Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Sodium phenylbutyrate

Proprietary Product Name: Pheburane

Sponsor: Orpharma Pty Ltd

First round evaluation: 8 August 2016

Second round evaluation: 19 January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

Contents

List of common abbreviations

Abbreviation	Meaning
°C	degree Celsius
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARRB	Allergic Reaction Review Board
ASL	argininosuccinate lyase
ASS	argininosuccinate synthetase
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BCAA	Branched chain amino acid
CL	total clearance of drug after intravenous administration
C_{max}	observed maximum plasma concentration
CNS	central nervous system
CP	carbamyl phosphate
CPS-I	carbamyl phosphate synthetase I
CRA	Clinical Research Associate
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECHO	echocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GPB	glycerol phenylbutyrate
HAQ	Health Assessment Questionnaire
IAR	Infusion associated reaction
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
NAGS	N-acetylglutamate synthase
NaPB	sodium phenylbutyrate
NaPBA	sodium phenylbutyrate
NH3	ammonia
OTC	ornithine transcarbamylase deficiency
PAA	phenylacetic acid
PAGN	phenylacetylglutamine
PBA	phenylbutyric acid
PD	pharmacodynamics
PK	pharmacokinetics
PP	per-protocol
qow	every other week
REB	Research Ethics Board

RFTs	respiratory function tests
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
$T_{½}$ or $t_{½}$	elimination half-life
T_{max}	time to reach C_{max}
UCD	Urea Cycle Disorders
Vd	apparent volume of distribution
Vdz	apparent volume of distribution based upon the terminal phase
Vdz	apparent volume of distribution based upon the terminal phase
WHO	World Health Organization

1. Submission details

Submission number	PM-2016-00417-1-3
Sponsor	Orpharma Pty Ltd
Trade name	Pheburane
Active substance	Sodium phenylbutyrate 174g granules

Pheburane is a new chemical entity in Australia.

This is a hybrid dossier with literature-based submission and a single bioequivalence study.

The clinical submission was based upon a single bioequivalence study between Pheburane and the innovator product Ammonaps. Ammonaps is not a registered medicine in Australia and so the sponsor has requested that they supplement the bioequivalence study with evidence of the efficacy and safety of the innovator drug (Ammonaps) from the literature (as they do not have access to the initial Ammonaps application). The literature search strategy was developed in consultation with the TGA.

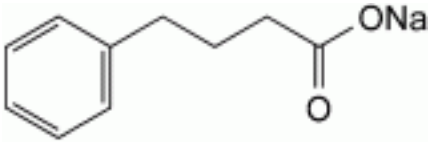
The proposed indication is urea cycle defects (UCDs), which are severe, rare and for which there are few effective therapies for treating the hyperammonaemia. Because of this, sodium phenylbutyrate has become a standard treatment without the support of randomised placebo-controlled trials.

1.1. Drug class and therapeutic indication

1.1.1. Drug class

Pheburane, sodium phenylbutyrate (sodium 4-phenylbutanoate), is an ammonia scavenger. It has an empirical formula of $C_{10}H_{11}NaO_2$ and a molecular weight of 186.2. The chemical structure is shown in Figure 1.

Figure 1: The chemical structure of sodium phenylbutyrate



Sodium phenylbutyrate is a pro-drug that is rapidly metabolised to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine which is then excreted by the kidneys. On a molar basis, phenylacetylglutamine's ability to bind nitrogen is comparable to urea (each containing 2 moles of nitrogen) and therefore provides an alternate vehicle for waste nitrogen excretion

1.1.2. Indication

Pheburane (sodium phenylbutyrate) is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase. Pheburane should be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline, and protein-free calorie supplements).

Pheburane is indicated in patients with *neonatal-onset* presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with *late-*

onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

1.2. Dosage forms and strengths

Pheburane granules are sugar-coated spheres containing sodium phenylbutyrate. The granules contain the following excipients: ethylcellulose, hydroxypropyl ethylcellulose, macrogol, maize starch, povidone and sucrose. Pheburane contains sodium phenylbutyrate 483 mg/g granule bottle and is in a pack size of 174 g.

1.3. Dosage and administration

Pheburane is administered orally. The usual total daily dose of sodium phenylbutyrate is:

- 450 - 600 mg/kg/day in neonates, infants and children weighing less than 20 kg;
- 9.9 - 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults

The safety and efficacy of doses in excess of 20 g/day have not been established.

The recommended doses for oral administration of Pheburane granules are shown in Tables 1-2. The recommended doses for administration of Pheburane solution through nasogastric or gastrostomy tube are shown in Tables 3-4.

Table 1: Recommended doses of Pheburane granules (expressed in mg of sodium phenylbutyrate) for oral dosing in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval	
	Minimum dose (mg) per day	Maximum dose (mg) per day
3	1350	1800
4	1800	2400
5	2250	3000
7.5	3375	4500
10	4500	6000
15	6750	9000
20	9000	12000

Table 2: Recommended doses of Pheburane granules (expressed in grams of sodium phenylbutyrate) for oral dosing in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval	
	Minimum dose (g) per day	Maximum dose (g) per day
0.8	7.9	10.4
1.05	10.4	13.7
1.27	12.6	16.5
1.48	14.7	19.2
1.66	16.4	20.0*
1.84	18.2	20.0*
1.97	19.5	20.0*

*The safety and efficacy of doses in excess of 20 g/day have not been established.

Table 3: Recommended doses of Pheburane solution (50 mg/ml of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
3	27.0	36.0
4	36.0	48.0
5	45.0	60.0
7.5	67.5	90.0
10	90.0	120.0
15	135.0	180.0
20	180.0	240.0

Table 4: Recommended doses of Pheburane solution (50 mg/ml of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
0.8	158.4	208.0
1.05	207.9	273.0
1.27	251.5	330.2
1.48	293.0	384.8
1.66	328.7	400.0*
1.84	364.3	400.0*
1.97	390.1	400.0*

*The safety and efficacy of doses in excess of 20 g/day have not been established.

2. Background

2.1. Information on the condition being treated

The submission describes Urea Cycle Disorders as follows.

> Ureagenesis follows a cycle: in the mitochondrial matrix, the first step of ammonia detoxification carbamyl phosphate synthetase I (CPS-I) converts ammonium and bicarbonate to carbamyl phosphate (CP). The second step ornithine transcarbamylase (OTC) catalyses the condensation reaction between CP and ornithine to yield citrulline. Citrulline is transported to the cytosol where it is conjugated with aspartate to form argininosuccinic acid via argininosuccinate synthetase (ASS). Subsequently, arginine is produced by the action of argininosuccinate lyase (ASL). The final step involves the cleavage of arginine by arginase to form urea and ornithine. Ornithine must be then transported to the mitochondrion for the next turn of the cycle. In addition, another intra-mitochondrial enzyme N-acetylglutamate synthase (NAGS) catalyses the formation of N-acetylglutamate, the essential cofactor for CPS-I activity.
>
> The urea cycle serves two purposes: (1) it contains, in part, the biochemical reactions required for the de novo biosynthesis and degradation of arginine, and (2) it incorporates nitrogen atoms not retained for net biosynthetic purposes into urea, which serves as a waste nitrogen product. Excess dietary protein and the nitrogenous substances produced by endogenous protein turnover are normally metabolised to yield

energy and the by-product ammonia is transformed into nontoxic urea which is freely excreted in the urine.

Urea Cycle Disorders (UCD) are inherited deficiencies of one of the 6 enzymes involved:

§ N-Acetyl glutamate synthetase (NAGS)

§ Carbamyl phosphate synthetase (CPS-I)

§ Ornithine transcarbamylase (OTC)

§ Argininosuccinate synthetase (ASS)

§ Argininosuccinate lyase (ASL)

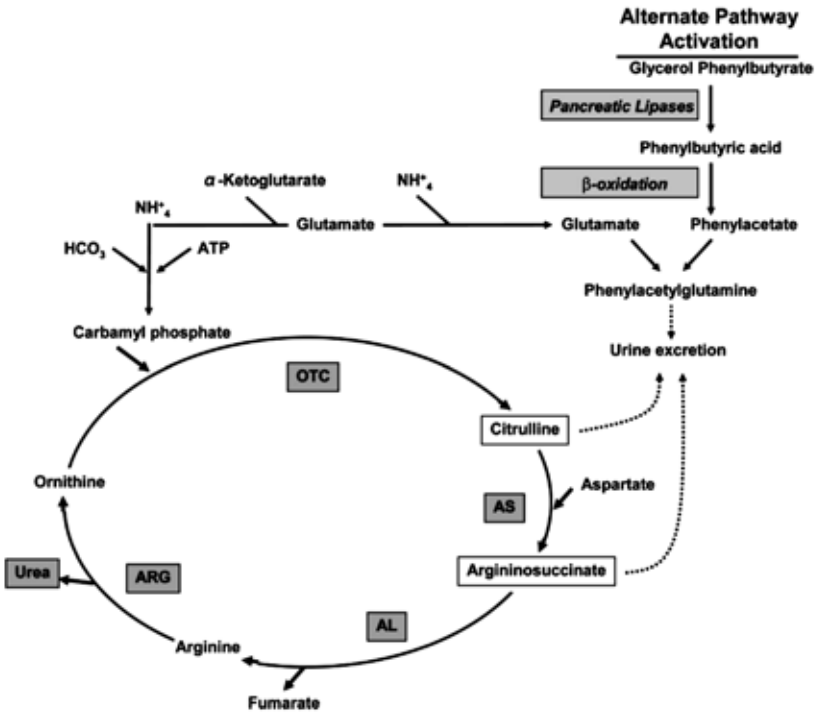
§ Arginase.

At each cycle one molecule of urea which contains two atoms of waste nitrogen (that is, nitrogen not used for net protein synthesis) is cleared. A defect in the ureagenic pathway has two consequences: arginine becomes an essential amino acid (except in arginase deficiency, where the enzyme defect results in a failure of degradation of arginine) and nitrogen atoms accumulate in precursors the pattern of which varies according to the specific enzymatic defect. Nevertheless, plasma levels of ammonium and glutamine are increased in all UCD not under metabolic control.

Severe, prolonged and/or repeated episodes of hyperammonaemia could lead to cerebral oedema and death or mental retardation.

Five enzyme-catalysed reactions that constitute the urea cycle function primarily to prevent the accumulation of toxic nitrogenous entities by incorporating them into urea. Inherited defects in four of the five enzymes that constitute the urea cycle function (carbamyl phosphate synthetase [CPS], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [AS], and argininosuccinate lyase [AL]) (Figure 2) lead to protein intolerance and massive accumulation of ammonia, with most catastrophic presentations in full-term infants in the first week of life. Inheritance for all UCDs is autosomal recessive, except for OTC deficiency, which is X-linked.

Figure 2: Urea cycle and alternate pathway activation. Deficiencies of these enzymes lead to hyperammonaemia and protein intolerance



The initial presentation varies widely. This is a challenge for rapid diagnosis and early start of treatment. Severe acute hyperammonaemia causes a rapidly progressive, often fatal, encephalopathy with brain oedema. Chronic milder hyperammonaemia causes a neuropsychiatric illness. Survivors of severe neonatal hyperammonaemia have structural brain damage. There is wide genotypic and phenotypic heterogeneity, such that milder forms of these urea cycle disorders (UCDs) may present in childhood or in adults manifesting as dietary protein aversion and encephalopathy that may be misdiagnosed for years. Clinical manifestations range from mild (for example, failure to thrive, intellectual disability and episodic hyperammonaemia) to severe (for example, altered mental status, coma, death) illness.

The overall prevalence of UCDs is approximately 1/35,000, with 2/3 presenting initial symptoms after the newborn period. The mortality rate is 24% in neonatal onset cases and 11% in late onset cases. It is estimated that there are only 1000-2000 patients with UCDs in the United States, approximately half of whom are diagnosed and approximately 400 of whom are taking sodium phenylbutyrate.

Currently available data suggest that the overall prevalence of UCDs and distribution of subtypes is similar in Japan, North America and Europe (European Medicines Agency, 2015). It is estimated that the number of UCD patients in Europe is about 3400 patients, approximately half of whom are diagnosed and less than 700 patients are taking sodium phenylbutyrate (European Medicines Agency, 2015). In Australia, there are likely to be only 100-150 UCD patients. Around one in 50,000 babies born in Australia and New Zealand has a UCD (Australasian Society for Inborn Errors of Metabolism, 2007; Wilcken, 2004). This means that only six to seven babies a year are diagnosed in Australia.

2.1.1. Clinical outcome in patients with UCDs

Prior to the availability of waste nitrogen excretion stimulation, the natural history of UCD was established among 28 patients (5 CPS-I, 10 OTC, 6 ASS, 7 ASL; Shih 1976). The one-year survival

rate was 14% and 3 of the 4 survivors were mentally retarded. After implementing alternative-pathway therapy (Msall 1984) the one-year survival rate was 92% in 26 children with complete UCD and neonatal hyperammonaemic coma (3 CPS-I, 7 OTC, 8 ASS, 8 ASL). Among the 24 who survived at least one year (2 male OTC died of hyperammonaemic coma) there were 4 further deaths, 1 from each diagnosis: 2 from hyperammonaemic coma, 1 from overdose of waste nitrogen excretion drugs, and 1 from pneumonia. Of those 24 children 19 had one or more developmental disabilities and mean IQ score was 53±6 (Table 5).

Table 5: Neurological long-term outcome in UCD as a function of diagnosis and coma duration (Msall 1984)

Deficient enzyme	N of patients	Age (months)	Duration of coma (days)	IQ at 12 months	Developmental disabilities (%)*
CPS-I	3	19±5	12±9	58±24	100
OTC	5	21±4	3±1	70±18	40
ASS	8	30±4	5±1	44±10	88

*Normal function (21%), cerebral palsy (46%), mental retardation (79%), seizure disorder (17%), blindness (4%) microcephaly (54%), multiple handicaps (46%)

No correlation was found between peak ammonium levels (351-1800 µmol/L) and IQ score at 1 year, however these scores were directly correlated with the length of time in neonatal hyperammonaemic coma: a good prognosis (normal IQ in 4/5 children) was observed in the group with coma lasting less than 3 days. Conversely patients in stage III-IV coma for longer than 5 days were all handicapped with abnormal CT-scans.

In a retrospective survey in Japan (Uchino 1998) on a larger group of 216 UCD patients including 116 with late-onset (26 CPS-I, 95 male OTC, 52 female OTC, 24 ASS, 12 ASL, 7 AG), the one-year survival was 43% for neonatal onset and 75% for late-onset; the long-term 5-year survival rates were 22% and 41%, respectively. The survival rate of patients with neonatal ASS or ASL was 85% versus 14% for those with neonatal CPS-I or OTC. A retrospective survey in France (Nassogne 2005) from a group of 217 UCD patients including 96 with late-onset (14 CPS-I, 112 male OTC, 38 female OTC, 33 ASS, 20 ASL) retrieved similar long-term survival rates (16% for neonatal onset and 40% for late-onset).

Similar survival rates were observed in a Swiss-coordinated survey on 88 UCD (Bachmann 2003). In this latter series, the effect of extensive treatment was significantly improving survival in neonatal presentation cases (p=0.045) but not in post-neonatal cases. Extensive treatment had not been effective in preventing mental retardation, with a significantly (p=0.0325) higher incidence of mental retardation in patients receiving extensive treatment versus patients on diet alone.

2.2. Current treatment options

The submission describes three key components to therapy for UCDs:

a. pharmacological intervention, or so-called nitrogen scavenger therapy;

b. nutritional supplementation with the amino acids l-citrulline or l-arginine; and

c. a low-protein diet that balances nitrogen restriction with growth requirements.

The only known 'cure' for UCDs is liver transplantation, which in itself carries a significant morbidity and mortality and does not correct all metabolic abnormalities.

2.3. Clinical rationale

The submission gives a clear rationale for the development of Pheburane. As described below, Ammonaps was the original formulation of sodium phenylbutyrate used for the treatment of urea cycle defects (UCDs) as a nitrogen scavenger. However, Ammonaps has an objectionable taste and this resulted in poor compliance and potentially poor outcomes in the treatment of UCDs. Pheburane was developed as an encapsulated version of sodium phenylbutyrate which avoided the taste but did not alter the bioavailability of the medicine.

2.3.1. Alternate pathways of nitrogen waste excretion

The existence of such potentially useful pathways exist was shown one century ago (Lewis 1914, Sherwin 1919) via the stoichiometric relationship between the administration of benzoate or phenylacetic acid and the resulting decreased urea nitrogen excretion, accounted for by the respective appearance of hippurate nitrogen and phenylacetylglutamine nitrogen in the urine. It was suggested that these pathways may be useful in patients with defective ureagenesis where the amino acid acylation products (hippurate and phenylacetylglutamine) may substitute for urea nitrogen excretion in all UCD. To date, however, they have been mostly used in CPS-I, OTC and ASS (Brusilow 1980).

Since phenylacetate has an offensive odour, sodium phenylbutyrate was developed. This compound was selected as it is rapidly oxidised in vivo to phenylacetate but has a less offensive odour. Sodium phenylbutyrate had been used since 1987 under an IND and was approved for Marketing as Buphenyl in the USA in 1996 and as Ammonaps in the European Union in 1999. Two presentations (both uncoated) are available: 500 mg tablets and powder/granules 94% w/w. Granules are usually prescribed in infants and children, and in adults when large dose is required. Pheburane was developed as a hybrid generic formulation of the granule presentation of Ammonaps.

2.3.2. Pheburane granules

Bad taste or taste aversion are amongst the most frequent adverse events (AE) reported with Ammonaps. Moreover, this very bitter taste cannot be easily disguised and dietician support is often necessary (Dover 1994, Guffon 2011).

Sodium phenylbutyrate is notoriously bitter and in patients in whom it cannot be tolerated the medication has to be administered via nasogastric tube or gastrostomy (Brusilow 1996). In children, extemporaneously prepared sweetened suspensions of the oral powder may be needed in an effort to improve compliance (Caruthers 2007).

Rejection of unpalatable medications is a reflection of basic biology. From an evolutionary perspective, the senses that evaluate what is put into the mouth have evolved to reject that which is harmful and seek out that which is beneficial. Particularly, rejection of bitter-tasting and irritating substances is thought to have evolved to protect the animal from being poisoned and the plant producing these chemicals from being eaten. Moreover, bitter compounds stimulate rejection reflexes such as nausea and vomiting, and children are more sensitive to bitter taste than adults (Menella 2008).

Since Ammonaps granules have an offensive taste the sponsor has developed an improved granule of sodium phenylbutyrate whereby coating of individual granules results in a formulation which has no immediate taste (that is, when swallowing the drug). The active ingredient remains sodium phenylbutyrate therefore, it was essential that the new product be bioequivalent to the reference product, which was subsequently demonstrated.

2.4. Formulation

2.4.1. Formulation development

Sodium phenylbutyrate has a very bitter taste resulting in serious difficulties in compliance with treatment, especially for children. Pheburane granules were developed specifically to have no taste, this being achieved by the use of pellets initially coated with sodium phenylbutyrate and further coated with film coating agent (taste masking agent).

2.4.2. Excipients

The qualitative and quantitative composition of Pheburane granules is shown in Table 6.

Table 6: The qualitative and quantitative composition of Pheburane granules

Name of Ingredients
Active ingredient
Sodium 4-phenylbutyrate
Other ingredients
Sugar spheres 250-355 Hypromellose Purified water* Ethylcellulose N7 Macrogol 1500 Povidone K25 Ethanol 96%*

*Evaporated during process

2.5. Guidance

The sponsor, in consultation with the TGA, developed a hybrid application and has relied upon specific TGA guidance on the development and presentation of the literature based section of the application.

2.6. Evaluator's commentary on the background information

The background information is adequate to explain the proposed indications, the development of Pheburane and the rationale for the current hybrid application.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier contains the following:

- 1 bioequivalence study
- 14 Literature based study reports relating to pharmacokinetics, efficacy and safety
- 69 Clinical references

- The First EU Periodic benefit-risk evaluation report (PBRER), 2016

3.2. Paediatric data

Paediatric data are included in several of the submitted papers on the efficacy of sodium phenylbutyrate. There is no separate commentary about the use of sodium phenylbutyrate in children and the data are pooled with the adult data.

There is one specific study that includes data on the use of Pheburane in children (Kibleur 2014). This was a follow-up study of a French premarketing authorisation.

- *The sponsor should provide a separate commentary about the use of sodium phenylbutyrate in children.*

3.3. Good clinical practice

The submitted application stated the following:

> **Ethics Certification**
>
> The key clinical studies of NaPB versus GPB were conducted by the same USA study group and the National Urea Cycle Disorders Foundation in a multi-centre collaboration across many US investigative centres. Studies were conducted around 2009 to 2012 and ethics certification and informed consent were all in line with ICH GCP Guidelines for these USA multicentre trials.
>
> All protocols were conducted under a US IND and were reviewed and approved by the appropriate Institutional Review Board. A Data Safety Monitoring Board was engaged throughout the studies and reviewed all safety results periodically. All patients or their parents signed a consent or assent form, which had been approved by local Institutional Review Boards, prior to enrolment and initiation of any protocol-specific activities

- *The evaluator was unable to verify that all of the presented data complied with GCP.*

3.4. Evaluator's commentary on the clinical dossier

The dossier was poorly constructed and difficult to follow. All of the appropriate papers except one were included in the dossier. The PDF links from the table of contents in the dossier did not always function correctly and the appropriate paper had to be sourced manually through searching the files.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 7: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence †- Single dose	LUC1001 (Guffon 2012)	*
PK in special	Target population § - Single		

populations	dose		
	- Multi-dose	Gilbert 2001 Lee 2010 Smith 2013	
Population PK analyses	Target population	Monteleone 2102 Mokhtaraini 2012	* *

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Phenylbutyrate is an aromatic short-chain fatty acid which is a chemical derivative of butyric acid naturally produced by colonic bacteria fermentation. Sodium phenylbutyrate is an off-white crystalline substance which is soluble in water and has a strong salty taste. Sodium phenylbutyrate also is freely soluble in methanol and practically insoluble in acetone and diethyl ether. It is known chemically as 4-phenylbutyric acid, sodium salt with a molecular weight of 186 and the molecular formula $C_{10}H_{11}O_2Na$.

4.2.2. Pharmacokinetics in healthy subjects

The submission confirms that formal ADME studies were not provided. Plasma and urine concentration of phenylbutyrate and its metabolites were obtained from fasting normal adults and from patients with UCD, haemoglobinopathies, cancer, cystic fibrosis (CF) and cirrhosis receiving single and repeated oral doses up to 45 g/day; this is over double the recommended daily dose of 20 g/day for the current indication.

4.2.2.1. Study, LUC1001

The bioequivalence study, LUC1001, defined the basic pharmacokinetic parameters in normal adult volunteers after a single dose (Table 8). McGuire found similar results in 22 healthy adults receiving a single dose of phenylbutyrate (not Pheburane) 3 g/m2 (Table 9).

Table 8: Pharmacokinetics of sodium phenylbutyrate in healthy volunteers according to gender (Study LUC1001)

Ref.	Parameter		Plasma concentrations		
			phenylbutyrate	phenylacetate	phenylacetylglutamine
LUC1001	AUC µmol/L x h	Males	2578.4	1134.0	1049.7
		Females	3341.0	1805.4	1105.4
	C_{max} µmol/L	Males	1033.8	287.9	250.3
		Females	1302.9	404.7	248.4

Ref.	Parameter		Plasma concentrations		
			phenylbutyrate	phenylacetate	phenylacetylglutamine
	T_{max} h	Males	1.18	3.62	3.25
		Females	1.21	3.73	3.43
	$t_{1/2}$ h	Males	0.78	1.2	2.12
		Females	0.82	1.26	2.66

Table 9 Pharmacokinetics of sodium phenylbutyrate in healthy volunteers according to gender (McGuire 2010)

Ref.	Parameter		Plasma concentrations		
			phenylbutyrate	phenylacetate	phenylacetylglutamine
McGuire 2010	AUC (µmol/L x h)	22 HV*	2890±599	1958±422	1411±221
	C_{max} (µmol/L)		1187±236	432±76	234±27
	T_{max} (h)		0.9±0.61	3.9±0.3	3.2±0.4
	$t_{1/2}$ (h)		0.7±0.1	1.2±0.2	1.7±0.5

* HV=healthy volunteers, gender not specified

4.2.2.2. Absorption

Sites and mechanism of absorption

The mechanism of absorption was not addressed in the clinical studies. As a small molecule, it is likely to be mostly absorbed at the small intestine.

4.2.2.3. Bioavailability

Absolute bioavailability

Absolute Bioavailability data were not provided in healthy subjects. However, intravenous data were available in cancer patients.

Piscitelli 1995

In 14 cancer patients (51.8±13.8 years) receiving a 30-min infusion at 3 dose levels (0.6, 1.2, and 2 g/m2), phenylbutyrate peak concentrations ranges were 500-2000 µmol/L. Metabolism into phenylacetate was rapid and extensive (80±12.6%) with median (range) T_{max} for phenylacetate and phenylacetylglutamine of 1 (1-2) and 2 (1-3.5) hours, respectively. Elimination was saturable, therefore pharmacokinetics was nonlinear. Plasma phenylacetate was low because of its rapid conversion into phenylacetylglutamine.

Carducci 2001

Ascending doses were studied in 24 patients (23 males; 48-80 years) with refractory prostate cancer (19) or other solid tumours (5) after a first 120-h infusion. In most patients, plasma

phenylbutyrate curves achieved a plateau within 4–6 h into the infusion followed by a substantial decline starting approximately 24 h into the infusion. This pattern was not seen at 150 or 225 mg/kg/day, and appeared in 1 patient at 285, 3 at 345, and 5 of 7 patients at 410 mg/kg/day, which suggested that the plasma clearance of phenylbutyrate increased and a saturable elimination.

Phenylacetate maintained a steady concentration throughout the infusion and displayed a zero order pharmacokinetics suggesting it could accumulate in patients whose V_{max} was lower than the dosing rate, which occurred in one patient.

Gore 2001

Patients with myelodysplasia (n = 11) and acute myeloid leukaemia (n = 16) were treated with phenylbutyrate as a 7-day continuous intravenous infusion repeated every 28 days in a Phase I dose escalation study. The maximum tolerated dose was 375 mg/kg/day; higher doses led to dose-limiting reversible neurocortical toxicity. Phenylacetate exhibited nonlinear elimination, clearance decreasing with dose. At a dose of 500 mg/kg/day, there also seemed to be nonlinear elimination for phenylbutyrate, with an increase in the elimination half-life to 2 hours (Table 10).

Table 10: AUC and half-life of phenylbutyrate and phenylacetate with 7-day continuous intravenous infusion (Gore 2001)

Dosage (mg/day)	n	PB		PA	
		AUC[a]	$t_{1/2}$	AUC	$t_{1/2}$
125	5	13,605 (3,002)	0.9 (0.84)	6,053 (1,682)	0.80 (0.35)[b]
		14,723 (8,368–15,609)	0.49 (0.44–2.16)	6,003 (3,916–8,292)	0.64 (0.53–1.39)[c]
250	6	38,838 (21,081)	0.81 (0.75)	52,505 (63,211)	1.25 (0.79)
		37,639 (17,322–72,812)	0.55 (0.35–2.31)	28,704 (17,453–180,891)	0.95 (0.83–2.86)
375	6	40,817 (18,848)	0.52 (0.25)	104,366 (77,290)	1.38 (0.44)
		34,082 (20,163–68,000)	0.49 (0.17–0.81)	104,933 (17,694–216,620)	1.28 (0.84–2.05)
440	3	51,263 (8,922)	0.32 (0.07)	609,790 (312,248)	4.11 (3.25)
		55,070 (41,069–57,652)	0.32 (0.27–0.38)[d]	485,181 (379,087–965,102)	3.23 (1.39–7.7)
500	3	96,006 (28,170)	2.19 (2.08)	460,092 (320,809)	4.40 (3.77)
		102,417 (65,183–120,419)	2.06 (0.18–4.33)	560,338 (101,130–718,810)	3.01 (1.53–8.67)

[a] AUC values are represented as μmol h/liter.
[b] Mean and SD.
[c] Median and range.
[d] n = 2.

Gore 2006

A continuous 7 day-infusion of 375 mg/kg/day in 36 patients (41-85 years) with myelodysplastic syndrome or acute myeloid leukaemia provided mean ±SD, median (range) of steady-state concentrations for phenylbutyrate, phenylacetate, phenylacetylglutamine (and an unidentified metabolite in 6 patients) as given in Table 11Table 11:.

Table 11: Pharmacokinetics of infusions of phenylbutyrate in haematological malignancies (Gore 2006)

Steady-state plasma concentrations (μmol/L)			
phenylbutyrate	phenylacetate	phenylacetylglutamine	unidentified metabolite
562.7 ± 818.9	1617.1 ± 1987.6	677.6 ± 457.1	192.8 ± 71.6
322.5 (19.5-4371.2)	723.9 (250.2-6,769.2)	440.3 (153.4-1520.9)	187.1 (84.6-292.9)

Lin 2009

In 27 patients (34-82 years) with advanced refractory solid tumour malignancy the drug was given in various dose regimen at 200 or 400 mg/m2/day as a 24-h infusion on 2 or 3 days (21 patients), or for one week (6 patients). After 24-hour infusion there was no statistically significant difference in phenylbutyrate, phenylacetate, or phenylacetylglutamine pharmacokinetic variables across dose levels which then could be pooled. C_{max} and AUC_{inf} for

phenylbutyrate, phenylacetate, phenylacetylglutamine and an unidentified phenylbutyrate metabolite in 4 patients, only in 24h-infusion schedule are shown in Table 12. The Vd for phenylbutyrate was 14±8 L. Mean AUC ratios over phenylbutyrate of phenylacetate and phenylacetylglutamine were 1.71±0.92 and 1.85±1.78, respectively. Four patients had an unidentified metabolite in plasma with C_{max} of 316 µmol/L at 24.2 hours.

Table 12: Pharmacokinetics of infusions of phenylbutyrate in solid malignancies (Lin 2009)

24h-infusion plasma concentrations (all doses pooled)			
parameter	phenylbutyrate	phenylacetate	phenylacetylglutamine
C_{max} µmol/L	775 ±467	1395 ± 594	997 ± 507
AUC_{inf} µmol/L . h	17722 ± 8345	26680 ± 11236	25609 ± 16771
7-day infusion steady-state plasma concentrations (µmol/L)			
mg/kg/d	phenylbutyrate	phenylacetate	phenylacetylglutamine
200	210 ± 73.8	184 ± 85.2	427 ± 103
400	446 ± 211	1464 ± 1285	1217 ± 244

The dossier states that intravenous phenylbutyrate pharmacokinetics of doses between 150 mg/kg and 500 mg/kg is associated with initial plasma concentration ranging between 300 and 2000 µmol/L rising to a plateau within 4-6 h of infusion. Plasma clearance increases with time into infusion and with dose, indicating a saturable elimination with nonlinear pharmacokinetics. Mean distribution volume is 14L. Metabolism into phenylacetate represents a mean 80% of phenylbutyrate administered. Metabolites phenylacetate and phenylacetylglutamine appear after a median 1 (1-2) and 2 (1-3.5) hours, and correspond to 70-85% higher exposures than to the parent compound.

Bioequivalence of clinical trial and market formulations

One study was a bioequivalence study of Phebuterone.

Study LUC1001

This study was a two-stage bioequivalence study of 14 healthy non-smoking male and female Caucasian subjects who were entered into the first stage of the study and assigned to treatment sequence according to the randomisation schedule. Based on the results of this first cohort, the option of including additional subjects was not exercised as bioequivalence was already achieved, as demonstrated in the analysis of data obtained from the first cohort. Subjects were admitted to the clinic approximately 11.5 hours before dosing to ensure an overnight fast of minimum 10 hours (a food- and beverage-free period, with the exception of 240 mL water which was taken upon waking on clinic days, approximately 90 minutes before study drug administration). On admission to the clinic, on the pre-profile night of each treatment period, a pregnancy test was performed on each female subject.

For pharmacokinetic analysis a total of 16 venous blood samples, 9 mL each, were collected through the indwelling venous cannula into heparinised, labelled, plastic tubes at baseline and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 hours post dose. Blood samples were handled on ice between collections and centrifuged within one hour at ~2700 g for 10 minutes (at 0°C to 8°C) Plasma samples were stored frozen at -20 until phenylbutyrate was assayed.

Quantitative analyses of phenylbutyrate in the plasma samples and in suitable quality controls were performed using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Primary Variables:

· Maximum observed plasma concentration (C_{max}).

- Area under the plasma concentration versus time data pairs [AUC_t], where *t* is the time of the last quantifiable concentration.

Secondary Variables:

- Area under the plasma concentration versus time data pairs, with extrapolation to infinity [AUC_{inf}]
- Residual area [(AUC_{inf}] – AUC_t) / $AUCi_{nf}$].
- Time to maximum observed plasma concentration (T_{max}).
- Terminal elimination rate constant (l_z).
- Apparent terminal half-life ($t_{½}.z$).
- Number of points used to estimate the terminal rate constant (l_z)

The decision rule of bioequivalence (all subjects) was based on characteristics C_{max} and AUC_t, AUC_{inf} and $t_{½}.z$ on log-transformed data of phenylbutyrate, using ANOVA with sequence, subject, treatment and period effects. The respective 94.12% (adjustment of alpha level due to multiple testing) confidence intervals were calculated and compared to the regulatory interval [0.8-1.25]. For T_{max} a non-parametric Wilcoxon signed rank test was used and the calculated p-value reported.

After single dose (2.5 g, n=2; 5 g, n= 21) under fasting conditions, phenylbutyrate was rapidly absorbed with measurable plasma levels 15 minutes after administration. Peak concentrations of approximately 1000 µmol/L were reached after 1 h. The elimination half-life was estimated to be 0.8 h. Measurable plasma levels of phenylacetate and phenylacetylglutamine were detected 30-60 min after oral dosing of phenylbutyrate (the mean peak concentration is 45.3 and 62.8 µg/mL, respectively). T_{max} increased with the dose of phenylbutyrate and was around 3.5 h for both metabolites after 5 g phenylbutyrate. Elimination half-lives were estimated to be 1.3 and 2.4 hours, respectively (see Table 13 and Figure 3).

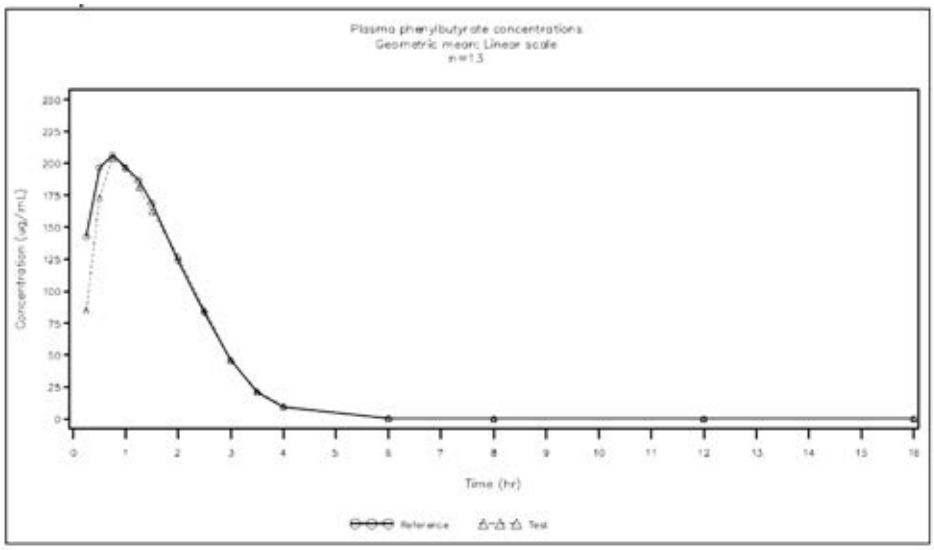
Table 13: Pharmacokinetics of Phebuterone and Ammonaps in healthy volunteers (Study LUC1001)

Ammonaps® (Reference product)		
Variable	**Geometric mean (SD)**	**Range**
C_{max} *(µg/mL)*	225.150 (49.282)	146.000 – 326.000
$AUC_{(0-t)}$ *(h·µg/mL)*	464.880 (190.356)	265.498 - 867.064
$AUC_{(0-\infty)}$ *(h·µg/mL)*	466.920 (190.356)	267.214 - 867.744
t_{max} *(h)*[*]	0.500	0.250 – 1.250
Sodium Phenylbutyrate (Test product)		
Variable	**Geometric mean (SD)**	**Range**
C_{max} *(µg/mL)*	212.453 (46.606)	137.000 – 318.000
$AUC_{(0-t)}$ *(h·µg/mL)*	445.427 (172.434)	234.898 - 809.492
$AUC_{(0-\infty)}$ *(h·µg/mL)*	448.220 (171.880)	235.605 - 810.507
t_{max} *(h)*[*]	0.750	0.500 – 1.250

Variable	**Point estimate (%)**	**94.12% Confidence interval**
C_{max} *(µg/mL)*	94.32	(86.95 ; 102.31)
$AUC_{(0-t)}$ *(h·µg/mL)*	95.61	(90.34 ; 101.19)
$AUC_{(0-\infty)}$ *(h·µg/mL)*	95.80	(90.80 ; 101.08)
t_{max} *(h)*[*]	p-value = 0.5205	

[*] Medians and p-value according to Wilcoxon signed rank test.

Figure 3: Bioequivalent pharmacokinetics curves of 2 different products sodium phenylbutyrate granules in healthy volunteers (Study LUC1001)



The study also assessed the taste of the test product (Pheburane) with Ammonaps. The parametric comparison of taste of the test and reference products shows that acceptability, bitterness and saltiness of the two products immediately after administration of the IMP, are significantly different and indicate a preference for the test. The evaluation of Sweetness showed no difference immediately after dosing.

4.2.2.4. Guffon 2012

Guffon N. et al, Developing a new formulation of sodium phenylbutyrate Archives of Disease in Childhood (2012) 97:1081-85

This is the published report of the Study LUC1001, the bioequivalence study conducted for Pheburane versus Ammonaps.

Influence of food

The submission acknowledged that there was no formal food interaction studies presented. It states that the suggestion for administration with food is based on clinical practice. In addition, the dose is to be titrated against metabolic status and an important principle would seem to be that the administration with or without food is kept constant.

Dose proportionality

There was no data presented investigating dose proportionality.

4.2.2.5. Distribution

The distribution of sodium phenylbutyrate was not addressed in the pharmacokinetic studies supplied in the dossier.

4.2.2.6. Metabolism

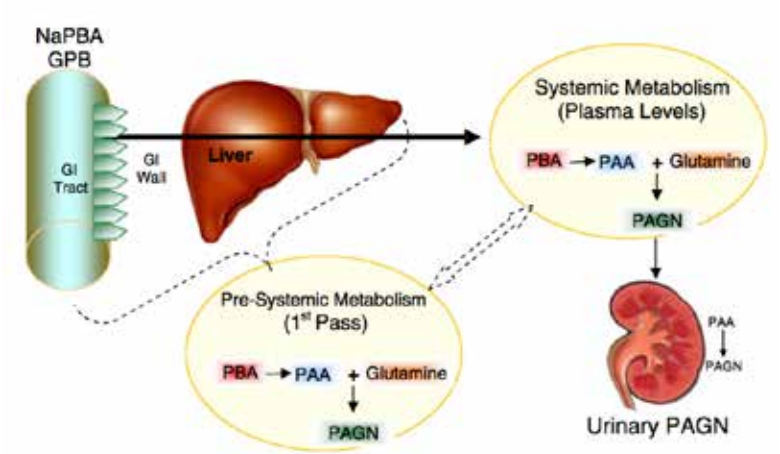
Sites of metabolism and mechanisms / enzyme systems involved

Phenylbutyrate is rapidly converted via β-oxidation by medium chain acyl-CoA dehydrogenase to its active metabolite phenylacetic acid which is conjugated with glutamine to form phenylacetylglutamine, which mediates waste nitrogen removal through urinary excretion (Figure 1). It has been demonstrated that, in most subjects, the kidneys excrete 80-100% of the drug as the conjugated product, phenylacetylglutamine, within 24 hours (Piscitelli1995) (see Figure 4). The elimination half-life of phenylbutyrate is 1 to 1.5 hours and unchanged drug is not detected in the urine of normal subjects or patients with UCDs (European Medicines Agency,

2009). There could be up to 20 minor metabolites of Phenylbutyrate. There is evidence of substantial yet variable presystemic (first pass) conversion of phenylbutyrate to phenylacetic acid.

The formation of phenylacetylglutamine from phenylacetate is saturable which may impact the ability to clear phenylacetic acid from the circulation. However, the accumulation of phenylacetic acid is not appreciable among any age groups (Diaz 2013; Smith 2013). At very high intravenous doses (for example, 500 mg/kg/day or 2000 mg/m^2), there also seemed to be saturable metabolism of phenylbutyrate to phenylacetate.

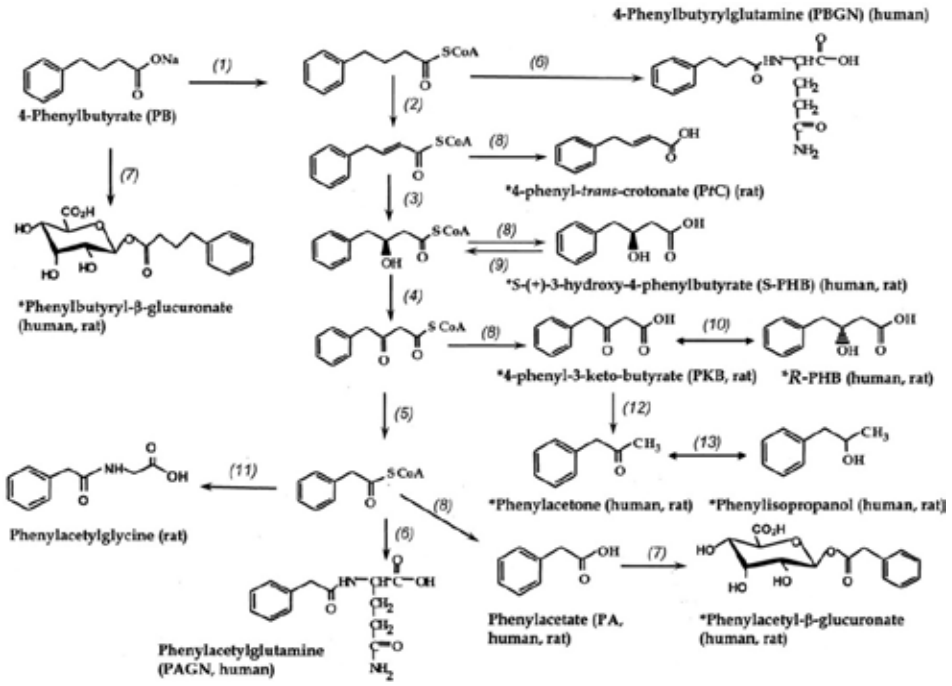
Figure 4: Presystemic and systemic metabolism of glycerol phenylbutyrate and sodium phenylbutyrate (Mokhtarani 2012)



Metabolites identified in humans: active and other

The main metabolites of phenylbutyrate are shown in Figure 5.

Figure 5: Metabolic pathway of phenylbutyrate



Pharmacokinetics of metabolites

Gilbert 2001

This was a Phase I trial of oral sodium phenylbutyrate in 28 patients with refractory solid tumour malignancies to evaluate toxicity, pharmacokinetic parameters, and feasibility of oral administration (Gilbert 2001). Five dose levels of phenylbutyrate were studied: 9 g/day (n = 4), 18 g/day (n = 4), 27 g/day (n = 4), 36 g/day (n = 12), and 45 g/day (n = 4). Pharmacokinetic studies were performed and included an oral bioavailability determination. Absorption was rapid, and the oral bioavailability of phenylbutyrate was 78% for all dose levels. Phenylbutyrate pharmacokinetics were linear within the dose range studied, as evidenced by a 4.4-fold increase in AUC values as the sodium phenylbutyrate dose was increased 4-fold from 9 to 36 g/day. After oral administration on Day 1 or 2, the average elimination half-life was 1 h and 'apparent' oral clearance was 15 L/hr. These parameters were independent of phenylbutyrate dose. Phenylbutyrate pharmacokinetic parameters were similar after administration of a single IV or oral dose (Table 14) and after administration of the first oral dose on day 3 (Figure 6). The formation of phenylacetylglutamine from phenylacetate was saturable; phenylacetate AUC increased disproportionately with phenylbutyrate dose. When the phenylbutyrate dose was increased 4-fold from 9 to 36 g/day, the average phenylacetate AUC value increased 8-fold. After intravenous and oral administration, mean systemic exposure (AUC) to phenylacetate represented approximately 46–66% of that for phenylbutyrate; at the highest dose level (45 g/day), phenylacetate represented an average of 77-95% of phenylbutyrate exposure, which is consistent with a disproportionate increase in phenylacetate exposure at the higher phenylbutyrate dose-levels (Figure 7). Exposure to phenylacetylglutamine represented 70-100% of that for phenylbutyrate and appeared to be independent of phenylbutyrate dose.

Consequences of genetic polymorphism

In a pharmacokinetic study in CNS-malignancies the co-administration with p-450 inducing anticonvulsants led to a higher clearance and higher conversion of phenylbutyrate to phenylacetate (Phuphanich 2005) than in the previous study in non-CNS malignancies without anticonvulsants (Gilbert 2001). It appears that the pharmacokinetics of phenylbutyrate may be affected by the concurrent administration of anticonvulsants.

Table 14: Oral bioavailability & pharmacokinetic parameters for phenylbutyrate & metabolites determined using non-compartmental method (Gilbert 2001)

	PB dose (g/day)					
PK Parameter[a]	9 (n = 4)	18 (n = 4)	27 (n = 4)	36 (n = 7)	45 (n = 4)	All dose levels
i.v. period						
PB						
C_{max} (μmol/liter)[b]	826 (35)	1671 (305)	2327 (488)	3508 (1188)	2603 (903)	
T_{max} (hr)	1.0 (0.06)	1.0 (0.06)	0.95 (0.03)	1.2 (0.36)	1.5 (1.1)	1.1 (0.47)
AUC (μmol/liter × hr)	1330 (285)	2978 (1246)	4517 (1388)	7954 (1651)	6008 (1313)	
T > 0.5 mM (hr)	1.7 (0.1)	2.2 (0.8)	2.4 (0.8)	3.9 (0.3)	3.7 (1.0)	
PA						
C_{max} (μmol/liter)	107 (37)	218 (72)	510 (252)	419 (51)	683 (173)	
T_{max} (hr)	1.8 (0.55)	2.7 (0.98)	3.3 (0.92)	4.1 (0.10)	5.3 (1.5)	3.5 (1.4)
AUC (μmol/liter × hr)	374 (74)	883 (502)	2201 (1545)	2614 (278)	4696 (962)	
PA:PB AUC ratio	0.27 (0.15)	0.29 (0.05)	0.45 (0.24)	0.33 (0.06)	0.77 (0.22)	0.46 (0.25)
PG						
C_{max} (μmol/liter)	189 (33)	324 (86)	503 (138)	507 (202)	508 (243)	
T_{max} (hr)	2.3 (0.41)	3.7 (0.77)	3.7 (0.50)	5.5 (1.7)	6.8 (2.6)	4.6 (2.1)
AUC (μmol/liter × hr)	955 (125)	1854 (641)	3384 (1771)	4524 (2819)	4736 (2968)	
PG:PA AUC ratio	0.74 (0.25)	0.68 (0.29)	0.72 (0.20)	0.59 (0.41)	0.84 (0.58)	0.70 (0.32)
p.o. period						
PB						
C_{max} (μmol/liter)	517 (243)	771 (254)	1574 (639)	1906 (996)	1495 (584)	
T_{max} (hr)	1.5 (0.90)	1.5 (0.19)	1.4 (0.79)	1.5 (0.46)	1.9 (0.37)	1.8 (0.72)
AUC (μmol/liter × hr)	1127 (491)	2176 (1096)	4098 (1870)	5613 (2380)	5321 (1210)	
T > 0.5 mM (hr)	1.1 (0.7)	2.4 (0.8)	3.9 (0.8)	4.1 (0.6)		
F	0.88 (0.24)	0.71 (0.15)	0.89 (0.22)	0.69 (0.20)	0.94 (0.36)	0.78 (0.24)
PA						
C_{max} (μmol/liter)	98 (39)	181 (54)	503 (202)	449 (209)	715 (174)	
T_{max} (hr)	2.7 (0.64)	3.8 (1.5)	3.8 (1.4)	5.3 (1.8)	5.6 (1.1)	4.4 (1.6)
AUC (μmol/liter × hr)	350 (106)	879 (434)	2704 (1713)	2906 (1441)	5420 (1502)	
PA:PB AUC ratio	0.38 (0.22)	0.43 (0.14)	0.63 (0.20)	0.54 (0.18)	0.95 (0.25)	0.66 (0.31)
PG						
C_{max} (μmol/liter)	188 (47)	303 (62)	511 (195)	475 (193)	621 (329)	
T_{max} (hr)	2.9 (0.28)	3.7 (1.5)	3.8 (1.5)	6.2 (0.24)	6.3 (3.1)	4.8 (2.0)
AUC (μmol/liter × hr)	1067 (211)	2056 (629)	3840 (1979)	4253 (2340)	6547 (5456)	
PG:PB AUC ratio	1.1 (0.38)	1.1 (0.48)	0.92 (0.28)	0.85 (0.47)	1.1 (0.71)	1.0 (0.42)

[a] Values are mean (SD).
[b] T > 0.5 mM, time plasma concentration remains above 0.5 mM; F, bioavailability.

Figure 6: Representative phenylbutyrate plasma concentration- time profiles at the 27 g/day (A) and 36 g/day (B) dose levels (Gilbert 2001)

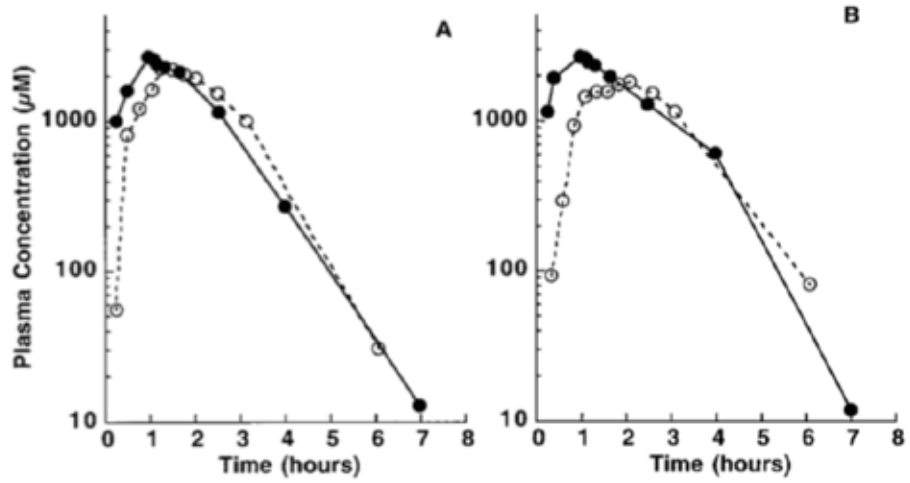
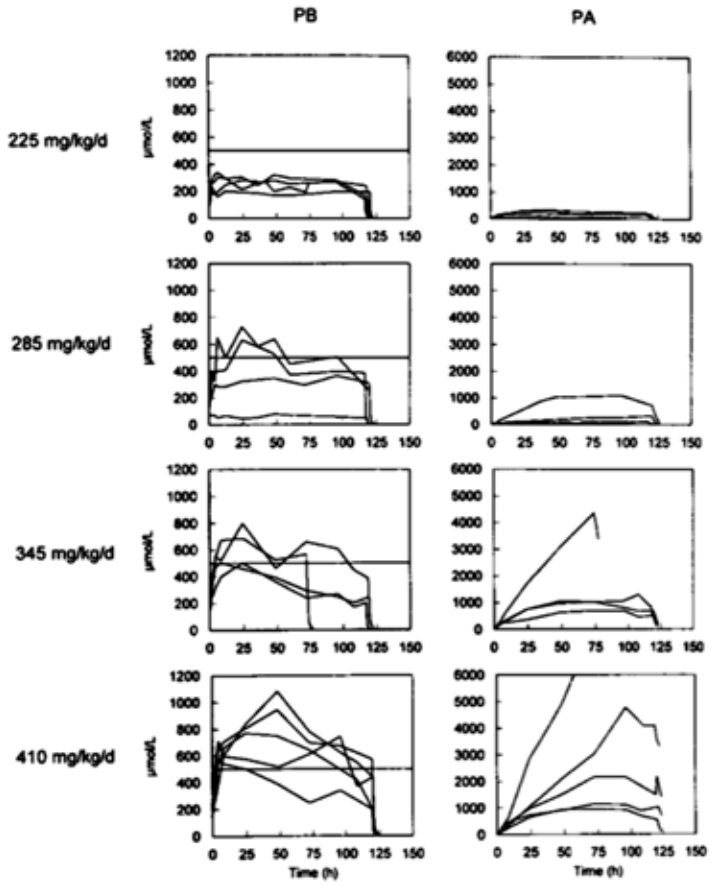


Figure 7: Cumulative disposition curves of phenylbutyrate (PB) and phenylacetate (PA) for all evaluable patients with phenylbutyrate administered IV as a 120 hour infusion every 21 days (Carducci 2001)



4.2.2.7. Excretion

Routes and mechanisms of excretion

Approximately 80-100% of the medicinal product is excreted by the kidneys within 24 hours as the conjugated product, phenylacetylglutamine.

4.2.2.8. Intra and inter individual variability of pharmacokinetics

Pharmacokinetic variability was addressed in the study by Mokhtarani 2012 which demonstrated high inter- and intra-subject variability noted in plasma metabolite levels. They explained the inter-subject variability by a wide range of doses that the study population received and differences in first pass metabolism. The intra- subject variability was explained by the short metabolite half-life and limits the utility of random measurement of plasma metabolite.

4.2.3. Pharmacokinetics in the target population

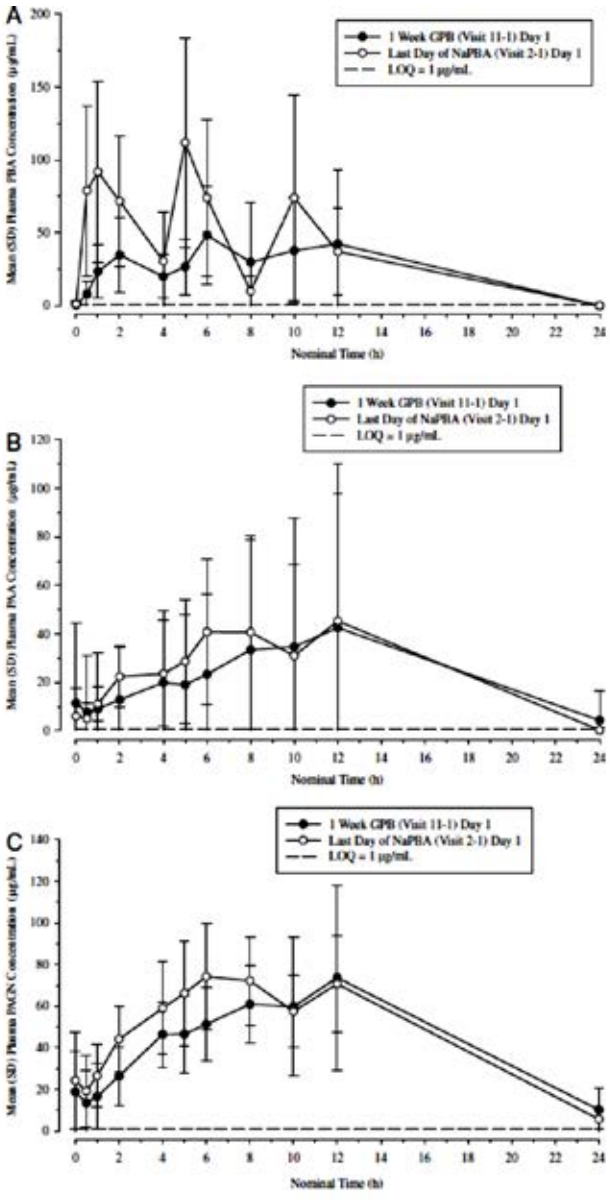
4.2.3.1. Lee 2010

Lee B, Rhead W, Diaz GA, Scharschmidt BF, et al.: Phase II comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. Mol Genet Metab 2010; 100(3): 221-8

Glycerol phenylbutyrate was compared with sodium phenylbutyrate in a Phase II, open label, fixed sequence, switch-over study in patients being treated with sodium phenylbutyrate for a UCD (Lee et al., 2010). Subjects 18 years old or older who had been treated with sodium

phenylbutyrate for at least 2 weeks were eligible. After enrolment, subjects received sodium phenylbutyrate for at least 7 days, three times daily with meals. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of dosing on either drug, both dosed to deliver the same amount of phenylbutyric acid. Ten subjects completed the study. Adverse events were comparable for the two drugs. Systemic exposure (AUC_{0-24}) to phenylbutyrate on glycerol phenylbutyrate was 27% lower than on sodium phenylbutyrate (540 versus 739 µg.h/mL), whereas exposure to phenylacetate (575 versus 596 µg.h/mL) and phenylacetylglutamine (1098 versus 1133 µg.h mL) were similar (Figure 8). Urinary phenylacetylglutamine excretion accounted for approximately 54% of phenylbutyrate administered for both sodium phenylbutyrate and glycerol phenylbutyrate; other metabolites accounted for <1%. Blood ammonia correlated strongly and inversely with urinary phenylacetylglutamine (r=-0.82; P<0.0001) but not with blood metabolite levels.

Figure 8: Plasma phenylbutyric acid (PBA), (B) phenylacetic acid (PAA) and (C) phenylacetylglutamine (PAGN) measured for 24 h following one week of oral sodium phenylbutyrate (NaPB) and glycerol phenylbutyrate administration for one week (Lee 2010)

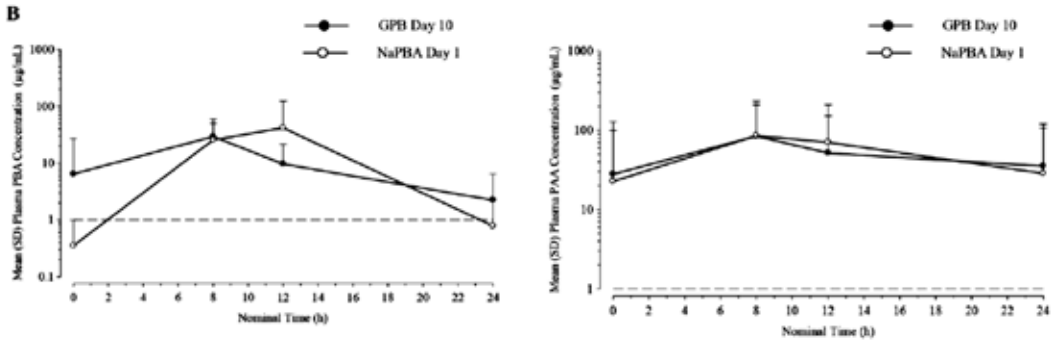


4.2.3.2. Smith 2013

Smith W et al, Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Journal of Pediatrics. 162(6):1228-34, 1234.e1, 2013.

In an open label switch-over study, Smith et al. examined ammonia levels, pharmacokinetics, and safety of glycerol phenylbutyrate and sodium phenylbutyrate in young children with UCDs (Smith et al., 2013). Eligible patients included children aged below 6 years with a confirmed or clinically suspected UCD who had been receiving a stable dose of sodium phenylbutyrate powder for at least 5 days. Patients underwent 24- hour blood and urine sampling on sodium phenylbutyrate and again on a phenylbutyric acid-equimolar dose of glycerol phenylbutyrate and completed questionnaires regarding signs and symptoms associated with sodium phenylbutyrate and/or their UCD. Mean systemic exposure to phenylbutyric acid, phenylacetic acid, and phenylacetylglutamine was similar (Figure 9).

Figure 9: Systemic exposure to phenylbutyrate and phenylacetate during dosing with sodium phenylbutyrate (NaPB) and glycerol phenylbutyrate (GPB), resulting in similar levels (Smith 2013)



4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

In male patients with hepatic cirrhosis after oral administration of 20 g/day sodium phenylbutyrate in three doses, plasma levels of phenylbutyrate followed the peak and trough pattern familiar from healthy subjects and UCD patients (EMEA 2005). The conversion to phenylacetylglutamine was relatively slower as evidenced by progressive accumulation of phenylacetate in 3 out of the 6 patients, and phenylbutyrate and phenylacetate were detected in urine. This suggests that in patients with cirrhosis the capacity of the metabolic pathway of phenylacetate is reduced.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

The pharmacokinetics of phenylbutyrate has not been studied in patients with renal impairment. However, given that the major metabolite phenylacetylglutamine is excreted via the kidneys, caution would be advised in prescribing in patients with renal impairment.

4.2.4.3. Pharmacokinetics according to age

Pharmacokinetic data from 2 months into adulthood were described.

No data in elderly patients were presented.

4.2.4.4. Pharmacokinetics related to genetic factors

No pharmacogenomics studies were presented.

4.2.4.5. Pharmacokinetics in other special populations / with other population characteristics

No other studies were presented

4.2.5. Population pharmacokinetics

4.2.5.1. Monteleone 2012

Monteleone J.P.R. et al, Population PK analysis of glycerol phenylbutyrate (GPB) and sodium phenylbutyrate(NAPB) in adult and pediatric patients with urea cycle disorders (UCD)Molecular Genetics and Metabolism (2012) 105:3 (343-344).

Population PK model building was performed using NONMEM (version 7.2) based on 2981 (PBA, PAA, PAGN and urine PAGN [UPAGN])) data points from 53 adult and 11 paediatric UCD patients (ages 6-17) who participated in Phase II (UP 1204-003; HPN-100- 005) or Phase III (HPN-100-006) switchover comparisons of the pharmacokinetics of NaPB and GPB.

The main objective of this PK modelling was to compare GPB with NaPB as the registered product. Via this process, useful information in relation to NaPB is also provided. Using the final popPK model and parameter estimates, Monte Carlo simulations were performed in ~1000 virtual patients for a range of NaPB and GPB doses to predict systemic metabolite exposure and UPAGN output. The final model that best fit the data was characterised by

a. partial conversion of PBA to PAGN prior to reaching the systemic circulation
b. saturable conversion of PAA to PAGN (Km ~161 μg/ml)
c. ~60% slower PBA absorption when delivered as GPB versus NaPB.

Body size (that is, BSA) was a significant covariate such that metabolite clearance was proportionally related to BSA, that is, larger BSA corresponds to more rapid metabolite clearance. Fractional presystemic metabolism of PBA was higher for adults than for paediatric patients receiving GPB (43% versus 14%), whereas the reverse was true for NaPB (23% versus 43%).

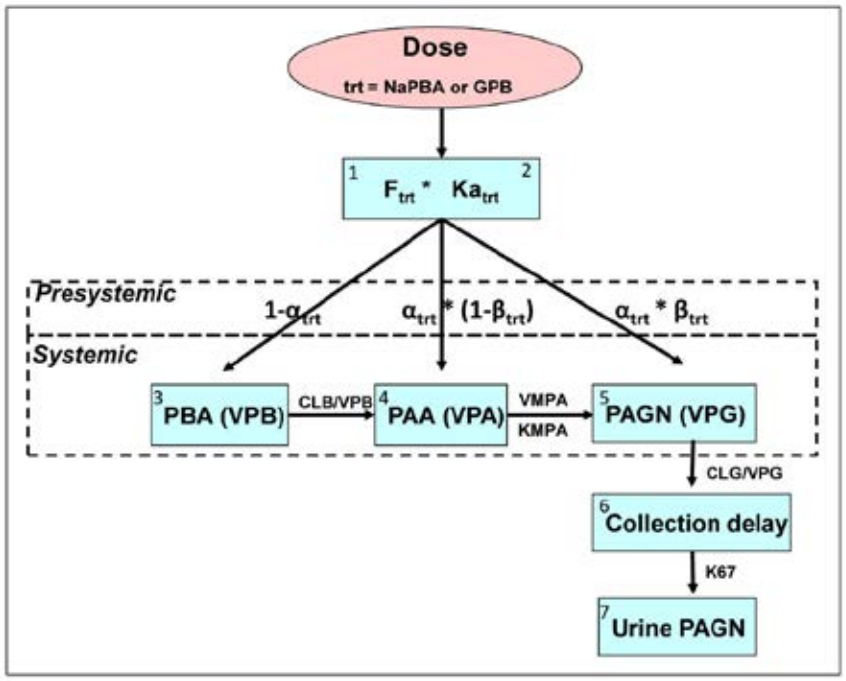
As compared with NaPB, predicted median PAA exposure based on simulated GPB dosing at the PBA equivalent of 13 g/m2 of NaPB was ~13%-22% lower in adults and ~13% higher in paediatric subjects ages 6-17; predicted upper 95th percentile PAA exposure was 25%-40% lower for adult subjects on GPB vs NaPB and similar for paediatric subjects. Simulated dosing at the PBA equivalent of ~5 g/m^2 of NaPB yielded generally similar and less variable predicted PAA exposure for both drugs and for paediatric and adult patients. Recovery of PBA as UPAGN was very similar whether delivered orally as GPB or NaPB.

The study found that PAA to PAGN conversion is saturable, and the higher PAA levels in paediatric as compared with adult UCD patients for both GPB AND NaPB reflect BSA-related changes in PAA clearance and higher per weight dosing in paediatric patients. Differences in the proportion of PBA metabolised pre-systemically appear to account for the drug-related differences in PAA levels, which are modest in relation to inter-subject variability observed with both drugs. Even with dosing at the upper end of the labelled range for NaPB (that is, 13 g/m^2 of NaPB; not to exceed 20 g/day) where PAA exposure shows greatest variability, the upper 95th percentile for PAA exposure, assessed as C_{max}, is less than 500 μg/ml.

The pharmacokinetic model approximated the biotransformation of GPB and NaPBA; including the absorption of PBA, conversion of PBA to PAA via β-oxidation, enzymatic conjugation of PAA with glutamine to form PAGN and the urinary excretion of PAGN. Conversion of PAA to PAGN is concentration-limited, saturable and described using a Michaelis–Menten relationship; whereas, the rate of β-oxidation of PBA to PAA was hypothesised to be linear due to the widespread prevalence of the enzymes. One hundred percent PBA to PAA conversion via β-oxidation was assumed, that is, no alternative metabolic pathways were included. The elimination rate for

PAGN (CLG/VPG) was determined to be a linear process, consistent with renal elimination of PAGN (Figure 10).

Figure 10: Simultaneous modelling of parent and metabolite data in plasma and urine following administration of two different treatments (Monteleone 2012)



4.2.5.1. Mokhtarani 2012

Mokhtarani M, Diaz GA, Rhead W, Lichter-Konecki U, Bartley J, Feigenbaum A, et al. Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders. Mol Genet Metab 2012; 107(3):308-14.

A total of 65 UCD patients, including 11 paediatric patients aged 6-17, were enrolled in a pharmacokinetic study for glycerol phenylbutyrate and sodium phenylbutyrate. Each patient received an equivalent amount of sodium phenylbutyrate or glycerol phenylbutyrate; the dose of glycerol phenylbutyrate was calculated based on each patient's prescribed dose of sodium phenylbutyrate at the time of enrolment, which ranged from 197 to 476 mg/kg/day (1.3 to 31.7 g/day), with a mean of 321 mg/kg/day (Mokhtarani et al., 2012).

Plasma metabolite concentrations varied greatly during the day after three times daily dosing with either sodium phenylbutyrate or glycerol phenylbutyrate, with average fluctuation indices ranging from 1979% to 5690% for phenylbutyric acid, 843% to 3931% for phenylacetic acid, and 881% to 1434% for phenylacetylglutamine. There was high inter- and intra-subject variability noted in plasma metabolite levels (Table 15). The high inter-subject variability is explained in part by a wide range of doses that the study population received and differences in first pass metabolism. However, the intra- subject variability, as reflected in the high fluctuation indices, is explained by the short metabolite half-life and limits the utility of random measurement of plasma metabolite. By contrast, 24-hour urinary phenylacetylglutamine and morning spot urine phenylacetylglutamine correlated strongly with dose and appear to be clinically useful non-invasive biomarkers for compliance and therapeutic monitoring (Figure 11).

Unlike most other drugs which need to reach the systemic circulation to exert their effect, PBA delivered either as GPB or NaPB does not need to reach the systemic circulation to mediate urinary excretion of waste nitrogen in the form of PAGN. Rather, phenylbutyric acid (PBA) released by dissolution of sodium phenylbutyrate (NaPB) or by pancreatic lipases via hydrolysis

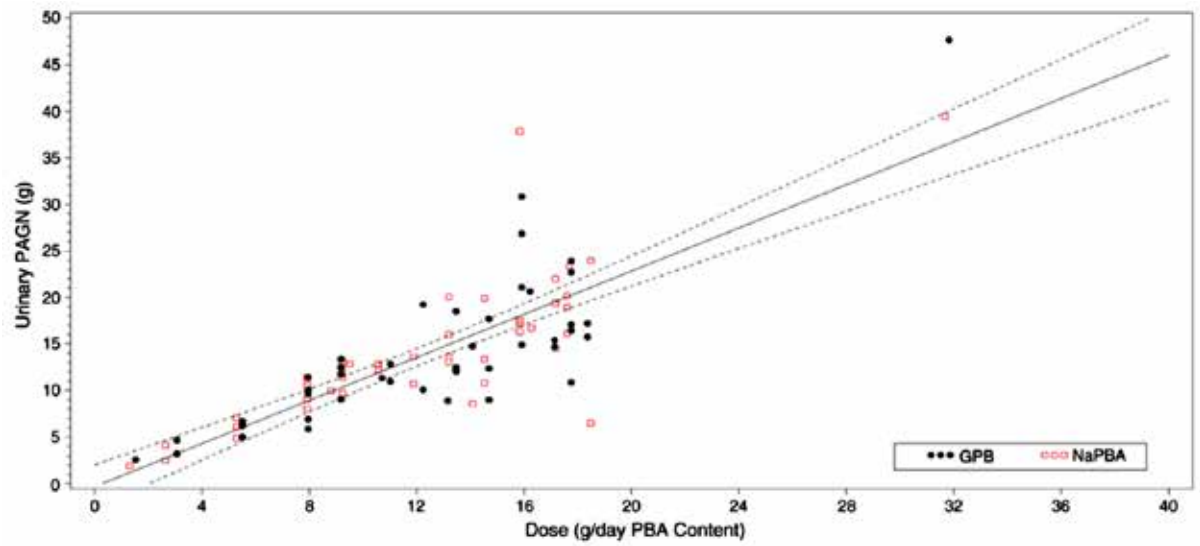
of glycerol phenylbutyrate (GPB) undergoes partial pre-systemic (1st pass) metabolism to phenylacetic acid (PAA) and/or phenylacetylglutamine (PAGN) in enterocytes and/or hepatocytes. Patient to patient variability in the degree of 1st pass metabolism accounts for differences in systemic exposure to PBA, PAA, and PAGN despite similar urinary recovery of PAGN. The kidney is also enzymatically equipped to conjugate PAA with PAGN to form PAGN.

Table 15: Pharmacokinetics of glycerol phenylbutyrate (GPB) or sodium phenylbutyrate (NaPB) in adult and paediatric patients with UCDs (Mokhtarani 2012)

PK variable	Study UP 1204-003 Adult patients (N = 10)		Study HPN-100-006 Adult patients (N = 44)		Study HPN-100-005 Pediatric patients (N = 11)	
	GPB	NaPBA	GPB	NaPBA	GPB	NaPBA
Plasma PBA – mean (%CV)						
$AUC_{0\text{-}24}$ (µg·h/mL)	540 (60)	739 (49)	433 (77)	508 (73)	631 (45)	236 (105)
C_{maxss} (µg/mL)	70.1 (65)	141 (44)	51.9 (67)	80.9 (65)	95.6 (42)	37.4 (102)
C_{minss} (µg/mL)	2.87 (265)	0.59 (255)	1.44 (201)	0.09 (392)	1.50 (100)	0.37 (171)
% fluctuation	3016 (107)	4864 (70)	2582 (85)	3579 (114)	5690 (57)	1979 (124)
Plasma PAA – mean (%CV)						
$AUC_{0\text{-}24}$ (µg·h/mL)	574.6 (169)	595.6 (124)	447 (130)	599 (92)	964 (64)	773 (73)
C_{maxss} (µg/mL)	40.5 (148)	53.0 (95)	38.5 (103)	52.2 (80)	90.5 (69)	75.1 (64)
C_{minss} (µg/mL)	7.06 (311)	3.56 (194)	2.11 (381)	0.903 (378)	2.99 (122)	0.674 (131)
% fluctuation	843 (72)	956 (62)	1368 (92)	2150 (103)	3483 (53)	3931 (85)
Plasma PAGN – mean (%CV)						
$AUC_{0\text{-}24}$ (µg·h/mL)	1098 (44)	1133 (31)	1127 (62)	1252 (57)	1378 (40)	1015 (45)
C_{maxss} (µg/mL)	71.9 (56)	83.3 (26)	78.6 (56)	86.8 (52)	105 (34)	74.8 (37)
C_{minss} (µg/mL)	12.1 (134)	16.8 (86)	15.1 (138)	9.09 (155)	13.1 (65)	4.6 (66)
% fluctuation	1145 (85)	952 (120)	881 (74)	1434 (58)	1001 (85)	1917 (55)
U-PAGN $_{0\text{-}24\ h}$ excretion – mean (%CV)						
Ae (g)	10.8 (25)	12.2 (48)	13.5 (52)	13.6 (52)	12.5 (56.9)	12.5 (51)
Fe % dose	NA	NA	68.7 (25)	71.4 (26)	66.4 (24)	69.0 (24)

Ae = amount excreted after dose; AUC = area under the concentration versus time curve; CL/F = apparent clearance; C_{max} = maximum plasma concentration at a steady state; Fe = fraction excreted in urine; GPB = glycerol phenylbutyrate; min = minimum; NA = not available; NaPBA = sodium phenylbutyrate; PAA = phenylacetic acid; PAGN = phenylacetylglutamine; PBA = phenylbutyric acid; PK = pharmacokinetic; SD = standard deviation; SS = steady state; T_{max} = time maximum plasma concentration; UCD = urea cycle disorder; U-PAGN = urinary phenylacetylglutamine.

Figure 11: Urinary phenylacetylglutamine excretion versus total dose of glycerol phenylbutyrate or sodium phenylbutyrate administered (Mokhtarani 2012)



4.2.6. Pharmacokinetic interactions

No drug-drug interactions have been investigated. However, Phuphanich 2005 did describe evidence of interactions with inducing and inhibiting anticonvulsants.

4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of Pheburane is described through the following:

- A single bioequivalence study demonstrating that Pheburane was developed as a hybrid generic formulation of the granule presentation of Ammonaps.
- A series of literature articles describing the pharmacokinetics of sodium phenylbutyrate, often in comparator trials with glycerol phenylbutyrate.
- Some literature articles including higher doses used in the treatment of malignancies

There were no dose finding studies presented. There were higher doses used in the treatment of malignancies suggesting linear pharmacokinetics up to about 36 g per day (Gilbert 2001).

- *There are significant deficiencies in the presented pharmacokinetic data that need to be addressed*
  - *Clarify the proposed dosing schedule and linearity of Pheburane.*
  - *Clarify that the form of sodium phenylbutyrate used in all of the pharmacokinetic studies was the same the innovator product (Ammonaps) from the bioequivalence study.*
  - *Demonstration that the dosing of Pheburane can be scaled by weight and surface area as in the proposed dosing schedule.*
  - *Explain the dose-ranging in the proposed dosing schedule.*

5. Pharmacodynamics

Following oral administration, sodium phenylbutyrate is metabolised by β-oxidation in the liver into phenylacetate which is rapidly converted to its CoA ester, phenylacetyl-CoA. The latter compound is conjugated to glutamine to form phenylacetylglutamine, which is excreted by the kidney. Glutamine (and therefore phenylacetylglutamine) contains 2 waste nitrogen atoms, so 2 moles of nitrogen are removed for each mole of sodium phenylbutyrate administered (Batshaw 2001).

5.1. Studies providing pharmacodynamic information

5.1.1. Brusilow 1993

Brusilow SW, Valle DL, Batshaw M. New pathways of nitrogen excretion in inborn errors of urea synthesis. Lancet 1979; 2:452-4

Net urea synthesis was evaluated in one 38-year old OTC patient treated with 16.5 g phenylbutyrate over three 3-day periods (Brusilow 1993). In a first control period the patient received a fixed nitrogen intake (low protein diet only 120 g plus citrulline); in period II, 49.5 g sodium phenylbutyrate was added; and in period III, an additional 45 g of dietary protein (7.2 g nitrogen) was added. The results are given in Table 16 and Figure 12.

Table 16: Net urea synthesis in a 38-year old man with OTC deficiency during three 3-day periods (Brusilow 1993)

	Dietary N, g/3d	PAG-N, g/3d	Net Urea Synthesis g/3d
Period I	20.8	0	6.85
Period II	20.8	6.97	1.83
Period III	28.0	6.67	7.95

Figure 12: Pharmacodynamics of phenylbutyrate in 1 OTC adult patient (Brusilow 1993)

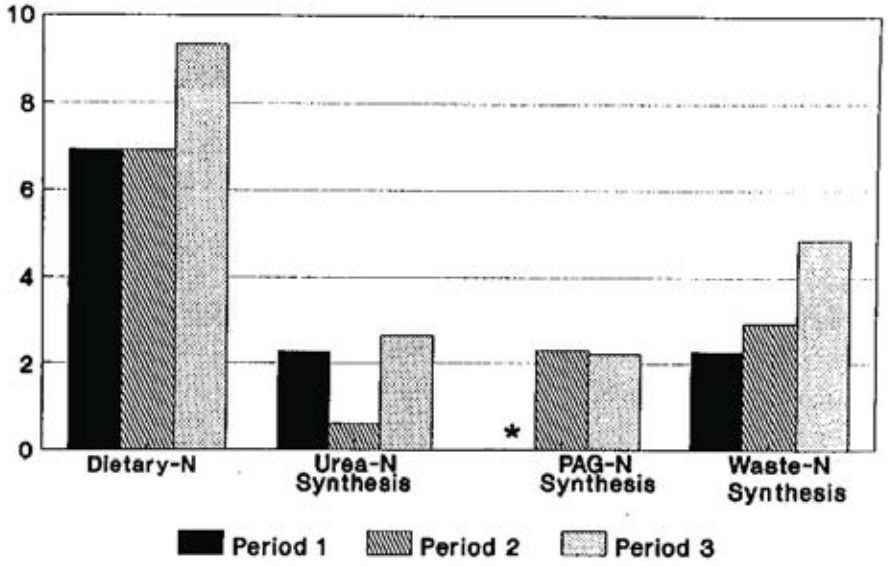


Table 17: Submitted pharmacodynamic studies

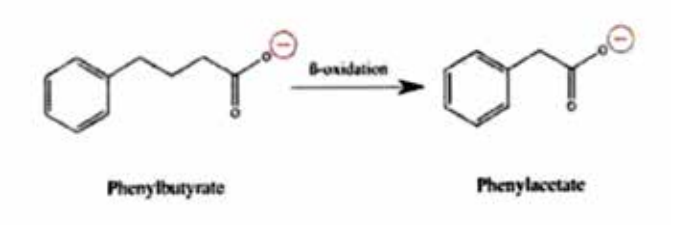
PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on PD Ammonia	Lee 2010 Brusilow 1993	

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Sodium phenylbutyrate is absorbed from the intestine and converted to the active moiety, phenylacetic acid via β oxidation (Figure 13). Phenylacetate is subsequently conjugated with glutamine in the liver and the kidney by way of N acyl-coenzyme A/L-glutamine N-acyltransferase to form phenylacetylglutamine. Like urea, phenylacetylglutamine incorporates two waste nitrogens and is excreted in the urine.

Figure 13: Conversion of phenylbutyrate to active phenylacetate by β oxidation (Matoori and Leroux, 2015)



5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The effect of sodium phenylbutyrate on ammonia levels was described in Lee 2010 (Table 18). Changes were not compared with a control group; however historically patients with UCDs have high serum ammonia and reduced nitrogen excretion.

Table 18: Pharmacokinetic parameters and ammonia following sodium phenylbutyrate (NaPB) and glycerol phenylbutyrate administration (Lee 2010)

PK/PD parameters	Arithmetic mean (CV%)	
	Glycerol phenylbutyrate (n = 10)	NaPBA (n = 10)
PBA in plasma		
AUC_{0-24} (μg h/mL)	540 (60.2)*	740 (49.1)*
$Cmax_{ss}$ (μg/mL)	70.1 (64.7)	141 (44.3)
$Cmin_{ss}$ (μg/mL)	2.87 (265)	0.588 (255)
PAA in plasma		
AUC_{0-24} (μg h/mL)	575 (169)*	596 (124)*
$Cmax_{ss}$ (μg/mL)	40.5 (147)	53.0 (94.7)
$Cmin_{ss}$ (μg/mL)	7.06 (310)	3.56 (194)
PAGN in plasma		
AUC_{0-24} (μg h/mL)	1098 (44.2) *	1133 (31.0)***
$Cmax_{ss}$ (μg/mL)	71.9 (55.9)	83.3 (25.8)
$Cmin_{ss}$ (μg/mL)	12.1 (134)	16.8 (86.3)
PAGN in urine		
Total excreted 0–24 h (μg)***	10 784 747 (25.9)	12 153 473 (48.2)
0–6 h (μg)	2381371 (61.3)	2452838 (41.6)
6–12 h (μg)	3027310 (44.9)	4859121 (54.7)
12–24 h (μg)***	5433033 (50.4)	4645447 (59.8)
Recovery of PBA as PAGN (%)	54 (15)	54 (16)
Total urinary nitrogen in 24 h		
Mean (SD) g	9.0 (3.0)**	9.6 (3.9)**
Ammonia		
TNAUC (μmol/L)	26.2 (38.9)	38.4 (51.0)
$Cmax_{ss}$ (μmol/L)	56.3 (49.5)	79.1 (50.6)
% normal ammonia values+	59.5 (34.04)	73.1 (27.04)
Mean ammonia ratio		
(Glycerol phenylbutyrate /NaPBA)	0.71	
95% CI of ratio	0.44–1.14	

AUC_{0-24}, area under the concentration from time 0 (pre-dose) to 24 h; $Cmax_{ss}$, maximum plasma concentration at steady state; $Cmin_{ss}$, minimum plasma concentration at steady state; TNAUC, time-normalized area under the curve.

+ % Normal ammonia values are presented as mean (SD).

* n = 8.

** n = 7.

*** n = 9.

5.3. Evaluator's overall conclusions on pharmacodynamics

There were literature based data to support the proposed mechanism of action of sodium phenylbutyrate, acting via its active metabolite phenylacetic acid, as an alternate pathway for the excretion of excess nitrogen. Brusilow 1993 did demonstrate increased nitrogen excretion in a single patient after receiving sodium phenylbutyrate.

- *The sponsor should reinvestigate the literature for further evidence of a dose response effect on nitrogen excretion with sodium phenylbutyrate.*

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The dossier states that there is no dose finding information. The submission includes the following justification for the dosing regimen.

> No dose-finding study has been performed in UCD patients. The proposed daily dosage was derived on the basis that one mole of phenylbutyrate will be metabolised to one mole of phenylacetylglutamine, and from the estimated nitrogen to be excreted on a restricted protein intake. On a molar basis phenylacetylglutamine is comparable to urea (each containing two nitrogen atoms) and provides therefore an alternate vehicle for waste nitrogen disposal. Children (6-24 months of age) receiving a diet of 0.2 g/kg/day of nitrogen (1.25 g/kg/day of protein) have been shown to excrete 0.094 g/kg/day of urea nitrogen, accounting for 47% of dietary nitrogen (Waterlow 1963). Children or adults receiving a low but adequate protein intake excrete 40-45% of their dietary nitrogen as urea nitrogen. Thus, a child receiving 1.25 g/kg/day of protein has the obligatory requirement to synthesize 93 mg/kg/day of waste nitrogen as urea. This requirement can be met by patients with the neonatal form of CPS-I and OTC deficiencies if they receive 600 mg/kg/day of sodium phenylbutyrate which if completely conjugated with glutamine will lead to the excretion of 90 mg/kg/day of phenylacetylglutamine nitrogen.
>
> These theoretical considerations were confirmed in an 8-year-old boy (of 27.2 kg body weight) with neonatal CPS-I (Brusilow 1991). When receiving 12 or 14 g/d of phenylbutyrate, 80-90% of the dose appeared in the urine as phenylacetylglutamine and phenylacetylglutamine nitrogen accounted for 42-44% of dietary nitrogen.

6.2. Phase II dose finding studies

No studies investigating alternative doses were supplied.

6.3. Phase III pivotal studies investigating more than one dose regimen

No studies investigating more than one dosing regimen were supplied.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

There was no dose finding studies on which to base the clinical dosing regimen. The recommended dosing regimen is based upon theoretical considerations and reported clinical experience.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

All of the evaluable efficacy data is based upon the literature search.

7.2. Pivotal or main efficacy studies

No Pivotal Efficacy Studies were submitted as part of the application.

7.3. Other efficacy studies

7.3.1. Lee 2010

Lee B, Rhead W, Diaz GA, Scharschmidt BF, et al.: Phase II comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. Mol Genet Metab 2010; 100(3): 221-8

This was a prospective open-label, fixed sequence switch-over study that was conducted in 10 adult UCD patients taking maintenance sodium phenylbutyrate (NaPBA). It compared glycerol phenylbutyrate (glyceryl tri (4-phenylbutyrate)) (GPB) with sodium phenylbutyrate. Blood ammonia and blood and urine metabolites were compared after 7 days (steady state) of TID dosing on either drug with both dosed to deliver the same amount of phenylbutyric acid. A total of 13 patients were enrolled but only 10 completed all of the study procedures.

7.3.1.1. Results

Ammonia values on GPB were ~30% lower than on NaPBA (time normalised AUC = 26.2 versus 38.4 µ mol/L; C_{max} = 56.3 versus 79.1 µ mol/L; not statistically significant), and GPB achieved non-inferiority to NaPBA with respect to ammonia (time normalised AUC) by post hoc analysis. Systemic exposure (AUC_{0-24}) to PBA on GPB was 27% lower than on NaPBA (540 versus 739 µg.h/mL), whereas exposure to phenylacetic acid (PAA) (575 versus 596 µg.h/mL) and phenylacetylglutamine (PAGN) (1098 versus 1133 µg.h/mL) were similar. Urinary PAGN excretion accounted for ~54% of PBA administered for both NaPBA and GPB; other metabolites accounted for < 1%. Intact GPB was generally undetectable in blood and urine. Blood ammonia correlated strongly and inversely with urinary PAGN (r=−0.82; p<0.0001) but weakly or not at all with blood metabolite levels. The mean plasma ammonia concentrations after 1-week treatment are shown in Figures 14-15.

Figure 14: Venous Ammonia Concentration Profiles Following One Week of NaPBA or Glycerol Phenylbutyrate Treatment (Lee 2010)

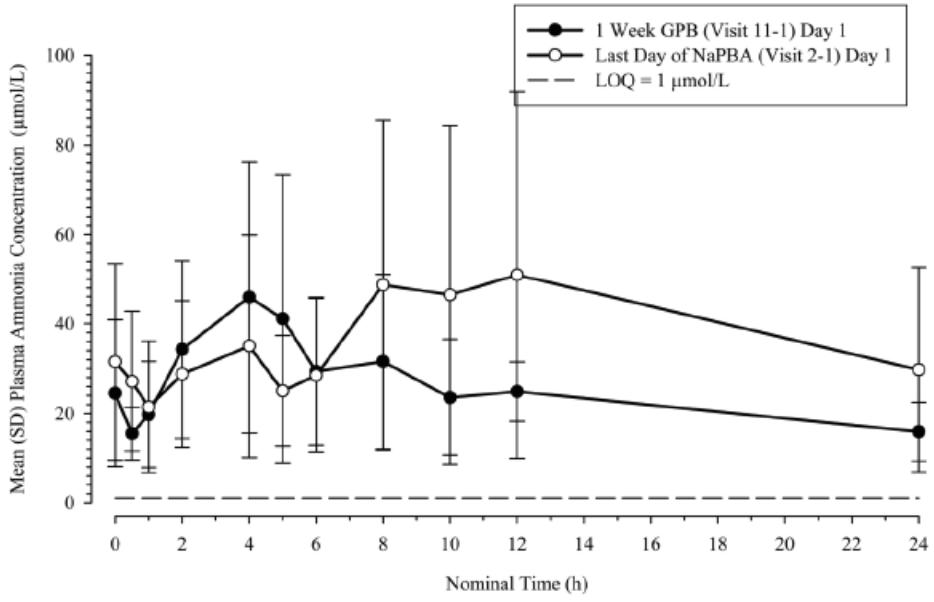
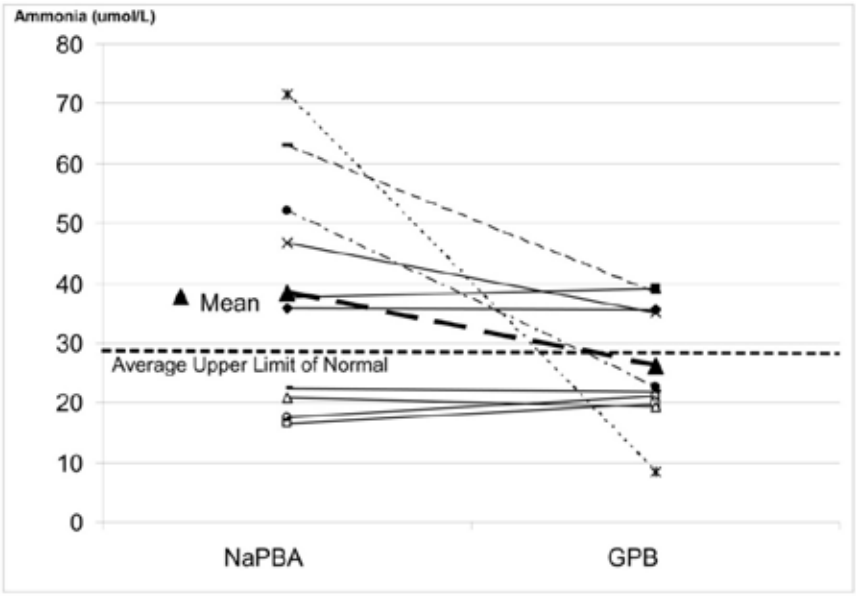


Figure 15: Venous Ammonia Concentrations in Individual Subjects Following One Week of Sodium Phenylbutyrate or Glycerol Phenylbutyrate Treatment (Lee 2010)



7.3.2. Lichter-konecki 2011

Lichter-Konecki U, et al Ammonia control in children with urea cycle disorders (UCDs); Phase II comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Genet Metab. 2011; 103

This was a prospective open label fixed-sequence switch-over from the prescribed NaPBA dose to a PBA-equimolar GPB dose with controlled diet. After 7 days on NaPBA or GPB, subjects underwent 24-hour blood sampling for ammonia and drug metabolite levels as well as measurement of 24-hour urinary phenylacetylglutamine (PAGN). A total of 11 children were enrolled but only 10 completed all of the study procedures. All 11 subjects (9 OTC, 1 ASS, 1 ASL) completed the switch-over from NaPBA (mean dose=12.4 g/d or 322 mg/kg/day; range=198–476 mg/kg/day) to GPB (mean dose=10.8 mL or 0.284 mL/kg/day or 313 mg/kg/day; range=192–449 mg/kg/day).

7.3.2.1. Results

Ammonia values were ~25% lower on GPB compared with NaPBA ($p \geq 0.1$ for ITT and $p < 0.05$ for per protocol population). The upper 95% confidence interval for the difference between ammonia on GPB versus NaPBA in the ITT population (95% CI 0.575, 1.061; p=0.102) was less than the predefined non-inferiority margin of 1.25 and less than 1.0 in the pre-defined per-protocol population (95% CI 0.516, 0.958; pb0.05). No statistically significant differences were observed in plasma phenylacetic acid and PAGN exposure during dosing with GPB versus NaPBA, and the percentage of orally administered PBA excreted as PAGN (66% for GPB versus 69% for NaPBA) was very similar. GPB and NaPBA dose correlated best with urinary-PAGN. The mean plasma ammonia concentrations after 1-week treatment are shown in Figures 16-17.

Figure 16: 24 Hour Ammonia Values on Sodium Phenylbutyrate and Glycerol Phenylbutyrate. Venous ammonia was measured for 24 h following one week of dosing with either sodium phenylbutyrate (NaPBA; continuous line) or glycerol phenylbutyrate (GPB; dotted line) (Lichter-Koneck 2011)

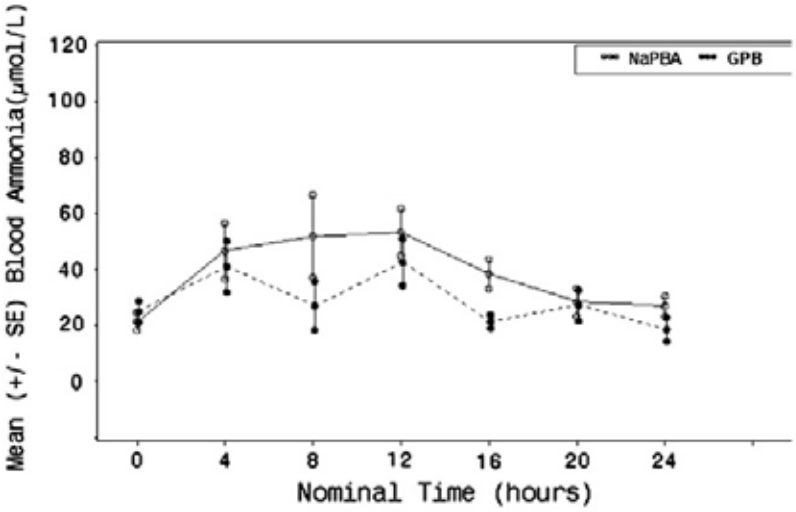
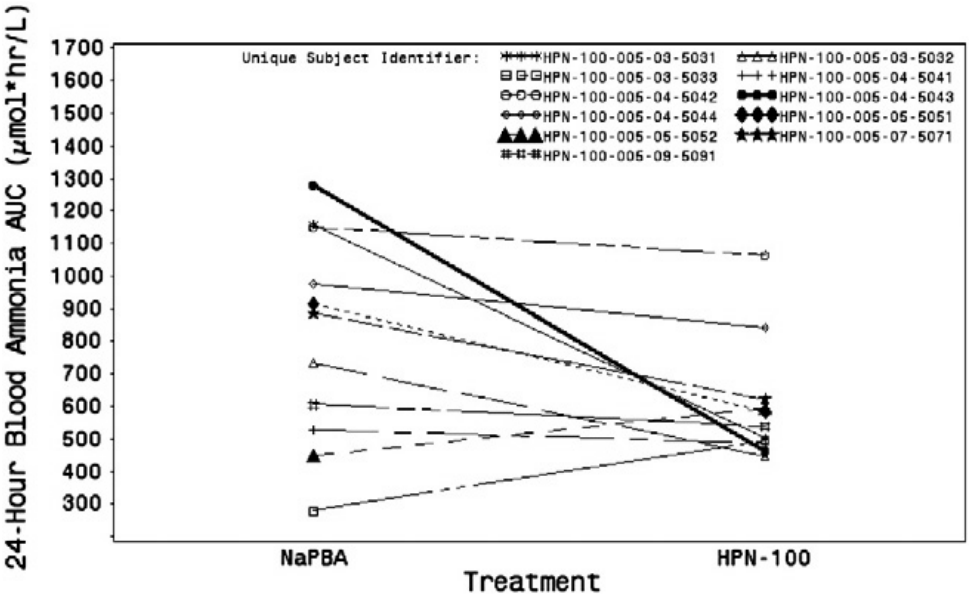


Figure 17: Venous ammonia in individual subjects following one week of dosing with either sodium phenylbutyrate (NaPBA; left) or glycerol phenylbutyrate (GPB; right). The values shown represent time-normalised area under the curve and are displayed as mean ±SD. Times 0 and 24 h correspond to just prior to dosing and breakfast (Lichter-Konecki 2011)



7.3.3. Smith 2013

Smith W et al, Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Journal of Pediatrics. 162(6):1228-34, 1234.e1, 2013.

This study was an open label cross-over study, which examined ammonia levels, pharmacokinetics, and safety of glycerol phenylbutyrate and sodium phenylbutyrate in young children with UCDs. Eligible patients included children aged below 6 years with a confirmed or clinically suspected UCD who had been receiving a stable dose of sodium phenylbutyrate

powder for at least 5 days. Patients underwent 24- hour blood and urine sampling on sodium phenylbutyrate and again on a phenylbutyric acid-equimolar dose of glycerol phenylbutyrate (Table 19) and completed questionnaires regarding signs and symptoms associated with sodium phenylbutyrate and/or their UCD (Table 20). Mean systemic exposure to phenylbutyric acid, phenylacetic acid, and phenylacetylglutamine was similar.

Table 19: Blood Ammonia by Treatment (Smith 2013)

Parameter	GPB (N=13)	NaPBA (N=15)
$NH3_{24\text{-hour AUC}}$ (µmol/L*hours)		
Mean (SD)	647.63 (379.944)	914.43 (630.206)
Median	543.08	604.96
Min, Max	258.6, 1513.5	189.3, 1974.8
Ratio of geometric means[b]	0.79	
P-values	0.075[c], 0.033[d]	
90% CI[b]	0.625, 1.002	
95% CI[b]	0.593, 1.055	
NH3 (umol/L)		
Mean daily ammonia	25	37
Mean Cmax[e]	39	53
Proportion of abnormal values		
Time zero	2/14 (14%)	7/15 (47%)
8 hours	1/14 (7%)	4/14 (29%)
12 hours	2/11 (18%)	6/14 (43%)
24 hours	3/14 (21%)	5/15 (33%)
All time points	8/53 (15%]	22/58 (38%)

[a] ANOVA with factors for treatment (fixed effect) and patient (random effect)

[b] Results on original scale obtained by exponentiating the corresponding log-transformed results of ammonia during treatment with GPB as compared with NaPBA

[c] Paired t-test

[d] Wilcoxon signed-rank test

[e] Cmax = maximal daily ammonia value

Table 20: Signs and Symptoms Associated with UCD or its Treatment (Smith 2013)

Symptoms	All Subjects (N=15)					
	Baseline	Improved* on day 10	Present at Day 1 and Unchanged	Not Present at Day 1 but present at Day 10	Not Present at either Day 1 nor Day 10	Unable to Assess
Body odor	6	5	1	0	9	0
Burning sensation in mouth/throat	1	1	0	0	9	5
Chronic or recurrent headache	1	1	0	0	7	0
Episodic lethargy or sleepiness	3	2	1	0	12	0
Heartburn	1	1	0	0	7	7
Irritability/agitation/excessive crying	3	0	3	0	12	0
Protein intolerance	4	2	2	0	7	4
Recurrent abdominal pain	3	3	0	0	9	3
Recurrent nausea	3	3	0	0	7	5
Recurrent vomiting	5	5	0	1**	9	7
Refuse to eat due to taste/smell of drug	3	3	0	0	10	0
Vomiting upon or after taking drug	5	3	2	1**	12	0
Total Symptoms	**38**	**29**	**9**	**2**		

* Improved denotes either complete resolution or decrease in frequency of the symptom

** Reported by a subject receiving NaPBA through a G tube and stated GPB orally for the first time.

7.3.4. Kibleur 2014

Kibleur Y.A. Dobbelaere D. Barth M. Brassier A. Guffon N. Results from a nationwide cohort temporary utilization authorization (ATU) survey of patients in France treated with Pheburane (sodium phenylbutyrate) taste-masked granules. Journal of Inherited Metabolic Disease (2014) 37:1 SUPPL. 1 (S81)

This study was a French descriptive nationwide system for pre-marketing follow-up (cohort temporary utilization authorization [ATU]) protocol of Pheburane and to analyse safety and efficacy in this treated cohort of patients with urea cycle disease (UCD).

A cohort ATU was established in October 2012 to monitor the use of Pheburane on a named patient basis. All treated UCD patients were included in a follow-up protocol developed by the Laboratory (Lucane Pharma) and the French Medicines Agency (ANSM), which recorded demographics, dosing characteristics of NaPB, concomitant medications, adverse events, and clinical outcome during the period of treatment. Following the granting of the Marketing Authorization in Europe, the cohort ATU was terminated approximately 1 year after its initiation, as the product was launched on the French market.

7.3.4.1. Results

The ease of administration and acceptability were reported to be better with Pheburane than with the previous treatment (Figure 18). No episodes of metabolic decompensation were observed over a treatment period which ranged from 3 to 11 months (Table 21). It was also reported that range of ammonia and glutamine plasma levels improved and remained within the normal range with Pheburane (Figure 19).

Figure 18: Differential (Pheburane –marketed NaPB) individual rating of acceptability just after drug intake in healthy volunteers (Kibleur 2014)

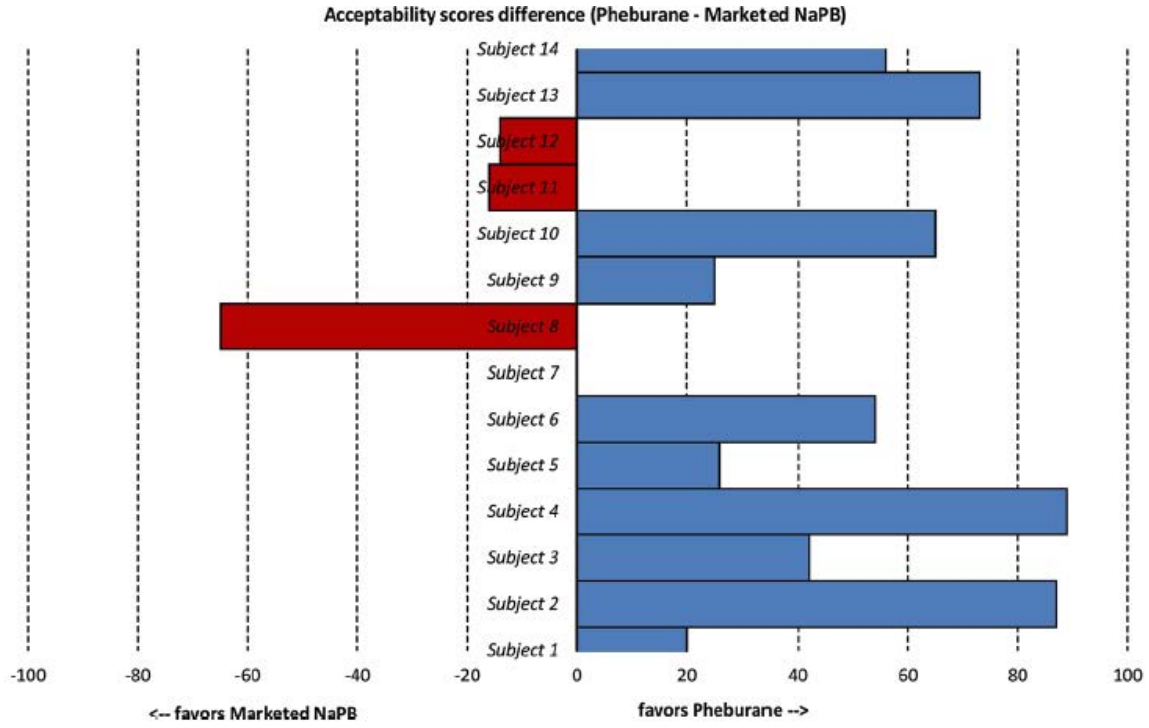
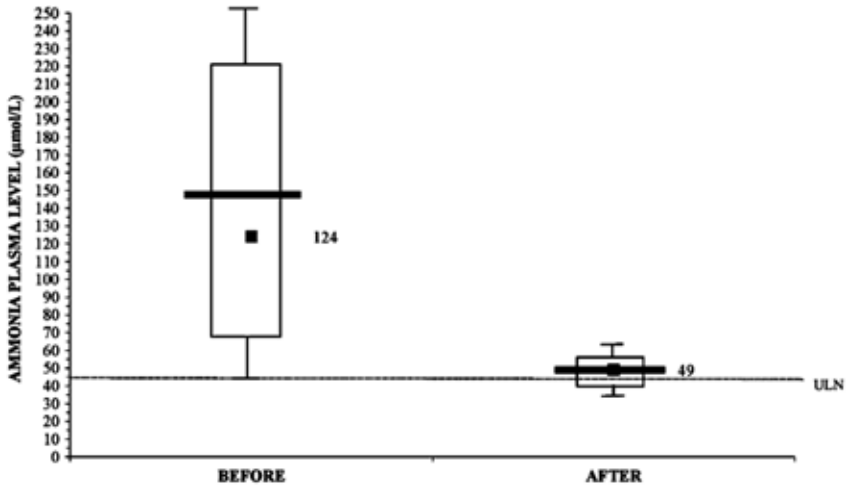


Table 21: Number of hyperammonaemic episodes under marketed NaPB and Pheburane (Kibleur 2014)

Patient No	Age (years)	Before Pheburane® (in previous 6 months)	Under Pheburane® (exposure duration)
5	11	3	None (6 months)
9	24	1	None (11 months)
10	4	2	None (11 months)
11	3	2	None (10 month)
17	15	1	None (8 months)
20	22	1	None (6 months)
22	64	3	None (3 months)
23	18	2	None (3 months)
24	4	1	None (3 months)
25	4	3	None (3 months)

NaPB sodium phenylbutyrate

Figure 19: Box–whisker plots of maximal plasma ammonia values in the 6-month period before inclusion in the cohort ATU and then under Pheburane (Kibleur 2014)



7.3.5. Evaluator commentary: other efficacy studies

The available studies support the fact that sodium phenylbutyrate results in low plasma ammonium, close to the normal range. Kibleur 2014 is supportive of Pheburane being at least as effective as the Ammonaps. This is probably explained by improved compliance with treatment rather than the inherent efficacy of Pheburane.

7.4. Analyses performed across trials: pooled and meta-analyses

7.4.1. Berry 2014

Berry SA; Lichter-Konecki U; Diaz GA; McCandless SE; et al. Glycerol phenylbutyrate treatment in children with urea cycle disorders: pooled analysis of short and long-term ammonia control and outcomes. Molecular Genetics & Metabolism. 112(1):17-24, 2014.

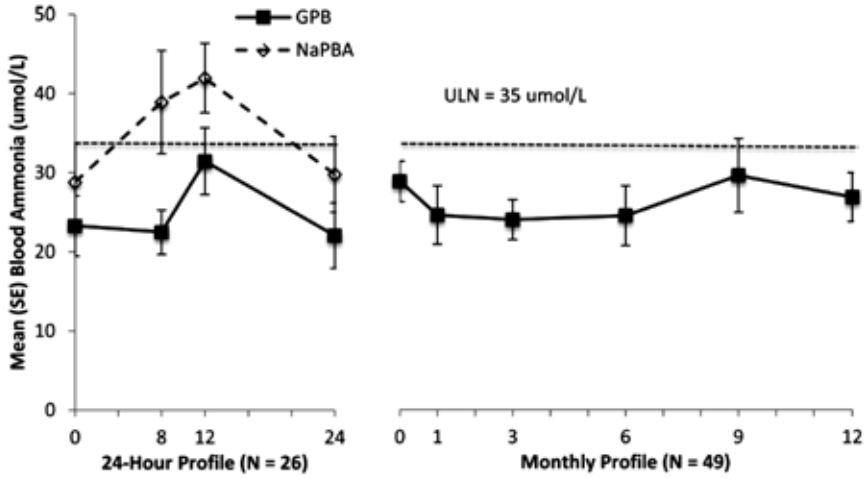
This study aimed to evaluate glycerol phenylbutyrate (GPB) in the treatment of paediatric patients with urea cycle disorders (UCDs) and enrolled 26 patients aged between 2 months and 17 years who were treated with GPB and sodium phenylbutyrate (NaPBA) in two short-term,

open-label crossover studies, which compared 24-hour ammonia exposure ($AUC_{0–24}$) and glutamine levels during equivalent steady-state dosing of GPB and sodium phenylbutyrate (NaPBA). These 26 patients plus an additional 23 patients also received GPB in one of three 12-month, open label extension studies, which assessed long-term ammonia control, hyperammonaemic (HA) crises, amino acids levels, and patient growth.

7.4.1.1. Results

Mean ammonia exposure on was significantly lower on GPB compared with NaPBA (mean [SD] $AUC_{0–24}$: 627 [302] versus 872 [516] µmol/L; p=0.008) with significantly fewer abnormal values (15% on GPB versus 35% on NaPBA; p = 0.02). Mean ammonia levels remained within the normal range during 12 months of GPB dosing and, when compared with the 12 months preceding enrolment, a smaller percentage of patients (24.5% versus 42.9%) experienced fewer (17 versus 38) HA crises. Glutamine levels tended to be lower with GPB than with NaPBA during short-term dosing (mean [SD]: 660.8 [164.4] versus 710.0 [158.7] µmol/L; p=0.114) and mean glutamine and branched chain amino acids levels, as well as other essential amino acids, remained within the normal range during 12 months of GPB dosing. Mean height and weight Z-scores were within normal range at baseline and did not change significantly during 12 months of GPB treatment (Figure 20).

Figure 20: Mean (SE) 24-hour ammonia levels following the morning dose of GPB (HPN-100) and NaPBA in paediatric UCD patients (n = 26; p=0.008) and long term GPB treatment (N=49). Dashed line indicates upper limit of normal range (35 µmol/L) (Berry 2014)



7.4.2. Diaz 2013

Diaz GA; Krivitzky LS; Mokhtarani M; Rhead W; et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology. 57(6):2171-9, 2013

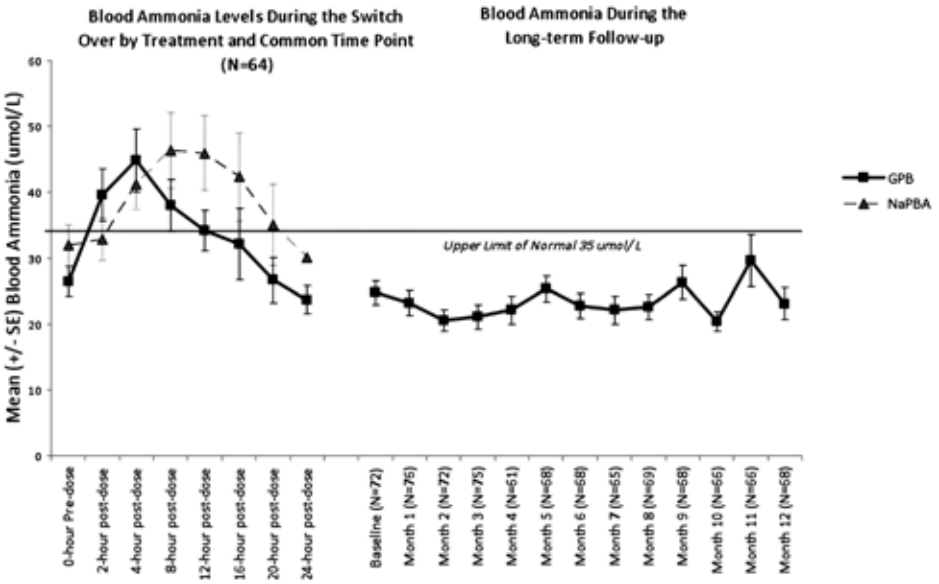
This was a Phase III, randomised double-blind, crossover trial comparing ammonia control, assessed as 24-hour area under the curve ($NH3\text{-}AUC_{0\text{-}24hr}$), and pharmacokinetics during treatment with glycerol phenylbutyrate versus sodium phenylbutyrate (NaPBA) in adult UCD patients and the combined results of 4 studies involving short- and long-term glycerol phenylbutyrate treatment of UCD patients ages 6 and above.

7.4.2.1. Results

Glycerol phenylbutyrate was equivalent to NaPBA with respect to ammonia control in the pivotal study, with mean (SD) $NH3\text{-}AUC_{0\text{-}24}$ of 866 (661) versus 977 (865) µmol·h/L for glycerol phenylbutyrate and NaPBA, respectively. Among 65 adult and paediatric patients completing 3 similarly designed short term comparisons of glycerol phenylbutyrate versus NaPBA, NH3-

AUC_{0-24} was directionally lower on glycerol phenylbutyrate in each study (Figure 21), similar among all subgroups, and significantly lower ($p<0.05$) in the pooled analysis, as was plasma glutamine. The 24-hour ammonia profiles were consistent with slow release behaviour of glycerol phenylbutyrate and better overnight ammonia control. During 12 months of open label glycerol phenylbutyrate treatment, average ammonia was normal in adult and paediatric patients and executive function among paediatric patients, including behavioural regulation, goal setting, planning and self-monitoring, was significantly improved.

Figure 21: Short- and Long-Term Blood Ammonia Levels in UCD Patients (pooled data) (Diaz 2013)



7.4.2.2. Nagamani 2015

Nagamani S.C.S. Diaz G.A. Rhead W. Berry S.A. et al. Self-reported treatment-associated symptoms among patients with urea cycle disorders participating in glycerol phenylbutyrate clinical trials. Molecular Genetics and Metabolism (2015) 116:1-2 (29-34).

This study involved the evaluation of a non-validated UCD-specific questionnaire in 100 adult and paediatric participants (Table 22). Patients or their caregivers responded to a pre-defined list of symptoms known to be associated with the use of these medications. Responses were collected at baseline (while patients were receiving sodium phenylbutyrate [NaPBA]) and during treatment with glycerol phenylbutyrate (GPB).

Table 22: Patient Demographics (*Nagamani 2015*)

	N = 100
Age at baseline: median (range)	18 yrs (2 mo–60 yr)
Age group (years): n (%):	
<2	7 (7.0)
3–5	16 (16.0)
6–7	10 (10.0)
8–11	7 (7.0)
12–18	9 (9.0)
18 +	51 (51.0)
Gender: n (%)	
Male	33 (33.0)
Female	67 (67.0)
Race: n (%)	
White	81 (81.0)
Non-white	19 (19.0)
Duration of prior NaPBA treatment: median (range) months	56 (0.2–300)
UCD subtype: n (%)	
OTC	69 (69.0)
ASL	13 (13.0)
ASS1	12 (12.0)
HHH	3 (3.0)
ARG1	2 (2.0)
CPS1	1 (1.0)
With symptoms: %	
No symptoms	31.0
At least 1 symptom	69.0
At least 2 symptoms	48.0
3 or more symptoms	36.0

ARG1: arginase 1; ASL argininosuccinate lyase; ASS1: argininosuccinate synthase 1; BUN: blood urea nitrogen; CPS: carbamoyl-phosphate synthase; HHH: hyperornithinemia–hyperammonemia–homocitrullinuria; OTC: ornithine transcarbamylase; UCD: urea cycle disorder.

7.4.2.3. Results

After 3 months of GPB dosing, there were significant reductions in the proportion of patients with treatment-associated symptoms (69% versus 46%; p b 0.0001), the number of symptoms per patient (2.5 versus 1.1; p b 0.0001), and frequency of the more commonly reported individual symptoms such as body odour, abdominal pain, nausea, burning sensation in mouth, vomiting, and heartburn (p b 0.05) (Figures 22-23). The reduction in symptoms was observed in both paediatric and adult patients. The presence or absence of symptoms or change in severity did not correlate with plasma ammonia levels or NaPBA dose.

Figure 22: Comparison of the most frequently reported symptoms reported by patients while on NaPBA therapy (baseline) compared with after 3 months of GPB therapy. A: all patients; B: paediatric patients (*p b 0.05; **p b 0.01; ***p b 0.001; ****p b 0.0001) (*Nagamani 2015*)

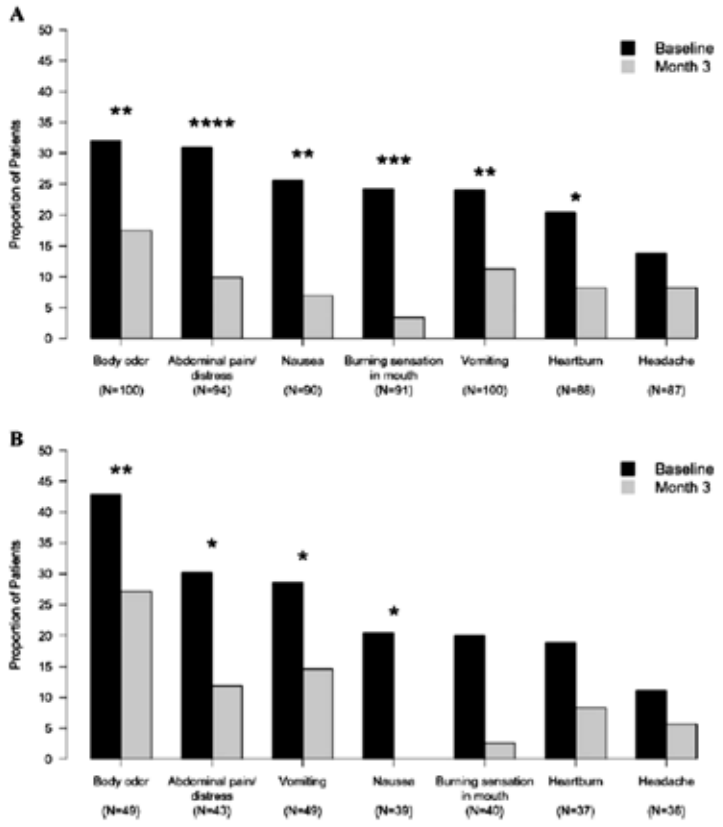
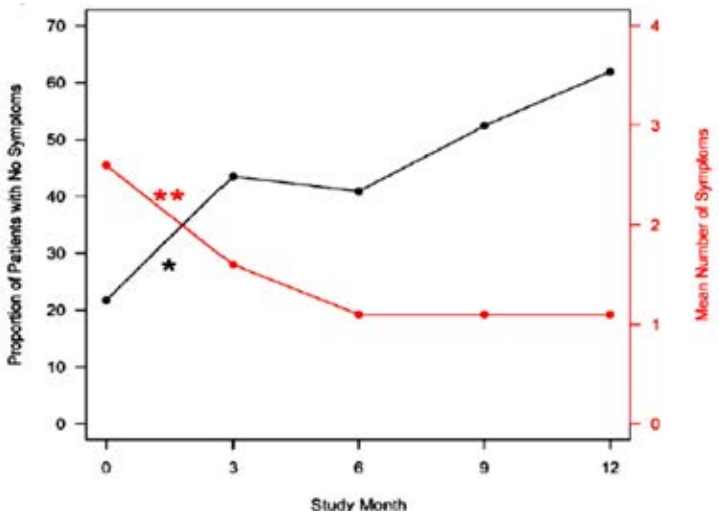


Figure 23: Changes in symptoms from baseline to quarterly visits in study HPN-100-012 in paediatric patients under 6 years of age (N=23). Left axis (black line) percentage of patients who reported symptoms at each visit; right axis (red line) corresponding mean number of symptom reported. (*p b 0.05; **p b 0.01 comparing month 3 and baseline) (*Nagamani 2015*)



7.4.3. Maestri 1991

Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr. 1991 Dec;119(6):923-8

This paper was a description of a diagnostic and therapeutic protocol designed to prevent clinical expression of inborn errors of urea synthesis in the neonatal period, and discuss the long-term developmental outcome of survivors. The families of 32 infants, among 43 identified prenatally as being at risk for a urea cycle disorder, were treated according to a diagnostic and therapeutic protocol, beginning at birth. This study did not involve the use of sodium phenylbutyrate in the treatment protocol (Table 23). There are no data presented directly relevant to the current application.

Table 23: Treatment protocol for treatment of neonatal urea cycle disorders (*Maestri 1991*)

	Diagnosis		
	CPSD or OTCD	ASD	ALD
Diet (per kg per day)			
Natural protein (gm)	0.7	1.5	1.5
Essential amino acids (gm)	0.7	—	—
Calories (kcal)	120	120	120
Medications (mg/kg/day)*			
Arginine freebase	170	700	700
Sodium benzoate	250	250	—
Sodium phenylacetate†	250	—	—

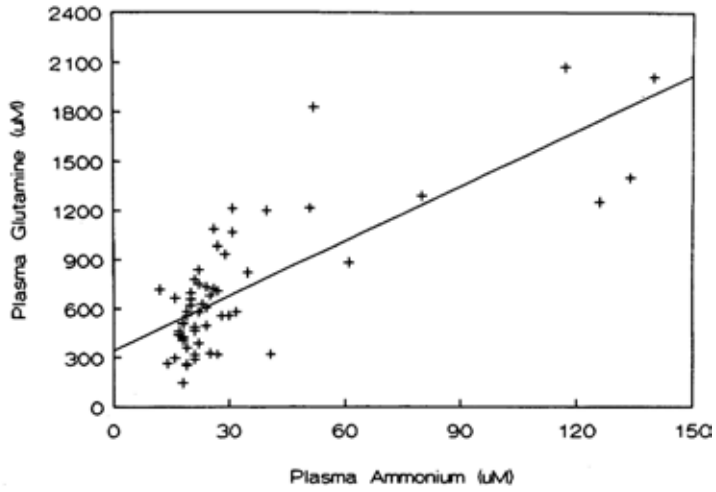
*Oral dosage.
†Sodium phenylacetate was added to the protocol in 1984.

7.4.1. Maestri 1992

Maestri NE, McGowan, KD, Brusilow. Plasma glutamine concentration: A guide in the management of urea cycle disorders. Journal of Pediatrics. 1992; 121:259-61

This was a single case report of a child born with OTC deficiency who was treated from the early neonatal period. The patient was the younger brother of a boy with known OTC deficiency. The patient was treated with a low protein diet (at times supplemented with essential amino acids), e-citrulline, 175 mg/kg per day, and sodium phenylbutyrate, 500 to 600 mg/kg per day. The study documents the relationship between plasma glutamine and ammonium concentrations (see Figure 24). At 19 months of age, the patient was at the 25th percentile for weight and below the 3rd percentile for height. He had been admitted to the hospital three times because of symptomatic hyperammonaemia.

Figure 24: Relationship between plasma glutamine and ammonium concentrations. For all values the Pearson co coefficient is 0.77 (p <0.0001). For plasma ammonium values less than 30 mol/L (p = 0.436; p <0.0001) (*Maestri 1992*)



7.4.1. Maestri 1995

Maestri NE; Clissold DB; Brusilow SW. Long-term survival of patients with argininosuccinate synthetase deficiency. Journal of Pediatrics. 1995; 127(6):929-35

This study reported on the long-term survival and outcome of patients with neonatal onset argininosuccinate synthetase deficiency (ASD) who were treated with specific therapeutic protocols designed to activate alternative pathways of waste nitrogen excretion (Table 24). Patients for this study included 24 infants born before 1990 and rescued from hyperammonaemic coma caused by neonatal-onset ASD; they were referred to a single centre for enrolment in ongoing clinical studies of sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. Collaborating physicians throughout the United States and Canada provided information on survival, intellectual development, intercurrent hyperammonaemic episodes, and anthropometric and biochemical measurements.

7.4.1.1. Results

The cumulative survival rate was 87.5% at 5 years and 72% at 10 years of age (Figure 25). Survivors include 15 patients currently treated with high doses of sodium phenylbutyrate; two patients have withdrawn. Among the treated group, 11 are classified as severely to profoundly mentally retarded. The remaining four patients have IQ measurements in the borderline to mentally retarded range. All patients have had intercurrent hyperammonaemic episodes; our data indicate that the frequency of the episodes has decreased with implementation of the current protocol (Tables 25-26). These patients are growth retarded but most have height-for-weight z scores within 2 SD of the mean. Laboratory studies of plasma amino acids and of hematopoietic, renal, and hepatic function are within normal limits with the exception of slightly elevated serum aminotransferase values.

Table 24: Long-term therapeutic protocols for study patients (*Maestri 1995*)

	Protocol I (1980)	Protocol IIa, b (1984)	Protocol IIIa, b (1987)
Diet (per kg per day)			
Natural protein (gm)	0.5-0.7	0.5-0.7	1.25-2.0
Essential amino acids	0.5-0.7	0.5-0.7	0
Calories (kcal)	As required	As required	As required
Medications (mg/kg/day)			
Arginine freebase	500-700	500-700	400-700
Sodium benzoate	250	250	
Sodium phenylacetate (a) or sodium phenylbutyrate (b)		250	450-600

Figure 25: Kaplan-Meier survival curve for 24 patients with neonatal onset of ASD. The diamond shapes represent the age at censoring of surviving patients (*Maestri 1995*)

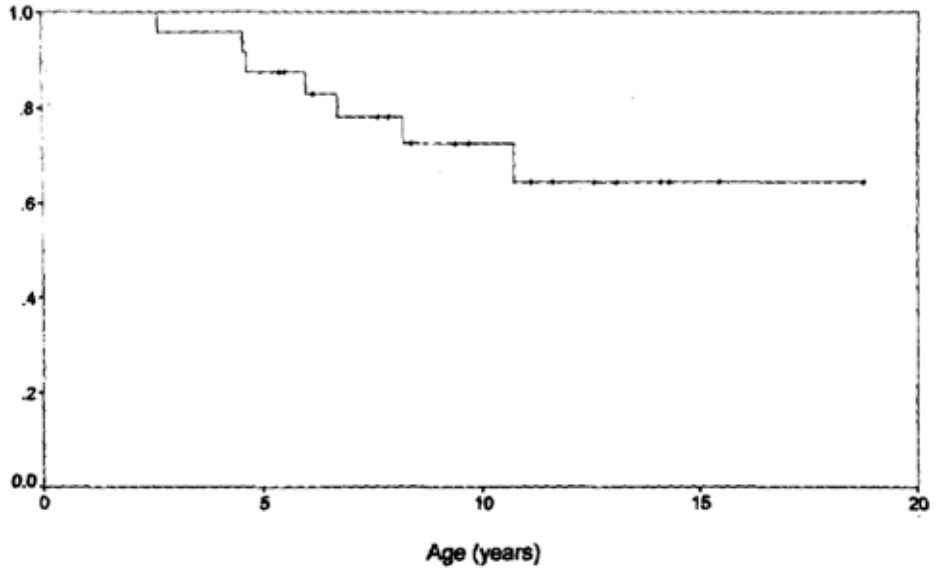


Table 25: Hyperammonaemic episodes during treatment protocols (*Maestri 1995*)

Therapeutic protocol	Patients	Total hyperammonemic episodes (No.)	Total patient-years of treatment	Frequency (episodes/patient-year)
I	12*	41	29.3	1.4
IIa	22*	71	74.7	1.0
IIIa	8*	3	7.0	0.4
IIb	7	18	25.9	0.7
IIIb	18*	52	71.7	0.7
TOTAL		185	208.6	0.9

*The data on patient 6 (died at 10.8 years of age) have been omitted from the calculations in this table. Her treatment included protocols I, IIa, IIIa, and IIIb. She had 15 hyperammonemic episodes during treatment with protocol IIIa and 7 episodes during protocol IIIb. Poor compliance with protocol, described in her chart, indicates that inadequate control of ammonia levels may be related to insufficient dosage of phenylacetate or phenylbutyrate.

Table 26: Current levels of plasma amino acids among surviving patients (*Maestri 1995*)

Amino acid (n = 15)	Result (μmol/L)	Normal values for plasma* (ages 6-18 yr)
Alanine	537 (205)	361 (87)
Arginine	188 (154)	89 (20)
Citrulline	3640 (2117)	35 (8)
Glutamine	688 (246)	596 (66)
Isoleucine	22.5 (11.3)	67 (13)
Leucine	41.0 (20.5)	127 (21)
Ornithine	93.4 (107.6)	49 (14)
Valine	87.1 (28.3)	223 (31)

Values are expressed as mean (±SD).
*Data from Armstrong MD, Stave U. A study of free amino acid levels. II. Normal values for children and adults. Metabolism 1973;22:259-61.

7.4.1. Maestri 1996

Maestri NE et al, Long-term treatment of girls with ornithine transcarbamylase deficiency. New England journal of medicine 1996 VL: 335 NO: 12 PG: 855-9

This study reported on 32 girls aged 1 to 17 years with ornithine transcarbamylase deficiency who had had at least one episode of encephalopathy. The patients were assigned to treatment that consisted of sodium benzoate, alone or in combination with sodium phenylacetate or sodium phenylbutyrate, or sodium phenylbutyrate alone. Collaborating physicians provided clinical, metabolic, and developmental data at specified intervals.

7.4.1.1. Results

The study reported that there was 90.6% survival at five years and that the patients maintained appropriate weight for height (Table 27). The frequency of hyperammonaemic episodes decreased with increasing age and with sodium phenylacetate or sodium phenylbutyrate treatment (Table 28). Although the mean IQ before treatment was in the low average range, 19 of the 23 girls in whom intelligence was tested longitudinally had stable test scores (Figure 26).

Table 27: Anthropometric measurements in girls with ornithine transcarbamylase deficiency, according to age* (*Maestri 1996*)

Measurement	No. of Patients	Mean Time after Initiation of Treatment (yr)	No. of Measurements	Mean z Score
Height-for-age z-score distribution				
<5 yr	16	1.4±0.9	39	−0.7±1.2
5–9.9 yr	20	3.8±1.9	66	−0.9±0.9
10–14.9 yr	15	7.6±3.3	62	−0.6±1.0
15–19.9 yr	13	7.6±4.1	28	−0.7±0.8
Weight-for-age z-score distribution				
<5 yr	17	1.4±0.9	43	−0.6±1.6
5–9.9 yr	21	3.9±2.0	73	−0.4±1.2
10–14.9 yr	15	7.5±3.3	65	−0.2±1.1
15–19.9 yr	13	7.2±4.1	28	−0.1±1.2
Weight-for-height z-score distribution†				
<5 yr	15	1.4±0.9	38	0.1±1.4
5–9.9 yr	20	3.8±1.9	60	0.5±1.3

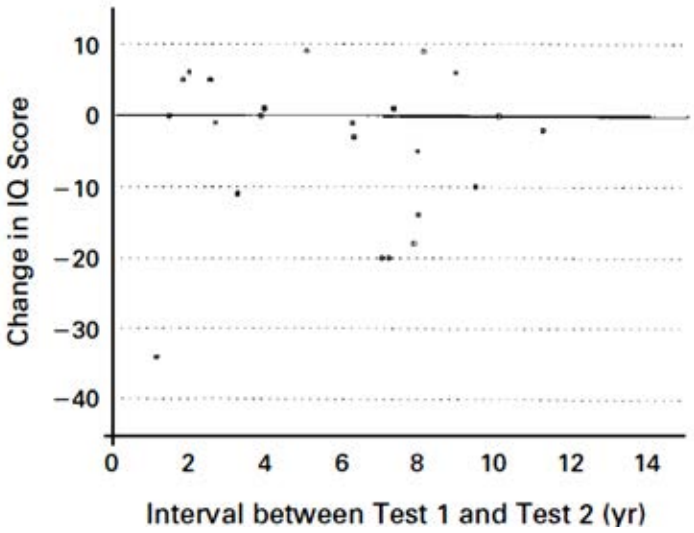
*Plus–minus values are means ±SD.
†Weight-for-height z scores are calculated from birth to the age of 10 years.[8]

Table 28: Hyperammonaemic episodes during treatment of girls with ornithine transcarbamylase deficiency, according to age* (*Maestri 1996*)

Age (yr)	No. of Patients	No. of Hyperammonemic Episodes	Patient-Years of Treatment	Frequency (Episodes/ Patient-Year)
<5	16	39	40	1.0
5–9.9	21	44	81	0.5
10–14.9	19	29	75	0.4
15–19.9	18	18	57	0.3
≥20	8	3	29	0.1
Total	82	133	281	0.5

*Data for Patient 3 were omitted from the calculations because she had more than 20 hyperammonemic episodes during treatment in protocols 1 and 2, despite excellent compliance.

Figure 26: change in IQ score for 23 girls with ornithine transcarbamylase deficiency who had at least two intelligence tests after enrolment in the treatment protocols (*Maestri 1996*)



7.5. Evaluator's conclusions on clinical efficacy

The data on the clinical efficacy of Pheburane are limited. Most of the presented studies relate to the use of glycerol phenylbutyrate versus sodium phenylbutyrate in which glycerol phenylbutyrate does appear to have some minor advantage in nitrogen excretion.

There is evidence of good survival and perhaps prevention of hyperammonaemic episodes in patients treated with sodium phenylbutyrate. The study by Kibleur 2014 does suggest that Pheburane may be better tolerated than standard sodium phenylbutyrate and this may lead to better compliance with treatment.

- *The sponsor should better quantify the outcomes of treatment with sodium phenylbutyrate compared to historical controls in terms of:*
  - *Ammonia levels*
  - *Nitrogen excretion*
  - *Hyperammonaemic episodes*

– *Neurodevelopmental outcomes*

8. Clinical safety

There are no safety studies related directly to Pheburane. There is only one submitted study (Bioequivalence Study LUC1001) including safety data on Pheburane. There are safety data related to Pheburane other formulations of sodium phenylbutyrate included in some of the published reports. In these reports, as they are uncontrolled for the use of sodium phenylbutyrate, it is not always possible to separate the effects of the underlying urea cycle defect from the effect from sodium phenylbutyrate or other therapies that the patients are receiving.
Finally, there is the first EU Periodic benefit-risk evaluation report (PBRER) Studies providing evaluable safety data from 31 July 2013 to 31 December 2015 which includes data from Study LUC1001 and published literature. There is overlap of patients between the reports, and not all overlap is clearly identified in the published reports.

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

No Pivotal Studies assessing safety were submitted as part of the application.

8.1.2. Pivotal and/or main efficacy studies

No Pivotal Efficacy Studies were submitted as part of the application.

8.1.3. Other studies

The overview of safety identifies adverse event reports in in the 3 comparative studies. The exposure of the patients to sodium phenylbutyrate is summarised in the table below (Table 29).

Table 29: Adverse event reports for Sodium Phenylbutyrate from the comparator studies (Safety Report, M2)

Reference (No of pts)	*Duration NaPB pre-study mths*	*Dose NaPB Mean (SD) g*		*Reported AEs*
		Pre-study	*During study*	
Lee 2010 (n=14 adult)	97.89 (88.4)	13.49 (6.08)	12.22 (4.05)	Total of 21 AE in 7 out of 10 adult UCD patients during NaPB prescribed for average 9.04 years at average dose of 191 mg/Kg/d. Most AE categorized as mild (19/21). Six of 21 AE were treatment emergent AE in 5 patients -dyspepsia (1), gastro-esophageal reflux (1), increased appetite (1), dizziness (1), dysgeusia (1), and chills (1)
Lichter-Konecki 2011 (n=11 paed)	74.68 (48.2)	12.41 (4.39)	10.90 (3.858)	Possibly-related AEs were reported in 2 subjects on NaPB and 4 subjects on GPB. All were mild, except for one moderate AE of vomiting on GPB related to an intercurrent illness. No clinically significant laboratory or ECG changes were observed.
Smith 2013 (n=15 paed)	19.3 (17.2)	5.28 (2.45)	4.63 (2.16)	On Day 112 of 15 patients reported a total of 38 symptoms associated with NaPB or their UCD, the most common of which were body odour (6 patients), recurrent abdominal pain, vomiting after taking drug and refusal to eat due to smell or taste of the drug (3 patients each). Most symptoms either improved or resolved on Day 10. Improvement was reported for body odor and recurrent vomiting (5 patients each), vomiting after taking drug, abdominal pain, recurrent nausea and refusal to eat (3 patients each), and 1 patient each experienced improvement in the remaining symptoms. One patient who received NaPB through a G-tube and who received GPB orally reported a new onset of occasional vomiting upon or after taking GPB.

8.1.3.1. Smith 2013

Details of this study are found in the Efficacy section.

On day 1, as part of the collection of data points of interest, 12 of 15 patients reported a total of 38 symptoms (Table 30) associated with sodium phenylbutyrate or their UCD, the most common of which were body odour (6 patients) followed by recurrent abdominal pain, vomiting after taking drug, and refusal to eat because of the smell or taste of the drug (3 patients each). Six patients experienced mild adverse events on glycerol phenylbutyrate.

Adverse events were reported by 61% and 51% of patients during glycerol phenylbutyrate and sodium phenylbutyrate treatment, respectively, with most being gastrointestinal and generally mild. Symptoms suggestive of gastrointestinal disorders, irrespective of treatment, included diarrhoea, flatulence, abdominal discomfort, dyspepsia, nausea, vomiting, and oral discomfort. No clinically significant laboratory or ECG changes were observed.

Table 30: Adverse Events reported during the study period related either to symptoms of UCD or its treatment (Smith 2013)

	All subjects (N = 15)					
Symptoms	Baseline	Improved* on day 10	Present at day 1 and unchanged	Not present at day 1 but present at day 10	Not present at either day 1 nor day 10	Unable to assess
Body odor	6	5	1	0	9	0
Burning sensation in mouth/throat	1	1	0	0	9	5
Chronic or recurrent headache	1	1	0	0	7	0
Episodic lethargy or sleepiness	3	2	1	0	12	0
Heartburn	1	1	0	0	7	7
Irritability/agitation/excessive crying	3	0	3	0	12	0
Protein intolerance	4	2	2	0	7	4
Recurrent abdominal pain	3	3	0	0	9	3
Recurrent nausea	3	3	0	0	7	5
Recurrent vomiting	5	5	0	1†	9	7
Refuse to eat due to taste/smell of drug	3	3	0	0	10	0
Vomiting upon or after taking drug	5	3	2	1†	12	0
Total symptoms	38	29	9	2		

*Improved denotes either complete resolution or decrease in frequency of the symptom.
†Reported by a subject receiving NaPBA through a G tube and started GPB orally for the first time.

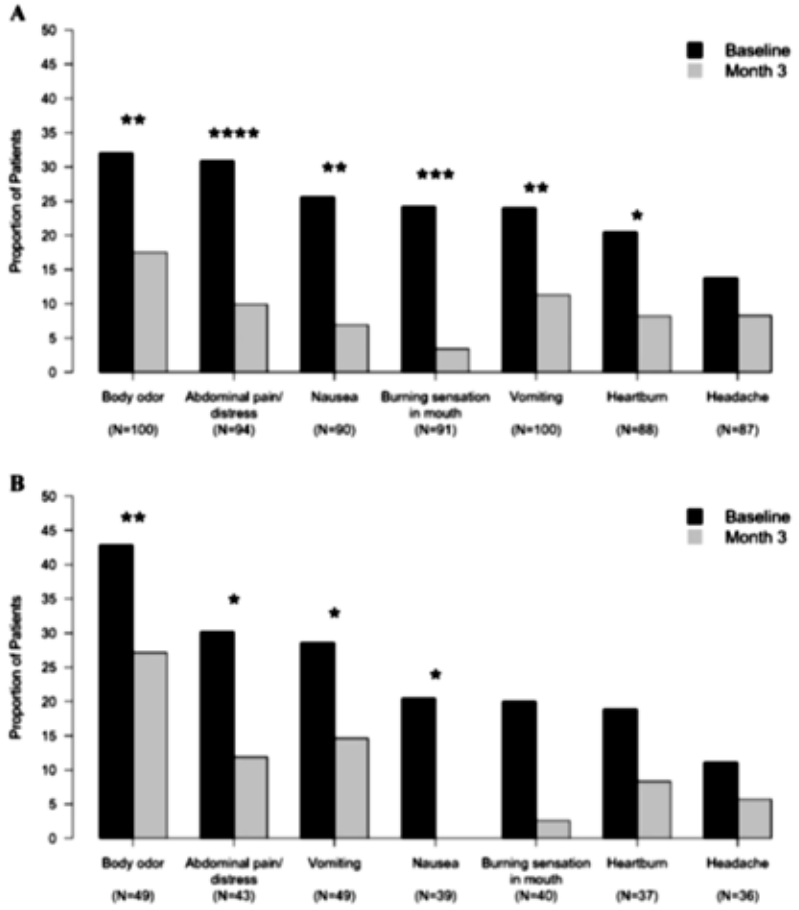
8.1.3.2. Nagamani 2015

Details of this study are found in the Efficacy section.

In this pooled analysis, a total of 100 patients with UCDs (77 aged ≥ 6 years; 23 aged < 6 years) were included from trials comparing sodium phenylbutyrate and glycerol phenylbutyrate (Berry 2014; Lee 2010; Lichter-Konecki 2011; Smith 2013). Treatment-associated symptoms from these studies were documented with baseline symptoms while on sodium phenylbutyrate.

The study reported that at baseline, 69% reported experiencing at least one of the treatment-associated symptoms compared with 46% of patients after 3 months of glycerol phenylbutyrate dosing (Figure 27).

Figure 27: Comparison of the most frequently reported symptoms reported by patients while on sodium phenylbutyrate (NaPB) therapy (baseline) compared with after 3 months of glycerol phenylbutyrate (GPB) therapy. A: all patients; B: paediatric patients (*p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001) (Nagamani 2015)



8.1.3.3. Studies with evaluable safety data: other diseases

The clinical safety overview stated the following

> During long-term phenylbutyrate therapy, 23% of menstruating females had irregular menses or became amenorrhoeic. Decreased appetite, taste disturbances, or disagreeable body odour occurred in approximately 4%. Abnormal electrolytes, increased serum hepatic enzyme levels, hypo-albuminaemia, and anaemia may occur but are difficult to differentiate from the primary disease itself. A variety of gastrointestinal disorders, aplastic anaemia, ecchymosis, arrhythmias, renal tubular acidosis, depression, and rash have been reported rarely (Anon, 1996).
>
> Renal Fanconi syndrome has been reported in 2 patients, and a few patients were reported to have oral mucositis (Feillet et al., 1998); there has been one report of chronic pancreatitis (Anadiotis et al., 2001). Neurotoxicity as described in adults receiving phenylacetate is unlikely to occur, because phenylacetate levels remain low after phenylbutyrate administration in therapeutic doses for UCDs (Gore 2001; Piscitelli 1995). Neurocortical toxicity attributable to accumulation of the metabolite phenylacetate has been associated with high doses of sodium phenylbutyrate (greater than approximately 400 mg/kg/day intravenously), predominantly in studies in adult patients with cancer (Gore 2001; Thibault 1994; Thibault 1995). The dosage of sodium phenylbutyrate in the management of UCDs is much lower (9.9 - 13.0 g/m^2/day in

patients weighing more than 20 kg, with a recommended maximum of 20 g/day; European Medicines Agency, 2015; FDA, 2009).

Sodium phenylbutyrate should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with oedema (FDA, 2009).

Burrage 2014 analysed plasma levels from 595 patients across the United States, Canada, and Europe. The analysis showed that plasma levels of the BCAAs were significantly lower in patients treated with PB, even when accounting for all covariates (Table 31). Although the consequences of decreased levels of BCAA in patients with UCDs are unclear, the results suggest that patients treated with sodium phenylbutyrate should be routinely monitored for BCAA deficiency and supplemented as required.

Table 31: Branched chain amino acid (BCAA) levels in patients taking sodium phenylbutyrate (NaPB; n = 212) versus patients not taking NaPB (n = 341) (*Burrage 2014*)

	NaPBA	No NaPBA	$p_{corrected}$ value
Leucine (µMol/L)	60 (40–85)	95 (72–121)	<0.005
Valine (µMol/L)	128 (92–169)	176 (142–217)	<0.005
Isoleucine (µMol/L)	31 (22–49)	49 (36–65)	<0.005

Walker 2009 is a review article published which included a table to toxicity associated with phenylbutyrate (Table 32).

Table 32: Toxicity of phenylbutyrate, phenylacetate and benzoate (*Walker 2009*)

Large doses
Nausea, vomiting, somnolence and headache [78,80]
Tinnitus and visual disturbances [67,117]
Hypokalaemia [118]
Massive overdose [119]
Irritability, lethargy and somnolence
Tachypnoea and Kussmaul respiration
Death

Carducci 2001 was a Phase I study of 24 patients with hormone refractory prostate cancer being the predominant tumour type. A total of 89 cycles were administered. The dose-limiting toxicity (DLT) was neuro cortical, exemplified by excessive somnolence and confusion and accompanied by clinically significant hypokalaemia, hyponatraemia, and hyperuricaemia. One patient at 515 mg/kg/day and another at 345 mg/kg/day experienced this dose limiting toxicity. The dose limiting neuro-cortical toxicity of excessive somnolence and confusion occurred suddenly and was noticed readily by family and staff. The metabolic changes of hypokalaemia, hyponatraemia, hypocalcaemia, and hyperuricaemia reversed with supportive measures on discontinuation of the drug. The neuro-cortical symptoms resolved promptly (within 12 hours of ceasing drug infusion), and the patients returned to their baseline mental status before discharge. Other toxicities were mild, including fatigue and nausea (Table 33). The maximum tolerated infused dose was 410 mg/kg/day for 5 days.

Table 33: Side effects with phenylbutyrate (Carducci 2001)

	150 mg/kg/d	225 mg/kg/d	285 mg/kg/d	345 mg/kg/d	410 mg/kg/d	515 mg/kg/d
Neurocortical				1		1[a]
Hypokalemia						1[a]
Hyperuricemia						1[a]
Nausea						1[a]
Neutropenia	1[b]					
Fatigue				2[c]		

[a] Toxicities occurred in the same patient.
[b] Lasted 2 days only.
[c] Felt to be related to disease progression rather than drug.

Camacho 2007 evaluated twice-daily intravenous sodium phenylbutyrate infusions for two consecutive weeks (Monday through Friday) every month at five dose levels (60, 120, 180, 240, 300, and 360 mg/kg/day). Twenty-one patients with the following malignancies were treated: colon carcinoma 4, non-small cell lung carcinoma 4; anaplastic astrocytoma 3, glioblastoma multiforme 3, bladder carcinoma 2, sarcoma 2, and ovarian carcinoma, rectal haemangiopericytoma, and pancreatic carcinoma 1 each. Common adverse effects included grade 1 nausea/vomiting, fatigue, and light-headedness (Table 34). Fatigue was almost universal, especially at the highest dose levels. Dose-limiting toxicities were short-term memory loss, sedation, confusion, nausea, and vomiting. However, these toxicities resolved after discontinuation of therapy. No significant myelosuppression was seen and no life-threatening or irreversible toxicity was observed. It was concluded that the administration of sodium phenylbutyrate in a twice-daily infusion schedule was safe. The maximum tolerated dose was 300 mg/kg/day.

Table 34: Toxicity with twice daily intravenous infusions of sodium phenylbutyrate (Camacho 2007)

Dose Level (enrolled patients)	Grade 1 Event	N	Grade 2 Event	N	Grade 3 Event	N
60 mg/kg/day (N = 4)	Disorientation	2	Thrombocytopenia	1		
	Fatigue	2	Neutropenia	1		
	Nausea	1	Edema	1		
	Vomiting	1	Metabolic	1		
	Lightheaded	1				
	Neurosensory	1				
	Dysgeusia	1				
120 mg/kg/day (N = 4)	Fatigue	3	Edema	1		
	Nausea	2	Fatigue	1		
	Vomiting	2				
	Constipation	1				
	Diarrhea	1				
180 mg/kg/day (N = 4)	Lightheaded	4	Fatigue	2		
	Fatigue	3				
	Nausea	2				
	Vomiting	2				
	Flushing	1				
	Edema	1				
240 mg/kg/day (N = 4)	Nausea	2	Lightheaded	2	Fatigue	1
	Vomiting	2	Fatigue	1	Headache	1
	Lightheaded	2	Flushing	1		
	Constipation	1	Nausea	1		
	Fatigue	1	Vomiting	1		
	Musculoskeletal	1				
	Flushing	1				
300 mg/kg/day (N = 3)	Constipation	2	Fatigue	2	Anemia	1
	Lightheaded	1	Lightheaded	2		
	Fatigue	1	Edema	2		
	Fever	1	Nausea	1		
	Flushing	1	Vomiting	1		
	Nausea	1	Orientation	1		
	Vomiting	1	Musculoskeletal	1		
	Musculoskeletal	1				
	Orientation	1				
	Pulmonary	1				
360 mg/kg/day (N = 2)	Nausea	2	Fatigue	2	Fatigue	1
	Vomiting	2	Nausea	2	Musculoskeletal	1
	Headache	2	Vomiting	2		
	Orientation	1	Lightheaded	2		
			Musculoskeletal	1		
			Flushing	1		

Gore 2001 assessed phenylbutyrate in a Phase I dose escalation study in myelodysplasia (n= 11) and acute myeloid leukaemia (n = 16) by 7-day continuous infusion repeated every 28 days. The maximum tolerated dose was 375 mg/kg/day; higher doses led to dose-limiting reversible neurocortical toxicity (Table 35). CNS toxicity completely reversed within 48 h of cessation of phenylbutyrate infusion.

Table35: Toxicity in a dose-finding study (Gore 2001)

	Dose Level 375					Dose Level 440					Dose Level 500				
NCI toxicity grade	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Nausea/Vomiting	9	1						4			2	3			
Mucositis	10					4					5				
Diarrhea	10					4					5				
Liver															
Billirubin	10					4					5				
Tranaminases	10					4					5				
Renal	10					4					5				
Skin	7		3			4					4		1		
CNS															
Headache	6	4				2	2				4	1			
Cortical	10					3			1		2	3			
Cardiac function	10										5				
Hypocalcemia	6	2	2			2		2			2	2		1	
Fever	9		1			3		1			4			1	
Hemorrhage	10					3			1		5				
Alopecia	10					4					5				
Other															
Hyperuricemia	8					4					5				
Thrombophlebitis	2					3									
Interstitial lung disease	1														
Abdominal pain	1					1					1				
Hiccup						1									
Auditory acuity											1				

Gore 2002 assessed phenylbutyrate in patients with acute myeloid leukaemia and myelodysplastic syndrome by a continuous intravenous infusion via ambulatory infusion pump. Sequential cohorts were treated for 7 consecutive days out of 14 or with 21 consecutive days out of 28. In the first schedule (7/14), patients received 7 days of phenylbutyrate, followed by 7 days of drug holiday. This schedule was repeated for a total of 12 weeks (total of 6 weeks of phenylbutyrate infusion alternating with 6 weeks of drug holiday). In the second schedule (21/28), patients received 21 consecutive days of phenylbutyrate infusion followed by a 7- day drug holiday. This schedule was repeated for a total of three cycles (12 weeks). Dose-limiting central nervous system toxicity developed in only 1 of 23 patients treated, and reversed within 48 h of cessation of phenylbutyrate infusion. Mild fatigue was experienced with greater frequency (Table 36).

Table 36: Toxicity in a prolonged infusion study (Gore 2002)

	7/14					21/28				
National Cancer Institute toxicity grade	0	1	2	3	4	0	1	2	3	4
Nausea/vomiting	10	3				10				
Mucositis	13					9	1			
Diarrhea	13					9	1			
Liver:										
Alkaline phosphatase						9		1		
Bilirubin						9				
Transaminases	13					10				
Skin	11		2			8	1		1	
CNS:										
Motor	8	5				5	5			
Cortical	10	2	1			10				
Hypocalcemia	6	4	3			8	2			
Fever	10	1	2			8	2			
Other:										
Hyperuricemia	9					3				
Edema	3					1				
Odor	2									
Urinary frequency	1									
Hypercholesterolemia	1									

* No >grade 0 toxicities were found in categories of renal, cardiac, hemorrhagic, or alopecia.

Maslak 2006 studied sodium phenylbutyrate in 10 patients with acute myeloid leukaemia or myelodysplastic syndrome. Patients were treated with seven consecutive daily subcutaneous injections of 5-azacytidine at 75 mg/m^2 followed by 5 days of sodium phenylbutyrate given intravenously at a dose of 200 mg/kg. The common toxicities of injection site skin reaction (90% of the patients) from 5-azacytidine, and somnolence/fatigue from the sodium phenylbutyrate infusion (80% of the patients).

Phuphanich 2005 studied oral sodium phenylbutyrate in patients with recurrent malignant gliomas. Twenty-three patients with supratentorial recurrent malignant gliomas were enrolled on this dose escalation trial. Four dose levels of phenylbutyrate were studied: 9, 18, 27, and 36 g/day (in three equally divided daily doses) with a cycle length of 28 days. At 36 g/day, two of four patients developed dose-limiting Grade 3 fatigue and somnolence. At the maximum tolerated dose of 27 g/day, one of seven patients developed reversible Grade 3 somnolence.

Gilbert 2001 conducted a Phase I trial of oral sodium phenylbutyrate in 28 patients with refractory solid tumour malignancies. Five dose levels of phenylbutyrate were studied: 9 g/day (n = 4), 18 g/day (n = 4), 27 g/day (n = 4), 36 g/day (n = 12), and 45 g/day (n = 4). The most common toxicities were grade 1-2 dyspepsia and fatigue. The maximum tolerated dose (MTD) was 27 g/day. Dose-limiting toxicities were seen at the higher dose levels of 36 and 45 g with two of seven patients and two of four patients experiencing dose-limiting toxicities, respectively. These were non-haematological in nature and consisted of individual episodes of grade 4 hypocalcaemia and Grade 3 nausea and vomiting at 36 g. At the 45 g dose level, there was 1 episode of Grade 3 fatigue and Grade 3 oedema in the same patient and neurocortical toxicity was dose-limiting in one of four patients at the highest dose level. That patient experienced Grade 3 decreased concentration, Grade 3 decreased coordination, and Grade 3 slurred speech. The patient received 2 dose reductions to 27 g/day with resolution of his neurocortical toxicity while remaining on the drug.

Zeitlin 2002 performed a randomised, double-blind, placebo-controlled, dose-escalation and safety study of oral phenylbutyrate in 19 adults with cystic fibrosis. Three dose levels (20, 30, or 40 g/day divided three times daily) of drug or placebo were given for 1 week. There were 12 men and 7 women randomized in the study, and all 19 completed the final study visit. Mean age ± SD was 28.5 years ± 7.1 and the average weight was 62.6 kg ± 7.1). Minor adverse events in the 20 g cohort included transient nausea, headache, and sleepiness after the initial dose, and body odour. The first three resolved with a dose of paracetamol, and hydration was encouraged. Body odour was an inconsistent complaint by family or friends of subjects. No dose adjustments were required. These complaints were also observed after the initial dose in the 30 g cohort. Several subjects reported visual disturbances that were transient after the first dose. One subject had severe headache that resolved with a reduction to 20 g daily. All three subjects in the 40 g cohort complained of nausea, headache, and visual disturbances, and one complained of cramps in the hands and fingers. One of these subjects tolerated 40 g of phenylbutyrate when it was divided into six daily doses. One tolerated a reduction to 30 g daily, and one subject found the symptoms to be so unpleasant that the drug had to be discontinued.

Rubenstein 1998 conducted a randomised, double-blind, placebo-controlled trial in 18 patients with cystic fibrosis with an oral dose of 19 g daily of phenylbutyrate (divided into three doses), and found that side effects due to phenylbutyrate therapy were comparable with placebo (Table 37).

Table 37: Side effects with phenylbutyrate versus placebo (Rubenstein 1998)

	Placebo ($n = 9$)	4PBA ($n = 9$)
Bad taste in mouth	2	1
Diarrhea	0	1
Nausea/stomach upset	0	0

Cudkowicz 2009 conducted an open-label study of escalating dosages of oral sodium phenylbutyrate in 26 patients with amyotrophic lateral sclerosis. Study medication was increased from 9 to 21 g/day. The most common adverse events included falls, dizziness, diarrhoea, oedema, dry mouth, headache, nausea, and rash (Table 38). There were no clinically

significant changes in laboratory values, electrocardiogram (ECG) or vital signs. No deaths or unexpected and related serious adverse events occurred.

Table 38: Early study medication terminations due to adverse events (Cudkowicz 2009)

Subjects	Weeks on study drug	Highest achieved NaPB dosage	Adverse event	Relationship to study medication*
1	1	9	Edema foot, under eyes	Possibly related
2	4	12	2nd degree heart block, Type II	Unrelated
3	5	15	Rash arm, legs, & trunk, Eyelid swelling	Possibly related
4	5	15	Increased arm weakness	Possibly related
5	7	15	Acute anemia, Gastrointestinal bleed	Possibly related
6	7	15	Headache (subarachnoid hemorrhage)	Unrelated
7	8	15	Abdominal discomfort, chills and nausea	Possibly related
8	12	15	Dizziness, shortness of breath	Possibly related
9	12	18	Lower extremity edema	Possibly related
10	14	18	Increased joint pain and stiffness	Unrelated

* Site investigator decision.

Hogarth 2007 conducted a dose-finding study in 21 subjects with Huntington's disease found that phenylbutyrate was safe and well tolerated up to 15 g/day (maximum tolerated dose). At higher doses, dose-limiting toxicity emerged in 5 of 11 subjects; toxicity included vomiting, light-headedness, gait instability and confusion. There was no significant laboratory or electrocardiographic abnormalities.

Collins 1995 treated eleven patients with homozygous beta thalassaemia and one sickle-beta-thalassaemia patient with 20 g/d of oral sodium phenylbutyrate for 41 to 460 days. Compliance with treatment was greater than 90% as measured by pill counts. Side effects of the drug included weight gain and/or oedema caused by increased sodium load in 2/12, transient epigastric discomfort in 7/12, and abnormal body odour in 3/12 subjects.

8.2. Patient exposure

Table 39: Exposure in clinical trials studying the use of sodium phenylbutyrate in the treatment of UCDs

Study	Condition	Sodium phenylbutyrate dose	Number of patients	Study Duration
Cohort of temporar utilization authorizat (ATUc)	15 OTC 5 ASS 2 CPS 1 ASL 1 HHH 1LPI	5.2g/d (SD)	N=25 (16F; 8M; 1 N/A) Age ranges: 2-6yrs: N=12 7-17yrs: N=8 18-64yrs: N=5	Mean exposure 15.0 years
Maestri (1995) Protocol IIb	24 ASD	250mg/kg/day	N=9 Neonates-infants (NOS)	Average treatment duration: 1.2 years

Study	Condition	Sodium phenylbutyrate dose	Number of patients	Study Duration
Maestri (1995) Protocol IIIb		450-600 mg/kg/day	N=19 Neonates-infants (NOS)	Average treatment duration: 3.9 yrs
Maestri (1996) Protocol II	32 OTC	250-300 mg/kg/day	N= 22* All F Age range: 1-17 yrs	Treatment: 81 patient-years
Maestri (1996) Protocol III		450-600 mg/kg/day	N=28 All F Age range: 1-17 yrs	Treatment: 165 patient-years
Lee (2010)	8 OTC 1 ASS 1 HHH	191 mg/kg/day = 7.54 g/m^2	N=10 (4M; 6F) Age range: 21-73 yrs 38.2 (SD)	7-day open label, fixed sequence, sodium phenylbutyrate to GBP switchover. sodium phenylbutyrate average treatment duration :9.04 yrs (SD)
Lichter-Konecki (2011)	9 OTC 1 ASS deficiency 1 ASL deficiency	12.4 g/d (SD) (=322mg/kg/d or 10.2g/m^2)	N=11 (10F; 1M) Age: 10.2 (SD) Age range: 6-17 yrs	7-day open label, fixed sequence, sodium phenylbutyrate to GPB switchover (sodium phenylbutyrate average treatment duration: 74.68 mths (SD)
Diaz (2013)	40 OTC CPS1 ASS1	12.33g/d (SD)	N= 45 (14M; 31F) Age: 32 (SD)	14-day (sodium phenylbutyrate and GBP) randomized, double blind, double dummy crossover. sodium phenylbutyrate average treatment duration: 128.57mths(SD)
Smith (2013)	6 ASL 2 ASS 2 OTC	5.27g/d (SD)	N=15 (8M;7F) Age ranges: 2mths-5yrs; (29d-< 2yrs: N=4 2-<6 yrs N=11)	Open label, fixed sequence, sodium phenylbutyrate to GPB switchover ≤ 7 days. sodium phenylbutyrate average treatment duration: 19.3mths (SD)

*Use of NaPA or NaPB; unspecified number of each. Switch from phenylacetate to phenylbutyrate occurred when sodium phenylbutyrate was introduced in 1985

8.3. Adverse events

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

The dossier in its current form does not allow for systematic analysis of all adverse events experienced by patients enrolled in all studies.

- *The sponsor should supply a complete summary of all of the Adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs.*

8.3.2. Treatment related adverse events (adverse drug reactions)

There is no overall summary of the treatment related adverse events.

The sponsor advises that most safety data of sodium phenylbutyrate in the treatment of UCD have been acquired from the case reports prepared by the investigators participating in the IND protocol covering 183 patients (EMEA 2005). The sponsor acknowledges that, since patients were not monitored under controlled conditions and were not provided a diary for recording AE, the reporting of these AE was not consistently documented.

The sponsor stated that Wiech 1997 found that menstrual disturbance was the most common AE (23%). Other problems included anorexia, biochemical abnormalities (acidosis, alkalosis, hypoalbuminemia, hyperphosphatemia, hypophosphatemia). The evaluator was not supplied with this paper (*Wiech NL, Clissold DM, MacArthur RB (1997) Safety and efficacy of buphenyl (sodium phenylbutyrate) tablets and powder (Abstract). Advances in Inherited Urea Cycle Disorders, Satellite to the 7th International Congress for Inborn Errors of Metabolism, Vie*nna).

There are data on higher doses of sodium phenylbutyrate in oncology patients resulting in dose-limiting neurotoxicity. This is documented above under *Safety, Other studies*.

- *The sponsor should tabulate all adverse events attributable to sodium phenylbutyrate. This should include exposure data including dose, dose by size (weight and/or surface area) and length of treatment.*

8.3.3. Deaths and other serious adverse events

No deaths due to sodium phenylbutyrate were identified in the dossier.

8.3.4. Discontinuations due to adverse events

Discontinuations due to adverse events were not clearly documented

- *The sponsor should tabulate all discontinuations due to adverse events attributable to sodium phenylbutyrate.*

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity

There are no data on the use of sodium phenylbutyrate in liver dysfunction. However, there are data to suggest that patients with cirrhosis have reduced capacity of the metabolic pathway of phenylacetate (see Pharmacokinetics section above).

8.4.2. Renal function and renal toxicity

There are no systematic data presented on the risk of renal toxicity. The sponsor identified two cases of Fanconi syndrome with no further details supplied.

8.4.3. Other clinical chemistry

No clinically significant abnormalities in laboratory tests were identified in the dossier.

8.4.4. Haematology and haematological toxicity

No significant haematological toxicities were identified in the dossier.

8.4.5. Other laboratory tests

No clinically significant abnormalities in laboratory tests were identified in the dossier.

8.4.6. Electrocardiograph findings and cardiovascular safety

No significant ECG abnormalities were identified in the dossier. The only potential cardiovascular risk related to the sodium load and fluid retention in patients with heart failure.

8.4.7. Immunogenicity and immunological events

Serious immunological events were not identified in the dossier.

8.4.8. Serious skin reactions

Serious skin reactions were not identified in the dossier.

8.5. Other safety issues

8.5.1. Safety in special populations

The dossier does not identify specific safety issues in children or in the elderly.

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

The dossier does not identify any specific safety issues related to drug-drug interactions. However, drug-drug interactions were not directly investigated. The issue of the use of liver inducing and inhibiting anticonvulsants was raised in Phuphanich 2005 (in the treatment of recurrent malignant gliomas) in terms of pharmacokinetics. The implications of this for safety are unclear.

8.6. Post marketing experience

8.6.1. FDA Label

The dossier included the following extract from the FDA's approved drug information (label) for sodium phenylbutyrate (Buphenyl; FDA, 2009).

> **ADVERSE REACTIONS**
>
> The assessment of clinical adverse events came from 206 patients treated with sodium phenylbutyrate. Adverse events (both clinical and laboratory) were not collected systematically in these patients, but were obtained from patient-visit reports by the 65 coinvestigators. Causality of adverse effects is sometimes difficult to determine in this patient population because they may result from the underlying disease, the patient's restricted diet, intercurrent illness, or sodium phenylbutyrate. Furthermore, the rates may be underestimated because they were reported primarily by the parent or guardian and not the patient.
>
> **CLINICAL ADVERSE EVENTS**
>
> In female patients, the most common clinical adverse event reported was amenorrhea/menstrual dysfunction, which occurred in 23% of the menstruating patients.
>
> Decreased appetite occurred in 4% of all patients. Body odour (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of patients.

Other adverse events reported in 2% or fewer patients were:

Gastrointestinal: abdominal pain, gastritis, nausea and vomiting; constipation, rectal bleeding, peptic ulcer disease, and pancreatitis each occurred in one patient.

Hematologic: aplastic anaemia and ecchymosis each occurred in one patient.

Cardiovascular: arrhythmia and oedema each occurred in one patient.

Renal: renal tubular acidosis

Psychiatric: depression

Skin: rash

Miscellaneous: headache, syncope, and weight gain

Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 250–300 mg/kg/day for 14 days, repeated at 4-week intervals. Manifestations were predominately somnolence, fatigue, and light-headedness; with less frequent headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of a pre-existing neuropathy. These adverse events were mainly mild in severity. The acute onset and reversibility when the phenylacetate infusion was discontinued suggest a drug effect.

8.6.2. First EU Periodic benefit-risk evaluation report (PBRER)

This report included safety information collected for the medicinal product Pheburane (sodium phenylbutyrate) covering the reporting period from date of authorisation 31 July 2013 to 31 December 2015. The report also included the French Compassionate Use Project (CUP) which was approved by the French Regulatory Agency in Sep 2012.

During the period under review, no actions have been taken or proposed by Lucane, or any Competent Authority for safety reasons.

The report stated that Pheburane is authorised in 34 countries: all the EU countries + Norway + Iceland, Canada, Israel, South Korea, New-Zealand. Pheburane is marketed in 17 countries: France, United Kingdom, Spain, Germany, Netherlands, Belgium, Italy, Portugal, Greece, Sweden, Finland, Czech Republic, Canada, South Korea, and distributed via compassionate use in Colombia and Turkey.

8.6.2.1. Exposure

The French Compassionate Use Project enrolled 25 patients as summarised below (Table 40).

Table 40: French Compassionate Use Project enrolment (PBRER)

Age group	No of Persons
<20 years	21
21-30 y	2
31 – 40 y	1
>41 y	1

In the PBRER, the total exposure estimate is based upon supplied bottles of Pheburane.

In Europe this calculated at 71,039 daily doses (5.2 g/day) (Table 41).

The Outside of European exposure is a total of 36,640 daily doses (5.2 g/day) and 10,947 daily doses (12 g/day) (Table 42).

There were also 8 cases of off-label use in a range of other metabolic disorders; however, the sponsor states that no adverse events or any particular patterns of use have come to their attention which is considered relevant for the interpretation of safety data.

8.6.2.2. Clinical trials

The PBRER reported that a single centre ([information redacted], France), pilot, open label, comparative, randomised, uncontrolled trial was initiated on Feb 2015 for 30 patients (2 groups of 15 patients) and was completed in September 2015. No SAE were observed during the trial. Two patients out of 13 at dose 15g/day who had to decrease to 7.5g/d for granularity issue with the product. The 13 (and 2 =15) patients at 7.5g/d had no TEAEs reported.

8.6.2.3. New literature

The following papers were identified in an updated literature search

- *Burrage. L.C, Jain.M, Gandolfo.L, Lee. B.H, Members of the Urea Cycle Disorders Consortium, and Nagamani.S.C.S. Sodium Phenylbutyrate Decreases Plasma Branched-Chain Amino Acids in Patients with Urea Cycle Disorders. Mol Genet Metab. 113(0): 131–135. 2014*
- *Ucar.S.K , Kose.M, Altinok.Y.K, Canda.E, Kagnic.M, Duyu.M et.al. A MSUD Case: Sodium phenylbutyrate treatment during attack period. Springer. Page 239*
- *Shneider.B.L, and Vockley.J. Possible Phenylacetate Hepatotoxicity during 4-Phenylbutyrate Therapy of Byler Disease. J Pediatr Gastroenterol Nutr. Page 1-16. 2015.*

This case was described as a case of hepatotoxicity received for sodium phenylbutyrate in an expanded access programme using a non-Marketing Authorisation Holder (MAH) marketed drug and the summary of the case is reproduced below.

> The case involved a 4-year-old boy diagnosed with Byler Disease (progressive familial intrahepatic cholestasis (PFIC)). The patient was started on Rifampin (rifampicin) on an unknown date. Liver biopsy at 44 months of age revealed Stage II/III fibrosis. Due to this (and following rejection of surgical intervention), Buphenyl (sodium phenylbutyrate) was prescribed at approximately 4 years and 6 months of age in a single patient expanded access compassionate (EAC) use. Buphenyl was discontinued after 6 months due to vomiting (due to poor palatability), although the patient was reported to have benefited from treatment. Following this, the patient was switched to an alternative EAC programme and administered glycerol phenylbutyrate. After 7 months on glycerol phenylbutyrate, Rifampin was discontinued to further assess the clinical response to glycerol phenylbutyrate. Thirty-five days after discontinuation of Rifampin, the patient was found to have significant hepatopathy and was admitted for supportive care. 24 hours after his last dose of glycerol phenylbutyrate, serum phenyl acetate was 719 µM, while serum 4-phenylbutyrate was undetectable. Hepatitis screening done was negative (Hep E testing not performed). Over 2 weeks, liver disease returned to baseline. His jaundice worsened (total bilirubin 7.1 mg/dL) and his pruritus returned approximately 40 days after discontinuation of glycerol phenylbutyrate. Rifampin was restarted and his pruritus resolved. Liver biochemistries returned to baseline. At follow up, the child had no pruritus, had no features of advancing liver disease. The authors theorised that discontinuation of Rifampin therapy led to a reduction in CYP3A4 activity and a commensurate reduction in phenylacetate metabolism thereby leading to the toxic accumulation of phenylacetate.
>
> There have been no other literature articles reporting the occurrence of hepatic toxicity following the use of sodium/glycerol phenylbutyrate.

The original articles were not supplied by the sponsor.

8.6.2.4. Signal and risk evaluation

The PBRER stated that no signals have been identified in the reporting period for Pheburane. In terms of a Risk Management Plan, The PBRER stated the following.

> There is no RMP in Europe for Pheburane. A Risk Management Plan (RMP) for Pheburane was submitted by Médunik to Health Canada. At the time of the MA, a number of minor deficiencies were identified. Overall, the RMP was considered to be acceptable. An updated version of the RMP was resubmitted in January 2016 and the review by Health Canada is on-going. The safety concerns summarised below are the risks consistent with the first version of the Canadian RMP which is the only one reviewed by their Authorities (Table 41).

Table 41: Summaries of Safety Concerns (PBRER)

Safety concerns	
Important identified risks	Risk of metabolic acidosis Risk of blood dyscrasias Risk of clinical lab abnormalities (changes in blood proteins, electrolytes, enzymes and hepatic enzymes) Risk of neurotoxicity
Important potential risks	Risk of medications errors Risk of drug interactions (probenecid, haloperidol, valproate, corticosteroids) Hyperbilirubinemia in neonates
Missing information	Use in patients with hepatic insufficiency Use in patients with renal insufficiency Use in patients with congestive heart failure/conditions of sodium retention with oedema Use in patients with DM/patients with sugar intolerance or malabsorption or sugar enzyme insufficiency Use in pregnancy Use during breastfeeding Use in elderly patients Off-label use

8.7. Evaluator's overall conclusions on clinical safety

The dossier presents limited data on the safety of Pheburane in the treatment of patients with UCDs. Of the data presented, the first EU Periodic benefit-risk evaluation report is the most useful and highlights some potentially important signals including hepatotoxicity, blood dyscrasias and neurotoxicity.

- *The sponsor should address the following questions:*
  - *The sponsor should supply a complete summary of all of the Adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs.*
  - *The sponsor should tabulate all adverse events attributable to sodium phenylbutyrate. This should include exposure data including dose, dose by size (weight and/or surface area) and length of treatment.*
  - *The sponsor should tabulate all discontinuations due to adverse events attributable to sodium phenylbutyrate.*
  - *The sponsor should submit a report on the single centre (Necker Hospital, France) pilot study of Pheburane, performed on 30 patients which was completed in Sep 2015*

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Urea Cycle Defects (UCDs) are a collection of rare and potentially life-threatening metabolic disorders with a raised ammonia as a common pathway in the disease process. *Pheburane offers a palatable form of sodium phenylbutyrate treatment as an alternative nitrogen excretor. It should be noted that phenylbutyrate is a standard component of the current protocols for treating UCDs*	*The strength of the application is the fact there is not a formulation of phenylbutyrate registered for use in Australia. Of the available formulations, Pheburane appears to offer significant advantages over other formulations of sodium phenylbutyrate but appears to be bioequivalent.* *There is significant uncertainty about both the actual efficacy and safety that Pheburane offers. Because the innovator product is not marketed in Australia, the regulatory authority (TGA) does not have access to the full original dossier on which sodium phenylbutyrate was approved in other countries. Because of this, the evaluation is based upon incomplete literature based data on which to assess both the efficacy and safety.*

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
The main risks are related to the lack of data and the poor quality of the available data as it is presented. Specifically, efficacy cannot be assured and the safety data are incomplete. There is also uncertainty around dosing as no dose efficacy data are available in the treatment of UCDs. However, data are available in other disease states (mostly cancer) identifying dose-limiting toxicity.	*The available data is presented in a suboptimal format to clarify the risks around efficacy and safety. A re-analysis of the available literature in tabular form may clarify the efficacy and safety data. This is important as it is unlikely that any further data from the literature will be forthcoming to change the risk assessment.* *Reassuringly, the first European PBRER stated that no signals have been identified in the reporting period for Pheburane.*

9.3. First round assessment of benefit-risk balance

Pheburane (sodium phenylbutyrate) is a novel treatment for the hyperammonaemia associated with urea cycle defects (UCDs) which are collection of rare and severe inborn errors of metabolism. There are no similar treatments registered for use in patients with UCDs in Australia and the registration of Pheburane would be a significant therapeutic advance for Australian patients. However, the dossier is based upon a single bioequivalence study comparing Pheburane to Ammonaps (the innovator product overseas but not registered in Australia). The sponsor has supplemented their application with literature about sodium phenylbutyrate, but this literature lacks the level of pharmacokinetic, efficacy and safety data which are usual in an application of this type. There are also significant deficiencies in the

analysis and presentation of the available data. If the deficiencies in the submission can be addressed, the benefit-risk balance would favour registration of Pheburane with careful post-approval surveillance for adverse events.

10. First round recommendation regarding authorisation

The evaluator does not currently recommend authorisation of Pheburane until the deficiencies in the data are addressed. However, with clarification of the questions about pharmacokinetics, efficacy and safety adequately addressed authorisation could be recommended.

11. Clinical questions

11.1. Pharmacokinetics

2. The sponsor should provide a separate commentary about the use of sodium phenylbutyrate in children.
3. The sponsor should clarify the proposed dosing schedule and linearity of Pheburane.
4. The sponsor should clarify that the form of sodium phenylbutyrate was the innovator product (Ammonaps) from the bioequivalence study.
5. The sponsor should demonstrate that the dosing of Pheburane can be scaled by weight and surface area as in the proposed dosing schedule.
6. The sponsor should explain the dose-ranging in the proposed dosing schedule.

11.2. Pharmacodynamics

7. The sponsor should reinvestigate the literature for further evidence of a dose response effect on nitrogen excretion with sodium phenylbutyrate.

11.3. Efficacy

8. The sponsor should better quantify the outcomes of treatment with sodium phenylbutyrate compared to historical controls in terms of:
   - Ammonia levels
   - Nitrogen excretion
   - Hyperammonaemic episodes
   - Neurodevelopmental outcomes

11.4. Safety

9. The sponsor should supply a complete summary of all of the adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs.
10. The sponsor should tabulate all adverse events attributable to sodium phenylbutyrate. This should include exposure data including dose, dose by size (weight and/or surface area) and length of treatment.
11. The sponsor should tabulate all discontinuations due to adverse events attributable to sodium phenylbutyrate.

12. The sponsor should submit a report on the single centre (Necker Hospital, France) pilot study of Pheburane, performed on 30 patients which was completed in Sep 2015

12. Second round evaluation

12.1. Clinical questions

12.1.1. Pharmacokinetics

13. The sponsor should provide a separate commentary about the use of sodium phenylbutyrate in children.

12.1.1.1. Sponsor Response

The sponsor stated the following:

> No formal pharmacokinetic studies were conducted in children with urea cycle disorders in order to support the use of sodium phenylbutyrate. However, data are available from bioequivalence studies in healthy volunteers (including Study LUC-1001), as well as pilot Phase I studies in patients with cancer or haemoglobinopathies (Gilbert 2001).
>
> A study by Berry was included in this submission for evaluation of pharmacokinetic parameters of sodium phenylbutyrate and of the glycerol conjugated form of the active. The study is a pooled analysis of two papers by Lichter-Konecki 2011 and Smith 2013 on paediatric patients aged between 2 months and 17 years of age. A total of 26 UCD patients aged 2 months to 17 years were treated with GPB and NaPB in the two short-term (7 or 10 day), open-label crossover studies, which compared 24-hour ammonia exposure (AUC_{0-24}) and glutamine levels during equivalent steady-state dosing of GPB and NaPB.
>
> Mean ammonia exposure on GPB was non-inferior to NaPB in each of the individual crossover studies. In the pooled analyses, it was significantly lower on GPB versus NaPB (mean [SD] AUC_{0-24}: 627 [302] versus 872 [516] µmol/L; p=0.008). Mean ammonia levels remained within the normal range during 12 months of GPB dosing and, when compared with the 12 months preceding enrolment, these lower ammonia levels likely reflect the slower absorption of phenylbutyric acid (PBA) when given orally as GPB compared with NaPB, which may be due to the fact GPB requires digestion by pancreatic lipases.
>
> The data presented for the NaPB phase of the cross-over studies supports the efficacy data available from earlier published reports including in paediatric patients.
>
> Kibleur (2016) published a follow up study on 11 patients from the compassionate use in France, all patients were paediatric patients. The data supports the continued/persistent/maintained protective effect of Pheburane against metabolic decompensation due to biochemical control. There was a further significant reduction in plasma ammonia levels, in addition to a decrease in plasma glutamine levels and improved neurodegenerative statuses.
>
> The above studies support the use of sodium phenylbutyrate in children. The product has been available for use in paediatric population since its development in the 1990s.

12.1.1.2. Evaluator's assessment

The sponsor's response is adequate in that it summarises the available paediatric data. There are limited efficacy and safety data in children and no specific pharmacokinetic data in the target population. The sponsor does identify pilot Phase I studies in patients with cancer and

haemoglobinopathies offering some extra but limited support for the use of sodium phenylbutyrate in children. The response is satisfactory.

12.1.2. Pharmacokinetics

14. The sponsor should clarify the proposed dosing schedule and linearity of Pheburane.

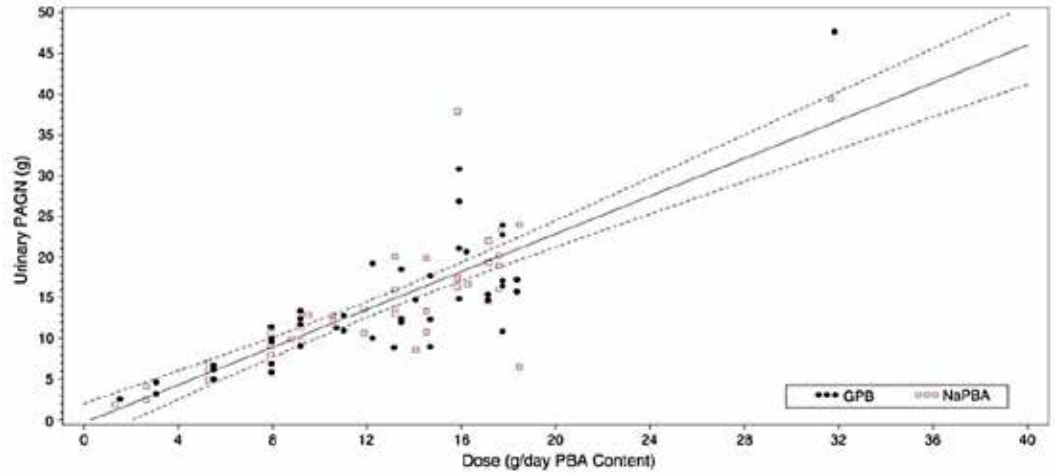
12.1.2.1. Sponsor response

The proposed dosing schedule of Pheburane lists the amount of sodium phenylbutyrate required rather than the actual amount of granules. A device is supplied with the medicinal product that enables the measurement of 0.5 g up to 3 g of the active substance. The device is called a 'spoonbox'; classically used for dispensing paediatric medicines. Hence, the 'spoonbox' provided within each pack is calibrated to measure out the volume of active rather than the volume of Pheburane granules.

For example, if the dosage calculated for an individual patient is 2500 mg of sodium phenylbutyrate then the granules are poured into the equivalent mark on the calibrated spoon provided to provide 2.5g of the active.

In terms of linearity of Pheburane, Mokhtarani (2012) analysed pharmacokinetic data for glycerol phenylbutyrate (and sodium phenylbutyrate) with respect to possible dosing biomarkers in patients with urea cycle disorders. These analyses are based on over 3000 urine and plasma data points from 54 adult and 11 pediatric UCD patients (ages 6-17) who participated in three clinical studies comparing ammonia control and pharmacokinetics during steady state treatment with glycerol phenylbutyrate or sodium phenylbutyrate. All patients received phenylbutyric acid equivalent doses of glycerol phenylbutyrate or sodium phenylbutyrate in a cross over fashion and underwent 24-hour blood samples and urine sampling for phenylbutyric acid, phenylacetic acid and phenylacetylglutamine. Patients received phenylbutyric acid equivalent doses of glycerol phenylbutyrate ranging from 1.5 to 31.8 g/day and of sodium phenylbutyrate ranging from 1.3 to 31.7 g/day. Plasma metabolite levels varied widely, with average fluctuation indices ranging from 1979% to 5690% for phenylbutyric acid, 843% to 3931% for phenylacetic acid, and 881% to 1434% for phenylacetylglutamine. Mean percent recovery of phenylbutyric acid as urinary phenylacetylglutamine was 66.4 and 69.0 for pediatric patients and 68.7 and 71.4 for adult patients on glycerol phenylbutyrate and sodium phenylbutyrate, respectively. The correlation with dose was strongest for urinary phenylacetylglutamine excretion, either as morning spot urine ($r = 0.730$, $p < 0.001$) or as total 24-hour excretion ($r = 0.791$ $p<0.001$), followed by plasma phenylacetylglutamine $AUC_{(24\text{-hour})}$, plasma phenylacetic acid $AUC_{(24\text{-hour})}$ and phenylbutyric acid $AUC_{(24\text{-hour})}$. Plasma phenylacetic acid levels in adult and pediatric patients did not show a consistent relationship with either urinary phenylacetylglutamine or ammonia control. Figure 28 below shows the linear relationship.

Figure 28: Urinary phenylacetylglutamine excretion versus total dose of glycerol phenyl- butyrate or sodium phenylbutyrate administered (Mokhtarani et al, 2012).



12.1.2.2. Evaluator's assessment

The sponsor did not address the pharmacokinetic basis for the proposed dosing schedule and this is a deficiency in their response. The sponsor should readdress this question. Their answer relates to a separate question about the administration of the dose using their 'spoonbox'.

The answer to evidence of dose linearity indicates that there is no blood or serum pharmacokinetic data to support dose linearity. There is urinary excretion data which does demonstrate a relationship between the dose of sodium phenylbutyrate and the urinary excretion of phenylacetylglutamine. However, it is unclear whether this relationship is linear and furthermore, the sponsor identifies that there is not a consistent relationship between serum concentrations of phenylacetic acid and its urinary excretion. In summary, the lack of data supporting a linear relationship between Pheburane dosing and serum concentrations of phenylacetic acid is a deficiency.

15. The sponsor should clarify that the form of sodium phenylbutyrate was the innovator product (Ammonaps) from the bioequivalence study.

12.1.2.3. Sponsor response

The form of sodium phenylbutyrate used in the trials (papers) presented as pharmacokinetic studies including the bioequivalence study used to bridge Pheburane's application to that of Ammonaps in Europe is Buphenyl. Buphenyl is same product as Ammonaps developed and manufactured by the same company but is marketed under different names in the USA and in the EU. It is clearly stated in the EPAR of Ammonaps that the data from the previous Buphenyl studies were used in support of its marketing approval as Buphenyl were representing the very same product with a different name for administrative considerations.

12.1.2.4. Evaluator's assessment

The sponsor has clarified that the innovator product (Ammonaps) was used in the bioequivalence study, albeit under a different brand name. The response is satisfactory.

16. The sponsor should demonstrate that the dosing of Pheburane can be scaled by weight and surface area as in the proposed dosing schedule.

12.1.2.5. Sponsor response

Regular monitoring of protein intake, growth and clinical status are essential, because protein requirements and tolerance vary with age, growth velocity, disorder nature and

severity and frequency of intercurrent illnesses (Häberle 2012). The appropriate dose of NaPB will be a function of dietary nitrogen and nitrogen retention (Brusilow 1991, 2.5 Clinical Overview, page 18).

Therefore, the therapy with Pheburane should be individualized according to the bodyweight and the metabolic state of the patient. The proposed daily dosage was derived on the basis that one mole of phenylbutyrate will be metabolized to one mole of phenylacetylglutamine, and from the estimated nitrogen to be excreted on a restricted protein intake. On a molar basis phenylacetylglutamine is comparable to urea (each containing two nitrogen atoms) and provides therefore an alternate vehicle for waste nitrogen disposal in patients with UCD. Children (6-24 months of age) receiving a diet of 0.2 g/kg/day of nitrogen (1.25 g/kg/day of protein) have been shown to excrete 0.094 g/kg/day of urea nitrogen, accounting for 47% of dietary nitrogen (Waterlow 1963). Children or adults receiving a low but adequate protein intake excrete 40-45 % of their dietary nitrogen as urea nitrogen. Therefore, a child receiving 1.25 g/kg/day of protein has the obligatory requirement to synthesize 93 mg/kg/day of waste nitrogen as urea. This requirement can be met by patients with the neonatal form of CPS-I and OTC deficiencies if they receive 600 mg/kg/day of sodium phenylbutyrate, which if completely conjugated with glutamine will lead to the excretion of 90 mg/kg/day of phenylacetylglutamine nitrogen.

These theoretical considerations were confirmed in an 8-year-old boy (of 27.2 kg body weight) with neonatal CPS-I (Brusilow 1991). When receiving 12 or 14 g/d of phenylbutyrate, 80-90 % of the dose appeared in the urine as phenylacetylglutamine, and phenylacetylglutamine nitrogen accounted for 42-44 % of dietary nitrogen.

12.1.2.6. Evaluator's assessment

The sponsor argued that the basis for dosing was mostly based upon theoretical grounds. No data was offered to support dosing on surface area calculations was to be preferred to dosing on a weight basis. The evaluator recognises that current guidelines for the use of sodium phenylbutyrate do include dosing recommendations on both a weight and surface area calculations. The lack of pharmacokinetic data in support of the proposed dosing regimen is a deficiency. The response is not satisfactory and the sponsor should conduct further pharmacokinetic studies justifying the dosing regimen. These could be conducted post-marketing.

17. The sponsor should explain the dose-ranging in the proposed dosing schedule.

12.1.2.7. Sponsor response

The sponsor did not address this question of the dosing range specifically.

12.1.2.8. Evaluator's assessment

The sponsor should be asked to address the basis of the dosing range proposed in the product information. The response is not satisfactory.

12.1.3. Pharmacodynamics

18. The sponsor should reinvestigate the literature for further evidence of a dose response effect on nitrogen excretion with sodium phenylbutyrate.

12.1.3.1. Sponsor response

The sponsor identified one further article not supplied in the original dossier (*Marini JC, Lanpher BC, Scaglia F, O'Brien WE, Sun Q, Garlick PJ, Jahoor F, Lee B. Phenylbutyrate improves nitrogen disposal via an alternative pathway without eliciting an increase in protein breakdown and catabolism in control and ornithine transcarbamylase-deficient patients. Am J Clin Nutr. 2011 Jun;93(6):1248-54.*).

This article investigated the effects of sodium phenylbutyrate administration on whole-body protein metabolism, glutamine, leucine, and urea kinetics in healthy and ornithine transcarbamylase–deficient (OTCD) subjects. Seven healthy control and 7 partial-OTCD subjects received either phenylbutyrate or no treatment in a crossover design. In addition, the partial-OTCD and 3 null-OTCD subjects received phenylbutyrate and phenylbutyrate plus BCAA supplementation. A multi-tracer protocol was used to determine the whole-body fluxes of urea and amino acids of interest. The study demonstrated that phenylbutyrate administration reduced ureagenesis and the transfer of 15N from glutamine to urea without parallel reductions in glutamine flux and concentration. There were no changes in total-body protein breakdown and amino acid catabolism.

12.1.3.2. Evaluator's assessment

The sponsor has identified one additional article in support of sodium phenylbutyrate in the treatment of ornithine transcarbamylase deficiency, demonstrating a reduction in ureagenesis. The dosing used in this study was 10 g phenylbutyrate /m^2/day.

12.1.4. Efficacy

19. The sponsor should better quantify the outcomes of treatment with sodium phenylbutyrate compared to historical controls in terms of:

- ***Ammonia levels***
- ***Nitrogen excretion***
- ***Hyperammonaemic episodes***
- ***Neurodevelopmental outcomes***

12.1.4.1. Sponsor response

During the evaluation of Ammonaps (reference product in the EU) it was noted that a coherent overview of efficacy was hindered by the heterogeneity of UCD patients, with different age of onset and the possible effect of prior treatment. The first treatment program (1985-1994) consisted of 162 patients, of which 148 were evaluable (87 with prior therapy and 61 without prior therapy). The following UCD had been diagnosed: OTC 99 patients, ASS 31 patients and CPS 18 patients. Of this population, 55% of patients were less than twelve years old at the time of the last visit to the investigator and 15% had received phenylbutyrate for five years or more. In a subsequent amendment, the overall population included 208 patients, out of which 183 were evaluable (EMEA 2005).

The following sections present the efficacy criteria in support of sodium phenylbutyrate:

§ incidence of hyperammonemic episodes,

§ cognitive development,

§ growth (anthropometric measurements),

§ plasma ammonia and glutamine levels

Hyperammonemic episodes

Any condition causing an increased nitrogen load to the urea cycle may trigger hyperammonemia. In 128 patients treated for 5 to 15 years (Maestri 1991, Maestri 1995, Maestri 1996, Feillet 1998), the annual incidence of hyperammonemic episodes ranged from 0.4/patient-year in the female OTC group treated with 250 mg/kg/day sodium benzoate and 250-300 mg/kg/day sodium phenylacetate or sodium

phenylbutyrate to 1.4/patient-year in the ASS treated in the earliest protocol (1980) with 250 mg/kg/day sodium benzoate alone.

In OTC (Maestri 1996), patients receiving sodium phenylacetate or sodium phenylbutyrate had a lower frequency of hyperammonemic episodes than those receiving sodium benzoate alone. The transfer to therapy with sodium phenylbutyrate instead of sodium phenylacetate was also associated with a decreased frequency of hyperammonemic episodes.

The same finding had been observed in ASS deficient patients (Maestri 1995) where on average the 15 surviving patients had one episode/year (range 2-30).

A retrospective study performed in 9 OTC patients (age at diagnosis ranging from 6 days to 14 years) to evaluate the efficacy of sodium phenylbutyrate in long-term treatment has been conducted. They had previously been treated with sodium benzoate and low protein diet and were switched to sodium phenylbutyrate at 8.9 and 4.9 years of age (median) in males and females, respectively. Clinical and biochemical data were analysed and the median follow-up duration was 26 months. During that time, there were no hyperammonemic episodes requiring hospitalization (Burlina 2001).

Cognitive development

Both acute and chronic hyperammonaemia result in alterations of the neurotransmitter system. These changes probably contribute to seizures, deterioration of intellectual function, decreased consciousness, and coma (Llansola 2007, Monfort 2009). Early identification and treatment of intercurrent hyperammonemic episodes is essential, both because treatment is more effective at lower ammonia levels and because neurologic outcome appears to be a function of duration of severe hyperammonemia and coma. In a study of 26 children with inborn errors of urea synthesis, 19/24 (79%) of the children surviving the first year had one or more developmental disabilities (Table 42).

Table 42: Neurological long-term outcome in UCD

Deficient enzyme	N of patients	Age (months)	Duration of coma (days)	IQ at 12 months	Developmental disabilities (%)*
CPS-I	3	19±5	12±9	58±24	100
OTC	5	21±4	3±1	70±18	40
ASS	8	30±4	5±1	44±10	88
ASL	8	41±7	3±1	50±7	88
Total	24	31±3	5±1	53±6	79

*Normal function (21%), cerebral palsy (46%), mental retardation (79%), seizure disorder (17%), blindness (4%), microcephaly (54%), multiple handicaps (46%)

In prospective treatment (Maestri 1991), children who appeared to be developing normally were evaluated less frequently than children with evident developmental delay. Nine patients out of 12 presented some developmental delay and almost all had problems with language.

Among the 15/24 surviving ASS patients (Maestri 1995), 12 had neonatal ammonium levels ranging from 400 to 2000 µmol/L and were in stage 3-4 coma. Eleven of those had an IQ<55 at age 8 years, 1 had an IQ=80 at 3.5 years and an IQ=55 at age 8 years. Three patients had neonatal ammonium levels ranging from 266 to 396 µmol/L and 2 had an IQ of 75-100 at 1st evaluation which then decreased to 50-70 as seen in the 3rd patient.

In Maestri 1996, 23 girls with OTC had at least two IQ tests. Results ranged at baseline from 56 to 111 (mean 84) and 10 girls had an IQ test <80. At follow-up, scores ranged from 36 to 116 and were positively correlated to respective baseline IQ ($p<0.001$). Only 4 children showed a decrease in IQ of more than 15 points (that is, of 1SD). The change in IQ was not affected by the number of years of treatment.

In 28 late-onset OTC (23 females, 5 males) 12 (among whom 5 treated prospectively with waste nitrogen excretion stimulation) were presenting a normal IQ (>85) and 16 were handicapped (Feillet 1998).

Nitrogen excretion

The submitted dossier included a number of papers supporting the safety and efficacy of sodium phenylbutyrate. Although some papers were provided for pharmacokinetic or safety evaluation, these papers could be evaluated for pharmacodynamics.

Marini (2011) investigated the effects of phenylbutyrate administration on whole-body protein metabolism, glutamine, leucine, and urea kinetics in healthy and ornithine transcarbamylase– deficient (OTCD) subjects. Phenylbutyrate administration reduced ureagenesis by ≈15% and the transfer of 15N from glutamine to urea was reduced by 35%.

Mokhtarani (2012) analysed pharmacokinetic data for glycerol phenylbutyrate (and sodium phenylbutyrate with respect to possible dosing biomarkers in patients with urea cycle disorders. Patients received phenylbutyric acid equivalent doses of glycerol phenylbutyrate ranging from 1.5 to 31.8 g/day and of sodium phenylbutyrate ranging from 1.3 to 31.7 g/day. Plasma metabolite levels varied widely, with average fluctuation indices ranging from 1979% to 5690% for phenylbutyric acid, 843% to 3931% for phenylacetic acid, and 881% to 1434% for phenylacetylglutamine. Mean percent recovery of phenylbutyric acid as urinary phenylacetylglutamine was 66.4 and 69.0 for pediatric patients and 68.7 and 71.4 for adult patients on glycerol phenylbutyrate and sodium phenylbutyrate, respectively. The correlation with dose was strongest for urinary phenylacetylglutamine excretion, either as morning spot urine ($r = 0.730$, $p < 0.001$) or as total 24-hour excretion ($r = 0.791$ $p<0.001$), followed by plasma phenylacetylglutamine $AUC_{(24\text{-hour})}$, plasma phenylacetic acid $AUC_{(24\text{-hour})}$ and phenylbutyric acid $AUC_{(24\text{-hour})}$.

McGuire 2010 reported a higher urinary excretion of PAGN following NaPBA (PAGN (0-24hours) amount excreted was 7,905) than following GPB (PAGN (0-24hours) amount excreted was 4130 and 4749.9) in patients on a dose of 3 g/m^2 equivalent in a The author concludes that assuming that dietary protein is ≈16% nitrogen by weight, that approximately 47% of dietary nitrogen is excreted as waste nitrogen.

Plasma ammonia and glutamine levels

Ammonia values, excluding those obtained during hospitalization for a hyperammonaemic episode, have been reported in 85 patients (281 measurements). 172/281 values (61 %) were within the normal range for the laboratory. A total of 45 patients (53 %) had at least one measurement exceeding the upper limit of normal and 6 % of the values were two-fold higher than the upper limit of normal.

Glutamine synthesis mediated by the astrocyte enzyme glutamine synthetase is the major pathway for ammonia detoxification in the brain and cerebrospinal fluid. For

therapeutic monitoring, plasma glutamine levels should be maintained under 1000 µmol/L. Higher levels will indicate that dietary or drug therapy requires modifications, such as increased dose of phenylbutyrate, increased calorie intake, or reduction of total nitrogen intake.

Plasma glutamine concentration has been shown to correlate with plasma ammonia concentration and it has been suggested that glutamine may represent a storage site for nitrogen accumulation (Maestri 1992). The mean ammonium level was normal for glutamine levels below 800 µmol/L. The mean (SD) ammonium level was 55 (36.3) µmol/L for plasma glutamine above 1000 µmol/L, with 86% of high ammonium levels (>30 µmol/L), thereby indicating approximately the threshold of glutamine above which ammonium accumulates.

In ASS patients (Maestri 1995) the current level of glutamine in surviving patients was 688 (246) µmol/L and 95% of plasma glutamine values were <1080 µmol/L, a level unlikely to be accompanied by hyperammonaemia.

12.1.4.2. Evaluator's assessment

The presented data for the use of sodium phenylbutyrate in the treatment of UCDs suggests that the outcomes are improved compared to historical controls, especially for neurodevelopmental outcomes. These data support the treatment of UCDs with sodium phenylbutyrate. The response is satisfactory.

12.1.5. Safety

20. The sponsor should supply a complete summary of all of the adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs.

12.1.5.1. Sponsor response

The sponsor provided a summary of the safety data for both the UCD and non-UCD populations.

During clinical trials with NaPB, the most frequently reported adverse reactions were those involving the reproductive system (23% of menstruating female patients reported amenorrhoea and/or irregular menstrual cycles) and gastrointestinal system (decreased appetite 4%, body odour 3% and bad taste/taste aversion 3%). An example of adverse events grouped by dosage of sodium phenylbutyrate [is shown in Table 43].

Table 43: Adverse events according to dose of sodium phenylbutyrate

Ref.	Dose g/kg/day	Number of patients Per group	Nausea and/or vomiting	Dyspepsia	Fatigue	Confusion/ drowsiness	Odour	Oedema	Hypocalcaemia
Gilbert 2001	9	4	3	3	4	0	0	0	0
	18	4	3	3	3	1	0	0	0
	27	4	2	3	3	3	2	0	0
	36	7	5	4	4	3	3	1	1
	45	4	4	0	4	1	0	1	0

Ref.	Dose g/kg/day	Number of patients Per group	Nausea and/or vomiting	Dyspepsia	Fatigue	Confusion/ drowsiness	Odour	Oedema	Hypocalcaemia
Phuphanich 2005	9	4			0	0			
	18	7			0	2*			
	27	7			1	0			
	36	4			2	0			

*lightheadedness/headache

12.1.5.2. Evaluator's Assessment

The sponsor has summarised the adverse events reported in all of the trials involving sodium phenylbutyrate in the treatment of UCDs. No new unexpected adverse events were identified. There was not a clear relationship between dosing and the rate or severity of the adverse events. The response is satisfactory.

21. The sponsor should tabulate all adverse events attributable to sodium phenylbutyrate. This should include exposure data including dose, dose by size (weight and/or surface area) and length of treatment.

12.1.5.3. Sponsor Response

All reported adverse reactions are listed by system organ class in Table 44 and by frequency in Table 45 below. Frequency is defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 44: Clinical trial adverse reactions reported with NaPB in UCD patients

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anaemia, ecchymosis
Metabolism and nutrition disorders	Common	metabolic acidosis, alkalosis, decreased appetite
Psychiatric disorders	Common	depression, irritability
Nervous system disorders	Common	syncope, headache
Cardiac disorders	Common	oedema
	Uncommon	arrhythmia
Gastrointestinal disorders	Common	abdominal pain, vomiting, nausea, constipation, dysgeusia
	Uncommon	pancreatitis, peptic ulcer, rectal haemorrhage, gastritis
Skin and subcutaneous tissue disorders	Common	rash, abnormal skin odor
Renal and urinary disorders	Common	renal tubular acidosis
Reproductive system and breast disorders	Very common	amenorrhea, irregular menstruation
Investigations	Common	Decreased blood potassium, albumin, total protein and phosphate. Increased blood alkaline phosphatase, transaminases, bilirubin, uric acid, chloride, phosphate and sodium. Increased weight

Table 45: AEs reported with phenylbutyrate in clinical studies for UCDs

Study	NaPB dose	Number of patients	AEs reported (n or % of n)
Weich (1997)	NR	12 (4M; 8F)	Menstrual Disturbances (23%) Anorexia Biochemical abnormalities
Feillet (1998)	NR	6 (5M; 1F)	Oral mucositis Fanconi syndrome (2)
Lee (2010)	191 mg/Kg/day equivalent to 7.54 g/m2 for an average of 9.04 years	6	Dyspepsia (1) gastro-esophageal reflux (1) increased appetite (1) dizziness (1) dysgeusia (1) chills (1).
McGuire (2010)		10	dizziness (5) headache (4) nausea (3)
Lichter-Konecki (2011)	mean dose =	28 (22M; 6F)	lymphadenopathy

Study	NaPB dose	Number of patients	AEs reported (n or % of n)
	12.4 g/d or 322 mg/Kg/day; range =198 – 476 mg/Kg/day)		(1) decreased appetite (1) cardiac murmur (1)
Diaz (2013)	(12.33 g/d) for an average of 128.57 months	45 UCD (40 OTC, 2 CPS-I, 3 ASS) patients; 51% reported AE	Diarrhea Flatulence abdominal discomfort dyspepsia nausea vomiting oral discomfort.
Pheburane vs Ammonaps Bioequivalence study		12	headache (15) ageusia (5) weakness (1) Vomiting (1)
ATUc (Autorisation Temporaire d'utilisation cohorte)			No AEs reported

12.1.5.4. Evaluator's assessment

The sponsor has tabulated the adverse events attributable to sodium phenylbutyrate. The dosing information was not available for all studies. The response is satisfactory.

22. The sponsor should tabulate all discontinuations due to adverse events attributable to sodium phenylbutyrate.

12.1.5.5. Sponsor response

All discontinuation due to use of sodium phenylbutyrate and reported in the literature are summarized in the table below.

Table 46: Discontinuation reported with phenylbutyrate in clinical studies

Study	Condition	Study dose	Adverse event
Dover 1994	sickle cell disease	initial therapy of 9 to 13 g/m2/day as 0.5-g tablets of PB.	One subject (C) developed a follicular pruritic rash over the arms and legs extending to the trunk at day 10 and discontinued treatment at day 14.
Carducci 2001	Hormone refractory prostate cancer predomina		The DLT was neuro-cortical (excessive somnolence and confusion and accompanied by clinically significant hypokalaemia, hyponatremia,

Study	Condition	Study dose	Adverse event
	nt tumor type)		and hyperuricemia) and was experienced by one patient at 515 mg/kg/day (grade 3) and another at 345 mg/kg/day (grade 3) and resolved <12 h after discontinuing the infusion. Both these patients developed the characteristic odour of PA which resolved promptly with discontinuation of the study drug.
Extracted from Pheburane SPC	UCDs		The major metabolite of sodium phenylbutyrate, phenylacetate, is associated with neurotoxicity. In a study of cancer patients administered phenylacetate intravenously, signs and symptoms of neurotoxicity were seen at plasma concentrations ≥ 3.5 mmol/l, including somnolence, fatigue, light headedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of pre-existing neuropathy. The adverse events were reversible upon discontinuation
Extracted from Ammonaps SPC	UCDs		A probable case of toxic reaction to AMMONAPS (450 mg/kg/day) was reported in an 18-year old anorectic female patient who developed a metabolic encephalopathy associated with lactic acidosis, severe hypokalaemia, pancytopaenia, peripheral neuropathy, and pancreatitis. She recovered following dose reduction except for recurrent pancreatitis episodes that eventually prompted treatment discontinuation.

12.1.5.6. Evaluator's assessment

The sponsor has tabulated 4 discontinuations from the clinical studies. The response is satisfactory.

23. The sponsor should submit a report on the single centre (Necker Hospital, France) pilot study of Pheburane, performed on 30 patients which was completed in Sep 2015

12.1.5.7. Sponsor response

The report is not available to Lucane or Orpharma as we did not sponsor the study which was done on a non-UCD population.

12.1.5.8. Evaluator's assessment

Given that the report is not available, the response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Pheburane, in the proposed usage are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Pheburane are unchanged from those identified in the first round evaluation.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Pheburane, given the proposed usage, is favourable.

Given the nature of the urea cycle disorders, the potential adverse neurological outcomes from untreated disease, and the limited available treatment. The available efficacy and safety data, albeit limited, supports the relative safety of Pheburane when compared to the poor neurological outcomes described for untreated urea cycle disorders. Pharmacokinetic data supporting the proposed dosing regimen is inadequate but could be improved through post-marketing pharmacokinetic studies.

14. Second round recommendation regarding authorisation

Approval of Pheburane is recommended as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.

The evaluator did not recommend authorisation of Pheburane in the first-round assessment until the deficiencies in the data are addressed. It is clear from the responses of the sponsor, that they have a limited ability to address these concerns (other than a single bioequivalence study) as the application is based upon the available literature. Given the nature of the UCDs, the potential adverse neurological outcomes from untreated disease, and the limited available treatments, the evaluator concludes that the authorisation could be recommended.

The sponsor should be encouraged to collect detailed ongoing safety and efficacy data as part of therapy. Furthermore, the sponsor should conduct a post-marketing pharmacokinetic study using a sparse-sampling technique to better characterise the dose-concentration relationship over the proposed dosing range in order to better justify the current dosing regimen.

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