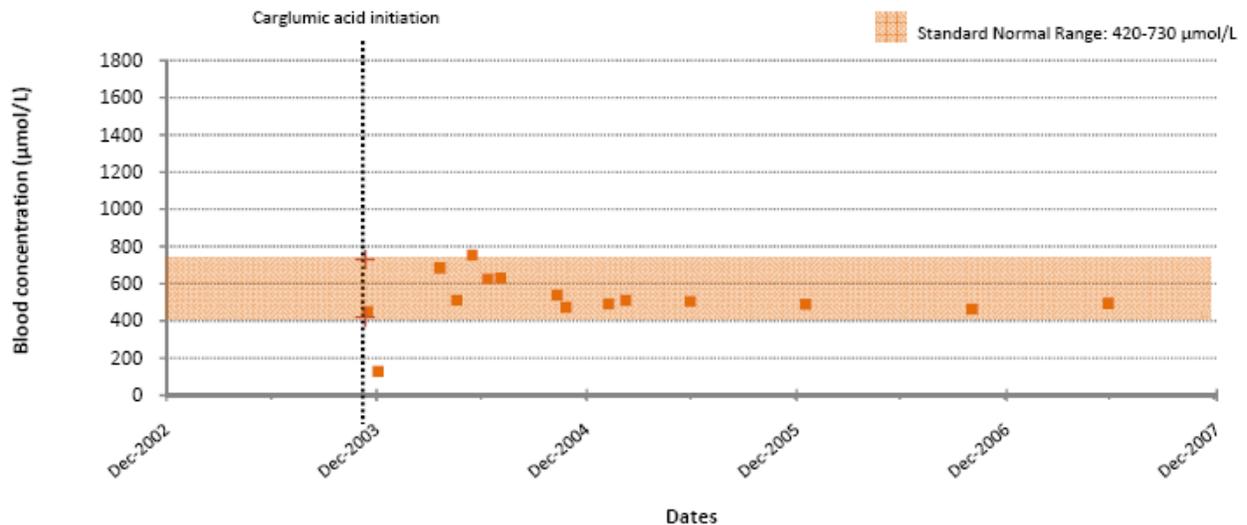
Since January 2004, carglumic acid was the sole therapy used to control the hyperammonemia. His ammonia levels remained in the range of 9 to 43 $\mu\text{mol/L}$ between May 19, 2004 and December 14, 2006.

Patient 35's Plasma Glutamine Levels

Patient 35 had plasma glutamine levels, which were within normal range post initiation of treatment with carglumic acid. No glutamine levels were reported prior to November 19, 2003.

Figure 59 depicts Patient 35's glutamine levels after treatment with carglumic acid.

Figure 59: Patient 35's Glutamine levels Post exposure to carglumic acid treatment

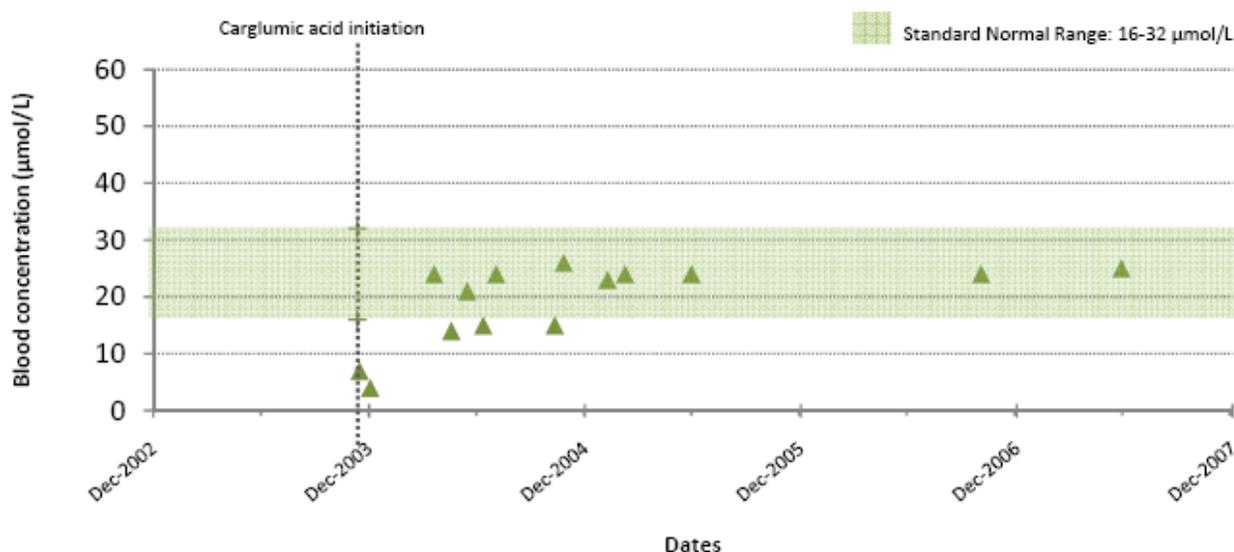


Sponsor's figure, Individual Patient Narrative, page 7

Patient 35's Plasma Citrulline Levels

The patient's citrulline levels were within normal range post initiation of treatment with carglumic acid except for a low citrulline value of 4 $\mu\text{mol/L}$ reported on December 7, 2003 (normal range 5 to 40 $\mu\text{mol/L}$). Figure 60 depicts Patient 35's citrulline levels after treatment with carglumic acid.

Figure 60: Patient 35's Citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Narrative for Patient 36

Patient 36 is a male born (b) (6). His birth weight was 2170 g but it is not known if he was born at term. On (b) (6) the patient was hospitalized presenting with vomiting, failure to thrive, mild hypotonia, tachypnea, and hepatomegaly. He had an ammonia level of 392 µmol/L, elevated glutamine, alanine, and lysine levels with a normal citrulline level. At six months of age, the patient underwent a protein load test. With ingestion of 23 grams of protein, he had an ammonia level of 196 µmol/L, with 15 grams of protein, his ammonia level was 191 µmol/L, and with 8 grams of protein, his ammonia level was 70 µmol/L. Despite a protein-restricted diet of 12 g/d and treatment with sodium benzoate, his ammonia levels remained elevated (73-122 µmol/L). Physicians suspected a diagnosis of hyperammonemia secondary to a urea cycle defect (CPS 1 or OTC deficiency).

A liver biopsy performed in January of 1999 with results shown in Table 43 revealed normal basal activity for OTC and low activity for CPS 1.

Table 43: Patient 36's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	0.68	µmol/h/mg prot	1.34-2.34
(b) (6)	Liver biopsy	OTC	39.9	µmol/h/mg prot	23.9-43.1

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

In May of 1999, the patient had another hyperammonemic crisis and received treatment with a combination of sodium benzoate (218 mg/kg/d; total daily dose 1824 mg) and carglumic acid (150 mg/kg/d; 400 mg tid). The protein in the diet was restricted to less than 2 g/kg/d as of the last report in May 2007.

Because of several episodes of hyperammonemic decompensations, his sodium benzoate was increased to a total daily dose of 5000 mg. During one of the episodes of decompensation on March 30, 2004, the dose of carglumic acid was 200 mg/kg/d; 1000 mg qid). Subsequently, the dose of carglumic acid was reduced to 139 mg/kg/d (800 mg qid) on April 9, 2004, and then on April 10, 2004, it was further reduced to a total daily dose of 1800 mg (600 mg tid). On April 28, 2004, a DNA test result shown in Table 44 confirmed a homozygous genetic mutation for NAGS deficiency.

Table 44: Patient 36's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
April 28, 2004	NAGS deficiency	c.791C>T (T264M)	Exon 3	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 2

By June 20, 2007, the dose of carglumic acid had been slowly reduced to 16 mg/kg/d for a total daily dose of 600 mg (300 mg bid).

Previous or Concomitant Therapy

Citrulline was added to his regimen and was discontinued in January 2006. The patient received 2 g/d starting in March 2004.

Medical officer comments

It is not clear from the information (individual patient narrative and subject profile) provided if Patient 36 was ever on monotherapy with carglumic acid. The patient appears to have remained on a combination of sodium benzoate, carglumic acid and protein restriction.

Growth and Development

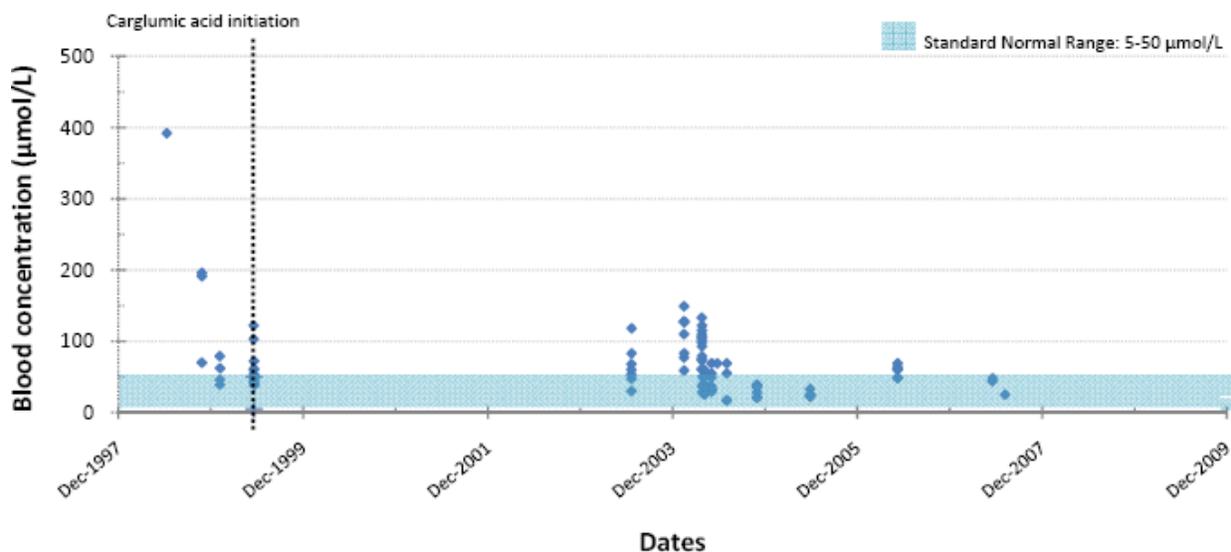
Despite protein restriction and an initial weight greater than 2 standard deviations (SD) below normal, the patient was 1+ SD at 4 years of age. Within the first month of life, Patient 36 had vomiting, failure to thrive, tachypnea, and hepatomegaly. The hepatomegaly regressed somewhat in March 2000 but was again present in (b) (6) following an episode of decompensation (3 cm below the costal margin). The multiple episodes of decompensation affected the patient's neurologic and psychomotor development. In (b) (6), the patient presented with psychomotor retardation, hyperactivity, and problems with concentration. In 2006, no major residual neurologic symptoms from previous decompensations were noted, but psychomotor performance was notable for the presence of dyslexia and dysorthographia.

Patient 36's Plasma Ammonia Levels

Patient 36 was first noted to have an elevated ammonia level at 392 µmol/L in (b) (6) in the newborn period. As Figure 61 below illustrates, there were numerous timepoints where fluctuations occurred in the plasma ammonia levels. After carglumic acid was initiated on May 26, 1999, plasma ammonia levels were within the normal range (38-41 µmol/L) until June of 2003 when the level increased to 118 µmol/L on June 26, 2003. In January 2004, the ammonia levels ranged between 59-149 µmol/L. Ammonia levels

again increased in March 2004 to a range of 73 to 133 $\mu\text{mol/L}$. There was a small increase in May of 2006 to a high of 69 $\mu\text{mol/L}$, and then his ammonia levels were within the normal range up until the last recorded report in July of 2007. Figure 61 depicts Patient 36's ammonia levels before and after treatment with carglumic acid.

Figure 61: Patient 36's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

Despite the initiation of carglumic acid on May 26, 1999 at TDD of 1200 mg (400 mg tid) and continuation of standard therapy (protein restriction and sodium benzoate), the patient had several hyperammonemic exacerbations. In spite of no reports of non-compliance, intolerance to treatment or discontinuations of carglumic acid, the numerous episodes of hyperammonemia may have affected the neurologic and psychomotor development of this patient.

Patient 36's Plasma Glutamine Levels

Prior to (b) (6) and on the day of initiation of carglumic acid therapy, patient had elevated glutamine levels at 799 $\mu\text{mol/L}$ and 891 $\mu\text{mol/L}$, respectively (normal range 323-675 $\mu\text{mol/L}$).

Patient 36's glutamine levels were also elevated at the following time points post initiation of carglumic acid therapy:

- June 25, 2003 (846 $\mu\text{mol/L}$) (normal range 334-666 $\mu\text{mol/L}$)
- January 20, 2004 (847 $\mu\text{mol/L}$)
- March 30, 2004 (1236 $\mu\text{mol/L}$)

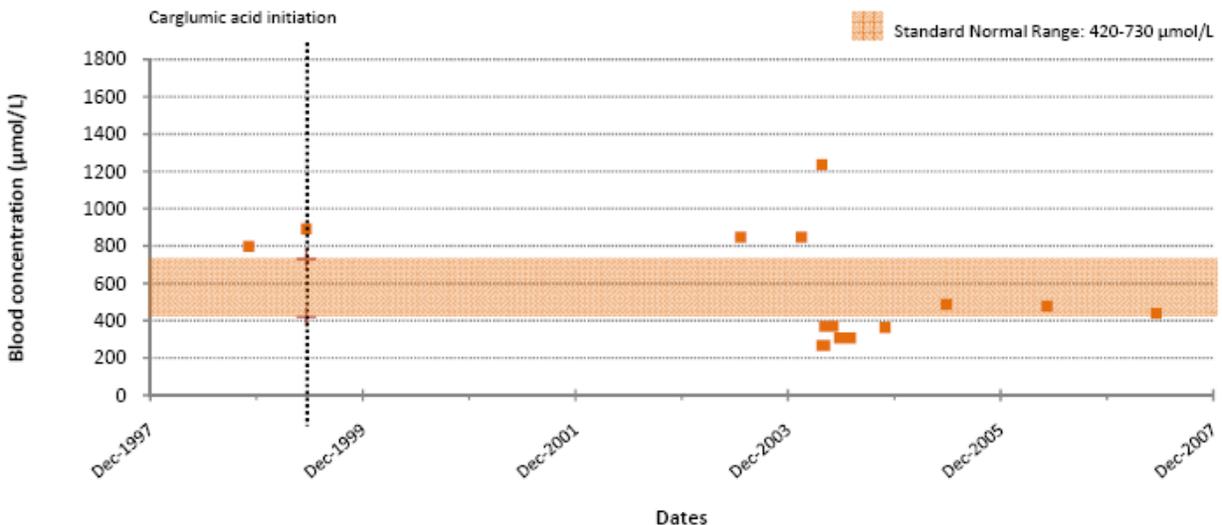
The patient also had low glutamine levels at 4 timepoints post initiation of carglumic acid therapy:

- March 30, 2004 (267 $\mu\text{mol/L}$) (normal range 334-666 $\mu\text{mol/L}$)

- April 9, 2004 (267 $\mu\text{mol/L}$)
- May 30, 2004 (307 $\mu\text{mol/L}$)
- July 6, 2004 (307 $\mu\text{mol/L}$)

Figure 62 depicts Patient 36's glutamine levels before and after treatment with carglumic acid.

Figure 62: Patient 36's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

Patient 36's Plasma Citrulline Levels

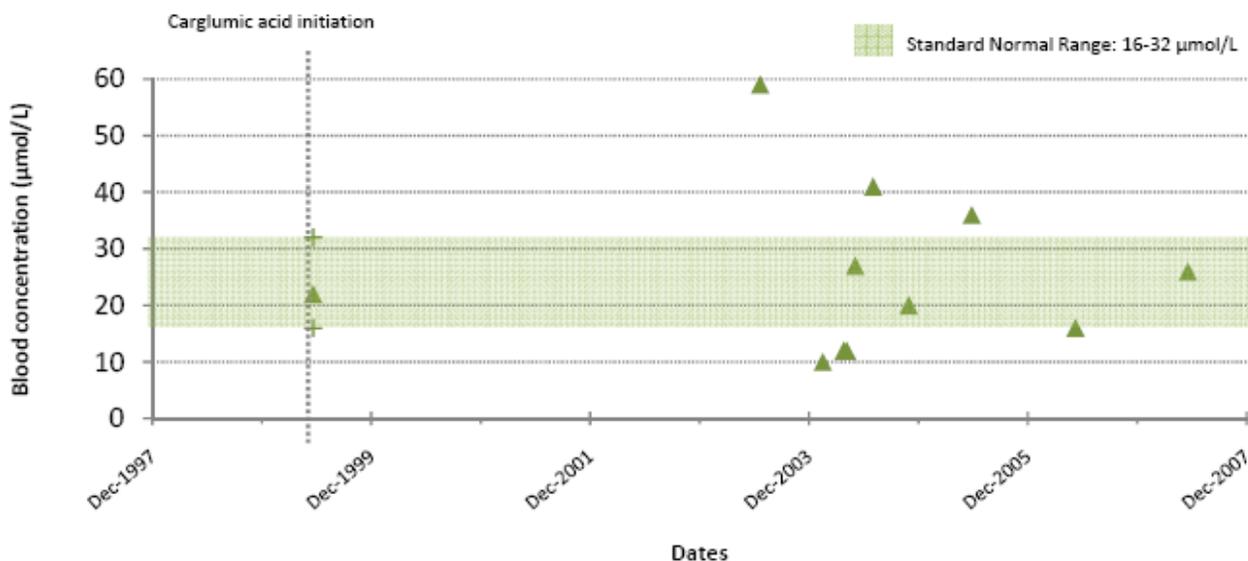
The patient's citrulline level was normal at the time of treatment initiation with carglumic acid. However, it was elevated at 2 timepoints while on treatment with carglumic acid:

June 25, 2003: 59 $\mu\text{mol/L}$ (normal range 16-40 $\mu\text{mol/L}$)

July 6, 2004: 41 $\mu\text{mol/L}$

He also had low citrulline levels at 3 timepoints in the range of 10 to 12 $\mu\text{mol/L}$ from January 20 to April 9, 2004. Figure 63 depicts Patient 36's citrulline levels on the day of carglumic acid treatment initiation and post treatment with carglumic acid.

Figure 63: Patient 36's Citrulline levels on day of initiation and post initiation of carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 8

Medical officer comments

Patient 36 received supplementation with citrulline concurrently with carglumic acid therapy; therefore, citrulline levels are difficult to interpret. When citrulline supplementation was discontinued in January 2006, patient had normal citrulline levels in the range of 16 to 26 µmol/L (normal range 10-42 µmol/L).

Narrative for Patient 39

Patient was a male born (b) (6). There is no birth weight, birth history, or family history available. In (b) (6) at the age of 5 years, the patient presented with unspecified psychiatric symptoms, fever, and hyperactivity. NAGS deficiency was suspected and this led to initiation of carglumic acid March 9, 2005 at a dose of 140 mg/kg/d (1200 mg bid). Due to the positive response, the dose was decreased to 94 mg/kg/d (800 mg bid). A DNA test result shown in Table 45 confirmed a homozygous mutation in the NAGS gene.

Table 45: Patient 39's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
March 30, 2005	NAGS deficiency	c.598T>C (C200R)	Exon 2	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

After 24 hours of treatment, the plasma ammonia decreased to a normal level at 29 µmol/L and remained within normal limits until the last recorded value in November 2007 except on September 24, 2006 when it was elevated at 110 µmol/L due to issues with drug access. In November 2006, the dose of carglumic acid was decreased to 55 mg/kg/d or 1200 mg a day. At the last report on November 30, 2007, the dose was 47 mg/kg/d for a total dose per day of 1200 mg.

Previous or Concomitant Therapy

Initially the protein intake was restricted to 1.1 g/kg/d. In November 2005, the protein intake was increased to normal (> 2 g/kg/d) and was still unrestricted as of the last reporting in November of 2007.

Growth and Development

Because of hyperammonemic decompensation, this patient suffered from behavioral problems associated with hyperactivity and had discipline problems in school. These were reported as residual sequelae that do not appear to have resolved following treatment with carglumic acid.

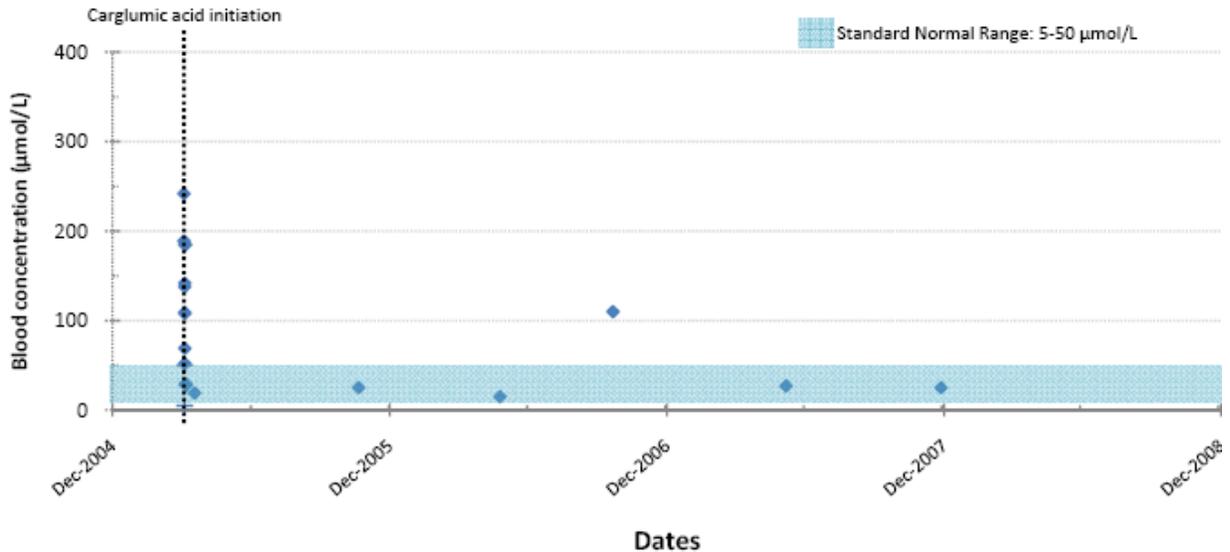
Medical officer comments

Despite being started on carglumic acid treatment at the age of 5 when he presented with his first symptoms, psychomotor retardation was documented in his subsequent follow-up visits (April 2006 to November 2006) and was attributed as residual sequelae of his hyperammonemia. No ammonia levels or description of any symptoms were available between the period of (b) (6) (his birth) and (b) (6) (age 5). Patient only had 2 elevated ammonia levels documented post treatment with carglumic acid (185 µmol/L and 110 µmol/L, (b) (6) respectively). It is unclear whether these 2 elevations in ammonia levels could account for his abnormal neurologic and psychomotor development.

Patient 39's Plasma Ammonia Levels

Twenty four hours (b) (6) prior to treatment with carglumic acid, Patient 39 had ammonia levels in the range of 189-242 µmol/L, which decreased rapidly hours after initiation of carglumic acid. There was a temporary rebound to 185 µmol/L on the first and second day of treatment, which decreased on the second day to 29 µmol/L. The ammonia levels remained since that time in the normal range with the exception of an elevation to 110 µmol/L on September 24, 2006 attributed to non-compliance. Figure 64 depicts Patient 39's ammonia levels before and after treatment with carglumic acid.

Figure 64: Patient 39's Ammonia levels Pre and Post exposure to carglumic acid treatment



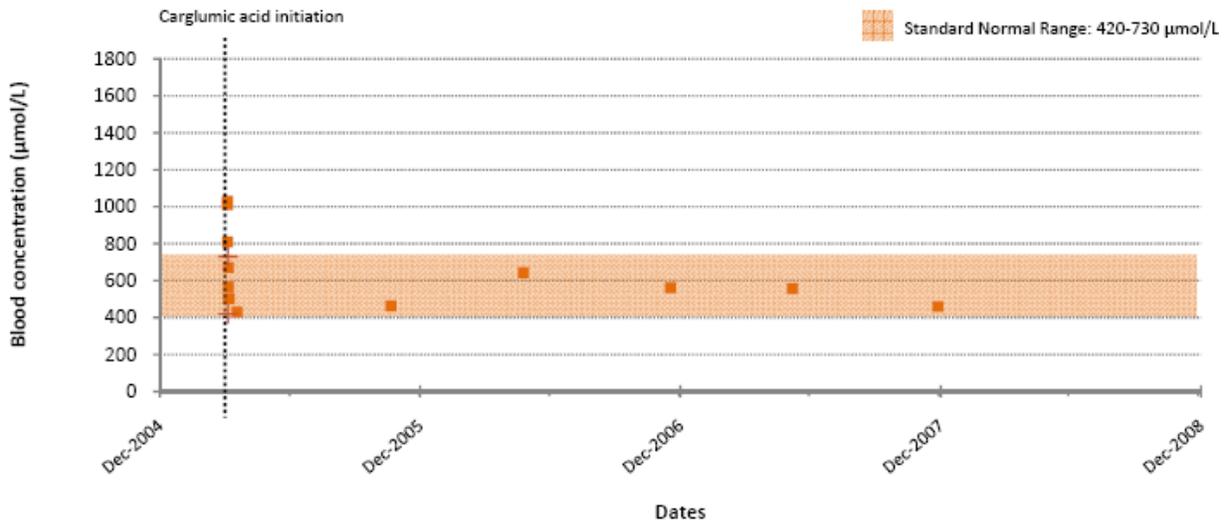
Sponsor's figure, Individual Patient Narrative, page 5

Patient 39's Plasma Glutamine Levels

Patient 39's glutamine levels were elevated in the range of 810 to 1030 µmol/L (normal range 432-705 µmol/L) prior to and on the day of initiation of carglumic acid therapy and then decreased to normal on the second day of therapy. The glutamine levels remained within normal limits as of the last report from November of 2007 except for a slightly low level of 430 µmol/L (normal range 432-705 µmol/L) on (b) (6).

Figure 65 depicts Patient 39's glutamine levels before and after treatment with carglumic acid.

Figure 65: Patient 39's Glutamine levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

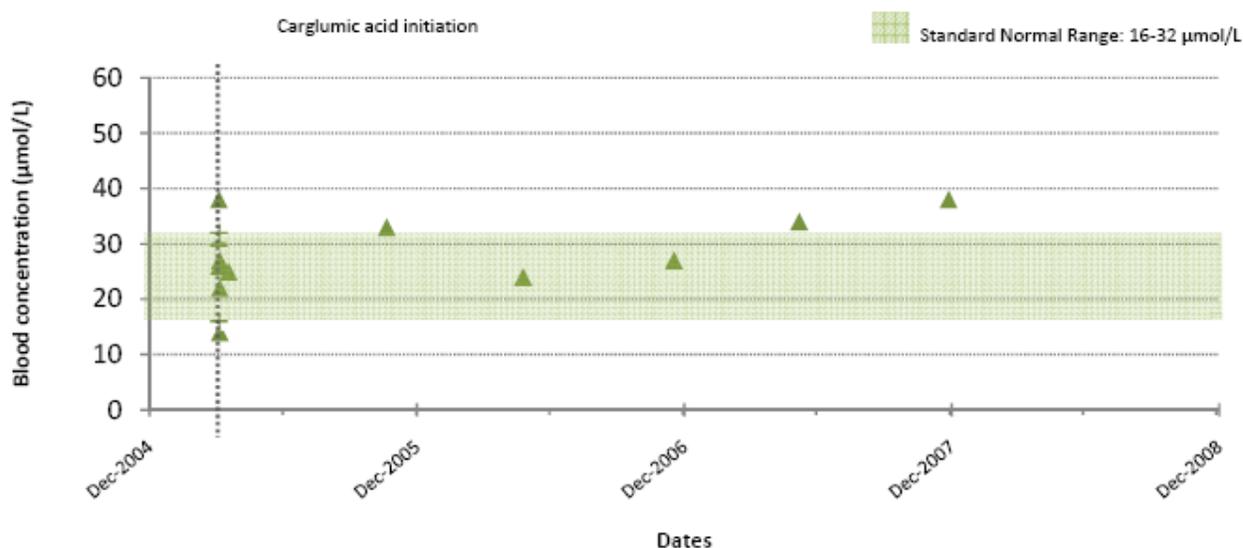
Medical officer comments

Glutamine levels decreased within 24 hours of initiation of carglumic acid therapy.

Patient 39's Plasma Citrulline Levels

The patient's citrulline levels were normal both on the day (March 9, 2005) carglumic acid therapy was started and for the duration of treatment with carglumic acid except for one low level of 14 µmol/L reported on March 10, 2005 (normal range 22-34 µmol/L). No citrulline levels were reported prior to initiation of treatment with carglumic acid. Figure 66 depicts Patient 39's citrulline levels at the start of and after treatment with carglumic acid.

Figure 66: Patient 39's Citrulline levels at initiation and post treatment with carglumic acid



Sponsor's figure, Individual Patient Narrative, page 5

Narrative for Patient 43

Patient 43 was a male born on (b) (6) with a birth weight of 3970 g. No further birth history was provided. This patient has a sibling (b) (6) who carries the diagnosis of NAGS deficiency. When his ammonia level increased to 103 µmol/L, a protein load test was performed. His plasma ammonia level increased to 157 µmol/L after one hour of protein administration and remained elevated at 102 µmol/L after 3 hours. At that point, a decision was made to initiate treatment with carglumic acid. No liver biopsy was performed to assess enzymatic activity; however, a DNA test was done. The DNA result shown below in Table 46 confirmed a homozygous mutation in the NAGS gene.

Table 46: Patient 43's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
April 6, 2005	NAGS deficiency	c.1552G>A (A518T)	Exon 7	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Due to frequent ammonia samples obtained on the day carglumic acid therapy was initiated, ammonia levels could be observed to decrease from a level of 102 $\mu\text{mol/L}$ to 67 $\mu\text{mol/L}$ approximately 1.5 hrs post first dose of carglumic acid.

Patient 43's Plasma Glutamine Levels

Patient 43 had glutamine levels that were within normal range prior to initiation of carglumic acid therapy. Post initiation of carglumic acid therapy, he maintained normal glutamine levels except at 3 timepoints:

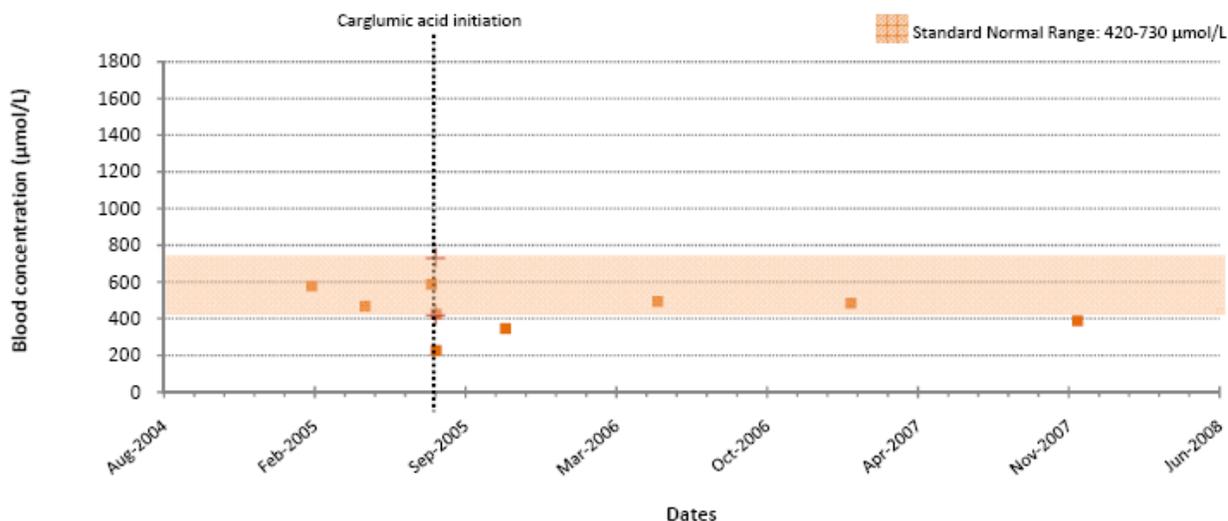
July 28, 2005: low at 227 $\mu\text{mol/L}$ (normal range 400-760 $\mu\text{mol/L}$)

October 28, 2005: low at 347 $\mu\text{mol/L}$

November 26, 2005: low at 388 $\mu\text{mol/L}$

Figure 68 depicts Patient 43's glutamine levels before and after treatment with carglumic acid.

Figure 68: Patient 43's Glutamine levels Pre and Post exposure to carglumic acid treatment



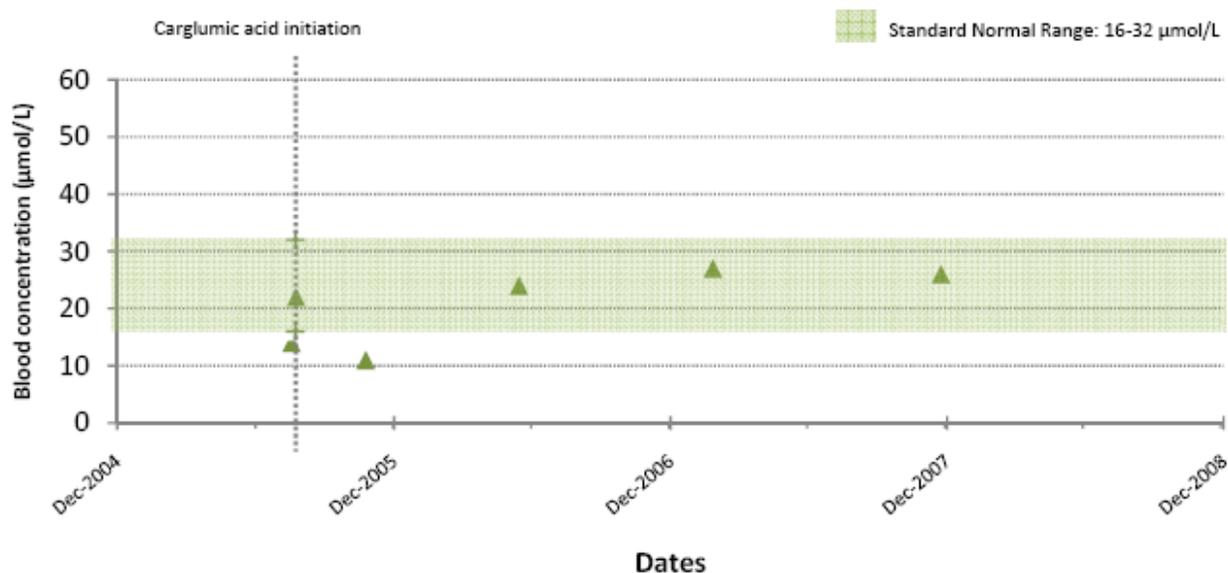
Sponsor's figure, Individual Patient Narrative, page 6

Patient 43's Plasma Citrulline Levels

The patient's citrulline level was normal at 14 $\mu\text{mol/L}$ (normal range 11-19 $\mu\text{mol/L}$) before initiation of treatment with carglumic acid. However, while on treatment with carglumic acid, the majority of the citrulline levels were elevated in the range of 22 to 32 $\mu\text{mol/L}$.

Figure 69 depicts Patient 43's citrulline levels before and after treatment with carglumic acid.

Figure 69: Patient 43's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 5

Narrative for Patient 60

Patient 60 was a female born on (b) (6). No birth weight or height, birth history or family history was provided. On DOL 4 (b) (6), the patient fed poorly, became lethargic, and was hypotonic. The plasma ammonia level was 600 µmol/L. Standard therapy was initiated and consisted of 20% glucose, arginine (350 mg/kg/d), and sodium benzoate (350 mg/kg) given intravenously. The patient continued to receive treatment with arginine (250 mg/kg/d) orally until it was discontinued on (b) (6). No liver biopsy was performed. Result of a DNA test shown in Table 47 confirmed a homozygous mutation for NAGS gene.

Table 47: Patient 60's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
June 2, 2006	NAGS deficiency	c.779C>T (P260L)	Exon 3	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

On July 31, 2006, the patient's ammonia level was elevated at 133 µmol/L. On August 5, 2006, treatment with carglumic acid was initiated at a dose of 100 mg/kg/d (335 mg bid). A total daily dose of 670 mg of carglumic acid was maintained until the last reporting on November 16, 2007. At that time, the dose was further reduced to a total daily dose of 200 mg.

Previous or Concomitant Therapy

As above the initial diet was hypercaloric (120 Kcal/kg/day) with protein intake restriction (< 1.4 g/kg/d). On September 11, 2006, the protein intake became unrestricted and had not been modified as of the last report in November of 2007.

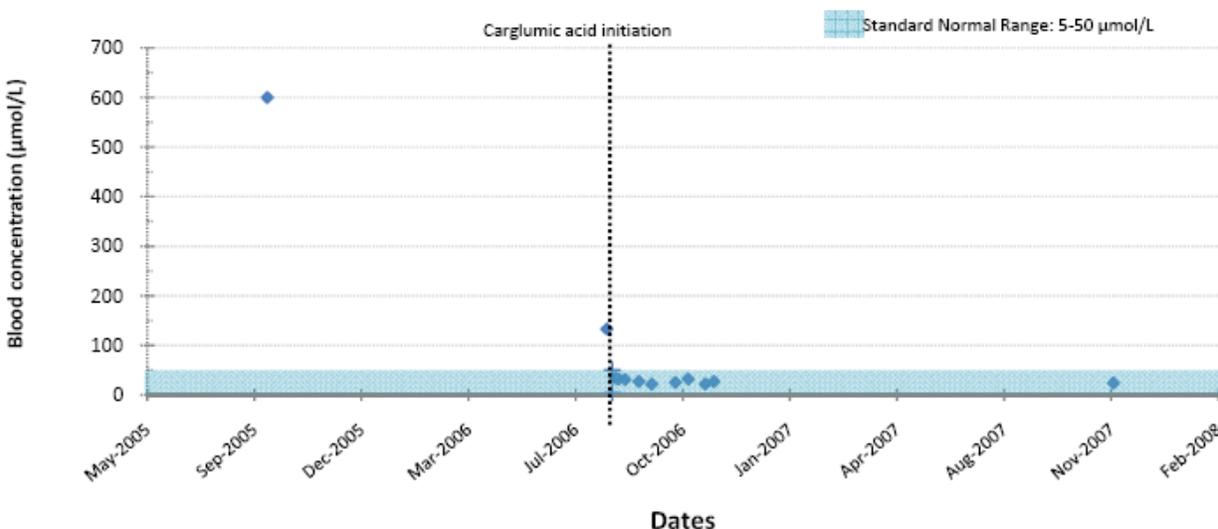
Growth and Development

This patient had normal growth and development without neurologic or psychomotor sequelae.

Patient 60's Plasma Ammonia Levels

Despite the initiation of standard therapy on DOL 4, the patient still maintained elevated ammonia levels at 133 $\mu\text{mol/L}$. Since the initiation of carglumic acid, however, the ammonia levels have been normal in the range of 22 to 34 $\mu\text{mol/L}$. Figure 70 depicts Patient 60's ammonia levels before and after treatment with carglumic acid.

Figure 70: Patient 60's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

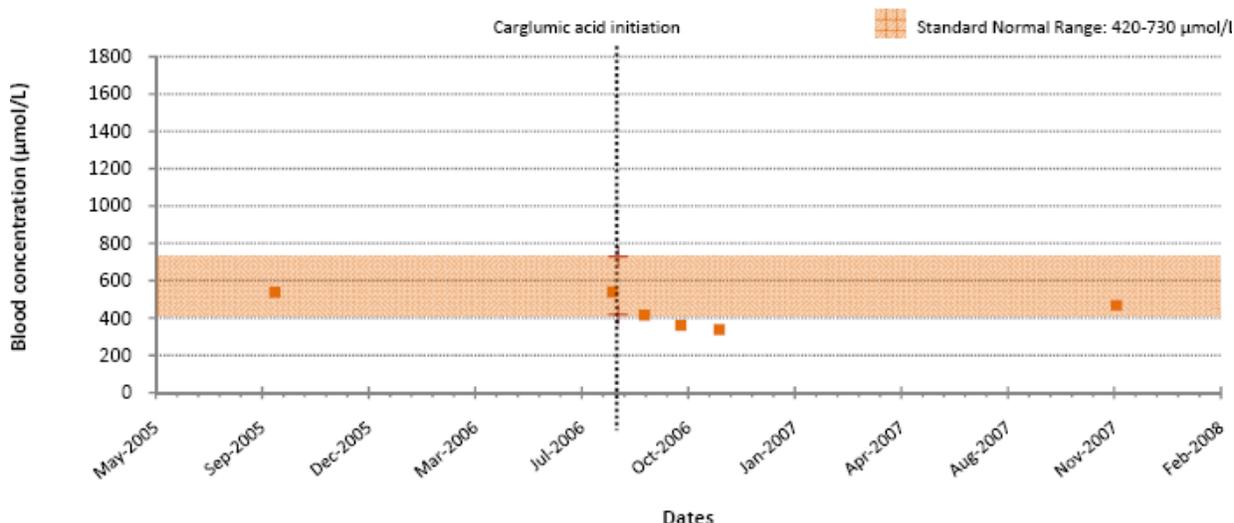
Medical officer comments

Without any treatment, this patient had an ammonia level that was extremely elevated at 600 $\mu\text{mol/L}$. With initiation of standard therapy (glucose, arginine, sodium benzoate), the ammonia level decreased to 133 $\mu\text{mol/L}$ but did not normalize. Three days post initiation of carglumic acid, the patient's ammonia level normalized at 34 $\mu\text{mol/L}$ and remained within normal range between 22 and 32 $\mu\text{mol/L}$. The patient has only one ammonia level of 24 $\mu\text{mol/L}$ recorded approximately 8 days after arginine was stopped and carglumic acid was continued as monotherapy.

Patient 60's Plasma Glutamine Levels

Patient 60 began therapy with carglumic acid while still being treated with arginine. Before the initiation of carglumic acid therapy, the glutamine levels were within the normal range between 537 to 540 $\mu\text{mol/L}$ (normal range 430-562 $\mu\text{mol/L}$). After starting carglumic acid therapy, the glutamine levels were below normal at 3 different timepoints in the range of 338 to 416 $\mu\text{mol/L}$. The glutamine level became normal again at 468 $\mu\text{mol/L}$ 8 days following discontinuation of arginine. Figure 71 depicts Patient 60's glutamine levels before and after treatment with carglumic acid.

Figure 71: Patient 60's Glutamine levels Pre and Post exposure to carglumic acid treatment

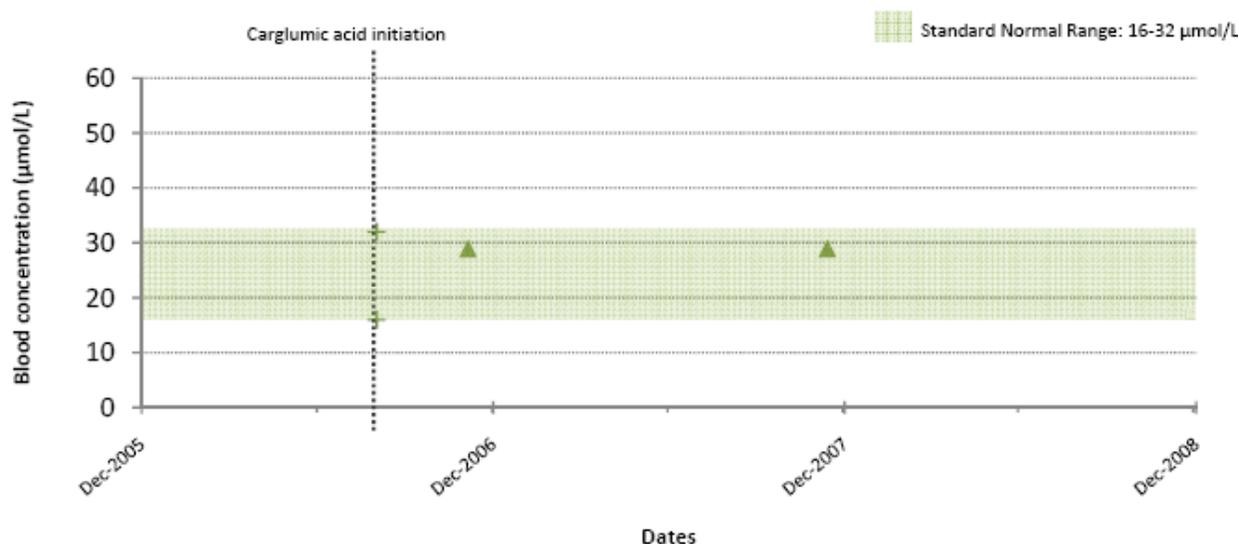


Sponsor's figure, Individual Patient Narrative, page 7

Patient 60's Plasma Citrulline Levels

Patient 60 had 2 citrulline levels obtained post initiation of carglumic acid treatment, and they were both within normal limits at 29 µmol/L. Figure 72 depicts Patient 60's citrulline levels after treatment with carglumic acid.

Figure 72: Patient 60's Citrulline levels Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Narrative for Patient 61

Patient 61 was born (b) (6), a female, with a birth weight of 1980 g. No further information about her birth and family history was provided. On DOL 2, the patient presented with focal seizures, hypoglycemia, hyperbilirubinemia, feeding problems, tachypnea, and fever. On DOL 4, the patient had repeated attacks of focal cramps, as

well as hypotonia and hepatomegaly. On (b) (6), the patient had generalized tonic-clonic seizures. On (b) (6), the patient who was described as "hypotrophic" had psychomotor retardation and atrophy of cerebral hemispheres noted on ultrasound, liver enlargement, and overall poor clinical status. In (b) (6), prior to initiation of carglumic acid therapy, the patient exhibited significant psychomotor retardation and microcephaly (-2 SD).

This patient received standard therapy with a combination of the following:

- Broad spectrum antibiotics
- Antifungals
- Corticosteroids
- Hemodialysis
- Arginine
- Carnitine
- Sodium benzoate
- Sodium phenylbutyrate
- Citrulline
- Protein-restricted diet

Despite the multiple interventions listed above, the patient remained hyperammonemic. The ammonia levels ranged as high as 724-739 $\mu\text{mol/L}$, and the glutamine level reached 1741 $\mu\text{mol/L}$. Physicians suspected a urea cycle defect, namely CPS 1 deficiency. The result of a DNA test shown below in Table 48 revealed a homozygous mutation in the NAGS gene.

Table 48: Patient 61's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
November 27, 2006	NAGS deficiency	c.544delC(fs204X)	Exon 2	homozygous

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

Two days before the DNA results came back, therapy with carglumic acid was initiated on November 25, 2006 at a dose of 142 mg/kg/d (total daily dose of 800 mg; 200 mg qid). No liver biopsy was performed. The last reported dose of carglumic acid was on July 24, 2007, and it was 81 mg/kg/d for a total daily dose of 600 mg.

Medical officer comments

This patient received various doses of the above listed medications, and the dosing of the interventions listed above were not adequately specified in the subject profile.

Because of the repeated hyperammonemic episodes, the patient was left with residual severe neurologic and psychomotor deficits. Despite the overall poor clinical status and impaired neurologic and psychomotor development, no further hyperammonemic exacerbations occurred following initiation of carglumic acid treatment.

Previous or Concomitant Therapy

Protein intake was completely restricted starting June 2006, but the restriction was discontinued following initiation of therapy with carglumic acid.

Growth and Development

This patient suffered from microcephaly. Ultrasound revealed normal structure, bilateral cerebral atrophy, mildly increased lateral ventricles, and normal structure of the "plump gyri".

Medical officer comments

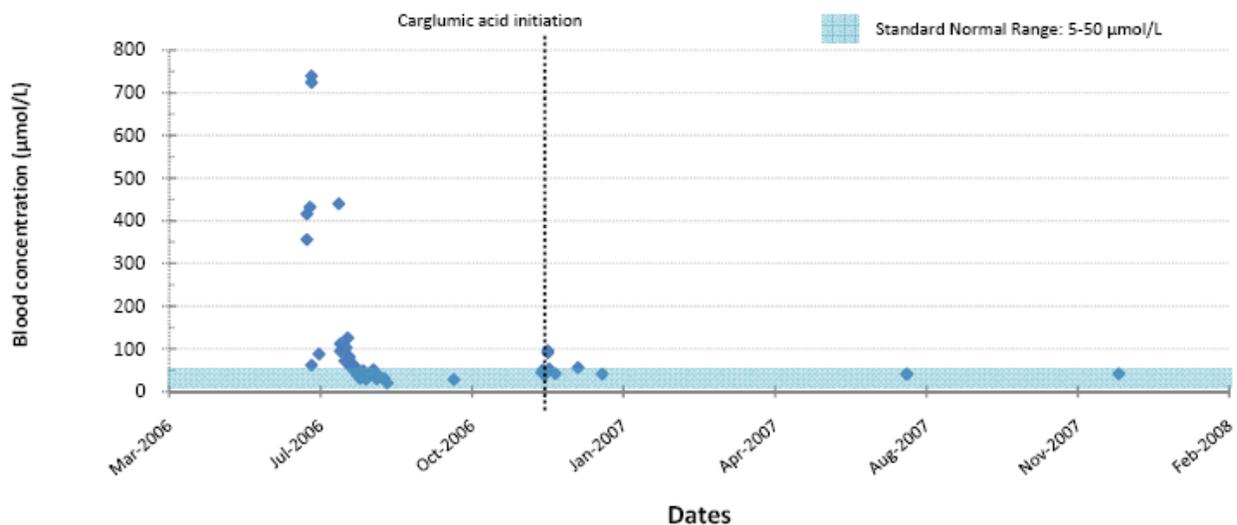
The description of the findings on ultrasound of the brain is difficult to interpret.

Patient 61's Plasma Ammonia Levels

Patient 61's first month of life involved severe episodes of hyperammonemic decompensation that did not respond to multiple standard therapies. Her levels ranged from 95-739 $\mu\text{mol/L}$. Approximately, five days (b) (6) after starting therapy with carglumic acid, her plasma ammonia levels decreased closer to the normal range at 53 $\mu\text{mol/L}$. From (b) (6), this patient had reported ammonia levels in the range of 41 to 56 $\mu\text{mol/L}$. Her last reported ammonia level on December 11, 2007 was 42 $\mu\text{mol/L}$.

Figure 73 depicts Patient 61's ammonia levels before and after treatment with carglumic acid.

Figure 73: Patient 61's Ammonia levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

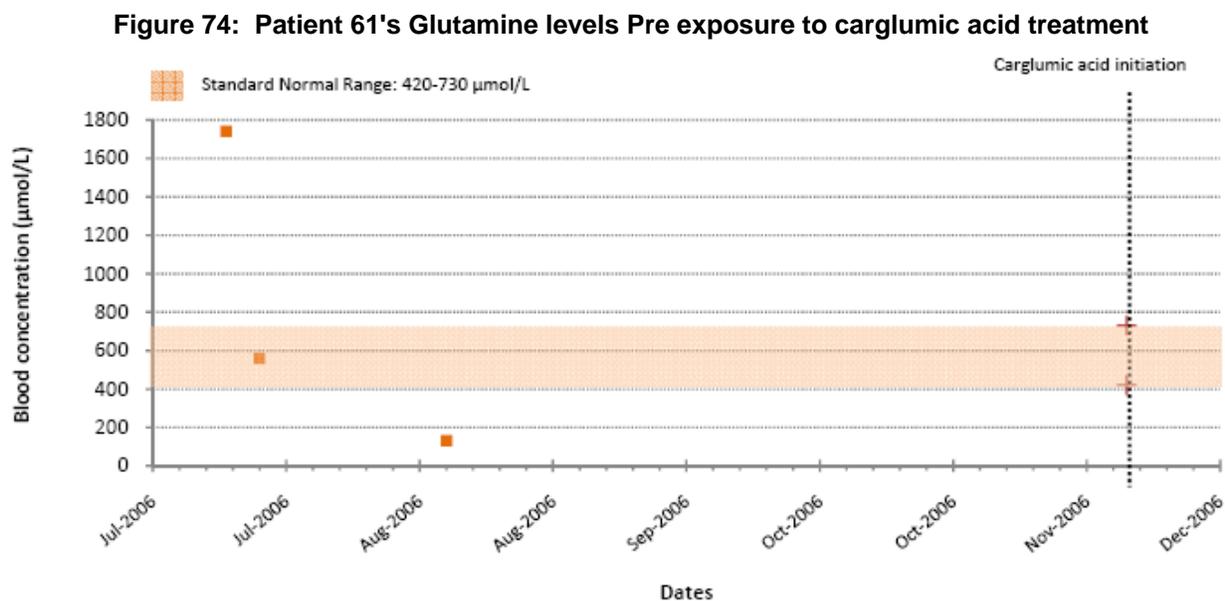
There appears to have been a 5 month delay prior to the initiation of carglumic acid therapy despite the patient exhibiting high levels of ammonia on standard treatment. By

the time carglumic acid was started on (b) (6) she had already sustained severe and irreversible neurologic and psychomotor retardation. Post initiation of carglumic acid treatment, her ammonia levels normalized. Her clinical condition has improved in terms of no further hyperammonemic exacerbations, but she has residual neurologic and psychomotor retardation.

Patient 61's Plasma Glutamine Levels

The highest glutamine level of 1741 $\mu\text{mol/L}$ occurred during her first month of life when standard therapy was initiated. Patient 61 had only 3 glutamine levels reported and none of them were obtained post treatment with carglumic acid.

Figure 74 depicts Patient 61's glutamine levels before treatment with carglumic acid.



Sponsor's figure, Individual Patient Narrative, page 7

Medical officer comments

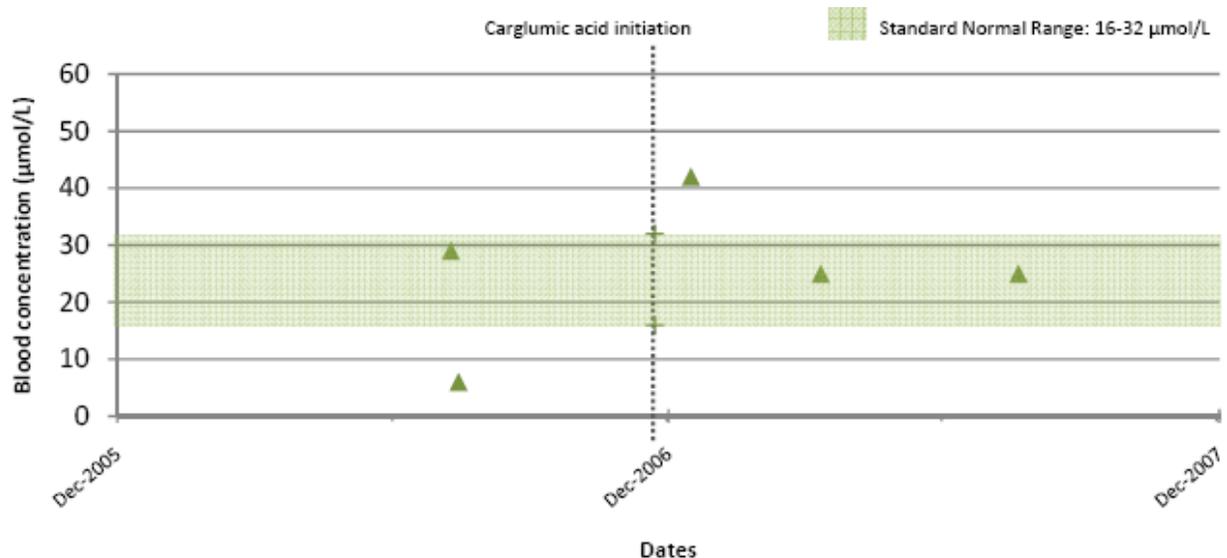
It appears that standard therapy decreased glutamine levels from a high of 1741 $\mu\text{mol/L}$ to 559 $\mu\text{mol/L}$ and then to a low level of 131 $\mu\text{mol/L}$ on August 15, 2006. However, there is a lack of glutamine data post treatment with carglumic acid to make any meaningful conclusions.

Patient 61's Plasma Citrulline Levels

Patient 61's citrulline level was normal prior to the initiation of carglumic acid therapy. Following initiation of carglumic acid, citrulline levels remained normal except for one high level at 42 $\mu\text{mol/L}$, which occurred on December 19, 2006 (normal range 3-35 $\mu\text{mol/L}$).

Figure 75 depicts Patient 61's citrulline levels before and after treatment with carglumic acid.

Figure 75: Patient 61's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

Patient 61 received supplementation with citrulline intermittently prior to and post initiation of carglumic acid therapy. It is difficult to interpret citrulline levels in light of on-going supplementation.

Narrative for Patient 74

Patient 74 was born (b) (6), a male weighing 3.19 kg. No other birth history or family history was provided. On (b) (6) he developed feeding problems, lethargy, and hyperammonemia (165-329 µmol/L). Physicians suspected a urea cycle disorder and the following standard therapies were initiated:

- Antibiotics
- lactulose
- Arginine (350 mg/kg/d IV)
- Carnitine (100 mg/kg/d IV)
- Citrulline (600 mg po)
- Sodium benzoate (250 mg/kg/d)
- Sodium phenylbutyrate (1410 mg po)

By (b) (6), his ammonia level normalized. The doses of the standard therapies listed above were slowly reduced. Result of the DNA test shown in Table 49 confirmed the presence of homozygous mutations in the NAGS gene.

Table 49: Patient 74's result of DNA test performed to confirm NAGS DNA mutation

Date	Diagnosis	Mutation	Location	Type
April 2007	NAGS deficiency	IVS4 + 20 G>C	N/A	homozygous
		IVS4 - 57 C>T		
		IVS6 + 9 C>T		
		c1264 G>T (p.E422X)		

Reviewer's table modified from Individual Patient Narrative sponsor's table, page 1

The patient also underwent a liver biopsy which demonstrated normal activity for the CPS 1 and OTC enzymes (see Table 50).

Table 50: Patient 74's results of liver biopsy

Date of result	Procedure	Enzyme	Value	Unit	Normal Range
(b) (6)	Liver biopsy	CPS 1	539.0	nmol/h/mg prot	310-1000
(b) (6)	Liver biopsy	OTC	41300.0	nmol/h/mg prot	18500-64800

Reviewer's table modified from Individual Patient Narrative, sponsor's table, page 1

Carglumic acid therapy began on May 21, 2007 at a dose of 105.3 mg/kg/d (150 mg qid). Citrulline was discontinued on June 1, 2007, and both arginine (240 mg/kg/d) and sodium benzoate (240 mg/kg/d) were discontinued on June 14, 2007. His positive response to treatment with carglumic acid led to decreases in dosing to 73 mg/kg/d on June 25, 2007, and then 59 mg/kg/d on June 26, 2007. Protein intake was initially restricted but then unrestricted by the end of April 2007.

Previous or Concomitant Therapy

See aforementioned list. The patient received unspecified doses of lactulose, antibiotics and ondansetron.

Growth and Development

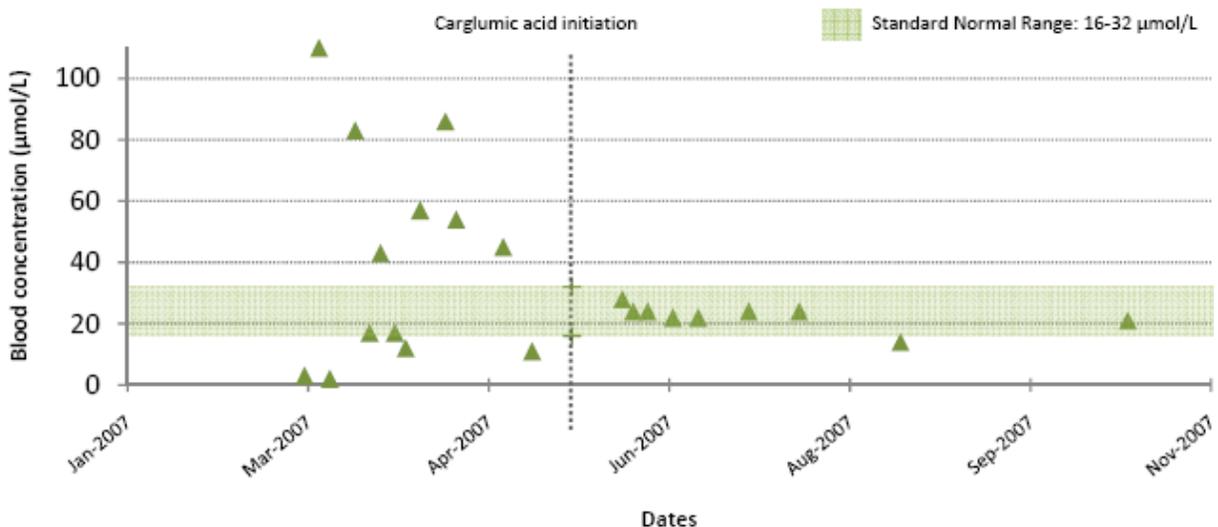
Besides the limited information regarding his initial presentation, in which he developed significant hyperammonemia in the newborn period, no other clinical symptoms, neurologic or psychomotor outcome data were provided.

Patient 74's Plasma Ammonia Levels

From March 8 to May 20, 2007 prior to initiation of carglumic acid, patient's ammonia levels were fluctuating in the range of 12 to 705 µmol/L despite use of antihyperammonemic standard therapies. Once carglumic acid therapy was started on May 21, 2007, the patient's ammonia levels decreased in the range of 17 to 124 µmol/L in the ten days post initiation of carglumic acid.

From June 1, 2007 to October 22, 2007, ammonia levels were in the range of 18 to 128 µmol/L. When carglumic acid was given as sole therapy and without any restriction to protein intake, his ammonia levels were in the range of 18 to 100 µmol/L.

Figure 77: Patient 74's Citrulline levels Pre and Post exposure to carglumic acid treatment



Sponsor's figure, Individual Patient Narrative, page 6

Medical officer comments

Citrulline level on the day standard anti-hyperammonemic therapy was started was low at 3 µmol/L (normal range 10-45 µmol/L). The patient was on citrulline therapy starting March 9, 2007 until it was discontinued on June 1, 2007. The oral citrulline therapy may have contributed to the high citrulline level

6 Review of Efficacy

Efficacy Summary

Plasma ammonia level was used as the primary efficacy endpoint to evaluate the treatment response to carglumic acid therapy. The product, carglumic acid, effectively lowers plasma ammonia levels acutely and maintains normal ammonia levels during chronic administration in patients with NAGS deficiency. In study IND 68,185, plasma ammonia levels decreased in 2 of the 3 NAGS deficiency patients (66.7%) after a 3 day treatment with carglumic acid. However, only 1 patient had an abnormal ammonia level at baseline.

Table 51: Ammonia levels pre and post 3 day treatment with carglumic acid

Ammonia Levels (µmol/L) Pre and Post carglumic acid exposure			
Patient	Baseline Average	Post-Baseline Average	Paired Difference (Post-baseline vs Baseline)
(b)	47	10	-37
(b)	12	16	3.9
(b)	105	46	-58.9

*Reference range for ammonia 17-60 µmol/L

In the retrospective case series, which consisted of 23 patients, two patients who remained asymptomatic and who later were discovered to have heterozygote NAGS gene mutation were excluded from the efficacy analysis. One patient had no ammonia level reported prior to treatment with carglumic acid. Of the 21 evaluable patients, 20 patients (95.2%) demonstrated a decrease in ammonia levels.

Table 52 below demonstrates that reduction in ammonia levels occurs as early as 24 hours post initiation of carglumic acid treatment, and the normal ammonia levels are achieved by day 3 in patients for whom data are available. The mean and median ammonia levels in Table 52 also demonstrate the sustained effect of carglumic acid therapy in the long term (last follow-up or last available ammonia level while on treatment with carglumic acid).

Table 52: Ammonia Levels pre and post exposure to carglumic acid

Timepoint	Statistics (N _{total} = 21*)	Ammonia** (µmol/L)	
Baseline	N	20	Change from baseline
	Mean (SD)	218.9 (299.0)	
	Median	142.0	
	Range	29.0-1428.0	
	Missing Data	1	
Day 1	N	14	14
	Mean (SD)	145.9 (303.1)	-92.0 (107.8)
	Median	61.5	-60.5
	Range	25.0-1190.0	-382.0-6.0
	Missing Data	7	7
Day 2	N	11	11
	Mean (SD)	64.7 (65.9)	-220.2 (335.4)
	Median	54.0	-128.0
	Range	11.0-255.0	-1173.0-6.0
	Missing Data	10	10
Day 3	N	6	6
	Mean (SD)	43.3 (40.8)	-332.7 (551.0)
	Median	29.5	-108.0
	Range	12.0-124.0	-1416.0-69.0
	Missing Data	15	15
Long-term (last available value on carglumic acid treatment)	N	21	20
	Mean (SD)	51.8 (88.6)	-167.0 (314.1)
	Median	25.0	-108.0
	Range	7.0-419.0	-1419.0-139.0
	Missing Data	0	1

*N=patients excluded from efficacy analysis are (b) (6)

**Mean normal range: 5 to 50 µmol/L

As previously described in section 2, prolonged hyperammonemic episodes have been associated with irreversible neurologic impairment. Although there were no

standardized and validated tools used at all centers to assess neurologic changes and/or neurocognitive development, it appears that decreasing ammonia levels improves acute hyperammonemic encephalopathy and long-term neurologic outcome. Of the 17 patients with neurocognitive/neurologic data available, 9 patients (53%) presented with neurologic impairment that improved post-initiation of carglumic acid therapy. Three patients (18%) had normal neurologic function at presentation and remained neurologically unimpaired post-initiation of treatment with carglumic acid. However, 5 patients (29%) sustained permanent neurologic impairment despite treatment with carglumic acid. The Applicant attributed permanent neurologic impairment in these patients to hyperammonemic episodes that occurred prior to the initiation of carglumic acid because these patients maintained normal plasma ammonia levels during continuous treatment with carglumic acid. Thus, 12/17 or (71%) of patients with long-term neurologic outcome information had an absence of clear neurologic impairment.

6.1 Indication

The Applicant proposed the following indication for carglumic acid:
“Carbaglu® (carglumic acid for oral use) is indicated for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency).”

6.1.1 Methods

The efficacy evaluation for carglumic acid was based on retrospective case series data collected by the Applicant on 23 patients in 8 European countries, and an open-label, on-going, Phase 2 clinical trial under IND 68,185, which is being conducted at Children's National Medical Center in Washington, D.C. by Mendel Tuchman, M.D.

Medical officer comments

Due to the rare and serious nature of the disease, the Agency agreed to review the efficacy of carglumic acid based on data from an uncontrolled, retrospective case series. Well-controlled, double-blind, multicenter Phase 3 trials were not conducted.

Study IND 68,185

Please see section 5.3, discussion of individual studies/clinical trials for methods on efficacy and safety analyses.

Retrospective Case Series

The Applicant evaluated the effect of carglumic acid on short and long-term plasma ammonia, glutamine and citrulline levels. Additional clinical information such as height and weight, protein restriction, neurologic, psychomotor, and hepatic status were assessed from baseline to last follow-up as secondary outcomes. Pharmacokinetic parameters, dose level and duration, and safety of carglumic acid were also evaluated.

There were no pre-specified efficacy endpoints or prospective assessment plan to evaluate efficacy. However, the applicant instituted a program to retrospectively collect all the data on the NAGS deficiency patients receiving carglumic acid. The Applicant created a statistical analysis plan and statistical analysis rules to provide a methodology for analysis of the data collected from 1991 through December 2007. This provided the basis for the descriptive statistics in the efficacy assessment.

Medical officer comments

The fact that this case series is retrospective, un-blinded, non-randomized and uncontrolled precludes any meaningful formal statistical analysis of the data. Any statistical inference from confidence intervals and/or p-values is uninterpretable.

6.1.2 Demographics

Study IND 68,185

Study IND 68,185 was designed to include patients with CPS deficiency, NAGS deficiency, propionic acidemia, and methylmalonic academia. Of the 7 patients enrolled in the study, only 3 NAGS deficiency patients have been enrolled. Table 53 summarizes the three adults and four pediatric patients who participated in the trial from January 2004 to November 2008.

Table 53: Baseline Demographics of study population in IND 68,185

Patient	Age (years)	Gender	Diagnosis	Mutation
(b) (4)	18	Female	NAGS Deficiency	compound heterozygote R509Q IVS4 nt-1 G>C
(b) (4)	51	Female	NAGS Deficiency	heterozygote IVS4-1 G>C
(b) (4)	58	Female	NAGS Deficiency	compound heterozygote V3501 L442V
(b) (4)	6	Male	Propionic Acidemia	homozygous G216fs mutation in PCCA gene
(b) (4)	11	Female	Propionic Acidemia	N/A
(b) (4)	8	Female	Propionic Acidemia	N/A
(b) (4)	5	Male	Propionic Acidemia	compound heterozygote c.183+3 G>C mutation in beta subunit of PCCB

N/A = not available

Reviewer's table constructed from data provided in Dr. Tuchman's IND 68,185

Retrospective Case Series

Table 54 summarizes the baseline demographics of the NAGS deficiency patients from whom the Applicant obtained retrospective data. The diagnosis of NAGS deficiency was confirmed by molecular genetic testing in 18 patients (78.3%). None of the patients from the United Kingdom had DNA testing performed. The majority of patients (14 of 23; 60.9%) had a homozygous mutation for the NAGS gene. Patient 16 was reported to have a homozygous mutation, but the DNA test result was not submitted to the Applicant.

Table 54: Baseline Demographics of NAGS deficient patients in Orphan Europe retrospective data

Patient	Current Age (years)	Age at time of diagnosis	Gender	Mutation
France (9 of 23 patients, 39.1%)				
(b)	16	6 months	Male	heterozygous c.278delC (110X) exon 1 c.499A>G exon 2
(b)	17	19 months	Male	homozygous c.598T>C (C200R) exon 2
(b)	14	3 weeks	Male	homozygous 1228T>C (S410P) exon 5
(b)	8	4 days	Female	homozygous 1552 G>A (A518T) exon 7
(b)	6	5 months	Male	homozygous 598T>C (C200R) exon 2
(b)	5	1 day	Female	homozygous 1228T>C (S410P) exon 5
(b)	9	1 year	Male	homozygous c.791C>T (T264M) exon 3
(b)	8	6 years	Male	homozygous 598T>C (C200R) exon 2
(b)	2	2 months	Male	homozygous c.1552 G>A (A518T) exon 7

Reviewer's table constructed from individual patient narratives and subject profiles data provided by the sponsor

Table 54 Continued: Baseline Demographics of NAGS deficient patients in Orphan Europe retrospective data

Patient	Current Age (years)	Age at time of diagnosis	Gender	Mutation
Germany (5 of 23 patients; 21.7%)				
(b) (4)	12	4 months	Female	homozygous W324X/W324X
(b) (4)	6	3 days	Male	heterozygous W324X
(b) (4)	3	7 days	Male	heterozygous W484R
(b) (4)	2	4 days	Female	heterozygous W484R
(b) (4)	1	5 months	Female	homozygous c.544delC (fs204X) exon 2
United Kingdom (4 of 23 patients; 17.4%)				
(b) (4)	15	1 day	Male	N/A
(b) (4)	9	0 day	Female	N/A
(b) (4)	33	13 years	Male	N/A
(b) (4)	11	2 months	Female	N/A
Austria (1 of 23 patients; 4.3%)				
(b) (4)	23	13 year	Female	homozygous A279P/A279P
Spain (1 of 23 patients; 4.3%)				
(b) (4)	20	12 year	Male	homozygous*
Sweden (1 of 23 patients; 4.3%)				
(b) (4)	4	3 weeks	Male	homozygous R414P/R414P exon 7
Italy (1 of 23 patients; 4.3%)				
(b) (4)	2	11 months	Female	homozygous c.779C>T (P260L) exon 3
Netherlands (1 of 23 patients; 4.3%)				
(b) (4)	9 months	1 month	Male	homozygous IVS4+20 G>C IVS4-57 C>T IVS6+9 C>T c1264 G>T (p.E422X)

N/A = not available

*Reported by treating physician and DNA test result not made available to sponsor

Reviewer's table constructed from individual patient narratives and subject profiles data provided by the sponsor

Medical officer comments

The current age of patients in the retrospective case series is based on the date of birth and the data cut-off date reported for the individual patients in the subject profiles submitted by the Applicant. Most of the patients were diagnosed prior to the age of six except for 3 patients (13 years for a male patient in United Kingdom and a female patient in Austria, and 12 years for a male patient in Spain).

Overall, the patients were predominantly male (14 of 23 patients, 60.9%). There were 9 females (39.1%). Race and ethnicity data were not collected.

6.1.3 Subject Disposition

Study IND 68,185

Total of seven patients have enrolled in study IND 68,185. All enrolled patients have completed the trial. There is no information provided regarding patients who failed the screening process.

Retrospective Case Series

A summary of patient disposition is presented below in Table 55. The majority of patients have continued treatment with carglumic acid (18 of 23 patients, 78.3%). Five NAGS deficiency patients discontinued treatment; three patients discontinued due to confirmation of heterozygote NAGS gene mutation by DNA testing, and two patients died.

Table 55: Disposition of NAGS deficiency patients in Orphan Europe retrospective data

Category				
On-going treatment with carglumic acid			18 patients (78.3%)	
Patient	Dose	Administration of dose per day	Total daily dose	Date of last dose
(b)	6 mg/kg/d	150 mg bid	300 mg	11/20/2007
(b)	16.3 mg/kg/d	N/A	800 mg	8/10/2007
(b)	25 mg/kg/d	600 mg bid	1200 mg	7/16/2007
(b)	20 mg/kg/d	300 mg bid	600 mg	12/18/2007
(b)	30 mg/kg/d	N/A	600 mg	11/30/2007
(b)	48 mg/kg/d	400 mg bid	800 mg	7/17/2007
(b)	16 mg/kg/d	200 mg tid	600 mg	6/20/2007
(b)	47 mg/kg/d	600 mg bid	1200 mg	11/30/2007
(b)	13 mg/kg/d	100 mg bid	200 mg	11/26/2007
(b)	10 mg/kg/d	N/A	600 mg	5/31/2007
(b)	81.1 mg/kg/d	N/A	600 mg	7/24/2007
(b)	N/A	250 mg bid	500 mg	12/31/2007
(b)	10 mg/kg/d	N/A	600 mg	4/17/2007
(b)	40 mg/kg/d	N/A	1800 mg	7/12/2007
(b)	14 mg/kg/d	333 mg tid	1000 mg	12/20/2004
(b)	57 mg/kg/d	400 mg bid	800 mg	5/30/2007
(b)	20 mg/kg/d	N/A	200 mg	11/16/2007
(b)	59 mg/kg/d	100 mg qid	400 mg	6/26/2007
Discontinued treatment with carglumic acid			5 patients (21.7%)	
Patient		Reason for Discontinuation		
(b)		heterozygous mutation		
(b)		heterozygous mutation		
(b)		heterozygous mutation		
(b)		death		
(b)		death		

N/A = not available

Reviewer's table constructed from individual patient narratives and subject profiles data provided by the sponsor

6.1.4 Analysis of Primary Endpoint(s)

Study IND 68,185

The primary objective of study IND 68,185 is to evaluate the effect of carglumic acid on ureagenesis based on incorporation of ¹³C/¹⁵N into urea in patients with NAGS deficiency, CPS deficiency, Propionic acidemia, and Methylmalonic acidemia. In addition to measurement of ¹³C urea (mmol/L), plasma ammonia (µmol/L) and alanine levels (µmol/L) were also measured.

Medical officer comments

Alanine levels pre and post treatment with carglumic acid were evaluated as an efficacy endpoint in patients with propionic acidemia but not for patients with NAGS deficiency. Therefore, results of alanine levels will not be presented in the efficacy assessment.

Table 56 provides the mean and range values for urea in 3 patients with NAGS deficiency and 4 patients with PA at baseline, and after 3-day treatment with carglumic acid.

Table 56: Mean Urea levels pre and post 3-day treatment with carglumic acid

3 NAGS deficiency patients		
Blood samples (N)	21	21
Timing of blood samples	Urea (mmol/L)*	Urea (mmol/L)*
	PRE-Carbaglu	POST-Carbaglu
Mean	2.2	4.1
(range)	(1.1-3.6)	(2.5-6.8)
4 Propionic Acidemia patients		
Blood samples (N)	36	36
Timing of blood samples	Urea (mmol/L)*	Urea (mmol/L)*
	PRE-Carbaglu	POST-Carbaglu
Mean	4.5	5
(range)	(2.9-6.1)	(3.2-7.1)

*Reference range for urea 1.2-7 mmol/L

Since the main objective of study IND 68,185 is to evaluate the restoration of ureagenesis, urea was also included as an endpoint measure.

Table 57 summarizes the individual patient mean and range urea levels during the course of the 3 day exposure to carglumic acid.

Table 57: Mean urea levels of each patient pre and post 3 day treatment with carglumic acid

Patient; Age (years)	Pre-Carbaglu Urea (mmol/L)*	Post-Carbaglu Urea (mmol/L)*	Blood samples
Diagnosis	Mean (range)	Mean (range)	N
(b) (6) NAGS Deficiency; compound heterozygote	1.2 (1.1-1.4)	2.7 (2.5-2.9)	6 pre; 6 post; 12 total
(b) (6) NAGS Deficiency; heterozygote	3.6 (3.6-3.6)	3.6 (3.2-3.6)	6 pre; 6 post; 12 total
(b) (6) NAGS Deficiency; compound heterozygote	1.7 (1.4-1.8)	6.0 (5.4-6.8)	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	4.7 (3.9-5.4)	4.3 (4.3-4.6)	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	5.2 (4.6-5.7)	5.8 (5.4-6.1)	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	5.3 (4.6-6.1)	6.4 (5.7-7.1)	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	2.9 (2.9-3.2)	3.5 (3.2-3.9)	9 pre; 9 post; 18 total

*Reference range for urea 1.2-7 mmol/L

Medical officer comments

In all 7 cases, the patients started their participation in the clinical trial with normal urea levels. Five out of seven (71.4%) patients demonstrated an increase in mean urea levels (indicated in bold in Table 57) following a three day exposure to carglumic acid. One patient with NAGS deficiency had no change in mean urea level post treatment with carglumic acid. One patient with PA had a small decrease in mean urea level post 3-day treatment with carglumic acid.

It is not clear, however, whether ureagenesis would have greatly improved, had the patients' baseline urea levels been abnormal. The clinical trial did not allow the participation of patients who were acutely ill. It is difficult to determine whether Carbaglu might have been more effective in restoring ureagenesis in more severely

affected patients with NAGS deficiency or PA who have abnormal baseline urea values, which would be expected to be more consistent with impaired ureagenesis.

Plasma ammonia level was another efficacy endpoint for study IND 68,185. Table 58 provides the mean and range values for ammonia pre and post 3-day treatment with carglumic acid in patients with NAGS deficiency (3 patients) and PA (4 patients).

Table 58: Mean ammonia levels at baseline and after 3-day treatment with carglumic acid

Category	Ammonia* (µmol/L)	
3 NAGS deficiency patients		
Blood samples, N	15	16
Timing of blood sample	PRE-carglumic acid	POST-carglumic acid
Mean	54.8	24.2
(range)	(7-159)	(6-69)
4 PA patients		
Blood samples, N	36	36
Timing of blood sample	PRE-carglumic acid	POST-carglumic acid
Mean	59.5	46.2
(range)	(32-95)	(24-73)

*Reference range for ammonia 17-60 µmol/L

Table 59 below summarizes the individual patient ammonia levels during the course of the three-day exposure to carglumic acid.

Table 59: Individual patient ammonia levels pre and post 3-day treatment with carglumic acid

Patient; Age (years) Diagnosis	Pre-Carbaglu	Post-Carbaglu	Reference Range	Blood Samples
	Ammonia (µmol/L) Mean (range)	Ammonia (µmol/L) Mean (range)	µmol/L	N
(b) (6) NAGS Deficiency; compound heterozygote	47 (20-70)	10.0 (8-11)	17-60	3 pre; 3 post; 6 total
(b) (6) NAGS Deficiency; heterozygote	12.3 (7-15)	16.3 (11-23)	17-60	3 pre; 4 post; 7 total
(b) (6) NAGS Deficiency; compound heterozygote	105.2 (79-159)	46.3 (29-69)	17-60	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	39.7 (32-47)	34.4 (24-40)	14-65	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	58.0 (53-68)	48.3 (37-52)	14-65	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	61.4 (53-71)	61.9 (52-73)	14-65	9 pre; 9 post; 18 total
(b) (6) propionic acidemia	78.8 (63-95)	40.1 (36-46)	14-65	9 pre; 9 post; 18 total

Medical officer comments

Two patients with NAGS deficiency experienced a decrease in mean ammonia levels, and one patient with NAGS deficiency experienced a small increase in mean ammonia level. However, the patient who experienced an increase in ammonia level had a normal baseline ammonia (7-15 µmol/L), and therefore, a small increase of 4 µmol/L is still a normal plasma ammonia level. The clinical trial was not designed to evaluate the effect of carglumic acid in patients with acute hyperammonemia. Only one patient (b) (6) had a baseline ammonia level that was abnormal. However, in this patient, the ammonia level normalized (105.2 to 46.3 µmol/L) after the 3-day treatment period.

Three of the four patients with propionic acidemia started the clinical trial with mean ammonia levels, which were within normal limits. Patient (b) (6) was the only patient with an elevated mean ammonia level at 78.8 µmol/L at baseline, which decreased to within normal limits at 40.1 µmol/L following 3-day treatment with Carbaglu. There was one patient, however, (b) (6) who had no change in mean ammonia level.

A post-hoc analysis of the data was performed by the Division's statistician (Vali Behrang) to further evaluate the effect of carglumic acid on plasma ammonia levels. Table 60 presents the analyses of the data for patients with NAGS deficiency.

Table 60: Analysis of ammonia levels pre and post 3 day treatment with carglumic acid

Ammonia Levels (µmol/L) Pre and Post Carbaglu Exposure			
Patient	Baseline Average	Post-Baseline Average	Paired Difference (Post-baseline vs Baseline)
(b) (6)	47	10	-37
(b) (6)	12	16	3.9
(b) (6)	105	46	-58.9

Medical officer comments

Study IND 68,185 is an open label, uncontrolled, non-randomized clinical trial that has few patients (3 NAGS deficiency patients and 4 propionic acidemia patients). It is difficult to draw any clear conclusions regarding ammonia levels since the majority of the NAGS deficiency patients (2 out of 3) had normal baseline ammonia levels. Any patient that was acutely ill was also excluded.

**Retrospective Case Series
 Primary Efficacy Evaluation**

The Applicant evaluated plasma ammonia level as a primary efficacy endpoint. In addition, the Applicant evaluated the effect of carglumic acid on both short-term and long-term plasma ammonia levels. Short-term treatment effect was defined as a response that occurred within 7 days after first carglumic acid therapy. Although certain authors and investigators consider the maximum normal ammonia level to be between 60-100 µmol/L in neonates and 50 µmol/L for infants, children, and adults, to standardize the "mean" normal ammonia level in all patients, the sponsor set the maximum normal ammonia level at 50 µmol/L. Since patients were treated at various facilities that used different laboratories and normal ranges, the Applicant calculated a "mean" ammonia normal range, which is the weighted average of all the normal ranges reported.

The Applicant applied the following rules to generate the summary statistics in Table 61:

- To determine the **baseline** ammonia values:
 - Baseline ammonia value was defined as an ammonia level obtained at the closest time point available prior to the first treatment with carglumic acid, this could include day 0 (the day treatment was initiated) ammonia value.

- If multiple ammonia values were obtained on the same day prior to initiation of treatment, the highest ammonia value was used in the analysis and not necessarily the ammonia level at the closest timepoint to first dosing.
- To determine the ammonia values **post-initiation** of carglumic acid:
 - In patients that had multiple ammonia samples on day 0 (the day treatment was initiated), any additional values obtained after the initiation of treatment on day 0 were excluded.
 - If multiple ammonia values were obtained on the same day post-initiation of treatment, example on day 3, the highest ammonia value was used in the analysis.

Table 61: Summary Statistics of Ammonia level in the short term

Timepoint	Statistics (N _{total} = 21*)	Ammonia** (µmol/L)	
Baseline	N	20	Change from baseline to short-term
	Mean (SD)	218.9 (299.0)	
	Median	142.0	
	Range	29.0-1428.0	
	Missing Data	1	
Day 1	N	14	14
	Mean (SD)	145.9 (303.1)	-92.0 (107.8)
	Median	61.5	-60.5
	Range	25.0-1190.0	-382.0-6.0
	Missing Data	7	7
Day 2	N	11	11
	Mean (SD)	64.7 (65.9)	-220.2 (335.4)
	Median	54.0	-128.0
	Range	11.0-255.0	-1173.0-6.0
	Missing Data	10	10
Day 3	N	6	6
	Mean (SD)	43.3 (40.8)	-332.7 (551.0)
	Median	29.5	-108.0
	Range	12.0-124.0	-1416.0-69.0
	Missing Data	15	15
Day 4	N	6	6
	Mean (SD)	42.3 (30.8)	-332.0 (550.0)
	Median	38.5	-117.0
	Range	10.0-96.0	-1418.0-51.0
	Missing Data	15	15
Day 5	N	5	5
	Mean (SD)	42.2 (18.5)	-106.8 (71.7)
	Median	47.0	-126.0
	Range	10.0-56.0	-187.0-8.0
	Missing Data	16	16

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 5 to 50 µmol/L

Reviewer's table modified from sponsor's tables 3, 7a and 8a Carbaglu final, pages 9, 74, and 86

Table 61 Continued: Summary Statistics of Ammonia level in the short term

Timepoint	Statistics (N _{total} = 21*)	Ammonia** (µmol/L)	Change from baseline to short-term
Day 6	N	3	3
	Mean (SD)	32.3 (4.5)	-61.3 (41.6)
	Median	32.0	-65.0
	Range	28.0-37.0	-101.0 - -18.0
	Missing Data	18	18
Day 7	N	2	2
	Mean (SD)	41.5 (29.0)	-51.0 (82.0)
	Median	41.5	-51.0
	Range	21.0-62.0	-109.0-7.0
	Missing Data	19	19

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 5 to 50 µmol/L

Reviewer's table modified from sponsor's tables 3, 7a and 8a Carbaglu final, pages 9, 74, and 86

Medical officer comments

There was a wide range of baseline ammonia levels (29-1428 µmol/L), however, 3 patients (b) (6) had normal ammonia levels at baseline. In all patients with an elevated ammonia level at baseline and at least one follow-up level at 24 hours, a reduction of ammonia level was seen at day 1. The overall mean and median ammonia levels decreased within 24 hours after initiation of carglumic acid therapy. On day 2, the mean and median ammonia values were lower than the baseline and 24 hour ammonia levels. At all time points measured, there are missing values. Indeed, there are only 2-6 patients with data available at each sampling point after day 2. Days 3 to 7, there is a substantial amount of missing values. However, once the ammonia levels normalized by day 3 in patients for whom data were available, the mean and median ammonia levels remained within the normal range of 29.5 to 47 µmol/L from days 3 to 7.

6.1.5 Analysis of Secondary Endpoints(s)

Study IND 68,185

There were no pre-specified secondary endpoints in study IND 68,185. Blood samples were collected on amino acids. Since the results on glutamine and citrulline levels were available, assessments were performed on glutamine and citrulline levels pre and post 3-day therapy with carglumic acid.

Table 62 provides the mean and range values for glutamine and citrulline at baseline and after 3-day treatment with carglumic acid in 3 patients with NAGS deficiency and 4 patients with PA.

Table 62: Mean glutamine and citrulline levels pre and post treatment with carglumic acid

Category	Glutamine level* (µmol/L)		Citrulline level** (µmol/L)	
3 N-Acetylglutamate Synthase deficiency patients				
Blood samples, N	19	21	19	21
Timing of blood sample	PRE-carglumic acid	POST-carglumic acid	PRE-carglumic acid	POST-carglumic acid
Mean	517.9	397.6	49.1	38.5
(range)	(399-670)	(307-483)	(20-151)	(8-174)
4 Propionic Acidemia patients				
Blood samples, N	36	36	36	36
Timing of blood sample	PRE-carglumic acid	POST-carglumic acid	PRE-carglumic acid	POST-carglumic acid
Mean	603.5	370.7	23.2	18.4
(range)	(524-731)	(289-519)	(17-31)	(13-23)

*Reference range for glutamine = (0-933 µmol/L, 0-4 months), (49-736 µmol/L, 4 months to 12 yrs), (414-863 µmol/L, 12 yrs and up)

**Reference range for citrulline = (0-92 µmol/L, 0-4 months), (0-67 µmol/L, 4 months to 12 yrs), (0-80 µmol/L, 12 yrs and up)

Medical officer comments

There appears to be a reduction in mean glutamine levels as well as mean citrulline levels after 3 days of treatment with carglumic acid in both NAGS deficiency and PA patients. Citrulline levels would be expected to increase in NAGS deficiency rather than decrease post treatment with carglumic acid, rendering the findings on mean citrulline levels difficult to interpret.

Retrospective Case Series

Effect of carglumic acid on short-term plasma glutamine and citrulline levels

The Applicant also evaluated the effect of carglumic acid treatment on plasma glutamine and citrulline levels. The short-term effect, defined as a response in glutamine and citrulline levels that occurred within 7 days after first carglumic acid therapy was assessed. The normal range for plasma glutamine varied from center to center. Therefore, the normal range table of amino acids for children from the National Institute of Health (NIH) dated 2006 was used for the mean normal range.

Table 63 demonstrates the results of glutamine levels at baseline and post initiation of first carglumic acid treatment.

Table 63: Summary Statistics of Glutamine levels in the short term

Timepoint	Statistics (N _{total} = 21*)	Glutamine** (µmol/L)	
Baseline	N	16	Change from baseline to short-term
	Mean (SD)	957.1 (452.5)	
	Median	998.0	
	Range	131.0-1961.0	
	Missing Data	5	
Day 1	N	6	6
	Mean (SD)	544.8 (101.9)	-437.2 (172.8)
	Median	526.5	-444.5
	Range	426.0-670.0	-640.0- -160.0
	Missing Data	15	15
Day 2	N	3	3
	Mean (SD)	479.7 (164.2)	-755.0 (235.3)
	Median	503.0	-741.0
	Range	305.0-631.0	-997.0- -527.0
	Missing Data	18	18
Day 4	N	3	2
	Mean (SD)	422.0 (113.9)	-267.0 (199.4)
	Median	449.0	-267.0
	Range	297.0-520.0	-408.0- -126.0
	Missing Data	18	19
Day 5	N	2	2
	Mean (SD)	275.0 (100.4)	-1114.0 (438.4)
	Median	275.0	-1114.0
	Range	204.0-346.0	-1424.0- -804.0
	Missing Data	19	19
Day 7	N	1	1
	Mean	470.0	-644.0
	Median	470.0	-644.0
	Range	470.0-470.0	-644.0- -644.0
	Missing Data	20	20

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 420 to 730 µmol/L

Reviewer's table modified from sponsor's tables 3, 7b, and 8b, Carbaglu Final, pages 9, 76, and 88

The normal range for citrullinemia varied from center to center. Therefore, the normal range table of amino acids for children from NIH dated 2006 was used as the mean normal range.

Table 64 demonstrates the results of citrulline levels at baseline and post initiation of first carglumic acid treatment.

Table 64: Summary Statistics of Citrulline levels in the short term

Timepoint	Statistics (N_{total} = 21*)	Citrulline** (µmol/L)
Baseline	N	13
	Mean (SD)	19.8 (16.5)
	Median	14
	Range	1.0-57.0
	Missing Data	8
Day 1	N	5
	Mean (SD)	19.0 (13.8)
	Median	27.0
	Range	3.0-32.0
	Missing Data	16
Day 2	N	1
	Mean (SD)	26.0
	Median	26.0
	Range	26.0-26.0
	Missing Data	20
Day 4	N	3
	Mean (SD)	15.0 (9.2)
	Median	13.0
	Range	7.0-25.0
	Missing Data	18
Day 5	N	1
	Mean (SD)	5.0
	Median	5.0
	Range	5.0-5.0
	Missing Data	20
Day 7	N	1
	Mean	7.0
	Median	7.0
	Range	7.0-7.0
	Missing Data	20

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 16 to 32 µmol/L

Reviewer's table modified from sponsor's tables 3 and 7c, Carbaglu Final, pages 9 and 78

Medical officer comments

Plasma ammonia levels have been used previously as an efficacy endpoint in clinical trials for products approved for the treatment of hyperammonemia due to urea cycle disorders. However, plasma glutamine and citrulline levels have not been clearly established as acceptable efficacy endpoints previously. The correlation of these levels with clinical outcome is not clear. The Reviewer evaluated both the effect of carglumic acid on plasma glutamine and citrulline as supportive measures to assess treatment effect of carglumic acid.

Treatment with carglumic acid is expected to decrease glutamine levels. Mean and median glutamine levels appear to decrease to normal range within 24 hours after the first treatment with carglumic acid; however, a substantial number of missing values between days 2-7 made interpretation of data difficult.

Citrulline levels are generally expected to be low at baseline in NAGS deficiency because citrulline is a product of carbamyl phosphate synthase and ornithine transcarbamylase (see Figure 1). Therefore, citrulline levels should increase with carglumic acid therapy; however, there was no clear trend demonstrated in the data. Baseline mean citrulline level was within normal range whereas baseline median citrulline level was slightly low. One day post treatment with carglumic acid, the mean citrulline level remained unchanged whereas the median citrulline level increased. Due to substantial missing values (n = 1 on days 2, 5 and 7) and conflicting results, it is difficult to establish any clear trend in citrulline levels with carglumic acid treatment. The citrulline levels were also confounded by concomitant citrulline supplementation at the time the values were obtained.

6.1.6 Other Endpoints

Neurologic and Psychomotor development Outcomes

There are no published outcome studies in NAGS deficiency patients due to the extreme rarity of this type of urea cycle disorder. Therefore, available published clinical outcomes are reported for all urea cycle disorders in aggregate. The degree of neurologic impairment in urea cycle disorders has been shown to correlate with peak levels of ammonia¹⁰ and the duration of hyperammonemic coma.¹¹ Hyperammonemia is the primary pathophysiologic consequence of NAGS deficiency and other urea cycle disorders. Hyperammonemia leads to multiple biochemical and structural changes in the brain, and is thought to cause swelling of astrocytes in the brain as well as pleomorphic changes in the mitochondria.

The natural history of urea cycle defects includes frequent episodes of hyperammonemia, which often result in permanent neurologic impairment. Generally, younger patients express a more severe phenotype. One study reports that 79% of children who presented with neonatal hyperammonemic coma had one or more developmental disabilities at 12-74 months of age and a mean IQ of 43 +/- 6.¹² Therefore, the Applicant attempted to measure neurologic outcomes in patients reviewed in the retrospective case series. However, there was no standardized and

10 Uchino T, et al. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. *J.Inher. Metab. Dis.* 1998; 21 (Suppl 1): 151-159

11 Msall M, et al. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. *N Engl J Med* 1984; 310: 1500-1505

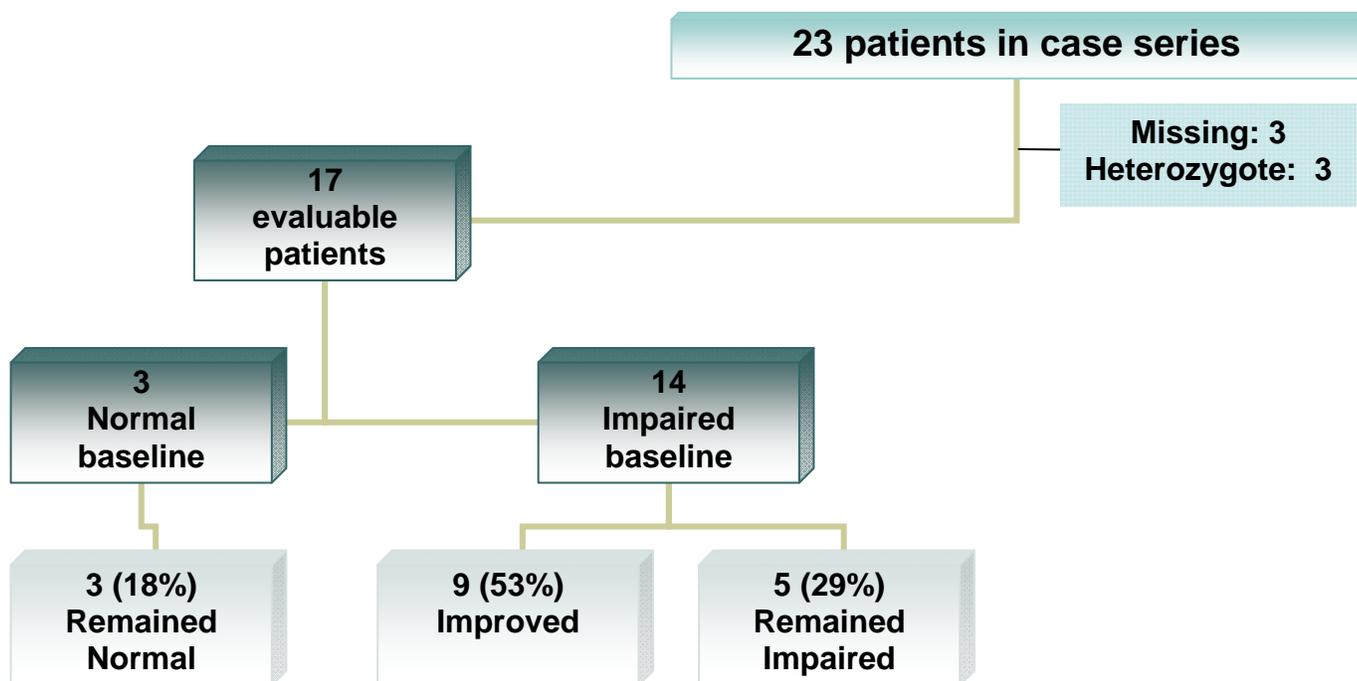
12 Msall M, et al. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. *N Engl J Med* 1984; 310: 1500-5

validated tool used at all centers to evaluate neurologic changes. Since there were multiple clinics, hospitals and physicians involved in treating the patients, the timing and type of neurocognitive assessments varied widely.

Medical officer comments

To evaluate neurologic outcome, the Reviewer evaluated data for all 23 patients. Six were excluded due to reasons listed in Figure 78. One patient (b) had missing neurologic and psychomotor development data at all timepoints (baseline and follow-up). Two patients who died with hyperammonemic encephalopathy in addition to other causes had no baseline or follow-up neurologic or psychomotor development documentations. Three patients were excluded from neurologic assessment due to their heterozygote NAGS mutation and discontinuation of carglumic acid therapy. Thus, in 17 patients with available data at last follow-up, 9 patients (53%) presented with neurologic impairment at baseline that improved after initiation of carbaglu therapy and for the duration of treatment. Three patients (18%) had normal neurologic function at presentation and remained neurologically unimpaired post initiation and continuation of treatment with carbaglu. Thus, 12/17 or (71%) of patients with long-term neurologic outcome information had an absence of clear neurologic impairment. This compares favorably with established natural history data. However, 5 patients (29%) who had sustained neurologic impairment attributed to hyperammonemic episodes continued to exhibit neurologic impairments despite normal ammonia levels and continued treatment with carbaglu. Given the lack of standardized measurement tools and intervals for neurologic and psychomotor evaluation, the degree of neurologic impairment that persisted in these 5 patients were described by the treating physicians using verbatim terms such as seizure disorders, inability to speak, sporadic incontinence, dyslexia along with hyperactivity disorder, limited communication skills, paraplegia of lower limbs, significant handicap for development parameters, psychiatric behavioral disorders with hyperactivity, lack of discipline at school with severe difficulty in school work and behavioral problems. Based on the type of neurologic and psychomotor evaluation data collected, it is not possible to make clear conclusions regarding the effect of carglumic acid on neurologic outcome. However, these data suggest that neurologic outcome may be improved in patients with NAGS deficiency treated long-term with carglumic acid.

Figure 78: Retrospective case series analyses of neurologic outcome



6.1.7 Subpopulations

Study IND 68,185 and Retrospective Case Series

See section 6.1.8 for a subgroup analysis of patients in the retrospective case series that received sole carglumic acid therapy.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Retrospective Case Series

Prior to and during treatment with carglumic acid, the majority of patients (18 of 23 patients, 78%) received one or more concomitant standard therapies, which are used to decrease ammonia levels. Only 5 patients in the case series did not have any antihyperammonemic therapy before or during treatment with carglumic acid. Table 65 provides a list of the interventions and therapeutic agents used in the various patients to decrease ammonia levels.

Table 65: Anti-hyperammonemic concomitant therapies

Anti-hyperammonemic	Total Patients = 23 (100%)
No Anti-hyperammonemic	5 Patients (21.7%)*
Concomitant therapies	N (%)
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)

(b) (6)

Reviewer's table modified from sponsor's table 19, Carbaglu Final, page 129

Six patients, however, received either carglumic acid treatment alone or carglumic acid with protein restriction without any other "anti-hyperammonemic" therapy within 7 days pre and post initiation of carglumic acid treatment. Table 66 summarizes the 7 days pre and post first carglumic acid treatment ammonia level data for these six patients who received carglumic acid treatment without any additional anti-hyperammonemic treatment. Three of these patients had concurrent protein restriction (b) (6) (b) (6) and 3 did not (patients (b) (6)). (b) (6) received standard therapy (arginine, carnitine, and sodium benzoate) for approximately 20 days (discontinued October 15, 1991) prior to the initiation of carglumic acid. He was then started on carglumic acid on June 19, 1992 without additional anti-hyperammonemia therapy, with the exception of protein restriction. Likewise, patients (b) (6) also received protein restriction during treatment with carglumic acid. Patient (b) (6) had protein restriction documented for 24 hours (January 20 to 21, 2002) after which he was on an unrestricted protein intake. (b) (6) had fluctuating ammonia levels on the day treatment was started and also 24 hours post initiation of carglumic acid therapy. Plasma ammonia level was noted to be abnormal (185 µmol/L) approximately 24 hours post-treatment with carglumic acid and no explanation was provided.

Table 66: Ammonia levels within 7 days pre and post first carglumic acid treatment in 6 patients without any anti-hyperammonemic concomitant therapies

Patient	Date and time* of first carglumic acid treatment	Date of ammonia levels and number of samples	Min and Max ammonia level (µmol/L)	Mean ammonia level (µmol/L)
(b)		6-17-1992; 8	74; 260	159
		6-18-1992; 6	64; 191	113
	Post first treatment with carglumic acid			
	6-19-1992	6-19-1992; 8	55; 85	67
		6-20-1992; 6	27; 63	46
(b) (6)		4-14-1999, 1	182	182
		4-15-1999, 1	182	182
	Post first treatment with carglumic acid			
	4-15-1999 at 19:30	4-15-1999, 1	184 (1hr post first dose at 20:30)	184
		4-15-1999, 3	158; 168	164
		4-16-1999, 2	58; 97	78
		4-17-1999, 1	54	54
	4-20-1999, 1	56	56	
(b) (6)		2-27-2002, 7	113; 367	255
		3-1-2002, 1	218	218
	Post first treatment with carglumic acid			
	3-1-2002 at 12:30	3-1-2002, 1	288 (1hr post first dose at 13:41)	288
		3-1-2002, 3	41; 126	84
		3-2-2002, 1	26	26
		3-3-2002, 1	11	11
	3-5-2002, 1	41	41	
(b) (6)		4-28-2002, 3	113; 130	124
		4-29-2002, 1	117	117
	Post first treatment with carglumic acid			
	4-29-2002	4-29-2002, 1	132 (1hr post first dose)	132
		4-29-2002, 6	55; 126	94
		4-30-2002, 4	25; 45	38
	5-06-2002, 1	21	21	
(b)		3-8-2005, 2	189; 242	216
	Post first treatment with carglumic acid			
	3-9-2005 at 12:00	3-9-2005, 1	69 (30 min post first dose)	69
		3-9-2005, 6	52; 185	122
		3-10-2005, 3	29; 185	81
	3-11-2005, 1	28	28	
(b ⁺)		7-22-2005, 1	40	40
		7-27-2005, 4	61; 157	107
	Post first treatment with carglumic acid			
	7-27-2005 at 11:40	7-27-2005, 1	67 (1hr 20 min post first dose)	67

*Time entered in military format if provided in sponsor's data

*Protein intake **Unrestricted**

Reviewer's table constructed from sponsor's data in subject profiles

Medical officer comments

Mean plasma ammonia levels decreased within 24 hours of the first treatment of carglumic acid in all 6 patients without any concomitant standard agents, except for protein restriction. Three of the 6 patients (b) (6) who received sole carglumic acid therapy and had no protein restriction intake implemented demonstrated a decrease in ammonia levels. In addition, these 3 patients had documented normal neurologic function at last follow-up.

The data on reduction or discontinuation of standard therapies and low protein diets were difficult to interpret due to missing information, such as accurate stop and re-start dates, and the variability in the timing of discontinuation of the standard therapies. These limited data in these six patients suggest that lowering of plasma ammonia levels appears to be an effect of carglumic acid and not other ammonia-lowering therapies. Therefore, a substantive analysis of the effect of confounders could not be performed. It is not possible to assess the independent effect of carglumic acid on the treatment of acute hyperammonemia associated with NAGS deficiency and clear conclusions regarding the effect of carglumic acid therapy as sole treatment for hyperammonemia due to NAGS deficiency cannot be made due to the limited quantity and quality of these data.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Study IND 68,185

The 3-day duration of this trial precludes any analysis of the persistence of efficacy.

Retrospective Case Series

To evaluate the persistence of efficacy, baseline plasma ammonia, glutamine and citrulline levels were compared to the last reported ammonia levels. Changes in these 3 laboratory values were evaluated in the long-term. The Applicant defined long-term as the last reported laboratory data while on carglumic acid therapy. The mean length of carglumic acid treatment was 8 years with a range of 1 month to 16 years.

All patients, except patients (b) (6) who had heterozygote NAGS mutation and were asymptomatic and discontinued treatment with carglumic acid, had at least one long term ammonia value while on carglumic acid treatment. Thus, patients (b) (6) were excluded from the summary statistics shown in Table 67, Table 68, and Table 69.

Effect of carglumic acid on long-term plasma ammonia level

The last available ammonia value on carglumic acid treatment was examined to assess the persistence of carglumic acid effect on plasma ammonia levels. Table 67 summarizes the last available ammonia value on carglumic acid treatment to assess the persistence of carglumic acid effect on ammonia levels.

Table 67: Summary statistics of ammonia levels in the long term

Timepoint	Statistics (N_{total} = 21*)	Ammonia (µmol/L)**
Baseline (nearest and/or maximal value before initiation of carglumic acid therapy)	N	20
	Mean (SD)	218.9 (299.0)
	Median	142.0
	Range	29.0-1428.0
	Missing Data	1
Long-term (last available value on carglumic acid treatment) (mean length: 8.0 years Range: 1 month – 16 years)	N	21
	Mean (SD)	51.8 (88.6)
	Median	25.0
	Range	7.0-419.0
	Missing Data	0
Change from baseline to long term	N	20
	Mean (SD)	-167.0 (314.1)
	Median	-108.0
	Range	-1419.0-139.0
	Missing Data	1

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 5 to 50 µmol/L

Reviewer's table modified from sponsor's tables 3, 7a, and 8a, Carbaglu Final, pages 9, 74, and 86

Medical officer comments

Based on the mean (51.8 µmol/L) and median (25.0 µmol/L) ammonia levels, carglumic acid appears to maintain mean and median ammonia levels closer to the normal range with on-going long term therapy. This may imply that once normal ammonia levels have been achieved, chronic therapy with carglumic acid maintains ammonia levels within the normal range.

Effect of carglumic acid on long-term plasma glutamine level

To further support the assessment of persistence of efficacy, the long-term effect of carglumic acid on plasma glutamine was also evaluated. The last available glutamine value on carglumic acid treatment was examined to assess the persistence of carglumic acid effect on glutamine levels. Table 68 summarizes the results of the last available glutamine value on carglumic acid treatment to examine the persistence of carglumic acid effect on glutamine levels.

Table 68: Summary statistics of glutamine levels in the long term

Timepoint	Statistics (N_{total} = 21*)	Glutamine (µmol/L)**
Baseline (nearest and/or maximal value before initiation of carglumic acid therapy)	N	16
	Mean (SD)	957.1 (452.5)
	Median	998.0
	Range	131.0-1961.0
	Missing Data	5
Long-term (last available value on carglumic acid treatment)	N	18
	Mean (SD)	561.0 (195.0)
	Median	516.5
	Range	353.0-1193.3
	Missing Data	3
Change from baseline to long-term	N	15
	Mean (SD)	-496.5 (403.7)
	Median	-570.0
	Range	-1532.0-203.0
	Missing Data	6

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 420 to 730 µmol/L

Reviewer's table modified from sponsor's tables 3, 7b, and 8b, Carbaglu Final, pages 9, 77, and 89

Medical officer comments

Median and mean glutamine levels normalized with long term carglumic acid treatment in patients for whom data were available.

Effect of carglumic acid on long-term plasma citrulline level

To further support the assessment of persistence of efficacy, the long-term effect of carglumic acid on plasma citrulline levels was also evaluated. The last available citrulline value on carglumic acid treatment was examined to assess the persistence of carglumic acid effect on citrulline levels. Table 69 summarizes the results of the last available citrulline value on carglumic acid treatment to examine the persistence of carglumic acid effect on citrulline levels.

Table 69: Summary statistics of citrulline levels in the long term

Timepoint	Statistics (N _{total} = 21*)	Citrulline (µmol/L)**
Baseline (nearest and/or maximal value before initiation of carglumic acid therapy)	N	13
	Mean (SD)	19.8 (16.5)
	Median	14
	Range	1.0-57.0
	Missing Data	8
Long-term (last available value on carglumic acid treatment)	N	19
	Mean (SD)	27.7 (9.1)
	Median	26.0
	Range	8.0-46.6
	Missing Data	2
Change from baseline to long-term	N	13
	Mean (SD)	5.7 (12.5)
	Median	4.0
	Range	-19.0-28.0
	Missing Data	8

*N = patients excluded from summary statistics are (b) (6)

**Mean normal range: 16 to 32 µmol/L

Reviewer's table modified from sponsor's tables 3, 7c, and 8c, Carbaglu Final, pages 9, 79, and 91

Medical officer comments

Baseline median citrulline levels were slightly low and baseline mean citrulline levels were within normal range. Treatment with carglumic acid might have resulted in an increase in mean and median citrulline levels to within normal range; however, long-term citrulline levels were difficult to interpret due to concomitant citrulline supplementation. Therefore, interpretation of the effect of carglumic acid on long-term citrulline levels is difficult, and clear conclusions regarding the effect of carglumic acid cannot be determined.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety of carglumic acid in the treatment of hyperammonemia due to NAGS deficiency has been adequately demonstrated in light of the ultra rare and serious nature of the disease. Despite the small sample size (30 patients total), the duration of exposure for the majority of patients exceeds 1 year. Based on the patients treated in Europe, there is adequate long term exposure, 21 of the 23 patients (91.3%) were

exposed for 1 year or greater with daily doses of carglumic acid. For study IND 68,185, no deaths, non-fatal SAEs or discontinuations were reported in this 3 day trial. The only AE reported in this trial was an episode of rhinorrhea, cough and congestion which was attributed to "strep throat" by the treating physician.

The retrospective case series includes long-term, uncontrolled exposure data for carbaglu. However, there were no serious safety issues identified in the submitted data for the 21 years (1987 to 2008) of exposure in 23 patients with NAGS deficiency.

Study IND 68,185 only includes short term exposure (3 days) in 7 patients (3 NAGS deficiency and 4 PA patients). The data submitted is derived from a case series and an open label trial without any concurrent control and with small sample sizes, which limit the ability to make clear conclusions regarding the overall safety profile of carbaglu.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study IND 68,185

Safety data from 7 patients who participated in an open-label 3 day treatment with carglumic acid were reviewed.

Retrospective Case Series

Safety data in 23 patients reviewed by the sponsor in a retrospective case series were compiled into individual patient narratives, subject profiles, and datasets. This information formed the basis of the safety evaluation.

7.1.2 Categorization of Adverse Events

Study IND 68,185

Adverse events (AEs) were reported as narratives without categorization using the MedRA dictionary. In addition, the clinical trial included the following secondary endpoints to evaluate the safety of carglumic acid following three day exposure:

- CBC, which consisted of hemoglobin, WBC and platelets
- Serum creatinine
- Plasma amino acids
- Liver function profile consisting of AST, ALT, total bilirubin, and conjugated bilirubin

The safety update report was submitted in October 2009, and includes updated safety data for patients enrolled from January 2004 until November 2008.

Retrospective Case Series

Individual patient narratives that described AEs were included by the applicant for review. Additionally, the Applicant coded all verbatim AE terms and descriptions in the subject profiles using the MedRA dictionary (version 11.0).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Study IND 68,185 and Retrospective Case Series

Since there are no control groups (active or placebo), it is not possible to report or compare incidences.

7.2 Adequacy of Safety Assessments

Study IND 68,185

Patients were monitored for serious adverse events such as a hypersensitivity reaction, severe vomiting, diarrhea, severe gastrointestinal complaints, or altered consciousness. Although hematology labs (hemoglobin, WBC, and platelets) were one of the safety parameters being monitored, they were not obtained in 4 out of the 7 patients at baseline and post treatment with carglumic acid. According to Dr. Tuchman, monitoring of hematology labs was added post protocol amendment and, therefore, were not consistently obtained in all patients.

Medical officer comments

The overall monitoring of safety appears adequate. There was only one AE reported in one patient in study IND 68,185, which is expected in light of the short duration and small sample size. Since this clinical trial included only 7 patients, the safety data are limited. In addition, the duration of the trial was short (3 days) and lacked a comparator arm.

Retrospective Case Series

Since NAGS deficiency is a rare disease, it is difficult to obtain a large sample size to adequately assess safety. However, most of the patients have had long term exposures to carglumic acid \geq 5 years (14 of 23 patients).

Medical officer comments

The small sample size and the source of the data (not from adequate and well controlled trials) are factors that limit the safety evaluation. In addition, the delayed diagnosis in some of the cases and use of concomitant medications that not only affect ammonia levels but could worsen the disease (impact the urea cycle products and cofactors) limit the interpretability of the AEs.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Retrospective Case Series

Because patients were treated individually and not as part of a clinical trial, the doses administered varied widely. Since the affected population tends to be in the pediatric age range, all dosing data are expressed in mg/kg. To understand dosing and exposure information, the sponsor divided the dosing data into within 7 days of initiation of treatment (or short term) and maintenance treatment (or long term). When short and long term dosing schedules were assessed, they ranged from once a day to six times a day dosing, but the most frequently used dosing schedule was qid.

Below is a breakdown of the number of patients that received doses between < 100 mg/kg/day and > 250 mg/kg/day. It should be noted that the same individual patient might be exposed to multiple dosing schedules and various doses throughout the duration of treatment with carglumic acid. Since the doses and dosing schedules outlined below are intended to comprehensively summarize the various dosing regimens prescribed, a patient might appear several times in the outline.

Initial and Maintenance Doses and Dosing Schedule, N = 23

Once daily administration (q d)

- 4 patients (17.4%) were treated with < 100 mg/kg/day
 - (patients (b) (6))
- 1 patient received between 100-250 mg/kg/day
 - (patient (b) (6))

Twice daily administration (bid)

- 16 patients (69.6%) received < 100 mg/kg/day
- 2 patients received between 100-250 mg/kg/day
 - (patients (b) (6))

Three times daily administration (tid)

- 14 patients (60.9%) received < 100 mg/kg/day
- 10 patients (43.5%) received between 100-250 mg/kg/day
- 1 patient received > 250 mg/kg/day
 - (patient (b) (6))

Four times daily administration (qid)

- 14 patients (60.9%) received < 100 mg/kg/day
- 12 patients (52.2%) received between 100-250 mg/kg/day
- 3 patients received > 250 mg/kg/day
 - (patients (b) (6))

Five times daily administration

- 2 patients received < 100 mg/kg/day
 - (patients (b) (6))

Listings of starting doses and schedules for the 23 patients with NAGS deficiency

(b) (6)	received 325 mg/kg/d administered in divided doses tid
(b) (6)	received 396 mg/kg/d administered in divided doses qid
(b) (6)	received 231 mg/kg/d administered in divided doses tid
(b) (6)	received 254 mg/kg/d administered in divided doses qid
(b) (6)	received 211 mg/kg/d administered in divided doses six times a day
(b) (6)	received 108 mg/kg/d administered in divided doses qid
(b) (6)	received 200 mg/kg/d administered in once daily
(b) (6)	received 130 mg/kg/d administered in divided doses tid
(b) (6)	received 100 mg/kg/d administered in divided doses tid
(b) (6)	received 100 mg/kg/d administered in divided doses tid
(b) (6)	received 182 mg/kg/d administered in unknown schedule
(b) (6)	received 122 mg/kg/d administered in divided doses qid
(b) (6)	received 34 mg/kg/d administered in divided doses tid
(b) (6)	received 294 mg/kg/d administered in divided doses qid
(b) (6)	received 40 mg/kg/d administered in divided doses qid
(b) (6)	received 144 mg/kg/d administered in unknown schedule
(b) (6)	received 134 mg/kg/d administered in divided doses qid
(b) (6)	received 200 mg/kg/d administered in divided doses qid
(b) (6)	received 140 mg/kg/d administered in divided doses bid
(b) (6)	received 122 mg/kg/d administered in divided doses tid
(b) (6)	received 100 mg/kg/d administered in divided doses bid
(b) (6)	received 142 mg/kg/d administered in divided doses qid
(b) (6)	received 105.3 mg/kg/d administered in divided doses qid

Initial Doses

The proposed starting dose of 100 to 250 mg/kg/day is based on clinical experiences with carglumic acid. In the listings above, NAGS deficiency patients have received starting doses ranging from, 34 mg/kg/day up to 396 mg/kg/day in divided doses. The mean and median starting doses were 165.7 and 140 mg/kg/day, respectively, with an interquartile range of 106.65 to 205.5 mg/kg/day.

Medical officer comments

Most patients' initial carglumic acid dose was the highest dose that they were exposed to, except for patients (b) (6) who started with doses of 150 mg/kg/day and 126 mg/kg/day, respectively. Those doses were later increased to the above listed doses. Although there is a wide range of starting doses for carglumic acid, most patients were started at a dose of ≥ 100 mg/kg/day, except for 2 patients (patient (b) (6) started at 34 mg/kg/day and patient (b) (6) started at 40 mg/kg/day). The highest starting doses were in the range of 325 to 396 mg/kg/day and occurred in 2 patients.

Patient (b) (6) had the lowest starting dose at 34 mg/kg/day and the lowest maintenance doses (between 4 and 6 mg/kg/d); however, this patient had parents who were reportedly non-compliant with treatment. Plasma ammonia levels fluctuated slightly above the normal range, and she experienced some hyperammonemic decompensations. This patient was probably underdosed throughout her treatment with carglumic acid.

Maintenance Doses

The maintenance dose varied widely among the 23 patients; however, there is a trend to reduce the daily administration (mg/kg/d) from the starting dose regimen. Dose reduction to achieve a maintenance dose was undertaken within days of initiation of carglumic acid therapy. It took anywhere from one day to 15 days for a dose reduction to be performed in the majority of patients (16 of 22 patients). In 5 patients, it took anywhere from 1 month to 10 months for the dose reduction process. In 1 patient, it took 2 years for dose reduction; however, this particular case (b) (6) was complicated by the fact that the patient was exposed to both chemical and pharmaceutical grades carglumic acid. (b) (6) was excluded from the evaluation of dose titration due to reported non-compliance and limited documentation.

In section 6.1.3, subject disposition, listings of the last doses with the recorded dates is provided in Table 55. The maintenance dose mean was 30.1 mg/kg/day with a range of 6 to 81.1 mg/kg/day in 17 patients who are on chronic Carbaglu treatment and have dosing data available in mg/kg/day.

Duration of exposure with carglumic acid

Table 70 below displays duration of treatment for the 23 patients in the retrospective case series database. Except for 2 patients, the majority of patients have had daily exposures to carglumic acid for ≥ 1 year.

Table 70: Exposure to carglumic acid therapy

Patient	Exposure (years)
< 1 year	
(b)	1 month
(b)	8 months
≥ 1 year but < 5 years	
(b)	1.3
(b)	2.3
(b)	2.5
(b)	2.7
(b)	3.5
(b)	3.6
(b)	4.9
≥ 5 years but < 10 years	
(b)	5
(b)	5.8
(b)	6.7
(b)	8
(b)	8.7
(b)	9
≥ 10 years	
(b)	10
(b)	11
(b)	11
(b)	14
(b)	15
(b)	15
(b)	16
(b)	20

Reviewer's table constructed from sponsor's subject profiles

7.2.2 Explorations for Dose Response

Study IND 68,185 and Retrospective Case Series

There were no dose finding studies conducted in the target patient population. Study IND 68,185 used the following dosing regimen for carglumic acid: 100 mg/kg/d for subjects weighing < 25 kg or 2.2 g/m²/day for subjects weighing ≥ 25 kg.

7.2.3 Special Animal and/or In Vitro Testing

There were no special animal or in vitro testing conducted for this submission.

7.2.4 Routine Clinical Testing

Study IND 68,185

The routine clinical testing of patients in study IND 68,185 was adequate. Dr. Tuchman performed adequate monitoring of safety parameters including vital signs and physical assessments.

Retrospective Case Series

Monitoring of safety parameters including physical assessments, psychomotor and neurologic developments was routinely done. Patients also had laboratory evaluations for amino acids, hematology parameters, liver function profiles and electrolyte and renal function parameters.

7.2.5 Metabolic, Clearance, and Interaction Workup

Dose-proportionality, dose-response, multiple-dose PK, and food effect studies were not conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Since there are no similar drugs approved in this class, no assessment of potential class effect of adverse events was performed.

7.3 Major Safety Results

7.3.1 Deaths

Study IND 68,185

There were no deaths reported in Dr. Tuchman's study IND 68,185.

Retrospective Case Series

Orphan Europe reported the deaths of 2 patients (8.7%) from their retrospective data collection. Both deaths were deemed "probably unrelated" to carglumic acid therapy.

Brief narratives of deaths are as follows:

Patient (b) (6) was admitted to the hospital for discontinuation of carglumic acid under medical supervision. As the patient was undergoing weaning from carglumic acid, her ammonia level increased from a normal level of 35 $\mu\text{mol/L}$ to a high of 233 $\mu\text{mol/L}$. During this same hospitalization, she became febrile and developed pneumonia. She required mechanical ventilation and experienced multi-organ system failure with encephalopathy leading to her death. No autopsy was performed. Chronic parental non-compliance with carglumic acid therapy was reported.

Patient (b) (6) experienced a worsening of her ammonia level to a high of 419 µmol/L in December 2007 as a consequence of pneumonia. Despite efforts to decrease her hyperammonemia with multiple interventions, the patient worsened and died. It is unknown whether an autopsy was performed.

7.3.2 Nonfatal Serious Adverse Events

Study IND 68,185

There were no non-fatal SAEs reported in Dr. Tuchman's study IND 68,185.

Retrospective Data

There were 10 patients who experienced non-fatal SAEs. Table 71 presents a description and preferred terms of all non-fatal SAEs reported.

Table 71: Listings of non-fatal SAEs

Patient	Preferred Term	Verbatim (AE description)	Causality Assessment	Outcome
(b)	vomiting	vomiting	unrelated	recovered/ resolved
	asthenia	asthenia	unrelated	recovered/ resolved
(b)	convulsion	hypertonic convulsive fit	unrelated	N/A
	Petit Mal Epilepsy	epileptic absence	unrelated	N/A
	abnormal behavior	behavior disorders	unrelated	Not recovered/ not resolved
	ear infection	otitis	N/A	N/A
	psychomotor hyperactivity	hyperactivity	unrelated	Not recovered/not resolved
	Pain	Pain of right hemiface	unrelated	recovered/resolved
(b)	headache	headache	unrelated	recovered/resolved
	vomiting	vomiting	unrelated	recovered/resolved
	gait disturbance	gait disturbance	unrelated	recovered/resolved
	somnolence	somnolence	unrelated	recovered/resolved
	Urethral fistula	cutaneous fistula of urethra	unrelated	recovered/resolved
(b)	vomiting	vomiting	unrelated	recovered/resolved
	appendicitis	acute appendicitis	unrelated	recovered/resolved
(b)	Abnormal feces	Pink feces	unrelated	recovered/resolved
	vomiting	vomiting	unrelated	recovered/resolved
	somnolence	drowsiness	unrelated	recovered/resolved
(b)	Nervous system disorder	gross cerebral dysfunction	N/A	N/A
	Paraplegia	Paraplegia	N/A	Not recovered/not resolved
	Urinary incontinence	Bladder incontinence	N/A	N/A
	Fecal incontinence	Bowel incontinence	N/A	N/A
(b)	vomiting	vomiting	unrelated	recovered/resolved
	dehydration	dehydration	unrelated	recovered/resolved
(b)	abdominal pain	abdominal pain	unrelated	recovered/resolved
	vomiting	vomiting	unrelated	recovered/resolved
(b)	pneumonia	pneumonia	N/A	N/A
	pneumonia	pneumonia	N/A	N/A
(b)	hallucination	hallucinations	unrelated	N/A
	dyskinesia	extension movements of the limbs	unrelated	N/A

N/A = not available

Reviewer's table constructed from sponsor's subject profiles and Carbaglu Final, table 13 SAEs page 115

Medical officer comments

Vomiting was the most frequently reported non-fatal SAE. It was reported once by 6 different patients. All non-fatal SAEs reported were thought to be unrelated to carglumic acid therapy. It is difficult to attribute vomiting to carglumic acid therapy since it can also be associated with hyperammonemia. The timing of vomiting relative to carglumic acid dosing is unclear based on the reported safety information.

7.3.3 Dropouts and/or Discontinuations

Please see section 6.1.3, subject disposition and Table 55 for details.

7.3.4 Significant Adverse Events

Study IND 68,185

There were no significant adverse events reported in Dr. Tuchman's study IND 68,185.

Retrospective Case Series

An overall summary of significant adverse events, defined as those reported by at least 3 subjects, is presented below in Table 72.

Table 72: Adverse Events reported by 3 or more patients

System Organ Class	Subjects N (%)
Total	23 (100)
Gastrointestinal disorders	10 (43.5)
vomiting	6 (26.1)
abdominal pain	4 (17.4)
diarrhea	3 (13.0)
Infections and Infestations	10 (43.5)
tonsillitis	4 (17.4)
infection	3 (13.0)
nasopharyngitis	3 (13.0)
General disorders and administration site conditions	7 (30.4)
Pyrexia	3 (13.0)
Nervous System disorders	6 (26.1)
headache	3 (13.0)
Ear and labyrinth disorders	4 (17.4)
ear infection	3 (13.0)
Blood and lymphatic system disorders	5 (21.7)
anemia*	3 (13.0)

*Note that anemia was reported in 2 patients and hypochromic anemia was reported in 1 patient, reviewer combined the 2 preferred terms under anemia.

Reviewer's table modified from sponsor's table 16, Carbaglu Final, page 120

7.3.5 Submission Specific Primary Safety Concerns

Study IND 68,185

There are no specific primary safety concerns reported in Dr. Tuchman's study IND 68,185.

Retrospective Case Series

There are no specific safety concerns identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study IND 68,185

Patient (b) (6) was diagnosed with "strep throat" on May 9, 2006 by his local pediatrician. On the first and fourth day of his participation in Dr. Tuchman's trial, the patient experienced rhinorrhea, cough, and congestion. No other AEs were reported in study IND 68,185.

Retrospective Case Series

There were no AEs reported for 6 patients (patients (b) (6)) in the retrospective case series (26.1%). Fifteen patients reported non-fatal, non-serious AEs. (b) (6) had the most reported non-fatal, non-serious AEs. Table 73 displays all non-fatal, non-serious AEs reported by SOC, preferred term, and AE description.

Table 73: Listings of Non-fatal, Non-serious AEs reported in 15 patients

Patient	SOC	Preferred Term	Verbatim AE description
(b)	Social Circumstances	Treatment Noncompliance	Poor acceptance (product acidity)
	General disorders and administration site conditions	asthenia	asthenia
	Metabolism and Nutrition disorders	Anorexia	Anorexia
	Gastrointestinal disorders	diarrhea	diarrhea
	Investigations	Weight decreased	weight loss
	Infections and Infestations	tonsillitis	tonsillitis
(b)	Nervous System Disorders	headache	headache
	Ear and Labyrinth disorders	ear infection	Otitis
	Ear and Labyrinth disorders	ear infection	Otitis

Patient	SOC	Preferred Term	Verbatim AE description
(b)	Blood and Lymphatic System disorders	Polycythemia	microcytic polyglobulia
	Gastrointestinal disorders	abdominal pain	abdominal pain
	Gastrointestinal disorders	Vomiting	vomiting (2 episodes)
	Gastrointestinal disorders	Pharyngitis	Pharyngitis
	General Disorders and administration site conditions	asthenia	asthenia
	General Disorders and administration site conditions	hyperthermia	Post vaccine hyperthermia
	General Disorders and administration site conditions	pyrexia	fever (2 episodes)
	Infections and Infestations	Influenza	Flu syndrome
	Infections and Infestations	nasopharyngitis	febrile rhinopharyngitis
	Infections and Infestations	nasopharyngitis	rhinopharyngitis (2 episodes)
	Infections and Infestations	tonsillitis	tonsillitis
	Infections and Infestations	tracheitis	tracheitis
	Infections and Infestations	Varicella	Febrile Chicken Pox
	Injury, Poisoning and Procedural Complications	Wrist Fracture	Wrist Fracture
	Metabolism and Nutrition Disorders	decreased Appetite	decreased Appetite (2 episodes)
	Nervous System Disorders	agitation	agitation
	Nervous System Disorders	headache	headache (2 episodes)
	Psychiatric Disorders	disturbance in attention	lack of attention
	Psychiatric Disorders	sleep disorder	sleep disorders
	(b)	Skin and subcutaneous tissue disorders	eczema
Skin and subcutaneous tissue disorders		Rash	rash
(b)	General Disorders and administration site conditions	Hyperhidrosis	sweating increased
	Infections and infestations	infection	infection
(b)	Infections and infestations	infection	infection
	Blood and Lymphatic System Disorders	Anemia	Anemia
(b)	Musculoskeletal and Connective Tissue disorders	Arthralgia	Pain right knee
	Metabolism and Nutrition Disorders	Anorexia	Loss of Appetite
	Investigations	Weight Decreased	Loss of 2 Kgs
	Gastrointestinal disorders	Flatulence	Flatulence
	Psychiatric disorders	depression	seemed depressed
	Reproductive System and Breast Disorders	dysmenorrhea	dysmenorrhea

Patient	SOC	Preferred Term	Verbatim AE description
(b) (4)	Gastrointestinal disorders	regurgitation	regurgitation
	Blood and Lymphatic System Disorders	hypochromic anemia	microcytic hypochromic anemia
	Ear and Labyrinth disorders	ear infection	Otitis
	Gastrointestinal disorders	Dysgeusia	bitter taste
	General Disorders and administration site conditions	Hyperhidrosis	excessive sweating
	Gastrointestinal disorders	diarrhea	diarrhea
	Ear and Labyrinth disorders	ear infection	Otitis
(b) (4)	Investigations	Hemoglobin decreased	low hemoglobin level
(b) (4)	Investigations	Aspartate aminotransferase increased	Increased AST
	Investigations	hemoglobin decreased	low hemoglobin
	Infections and Infestations	nasopharyngitis	rhinopharyngitis
	Gastrointestinal disorders	Vomiting	vomiting
	Gastrointestinal disorders	abdominal pain	abdominal pain
	Infections and Infestations	impetigo	impetigo
	Gastrointestinal disorders	diarrhea	diarrhea
	Infections and Infestations	nasopharyngitis	rhinopharyngitis
	General Disorders and administration site conditions	pyrexia	fever
	Skin and subcutaneous tissue disorders	Rash	Macular eruption
	Ear and Labyrinth disorders	ear infection	Otitis
	Infections and Infestations	tonsillitis	tonsillitis
(b) (4)	Blood and Lymphatic System Disorders	Jaundice	Icterus
	Respiratory, Thoracic and Mediastinal disorders	Nasal congestion	Nasal congestion
	Gastrointestinal disorders	gastroenteritis	acute gastroenteritis
	Infections and Infestations	Bronchitis	bronchial infection
	Eye Disorders	Conjunctivitis	Conjunctivitis
	Infections and Infestations	nasopharyngitis	rhinopharyngitis
	Infections and Infestations	Influenza	Flu syndrome
(b) (4)	Gastrointestinal disorders	Abdominal pain	Recurrent abdominal pain
(b) (4)	Ear and Labyrinth disorders	Otitis Media	Otitis Media
	Hepatobiliary disorders	Hyperammonemia	Hyperammonemia
	Infections and Infestations	Infection	Infections

Patient	SOC	Preferred Term	Verbatim AE description
(b) (6)	Blood and Lymphatic System Disorders	Anemia	Anemia at 96 g/L
(b) (6)	Infections and infestations	tonsillitis	febrile tonsillitis
(b) (6)	Nervous System Disorders	headache	headache (2 episodes)
(b) (6)	Infections and infestations	Molluscum Contagiosum	Molluscum Contagiosum
(b) (6)	Gastrointestinal disorders	Tooth Injury	Injured teeth
(b) (6)	Infections and infestations	Skin Papilloma	Warts

Reviewer's table constructed from the sponsor's subject profiles

Medical officer comments

Two subjects (b) (6) reported bad taste, which were considered related to carglumic acid treatment by their respective treating physicians. Additionally, two patients (b) (6) reported hyperhidrosis. In patient 5's case, the hyperhidrosis was thought to be related to carglumic acid treatment; whereas, in patient (b) (6) case, it was thought to be unrelated to carglumic acid therapy by their respective treating physicians. It is not clear whether these findings can be clearly attributed to treatment with carglumic acid

7.4.2 Laboratory Findings

Study IND 68,185

Creatinine, hematology labs (hemoglobin, WBC and platelets), liver function profile (AST, ALT, total bilirubin, and conjugated bilirubin), were obtained prior to and post the 3 day treatment with carglumic acid. There were no clinically significant worsening of any of the laboratory measurements from baseline. All the aforementioned laboratory results were within normal range except ALT level in Patient (b) (6). Patient (b) (6) had an abnormal ALT at 111 U/L at baseline, and it decreased to 93 U/L post treatment with carglumic acid but remained abnormal.

Retrospective Case Series

Anemia was reported as an AE in the following 6 patients: (b) (6).

Patient (b) (6) experienced jaundice and had one elevated total bilirubin at 217 µmol/L (normal range 2-18 µmol/L). No liver transaminases or coagulation profile were obtained at that time. Ten days later, her icterus was reported to have spontaneously resolved, but no follow-up total bilirubin was provided.

Patient (b) (6) had an elevated AST at 57 IU/L (normal range 10-45 IU/L) without an associated increase in ALT. Total bilirubin and coagulation profile were not obtained at that time. His ammonia level was normal at 34 µmol/L, but he had a low hemoglobin at

103 g/L (normal range 115-155 g/L). A follow-up ALT level revealed that it was decreasing to 49 IU/L.

Medical officer comments

The anemia findings in the 6 patients could be the result of multiple blood draws or possibly due to protein intake restriction.

7.4.3 Vital Signs

Study IND 68,185

Routine vital sign (i.e. heart rate, blood pressure, respiration, and temperature) findings were not provided although they were reported as monitored throughout the conduct of the 3 day trial.

Retrospective Case Series

Routine vital sign (i.e. heart rate, blood pressure, respiration, and temperature) findings were not provided.

7.4.4 Electrocardiograms (ECGs)

A thorough QT/QTc study in humans was not conducted for this submission.

Study IND 68,185

ECGs were not obtained in Dr. Tuchman's study.

Retrospective Case Series

ECG data from the 23 patients with NAGS deficiency were not submitted. The sponsor reports that baseline ECGs were not collected in the NAGS deficiency patients. Follow-up ECGs post dosing with carglumic acid were not consistently performed.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were done.

7.4.6 Immunogenicity

No immunogenicity studies were done.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

At high doses of 650 to 750 mg/kg/d, carglumic acid has been associated with a clinical picture of glutamate intoxication, which includes symptoms of tachycardia, sweating, bronchial hypersecretion, elevated body temperature, and restlessness. These symptoms were experienced by the same patient at 2 different time points with 2 different N-carbamylglutamate doses of 750 mg/kg/d in the neonatal period as described in section 7.6.4 and 650 mg/kg/day in a published case report describing a 9 year follow-up.¹³

7.5.2 Time Dependency for Adverse Events

Study IND 68,185

Carglumic acid was only administered for 3 days; therefore, evaluation of time dependency for adverse events was not performed.

Retrospective Case Series

There were no AEs reported that appear to worsen over time or duration of treatment with carglumic acid. The highest doses of carglumic acid administered to patients were during the initial treatment period, which often lasted a few days. Once the ammonia levels normalized, lower doses of carglumic acid were used for maintenance treatment. Although the sample size is small, no AEs seem to get worse with longer duration of treatment.

7.5.3 Drug-Demographic Interactions

Pregnant and Nursing Female Subjects

- There have been no adequate and well-controlled trials of carglumic acid in pregnant women
- The excretion of carglumic acid or its metabolites in milk of nursing mothers has not yet been evaluated

Elderly Subjects

- Carglumic acid has not been investigated in elderly patients (both males and females \geq 65 years of age).

Renal and Hepatic Impaired Subjects

- No studies were conducted in renal or hepatic impaired patients

¹³ Schubiger G, et al. N-Acetylglutamate synthetase deficiency: diagnosis, management and follow-up of a rare disorder of ammonia detoxification. Eur J. Pediatr 1991; 150: 353-356

Race

- Comparisons of AEs in various race groups were not conducted due to the limited total sample size. Race and Ethnicity data were not provided in both study IND 68,185 and the retrospective case series.

Male and Female Subjects

- Comparisons of AEs in male and female patients did not demonstrate any differences. However, the number of patients evaluated in the safety population was too few to detect any gender differences in AEs.

7.5.4 Drug-Disease Interactions

No explorations were done.

7.5.5 Drug-Drug Interactions

No drug-drug interactions studies were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are no human carcinogenicity studies performed using carglumic acid.

7.6.2 Human Reproduction and Pregnancy Data

Study IND 68,185

Pregnancy was used as an exclusion criterion in Dr. Tuchman's study.

Retrospective Case Series

There have been no cases of carglumic acid exposure during pregnancy or lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

Study IND 68,185

Dr. Tuchman's study did not evaluate any growth measures. In light of the short duration of the study (3 days), no change in growth would be expected.

Retrospective Case Series

In general, the retrospective data from Orphan Europe suggests that when patients received early exposure to carglumic acid (often concomitantly with standard therapies), there was relatively "normal" growth (see individual patient narratives in section 5.3, discussion of individual studies).

Medical officer comments

Since growth is an important outcome measure in the pediatric population, the reviewer attempted to evaluate the effect of carglumic acid on growth. Clinical measurements of growth (i.e., weight, height, body mass index) were not consistently collected at baseline and follow-up visits, making an analysis of the effect of carglumic acid on growth uninterpretable. Therefore, an analysis of the effect of carglumic acid on growth could not be performed. Furthermore, growth has been correlated with the amount of protein intake in the pediatric population, especially in the neonate, infant and early childhood years when rapid growth is expected. Hence, the amount of protein restriction might have been a confounding factor for evaluation of growth and may not necessarily reflect the effect of carglumic acid.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence in either study IND 68,185 or in the retrospective case series that suggests any issues with drug abuse potential, withdrawal, or rebound effect.

Retrospective Case Series

The sponsor and the literature report one case of overdose that occurred in a male patient who was started on carglumic acid in the neonatal period. This patient demonstrated the first ever human use/experience with carglumic acid.¹⁴ According to the sponsor and the literature, the patient received 750 mg/kg/day of carglumic acid as a test case for a "dose-finding approach". He experienced clinical symptoms similar to that observed in "Chinese restaurant syndrome" (or Monosodium glutamate (MSG) intoxication).

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Carglumic acid has been approved in Europe since January 24, 2003. The sponsor reported that there have been no new safety issues identified or new safety labeling changes implemented. On review of the AEs reported to the sponsor during the post marketing period up to December 31, 2008, there were no new potential safety signals identified.

¹⁴ Buchman C, et al. N-acetylglutamate synthetase (NAGS) deficiency: diagnosis, clinical observations and treatment. *Advances in experimental medicine and biology.* 1982: 153: 39-45

Medical officer comments

Since the data cut-off date was December 2007, most of the safety review incorporates postmarketing experience in Europe (2003 to 2007). Safety data (deaths, non-fatal serious AEs, non-serious and non-fatal AEs) in other metabolic disease entities, except as described in Study IND 68,185 were reviewed but not incorporated in the safety review since these data were determined not to alter the safety conclusions in the target population.

The safety update (December 2007 to December 31, 2008) provided by the sponsor were also reviewed, and the reviewer did not identify any AEs (deaths, non-fatal serious AEs, non-serious and non-fatal AEs) that would alter the overall safety of Carbaglu in NAGS deficiency patients. There were 3 cases in which the treating physicians reported Carbaglu as being ineffective. One case was a confirmed CPS 1 deficiency, another case was methylmalonic acidemia, and the third case was a suspected NAGS deficiency (not confirmed by DNA analysis but with low CPS 1 enzymatic activity).

9 Appendices

9.1 Literature Review/References

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Enns G, et al. Survival after Treatment with Phenylacetate and Benzoate for Urea-Cycle Disorders. *N Engl J Med* 2007: 356: 2282-92

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Guffon N, et al. Neonatal Hyperammonemia: The N-Carbamoyl-L-Glutamic Acid Test. *J Pediatr* 2005: 147: 260-2

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Summar M and Tuchman M. Proceedings of a Consensus Conference for the Management of Patients with Urea Cycle Disorders. *The Journal of Pediatrics*. 2001; 138: S6-S10

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Plecko B, et al. Partial *N*-acetylglutamate synthetase deficiency in a 13-year-old girl: diagnosis and response to treatment with carbamylglutamate. *Eur J Pediatr* 1998; 157: 996-998

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Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic outcome in children with inborn errors of urea synthesis: outcome of urea-cycle enzymopathies. *N Engl J Med* 1984; 310: 1500-5

Buchman C, et al. *N*-acetylglutamate synthetase (NAGS) deficiency: diagnosis, clinical observations and treatment. *Advances in experimental medicine and biology*. 1982; 153: 39-45

Busilow S W, Horwich A L. "Urea Cycle Disorders" [Metabolic and Molecular Basis of Inherited Disease](#). Eighth Edition, Vol. II: 1936-1950

Clinical features and diagnosis of urea cycle disorders dated September 30, 2009 from www.uptodate.com

Clinical Review
Virginia Elgin, M.D. and Helen Sile, M.D
NDA 22-562/S-000
Carbaglu (carglumic acid)

Management of urea cycle disorders dated September 30, 2009 from
www.uptodate.com

Deputy Division Director/Team Leader Memo for NDA 20-645: Ammonul (sodium
phenylacetate and sodium benzoate) 10%/10% for injection

Clinical Review for NDA 20-645: Ammonul (sodium phenylacetate and sodium
benzoate) 10%/10% for injection

Medical Officer Review of IND 68,185: Carglumic Acid tablets dated October 21, 2003

Information on lactulose obtained from www.rxlist.com

Current Approved label for Buphenyl (sodium phenylbutyrate) tablets and powder

9.2 Labeling Recommendations

[Redacted] (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted]

[Redacted]

5 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)



(b) (4)



9.3 Advisory Committee Meeting

A meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) was held on January 13, 2010 to obtain advice from the committee regarding the adequacy of information to support the effectiveness of carglumic acid in the treatment of NAGS deficiency. Additionally, the Agency was seeking advice regarding the appropriate indication and use of carglumic acid. Below are the questions posed to the committee, and the voting outcomes for the specific questions along with summary statements for the reasons behind their votes. For detailed discussions, please refer to the advisory committee transcripts.

EFFICACY

1. The legal effectiveness requirement for drug approval is “substantial evidence,” defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, ... on the basis of which it could fairly and responsibly be concluded ... that the drug will have the effect it purports or is represented to have” In some cases, substantial evidence may be considered to be “data from one adequate and well-controlled clinical investigation and confirmatory evidence”

Do the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provide substantial evidence of efficacy?

Vote: Yes: **12** No: **0** Abstain: **0**

Discuss the rationale for your vote, and in your discussion please include responses to the following questions:

- A. What clinical data were persuasive?
- B. What deficiencies in the clinical data make you consider the evidence to be less than substantial?

The committee discussed the retrospective nature of the case series as well as the variable time points of data collection, and the lack of a consistent protocol. However, the committee agreed that the disease was extremely rare and the pathophysiology is well understood. In addition, the committee concurred that carglumic acid treatment is directed toward correcting the underlying pathophysiology. It was evident to the committee, despite the retrospective nature of the case series presented, that the ammonia levels decreased with Carbaglu treatment. The committee noted that elevated ammonia levels probably contributed to most of the neurologic impairments with this disease, and neurologic improvements were observed during treatment. The committee believed this application meets the legal and regulatory definition for substantial evidence.

2. Do the data support the effectiveness of Carbaglu for treatment of **acute** hyperammonemia (i.e., initial treatment and subsequent episodes of acute hyperammonemia) in NAGS deficiency?

Vote: Yes: **11** No: **1** Abstain: **0**

Discuss the rationale for your vote, and in your discussion please include responses to the following questions and issues:

- A. What clinical data were persuasive?
- B. If Carbaglu is approved for the treatment of acute hyperammonemia, the product labeling will need to include dosing recommendations for acute treatment. Please provide recommendations that address:
 - Starting dose of Carbaglu (if different from the Applicant's proposed starting dose of 100-250 mg/kg/day in divided doses)
 - Dose adjustments during acute hyperammonemia
 - Use of adjunctive ammonia lowering therapies during acute hyperammonemia

There was discussion concerning the definition of acute hyperammonemia. The committee thought the plasma ammonia levels decreased within several days when

patients with acute hyperammonemia were treated with Carbaglu. The committee agreed that the dose of 100 to 250 mg/kg/day is appropriate as long as this was titrated based on the clinical presentation of the patient along with the ammonia level. The committee also supported the use of concomitant ammonia lowering therapies during acute hyperammonemic episodes.

3. Do the data support the effectiveness of Carbaglu for **maintenance** treatment of hyperammonemia in NAGS deficiency?

Vote: Yes: **12** No: **0** Abstain: **0**

Discuss the rationale for your vote, and in your discussion please include responses to the following questions and considerations:

A. What clinical data were persuasive?

B. If Carbaglu is approved for the maintenance treatment of hyperammonemia, the product labeling will need to include dosing recommendations for maintenance treatment. Please provide recommendations that address:

- Dose during maintenance treatment
- Clinical monitoring necessary to guide maintenance dosing (e.g., plasma ammonia level, glutamate level, etc.)
- Use of adjunctive ammonia lowering therapies during maintenance treatment

The committee unanimously agreed the data, although the source was a retrospective case series, provided sufficient evidence that plasma ammonia levels decreased with long term Carbaglu treatment. They also agreed that neurological impairments tended to resolve over time with Carbaglu treatment. The committee noted that dose adjustments will depend on individual patients and plasma ammonia levels but may typically be modified to 20 – 50% of the acute dosing. There was a suggestion to include the actual dose ranges from the retrospective case series data.

SAFETY

4. Based on the overall safety data presented, do you have safety concerns that should be addressed? If so, please describe how these safety concerns should be addressed (i.e., further studies, product labeling, etc.)

Vote: Yes: **5** No: **5** Abstain: **2**

Although the committee was divided, there was consensus that Carbaglu appears safe for the NAGS deficiency indication as demonstrated from the retrospective case series data. However, many members of the committee expressed concerns regarding potential "off-label use"; Carbaglu has the potential to be used in patients without NAGS deficiency such as OTC and CPS 1 deficiencies or patients with PA and MMA. There

was an additional concern among committee members that Carbaglu might be used in women who could potentially become pregnant.

RISK/BENEFIT ASSESSMENT

5. Does the risk/benefit profile of Carbaglu support its approval for treatment of hyperammonemia in NAGS deficiency?

Vote: Yes: **12** No: **0** Abstain: **0**

The committee voted unanimously to approve Carbaglu based on the decline and normalization of plasma ammonia levels and the improved neurologic outcomes in the NAGS deficiency patients treated with carbaglu. They strongly suggested that plasma ammonia levels be monitored for NAGS deficiency patients receiving carbaglu treatment.

6. What additional studies, if any, should be performed to further evaluate the safety and/or efficacy of Carbaglu in the treatment of hyperammonemia due to NAGS deficiency? Please include in your answer whether these studies should be performed pre-approval or post-approval.

The committee agreed that wider use of Carbaglu, including long-term use over years and decades in NAGS deficiency, does raise concerns about potential adverse effects. Overall, the committee agreed that the 2 year animal carcinogenicity study should be performed. There was active discussion regarding the issue of chronic toxicity study in non-rodent species. Several committee members did not agree with the rationale presented for the need to have chronic toxicity study in nonrodent species as they felt there has already been chronic human exposure in the retrospective case series. The committee also recommended use of registry to monitor patients receiving Carbaglu.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22562	ORIG-1	ORPHAN EUROPE	CARBAGLU (CARGLUMIC ACID)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HELEN SILE
03/11/2010

LYNNE P YAO
03/12/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-562 Applicant: Orphan Europe Stamp Date: 19-June-2009
Drug Name: Carbaglu NDA/BLA Type: 505 (b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Paper submission with electronic datasets
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			Narrative data only
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			X	
5.	Are all documents submitted in English or are English translations provided when necessary?		X		Problems with incomplete translation and difficulties corroborating paper submission with datasets for accurate review of data
6.	Is the clinical section legible so that substantive review can begin?	X			The clinical section in Module 2 is legible; there are illegible portions however in Module 5.
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1); will use Mendel Tuchman's supporting data however (IND # 68,185)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: NO TITLE: CASE SERIES			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?				Unable to determine
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The data submitted contains pediatric information
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No rationale needed. This is a rare disease and the patients were studied in 8 different countries for that reason.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	Many of the actual CRFS are illegible or in non-standard format. This is a retrospective case

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					series and CRF blank forms were submitted retrospectively.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	See above.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	Case Series; no controlled study

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **Note a teleconference was held with the Sponsor, Orphan Europe, 5-July-2009, where they agreed to resubmit Module 5 data so that individual patient data is submitted separately to facilitate the review. This was the original plan following the Sept 26, 2008 face-to-face meeting. The Sponsor has submitted two versions 30-July-2009 (2 different patients) of this to this Reviewer and the current approach seems to correct the organizational problems. Information gaps remain but those will be review issues.**

Virginia Elgin, M.D. FAAP 30-July-2009

 Reviewing Medical Officer Date

Virginia Acting TL for Lynne Yao, M.D. 30-July-2009

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E ELGIN
07/30/2009

LYNNE P YAO
08/05/2009