EMA/76889/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Nugalviq (WD)

International non-proprietary name: govorestat

Procedure No. EMEA/H/C/006270/0000

Note

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

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List of abbreviations

Abbreviation	Definition
9HPT	9-Hole Pegboard Test
ADHD	Attention-deficit/hyperactivity disorder
ADL	Activities of Daily Living
AE	adverse event
AMH	antimullerian hormone
AR	aldose reductase
ARI	aldose reductase inhibitor
ATC	Anatomic Therapeutic Chemical
AUC	area under the plasma concentration curve
BASC-3	Behavior Assessment System for Children 3rd Edition
Bayley-4	Bayley Scales of Infant and Toddler Development
BMI	body mass index
BSI	Behavioral Symptoms Index
CG	Classic Galactosemia
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
COA	Clinical Outcome Assessment
CRC	Central Rating Committee
CRF	case report form
CSR	clinical study report
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	End-of-Study
FSH	follicle stimulating hormone
Gal-1-phoshate/gal-1P	galactose 1-phosphate
GALT	galactose-1-phosphate uridyltransferase

GCP	Good Clinical Practice
GIC	Global Impression of Change
GIS	Global Impression of Severity
GLOS	Galactosemia Lens Opacities System
Glu-1-phoshate	Glucose 1-phoshate
HSAC	Hepatic Safety Adjudication Committee
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPD	important protocol deviation
IRB	Institutional Review Board
LAR	legally authorized representative
LC	Listening Comprehension
LH	luteinizing hormone
LOCS/ LOCS-III	Lens Opacity Classification System (Version III)
logMAR	Logarithm of the Minimum Angle of Resolution
MAD	multiple ascending dose
MCIC	minimal clinically important change
MCID	minimally clinically importance difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NDA	New Drug Application
Nf-L	neurofilament light chain
NIH	National Institutes of Health
NIH-CB	National Institutes of Health Toolbox Cognitive Battery
NIH-MB	National Institutes of Health Toolbox Motor Battery
OAT	organic anion transporter
OE	Oral Expression
OLE	open-label extension
OTC	over-the-counter

OWLS-II	Oral and Written Language Scales
PK	pharmacokinetic(s)
PT	preferred term
Q6M	every 6 months
SAP	statistical analysis plan
SAE	serious adverse event
SARA	Scale for the Assessment and Rating of Ataxia
SD	standard deviation
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
US	United States
WCT	Worldwide Clinical Trial
WHO	World Health Organization
WHODDE	World Health Organization Drug Dictionary Enhanced

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Nugalviq an orphan medicinal product in the treatment of adults and children aged 2 years and older with a confirmed diagnosis of classic galactosemia, also known as galactose-1-phosphate uridylyltransferase deficiency:

is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

1. Module 3 is considered incomplete as presented. The level of detail and data presented in all subsections are considered critically low and the information provided in module 3 should convincingly demonstrate that the quality of the substance and the finished product are adequately controlled.
2. the proposed starting materials are not accepted since insufficient information is provided in the dossier. Further information has to be provided for each proposed starting material;
3. the information provided on the evaluation of potentially genotoxic impurities in the active substance is not considered to be sufficient. The control strategy for potentially genotoxic impurities should be discussed and implemented in line with the ICH M7 Guideline;
4. information on dissolution test development is not provided and discriminatory power of method is not demonstrated, therefore dissolution method to be used for routine control cannot be concluded. Dissolution limit acceptance criteria in the finished product specifications should be based on dissolution data obtained from batches used in the clinical studies/biobatch used in bioequivalence study, therefore tightening of specification limit should be considered;
5. no comparative dissolution studies are performed between different govorestat oral suspension formulations and pharmaceutical equivalence of these formulations is not demonstrated;
6. selection of two component preservative system should be justified; the antimicrobial preservatives concentration used should be justified in terms of efficacy and safety and the minimum concentration of preservatives that gives the required level of efficacy throughout the intended shelf life of the product should be used;
7. representative batch data of the finished product should be provided as a lot of relevant information currently is missing in the marketing authorisation dossier confirming that the process leads to a product that complies with the proposed and required specification limits;
8. risk assessment on potential presence of nitrosamine impurities in the active substance and finished product is not yet considered acceptable since no underlying documentation has been submitted, therefore it cannot be verified if the risk evaluation is complete;
9. no conclusion on finished product’s shelf life can be made as stability data provided by the Applicant cannot be considered as representative.
10. no conclusion on finished product’s in-use shelf life can be made as stability data provided by the Applicant cannot be considered as representative.

Non-clinical

1. The carcinogenic potential is not adequately addressed. . Relevant eCTD documents should be provided or updated, in module 2 and 4. The responses should refer to the data in the eCTD.

Clinical

11. In general, the Clinical Overview and Summary of Clinical Efficacy are incomplete, not containing the expected clinical information. This significantly hampers the assessment of the clinical section of this submission.
12. The benefit-risk balance of govorestat is negative in the claimed indication and should be thoroughly discussed by the applicant
13. The proposed posology is not well understood, impractical and prone to medication errors. The applicant should justify the posology and simplify the posology to reduce the risk of medication errors.
14. A mass-balance study, absolute bioavailability study are absent which leads to major pharmacokinetic uncertainties in the current dossier..
15. The PopPK model is insufficient and therefore is also currently not suitable to investigate the effect of the special populations on the PK. Furthermore as the PK/PD model is informed with the simulated PK data from the PopPK model the PK/PD relationship is currently also not acceptable.
16. No food effect study was conducted by the Applicant. It is therefore unknown if exposure from the commercial formulation (oral suspension) is affected by food.
17. The Applicant stopped the study at Month 18 in Part B as observed clinical benefit was substantial. However, there was no reason for such stop as a statistically insignificant result on 5% significance level was observed for primary composite endpoint which violates the statement in the study protocol.
18. During the study the primary endpoint changed a couple of times. Changing the primary endpoint during a confirmatory trial without proper planning will render the trial to be considered **exploratory.**
19. The study was formally performed at three sites. The results are mainly determined by one site (Rare disease research, LLC). This is surprising, given that the rarity of the disease is used to substantiate the absence of type I error control.
20. As all patients are on a lactose-free and galactose-restricted diet and as known from literature strictness of the diet may vary between doctors, institutions and countries. Therefore, compliance of the diet is not known.
21. The population included in the study are Caucasian, US residents from the higher socio-economic classes. The exclusion criteria do not allow for severely impaired patients to be included (IQ score < 50). All patients with a serious renal, hepatic or cardiac co-morbidity are excluded. Therefore the population included does not represent the population intended to be treated with the patients with the highest need (severely impacted cognition) excluded.
22. As a considerable group of patients appeared to be within the normal range (for the behavioural and motor assessments), therefore, the need for treatment is not evident.
23. It is well known that, in addition to diet, speech and physical therapy are an integral part of the care of patients with galactosemia. Speech and physical therapy have a positive effect on the patient's clinical condition. This non-pharmacological treatment was not standardized, nor was it required to be stable before the study initiation. This may also affect the assessment of the study endpoints.
24. No interpretable information over more than 18 months is available.
25. There are several issues identified that seriously question the GCP adherence and thus the reliability and the validity of the study results.
26. The request for CMA is currently not acceptable

1.1. Questions to be posed to additional experts

Currently no SAG or expert involvement is foreseen

1.2. Inspection issues

1.2.1. GMP inspection(s)

No GMP inspections are required.

1.2.2. GCP inspection(s)

Currently there is no GCP inspection triggered. The outcome of the GCP inspection to be performed by US FDA in relation to study AT-007-1002 at the main investigator site located in Georgia, US and at the sponsor site in New York will be considered during the next steps of the assessment together with the responses from the Applicant to the GCP related Major Objections (MOs) and Other Concerns (OCs).

1.3. New active substance status

Based on the review of the data, it is considered that the active substance Govorestat contained in the medicinal product Nugalviq is qualified as a new active substance.

1.4. Additional data exclusivity /Marketing protection

Not applicable.

1.5. Similarity with authorised orphan medicinal products

Not applicable.

1.6. Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition and epidemiology

GALT deficiency can be classified into three categories based on the residual enzyme activity: Classic Galactosemia (CG) (<1% enzyme activity), Clinical Variant Galactosemia (1%-10% enzyme activity), and Duarte Galactosemia (15-35%).

Classic Galactosemia (CG) is a rare disease (1:16,000-1:44,000 in Europe) (Murphy et al., 1999; Bosch et al., 2005; Honeyman et al., 1993; Schweitzer-Krantz, 2003). Patients have autosomal mutations in the gene encoding for galactose-1-phosphate uridylyltransferase (GALT).

Galactosemia is reported among all races and ethnicities. The distribution in the various races and ethnicities is comparable[1].

Patients with CG have severe deficiency in the GALT enzyme, defined as less than <1% activity. The lack of enzyme activity leads to accumulation of galactose which is metabolized by aldose reductase (AR) to its metabolite galactitol and by galactokinase (GALK) to galactose-1-phosphate (Gal-1-P). In untreated classical galactosemia patients the galactitol in plasma (120–500 µmol/l) is markedly elevated (controls 0.08–0.86 µmol/l); under treatment, the galactitol concentrations (4.7–20 µmol/l) remained above the control range[2].

The pathogenic mechanisms underlying the acute and long term complications are not fully understood. Galactitol has been assigned the role of main pathogenic agent, however other mechanisms such as accumulation of other metabolites (mainly gal-1-P), aberrant glycosylation and oxidative stress have also been postulated as potential disease mechanisms. Potentially, different mechanisms contribute to the clinical phenotype simultaneously.[3,4] Currently the role of Gal-1-P as the most important toxic metabolite is subject of discussion.

In affected infants, exposure to galactose from breast milk or infant formula results in severe and potentially life-threatening illness in the first weeks of life followed by death during infancy when untreated (Berry, Updated 2021; Demirbas et al., 2018). Clinical manifestations include feeding difficulties, failure to thrive, liver failure, renal disease, E. coli sepsis and bilateral cataracts. Upon initiation of a lactose-free and galactose-restricted diet, within the first 10 to 14 days of life, these acute symptoms resolve. (Berry 1997, Demirbas 2018). Despite early detection and life-long dietary restriction of lactose and galactose later in life other complications of the condition can become apparent.

These complications include speech/voice/language, cognitive impairment, behavioral symptoms (withdrawal, depression, ADHD, anxiety), tremor, and seizures. As a result part of the patients are unable to perform activities of daily living, to have gainful employment, to form social or emotional relationships with others, or to live independent, and as a result require lifelong care (Rubio-Gozalbo et al, 2019; Randall et al. 2022).

The spectrum of severity of the long term complications is extremely wide. For example, mean IQ scores are reported to be below average or in the low average range, but with considerable variability between individuals ranging from very low to above average.

A topic of debate is whether the long term outcomes are progressive. Concerning cognitive impairment, some cross-sectional studies report a negative correlation between age and performance. Other cross-sectional and longitudinal studies report no cognitive decline. With regard to speech and

[1] N. Stettner, D. Cutler, J. Fridovich-Keil. Racial and ethnic diversity of classic and clinical variant galactosemia in the United States. Mol Genet Metab. 2023 Apr;138(4):107542. doi: 10.1016/j.ymgme.2023.107542. Epub 2023 Feb 21.
[2] C. Jakobs, S. Schweitzer, B. Dorland. Galactitol in galactosemia. European Journal of Pediatrics 1995, Volume 154, pages S50–S52, (1995)
[3] B Delnoy, A Coelho, M Rubio-Gozalbo. Current and Future Treatments for Classic Galactosemia. J Pers Med. 2021 Jan 28;11(2):75.
[4] J Fridovich-Keil, G Berry. Pathophysiology of long-term complications in classic galactosemia: What we do and do not know. Mol Genet Metab 2022 Sep-Oct;137(1-2):33-39

language outcomes and motor function, most cross-sectional studies show no evidence of worsening with age.[5,6,7,8]

Since early diagnosis and treatment can prevent neonatal morbidity and mortality, newborn screening is performed in several countries in Europe. Other countries however chose not to include CG in the neonatal screening programme due to ongoing uncertainties about the balance between risks and benefits.

Controversy exists on the value of biochemical markers in CG. Markers measured most frequently in clinical practice include blood galactose, RBC Gal-1-P and/or urinary galactitol levels. Although the levels of these metabolites decrease rapidly after initiation of a galactose-restricted diet, the levels remain elevated compared to healthy people. Both gal-1-P and galactitol levels have a high inter- and intrapersonal variability. In current guidelines it is concluded that there is no clear association/correlation between galactose metabolites and other markers and the development of both acute and long-term complications in patients with classical galactosemia. In clinical practice, biochemical monitoring varies between treatment centers.[9]

In a GALT- null rat model of CG, galactitol accumulation was associated with cognitive and neurobehavioral deficits, similar to the defects observed in humans with CG (Rasmussen, 2020).

Other treatment options

There are currently no medicinal treatments approved for CG, patients are currently treated with a lactose-free and galactose-restricted diet.

Unmet medical need

CG represents an unmet medical need, since part of the patients experience cognitive and/or motor impairment or primary ovarian failure.

2.2. About the product

Govorestat is provided as 200 mg/ml oral suspension for once-daily oral administration in paediatric and adult patients. Each bottle contains 100 ml of oral suspension. Each pack contains 1 bottle of product, a syringe adaptor and up to 2 dosing syringes, as required to administer the appropriate does as specified in the product information.

Pharmacological Class

Pharmacotherapeutic group: Other alimentary tract and metabolism products, aldose reductase inhibitor.

Proposed ATC code: A16AX

[5] L Welling, L Bernstein, G Berry, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment and follow-up. J Inherit Metab Dis. 2017 Mar;40(2):171-176
[6] J Fridovich-Keil, G Berry. Pathophysiology of long-term complications in classic galactosemia: What we do and do not know. Mol Genet Metab 2022 Sep-Oct;137(1-2):33-39
[7] M Hermans, G Geurtsen C Hollak, A Bosch. Neuropsychological stability in classical galactosemia: A pilot study in 10 adult patients. JIMD Reports. 2024;1–6. DOI: 10.1002/jmd2.12410
[8] N. Smith, E Hendrickson, O Garrett, et al. Long-term complications in classic galactosemia are not progressive. Molecular Genetics and Metabolism 140 (2023) 107708
[9] L Welling, L Bernstein, G Berry, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment and follow-up. J Inherit Metab Dis. 2017 Mar;40(2):171-176

Mechanism of action

Govorestat is a CNS and retinally penetrant aldose reductase inhibitor (ARI). The administration of govorestat inhibits the function of aldose reductase and reduces the levels of galactitol.

Proposed Clinical Use

Nugalviq is indicated for the treatment of adults and children aged 2 years and older with a confirmed diagnosis of CG, also known as galactose-1-phosphate uridylyltransferase deficiency

2.3. The development programme/compliance with guidance/scientific advice

The Applicant received Scientific Advice on the development of Govorestat for the treatment of galactosaemia from the CHMP on 26/01/2023 (EMA/SA/0000113524). The Scientific Advice pertained to the following Quality, non-clinical and clinical aspects:

Quality

Components of the formulation, manufacturing, control of the drug product processes, and stability testing program of the oral formulation intended for the MAA. In general, scientific advice is followed, however, not all additional data mentioned in scientific advice regarding pharmaceutical development (characterisation of active substance, choice of preservatives), specification and stability of the finished product are provided in MAA, questions are raised regarding this matter.

Non-clinical

Overall acceptability of the non-clinical development plan to support a MAA for patients with classic galactosemia. In general, scientific advice was followed, however no carcinogenicity studies were conducted and questions are raised regarding this matter.

Clinical

Planned CMA for treatment of children who are 2 years of age and older, and adults with galactosemia based on the proposed biomarker endpoint and available clinical outcome data and evidence to convert the proposed CMA to a standard MA. In general the scientific advice was followed, however the advice concerning the proposed biomarker endpoint was not adequately discussed.

In the advise it was highlighted that:

- Even if elevated galactitol levels is a hallmark of the disease, and the toxicity of galactitol and its causality in the long-term complications of galactosemia is established, there is no established clear correlation between plasma levels of galactitol and the severity of signs and symptoms of galactosemia. Preliminary phase 3 data showed a reduction of 40-50% in galactitol plasma levels, and it is not known how such a decrease would translate into a clinical benefit.
- There is not either any established correlation between plasma levels of galactitol and corresponding levels in areas related to the symptomatology, especially the brain.
- Overall, Galactitol is not a validated biomarker and any govorestat-induced decrease in galactitol cannot be readily translated into a clinical benefit. Its sensitivity to change and validity are unknown. In this respect, it is underlined that, while an increase in galactitol has been associated with worsening symptoms of galactosemia, this has not been demonstrated for a normalization or reduction of galactitol concentrations. A clear target concentration to guide dosing or define responders based on this biomarker is thus not established.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Satisfactory GMP status is confirmed for manufacturing sites involved in the manufacturing process. A valid GMP certificate issued by EU Competent Authority covering the proposed activities is provided for the manufacturing site located in EU. For manufacturing sites located in Canada, the EU-Canada MRA is in operation. Screenshots from the Health Canada database are provided and are accepted as a MIA equivalent and valid proof of GMP compliance.

Drug substance

A QP declaration for EU GMP compliance is provided. The declaration includes a French site and is based on remote audit performed on 10-11/05/2022. The submitted QP declaration includes in Part B sites located outside the EU/EEA. According to the Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template", in Part B the relevant MIAHs for which the QP declaration is applicable should be listed and only EU/EEA sites are MIA holders. The included third country sites should be removed and updated QP declaration provided.

GLP

The pivotal nonclinical safety pharmacology and toxicology studies of govorestat (AT007) were performed according to GLP. All studies conducted under GLP conditions were in full compliance. No concerns were identified.

GCP

The applicant stated that the clinical trials conducted with Nugalviq (active substance: AT-007/govorestat) have been carried out in clinical sites located outside the European Union and met the ethical requirements of Directive 2001/20/EC.

Clinical trials were conducted in accordance with the protocol and amendments, applicable International Council for Harmonisation (ICH) Good Clinical Practice Guidelines and the principle enunciated in the Declaration of Helsinki.

No information on GCP inspection were submitted by the applicant. No issues for a triggered inspection are identified. Depending on the answers of the applicant such issue might arise. Further the FDA has planed an inspection of the main study site and the company's office.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

Not applicable.

2.5.4. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

See benefit/risk assessment, currently (D80) negative

- It is likely that the applicant will be able to provide comprehensive data.

The applicant is fully committed to continue generating comprehensive data supporting the CMA.

In line with the current stage of the clinical development of the product, the Applicant proposes the following post-authorisation activities in order to generate further comprehensive data.

- the Applicant has committed to performing a placebo-controlled clinical efficacy study in children under the age of 2 as part of the paediatric investigational plan.
- the Applicant will perform an additional long-term clinical outcomes study in adults with CG, evaluating the impact of govorestat on behavioural symptoms, daily living skills and tremor (as well as safety) as a post-marketing commitment.
- the Applicant will provide additional long-term follow up data on the children who participated in the placebo-controlled AT-007-1002 clinical study (which is now unblinded). Follow-up data on behaviour, daily living skills, tremor and safety will be provided at 18 month intervals to demonstrate sustained benefit of govorestat in the children who had been previously randomized to active treatment (who remain on active treatment in an expanded access program), and introduction of benefit in children who had been previously randomized to placebo, but were crossed to active treatment after study unblinding. Although the study no longer contains a placebo group, the trajectory of the placebo group through the blinded 18-month period will be modelled out to later timepoints using statistical modeling to simulate the progression of the placebo arm as a comparator.
- The Applicant will conduct a food effects study as a post-marketing commitment to support the label concerning govorestat administration.

The Applicant express the intention to further discuss the proposed post-authorisation development with the CHMP and agree on a final plan to provide further data to the CMA as soon as possible. In addition, it should be pointed out that the above proposals are feasible considering the limitations of clinical trials in unmet medical need conditions and the Applicant is also fully committed to continue applying the highest quality standards in order that the data generated support a future full MA.

- Unmet medical needs will be addressed, as

As above described in the previous section "Govorestat falls within the scope of the conditional marketing authorization", the product received an orphan designation for the treatment of CG patients (a copy of the Commission Decision is provided in Annex 5.18 of the Application Form). As discussed in the Orphan Drug Designation application, The reported prevalence of CG in Europe varies by country from 1 in 16,000 to 1:44,000 (Murphy et al., 1999; Bosch et al., 2005; Honeyman et al., 1993; Schweitzer-Krantz, 2003).

In addition, the medicine fulfils an unmet medical need because there is currently no medicine approved for the treatment of Galactosemia, which is a seriously debilitating disease.

Although dietary restriction of galactose prevents fatalities in the newborn period, it does not prevent long-term complications of disease, since the body produces galactose endogenously through de novo synthesis.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Because Galactosemia progressively worsens over time, there is an urgent need to offer a therapy to patients through a Conditional Marketing Authorisation (CMA). This was demonstrated most clearly by the placebo group in the pediatric study, which substantially worsened over the 18- month treatment period of the study, and the worsening of disease in this short period of time was detectable and clinically meaningful to caregivers in the context of daily life.

The granting of a CMA will allow this medicine to reach patients with the unmet medical need of Galactosemia earlier and will ensure that additional data on Govorestat are generated. With no approved treatment at all, patients will be left to the limited approach of diet restrictions. Unfortunately, long-term complications of the disease persist even when patients are maintained on a galactose-restricted diet from birth, due to endogenous production of galactose by the body through de novo synthesis.

According to the available data, there is no serious safety concerns.

2.5.5. Marketing authorisation under exceptional circumstances

Not applicable.

2.5.6. Biosimilarity

Not applicable

2.5.7. Additional data exclusivity/ marketing protection

Not applicable.

2.5.8. New active substance status

The applicant requested the active substance govorestat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Assessment of this claim is appended.

2.5.9. Orphan designation

Nugalviq was designated as an orphan medicinal product EU/3/22/2642 on 21 June 2022 in the following condition: Treatment of galactosaemia.

2.5.10. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.11. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.12. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0487/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-003365-PIP02-23 was not yet completed as some measures were deferred.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as oral suspension containing 200 mg/ml of govorestat as active substance.

Other ingredients are: microcrystalline cellulose, xanthan gum, carrageenan, carmellose sodium, citric acid, disodium phosphate, simethicone, potassium sorbate, methyl parahydroxybenzoate and purified water.

The product is available in amber-coloured polyethylene terephthalate (PET) 100 ml bottles with high density polyethylene (HDPE) screw child resistant closures. A multi-use snap-in bottle adapter and graduated 2.5, 5.0-, and 10.0-mL oral syringes are provided to dose the oral suspension.

3.1.2. Active Substance

3.1.2.1. General Information

Govorestat (INN) chemical name is 2-(4-oxo-3-((5-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)-3,4-dihydrothieno[3,4-d]pyridazin-1-yl)acetic acid.

Molecular formula: $C_{17}H_{10}F_3N_3O_3S_2$

Relative molecular mass: 425.4 g/mol

The structure is depicted below:

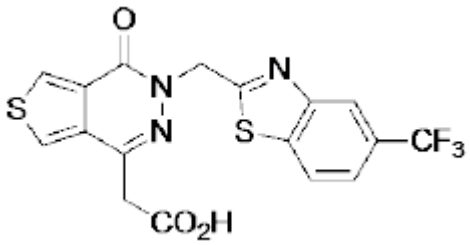


Figure 1: Govorestat structural formula

Govorestat is soluble in DMSO.

Govorestat is white to off white solid, has a defined melting point. It has been stated that the present process consistently produces only one crystalline form. Additional information regarding polymorphic form characterisation and stability is asked. Distribution coefficient has been mentioned, it should be clarified if the distribution coefficient has been established experimentally. Additional information is requested with respect to hygroscopicity, stereochemistry and optical rotation.

The full information in the dossier of the active substance is used.

3.1.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Compliance with current EU GMP for active substances used as starting materials is assured by the QP declaration issued by the company in charge of the batch release of the drug product.

The manufacturing process of govorestat consists of seven chemical synthesis steps followed by recrystallisation step.

The manufacturing process is in general well described including the used raw materials and quantities of raw materials, the reaction conditions. However, solvents are missing in the synthesis scheme and not all in-process controls are clearly described, as well as no information is provided regarding in-process test methods. These issues have to be clarified.

Reprocessing is not declared; recovered solvents are not used.

Batch size has to be declared since currently it is mentioned in the manufacturing process validation report only.

Two starting materials are stated. Both are stated commercially available, however, no further justification is provided anywhere in the dossier. The specification only is presented for both starting materials. Overall, the following information is missing on starting materials: characterisation, suppliers, route of synthesis, test methods, carry-over and control strategy of impurities originating from the starting material synthesis, justification of specification and justification as such on the proposed starting materials. Considering the above stated deficiencies, the proposed starting materials are not accepted since insufficient information is provided in the dossier. This is raised as a major objection.

In addition, two reagents are incorporated as relatively small structural elements in the active substance structure, but they are relatively simple reagents and introduced early in the synthesis. However, apparently, they have an impact on the purity profile of active substance. Therefore, the designation as reagents would be acceptable if the control strategy of these reagents is fully justified. Otherwise, they have to be classified as starting material and all necessary information has to be provided.

Specifications for most reagents and solvents are considered satisfactory with some exceptions where identification and purity/assay control has to be added. In addition, specifications of 3 components are asked. The specifications of n-heptane, methanol and acetone does not contain test for possible contaminant benzene (class I solvent). Parameter for benzene control NMT 2ppm is included in the specification of final active substance, therefore the control strategy of benzene is in compliance with Annex I: Specifications for class 1 and class 2 residual solvents in active substances (CPMP/QWP/450/03, EMEA/CVMP/511/03).

In the section 3.2.S.2.4, for critical process parameters in the steps 4, 5, 6 and 7, both- proven acceptable range (PAR) and normal acceptable range (NOR) are stated while in the manufacturing process description only one target set point is included. The same approach – target set points for process parameters - are used in the manufacturing process validation. It should be clarified whether the process will controlled via set points or normal operating ranges. The information is not considered

sufficient to justify any design space and PARs. There is an applicants' statement in the section 3.2.S.2.6 that the development is performed using Quality by Design approach taken to develop the normal operating range (NOR) for the synthesis of govorestat. The applicant is asked to delete PARs from section 3.2.S.2.4 the information is not considered sufficient to justify any design space and PARs. It is also requested to clarify and justify the control strategy using harmonised ICH terminology.

Specifications have been provided for five isolated intermediates. No justification/discussion is presented. Batch data were found in the manufacturing process validation reports. Test methods including validation information are not included in the dossier. There are several issues that have to be resolved before specifications can be accepted.

Process validation has been performed for all seven steps of the manufacturing process of govorestat drug substance. Process validation summary data have been presented. The results have indicated that the critical process parameters and the quality parameters are within standard limits and no reprocessing is necessary.

Manufacturing process development

Sufficient details on the manufacturing process development have been provided.

A clear overview has been presented of batches used in toxicological, clinical studies and stability studies. To date 26 batches of govorestat drug substance have been manufactured. All batches including those used in preclinical/clinical studies were manufactured according to the same manufacturing process as described in section 2.3.S.2.2.

The manufacturing process development has been performed using Quality by design approach taken to develop the process control strategy and the Normal operating ranges for the synthesis of govorestat. Design of experiments strategies are mentioned to define the multidimensional space. These experiments defined the PARs, from studies within the PARs – the NORs were developed. The information is not considered sufficient to justify any design space and PARs. No design space is proposed.

Characterisation

The drug substance has been characterized using the following techniques: infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, ultraviolet spectrophotometry, differential scanning calorimetry, powder X-ray diffraction (PXRD). Elemental analysis with theoretical values has to be added for drug substance characterisation studies. The polymorphism of active substance has been discussed. Govorestat is crystalline form. The performed study demonstrates that several crystalline forms are possible, but under the conditions of the proposed manufacturing process only one crystalline form may be formed. No changes in polymorphic form after dry milling, wet milling and compression were observed. Applicant is requested to provide the name of crystalline form obtained by the proposed manufacturing process; to provide 2θ values characteristic for Govorestat crystalline form XPRD pattern. Furthermore, the stability of polymorphic form of active substance should be demonstrated throughout storage of the active substance. Otherwise, control of polymorphic form should be included in the specification of final active substance. Further, particle size distribution has been measured for four batches involved in the process validation study. The results comply with limits set in the drug substance specification.

Potential, structurally related organic impurities have been listed along with structures, origin and control. Performed fate & purge studies are summarised. Following the obtained results and fate&purge studies, four impurities have been included in the active substance specification as specified impurities. The question is raised regarding demonstration of methods' ability to test several impurities. Additional information is requested with respect to impurities potentially originating in steps 1A to 4, also the chemical names of impurities have to be provided. Analytical methods used for spiking experiments

should be described and basic validation data provided. Discussion on degradation products has to be provided.

Nine impurities (the starting material and all process intermediates) were included in the QSAR analysis. However, there are genotoxic structural alerts identified also in the process impurities. In addition, reagent iodomethane has mutagenic potential. Therefore, it is not clear whether all substances with structural alerts were included in the risk assessment. It is also not known whether the impurities originating from starting material synthesis have been considered, since there is no starting material synthesis provided in the dossier. The information provided on the evaluation of potentially genotoxic impurities is not considered to be sufficient. The control strategy for potentially genotoxic impurities should be discussed and implemented in line with the ICH M7 Guideline. This is raised as a Major objection.

Nitrosamines evaluation has been presented. Different aspects including synthesis of starting material and final API, reagents, solvents and risk related to cross-contamination and cleaning procedures have been considered in the risk assessment. Nitrosatable amines or their precursors have been identified in the process. Since no presence of nitrosating agents is identified in the process, no risks for nitrosamine impurities is concluded. However, confirmatory testing has been performed, all results were below detection levels. The risk is determined to be very low and no analytical testing would be required. The applicant screened for 14 small molecule nitrosamines, however the some of them seem unlikely to be present based on reagents, solvents etc. Rather, the risk assessment should identify impurities which could be present and if a risk exists, confirmatory testing should be done. The approach to screen blindly is not endorsed. Additional information is requested regarding risk assessment of nitrosamines in proposed starting materials before this conclusion is agreed.

The risk assessment on elemental impurities has been provided in line with ICH Q3D requirements. The screening of all elements in the final drug substance batches has been considered. The ICP-MS method has been used and LOD, LOQ has been stated. All elemental impurities analyzed have been observed below 30% of the ICH limit, therefore, no routine testing is required. The control strategy of residual solvents used in active substance synthesis is summarised and is considered acceptable.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The govorestat release testing performed at the drug product manufacturer, in order to release the incoming API as a raw material, is exactly the same as the analytical release testing performed at the drug substance manufacturer.

The drug substance specification includes appearance, identification by IR, HPLC, particle size distribution, assay, related substances by HPLC, residual solvents, residue of ignition, water, and residual reagents. Tests included in the specification for the final API are in line with requirements of ICH Q6A. However, there are several issues identified with respect to parameters and limits. The specification is not considered acceptable.

Four specified impurities are included in the specification. There are no clear statements on the maximum daily dose of active substance. The recommended dose as per SmPC is 20 mg/kg once daily and the maximum dose mentioned in the dosing table appears to be 2 g (i.e., for adult with 100 kg bodyweight the dose would be 2 g). On the other hand, 2.4 g is mentioned in the genotoxic impurities section as the maximum daily dosage. In any case the reporting threshold 0.03%, identification threshold 0.05% and qualification threshold 0.05% proposed by applicant based on daily dose >2g/day is agreed as the worst-case approach.

The company proposes to justify the limits for four specified impurities (above qualification threshold) by results of batches used in pre-clinical and clinical studies. Those batches (manufactured in 2018 – 2020) were released without testing of individual impurities and were back-tested for individual related substance content once the identity of individual related substances was known. However, the proposed limits for one specified impurity is not considered qualified since it is higher than levels observed in batches used for preclinical and clinical studies. From a non-clinical point of view this impurity has not been adequately qualified, and the limits should be tightened in line with the results demonstrated in batches used for preclinical and clinical studies, or other qualification data should be provided. Acceptance limits for water content (NMT 0.5%) and residue on ignition (NMT 0.5%) have been justified based on the historical data. However, considering the obtained data these limits should be tightened. Acceptance limits for residual solvents are in line with the ICH Q3C guideline. DIPEA also refer to ICH guideline, however this limit should be justified as DIPEA is not presented there. The limit for sum of residual solvents is acceptable. The absence of microbiological control is not agreed and has to be introduced in the specification. Particle size distribution acceptance criterion is based on data obtained for the validation batches. However, the question is raised in the 3.2.P.2 asking the discussion (based on relevant batch data) on the drug substance particle size distribution impact on the manufacturability and quality of final product and justification for the proposed particle size of the drug substance.

Analytical procedures and reference standards

All in-house analytical methods for the test's parameters have been described only with the equipment operation conditions without the sample/standard preparation, SST criteria and calculation formula. The applied methods are in accordance with current technical and scientific requirements. However, some questions have been raised by assessor regarding to analytical method description of in-house methods and supplemental information regarding to water content determination.

It seems that requirements of ICH Q 2 (R1) are followed, however only summaries of validation reports (assay and related substances by HPLC, GC-MS, Colorimetry, Residual solvents by GC-MS, Acetic acid by GC-MS, N,N-Diisopropylethylamine by GC-MS, Benzene by GC-MS, water content and particle size distribution by Laser Diffraction) are submitted, therefore question is raised to submit full reports including corresponding data, representative chromatograms and used reference standard.

Batch STD-XI-195 is designated as the primary reference standard for Govorestat. It has been characterized according to Ph. Eur. 5.12. The values for purity by HPLC, residual solvents, water content by coulometry and residue on ignition used to establish the declared purity (assigned value) by applying principle of mass balance and it is acceptable. There are still some deficiencies regarding to reference standard used for testing for related substances and residual solvents which should be resolved.

Batch analysis

Batch results have been provided for twenty- six various batches – used in toxicological, clinical studies as well as stability studies and intended for commercial supply. All of them have been manufactured as per process described in section S.2.2. Results comply to the specifications valid at the time of testing. Batch analysis results confirm consistency and uniformity of the product; however, comments are raised on missing parameters as well on the applied limits (see above).

Container closure

The primary packaging is double low density polyethylene (LDPE) bags. The bags are closed by a plastic bond. Secondary packaging: The bags are placed in fibreboard drums closed by a steel lid. The LDPE bags are of food grade quality, they comply with the requirements of relevant European Directives (EU Commission Regulation Nº 10/2011, as amended). Relevant statements are included. The specification, a representative IR spectrum and an example CoA is provided. The containers proposed for routine

storage are those which have been used in the stability studies supporting the re-test period. The provided information is considered acceptable.

3.1.2.4. Stability

Proposed re-test period: 48 months

Proposed storage conditions: under the long-term conditions of 25°C/60% RH.

Long-term (25°C ± 2°C / 60% ± 5% RH) and accelerated stability studies 40°C ± 2°C / 75% ± 5% RH under ICH recommended storage conditions are presented for 14 batches of drug substance. The batches are of production scale and are considered representative. It has been declared that all batches were manufactured using the manufacturing process described in section 3.2.S.2.2. There has been changes in the specification and test methods over time. The results on long term conditions according to the current specification are available for four batches at 18 months, two batches at 24 and 36 months time point, and one batch at 36 and 48 months time point. The results for accelerated conditions according to current specification are available and show the compliance with the specification. Overall, the results are within the currently proposed specification. However, there are few remaining issues. The stability results for one impurity are at the proposed limit. However, the limit is not currently accepted, question is raised in 3.2.S.4.5 regarding appropriate qualification for this specified impurity. Furthermore, the stability of polymorphic form of active substance should be demonstrated throughout storage of the active substance. Data on particle size during stability testing has to be provided since could change on storage, especially for low solubility active substances. Taking into account the above mentioned, no conclusions can be taken on appropriate re-test period and storage conditions of active substance. Furthermore, photostability study in line with requirements of ICH Q1B Photostability Testing of New Active Substances and Medicinal Products has to be provided. Photodegradation has been part of the forced degradation studies, however not in line with requirements of ICH Q1B.

Forced degradation stability study has been carried out using HPLC method for related substances. Results obtained have shown degradation under basic and oxidative conditions.
Post-approval commitments have been adequately set.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Nugalviq 200 mg/ml oral suspension is white, opaque, liquid suspension. The formulation of oral suspension does not contain an overage of drug substance. The 5% overfill is used to yield the target deliverable volume (label volume). Fill volume development should be discussed in relation to the proposed dosing and treatment duration (OC).

Pharmaceutical development

Formulation development is described briefly. Initially, govorestat was developed as a powder in capsules with no other excipients for oral administration. The next step was to employ an aqueous suspension that would be easy to swallow for paediatric patients using a ready-to-use suspending vehicle. Further optimization of formulation was performed and suspension vehicle has been changed. Changes introduced in the formulation are explained and justified, however, several issues are raised with regards to components of drug product and formulation development. It is noted that the applicant did not know at early steps of the formulation development quantitative composition of a main part of its product. In such cases the finished product manufacturer should be in a close contact with the vehicle manufacturer to gain as much information about its product as possible due to 80% of the finished product being composed from the vehicle. Differences in any parameters between vehicles and their influence on the product characteristics should be discussed (OC). Questions concerning pharmaceutical development in the relation to drug substance was discussed with CHMP via scientific advice procedure in January 2023,

however, no additional data are provided in the dossier. In line with ICH guideline Q8 (R2) on pharmaceutical development the physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability should be identified and discussed. Further data are required on particle size distribution of API, solubility in different media and stability of polymorphic form. (OCs). In addition, functionality related characteristics (FRCs) of excipients should be discussed; considering the observed variability of viscosity results at release and during stability studies special attention should be paid on the critical characteristics of the excipients that ensures the viscosity. (OC)

In order to demonstrate safety of the proposed formulation for use in the paediatric population the Applicant has calculated daily intake of each excipient for 2 years old child with body weight of 12.5 kg. The calculated daily intakes from approximately 2.0 ml of drug product per day are well below the acceptable daily intake set forth by EFSA, therefore, in general, its safety for use in the intended population could be agreed. The formulation contains two preservatives, potassium sorbate and methylparaben. The quantity of selected antimicrobial preservatives is not considered adequately justified in accordance with guidelines EMEA/CHMP/QWP/396951/2006 and EMA/CHMP/ICH/167068/2004. The applicant is asked to discuss and assess suitability of antimicrobial preservative concentrations. Furthermore, it also should be discussed whether strategies were considered to allow a preservative-free formulation or formulation with single preservative. (MO)

No development of the dissolution QC method is presented in the dossier, instead it is only stated that the validated method is used. Dissolution method development data should be provided to conclude suitable dissolution conditions for routine control. Furthermore, no comparative dissolution studies are performed between different govorestat formulations. Consequentially, the pharmaceutical equivalence cannot be concluded based on the provided data. The applicant is also reminded that dissolution limit acceptance criteria in the finished product specifications should be based on dissolution data obtained from batches used in the clinical studies/registration/stability. Issues related to the development of the dissolution method and dissolution specifications, as well comparative dissolution studies are classified as major objections.

Brief discussion is given on physiochemical properties of the proposed formulation. Further data are requested on studies for sedimentation and re-dispersion of the suspension to support proposed instructions for shaking before use. (OC). The stability of the particle size of the drug substance should be demonstrated throughout the proposed shelf life with experimental data and the potential for particle growth should be discussed. (OC) Also pH of formulation should be addressed demonstrating balance between adequate stability of the drug product and suitability for the oral administration. (OC)

No manufacturing process development is provided for initial formulations (govorestat capsules and oral suspension). For the commercial suspension the recommended vehicle manufacturing process included in the monograph was followed. However, during scale-up from a 5 L pilot batch to 50 L, it was determined that the manufacturing process needed to be modified.

A separate risk assessment report of the manufacturing process, including critical quality attributes (CQAs), critical process parameters (CPPs) and key process parameters (KPPs), as well as a discussion of process controls is presented from a manufacturer. Relationship between that manufacturer and the proposed manufacturing site should be explained. (OC).

Container closure system development is described. According to the SmPC two presentations are available. One presentation contains a 100 mL bottle with two oral dosing syringes, i.e. a 2.5 ml oral syringe graduated in 0.1 ml and a 5 ml oral syringe graduated in 0.2 ml. This presentation should be prescribed for children and adolescents from 2 years to 17 years. The second presentation contains a 100 mL bottle with one 10 ml oral syringe graduated in 0.5 ml. This presentation should be prescribed for adults from 18 years. A syringe dosage study was performed to determine the accuracy of dosing

govorestat oral suspension with syringes of all sizes. The results from the experiments demonstrate that the reusable 2.5 ml, 5 ml & 10 ml oral syringes meet the Ph. Eur. 2.9.27 requirement for the uniformity and accuracy of delivered doses. Dosing recommendations prescribed in the SmPC (Table 3, Section 4.2) can be ensured. Although accuracy of the proposed oral syringes is demonstrated, currently no conclusions can be made on their suitability for intended purpose as major objection on dosing recommendations is raised (refer to Clinical and PK major objections). Furthermore, as the pack indicated for children and adolescents from 2 to 17 years contains two different oral syringes graduated differently (a 2.5 ml oral syringe graduated in 0.1 ml and a 5 ml oral syringe graduated in 0.2 ml), the risk of mix-match of syringes and consequentially potential errors in posology might exist, therefore, the suitability of the scale intervals in relation to the dosing advice or the dosage range and the ease of interpretation of the graduated scale should be discussed. (OC). The suitability of oral syringes will be re-assessed in the next step of the procedure.

Microbiological quality results of several batches of commercial formulation are provided (P.5.4), showing compliance with the acceptance criteria laid down. In addition, the applicant states that the preservative effectiveness testing (PET) has been performed during in-use and long term stability studies and results are included in the 3.2.P.8.3, however, mentioned data are not found in the dossier. (OC)

3.1.3.2. Manufacture of the product and process controls

The proposed commercial batch size of govorestat oral suspension is 100 L. Batch formula is presented.

Govorestat oral suspension is immediate release non-sterile oral dosage form manufactured by a conventional manufacturing process including preparation of suspension, mixing and filling. A flow chart of the manufacturing process indicating raw materials, chronology of operations and applied in-process quality controls is presented. Details of processing parameters such as mixing times and duration have been included. The critical process parameter and in-process control are indicated and are in line with those concluded in manufacturing process development studies.

However, the description of the manufacturing process does not contain all required information; details on used equipment should be provided, as well process parameters used to achieve the required quality should be specified. (OCs). Furthermore, control of viscosity of oral suspension and integrity of container closure system should be monitored during in-process control. (OC)

The applicant has proposed bulk holding time of 48 hours, nevertheless, no supportive data are provided in the dossier. Furthermore, it is not clear whether mixing is required during bulk storage. Due to lack of supportive data, it is not possible to assign a holding time and information about holding time should be removed from the dossier. (OC)

The manufacturing process is considered a standard process according to guideline EMA/CHMP/CVMP/QWP/BWP/70278/2012, therefore, no validation data at production scale is required in the dossier.

3.1.3.3. Product specification, analytical procedures, batch analysis

The proposed specification in general follows recommendations provided in ICH guidelines and European Pharmacopoeia and reflects common quality specifications for this type of products. Specification includes parameters to be tested, acceptance criteria and references to analytical methods used. It is proposed not perform tests for identification, uniformity of mass of delivered doses from multidose containers and content uniformity during stability studies. It is proposed to perform control of microbiological quality at initial and at the end during stability studies. Additionally, limit for fill volume of the container and tests for redispersibility and particle size distribution should be implemented in the specification of the finished product.

The limits for assay differ in the release and shelf-life specifications, wider shelf life limit for assay of the active substance and of preservative potassium sorbate are proposed, however they are not supported by stability data. Therefore, tightening of these limits is requested.

The control of specified, unspecified and total impurities is included in the specification of the finished product. The same specified impurities as in the active substance are controlled in the finished product with the same limits. Based on analytical data also limit for total impurities should be tightened. The Applicant should further justify the proposed limit for a specified impurity from non-clinical point of view, otherwise the proposed limit should be tightened in-line with results demonstrated in active substance batches used for preclinical and clinical studies.

Test for dissolution is included in the specification, however, no development of the dissolution method is described in the section 3.2.P.2, moreover, no batch data and stability data are provided where dissolution results are indicated. Therefore, no conclusion on the proposed dissolution limits can be made at this stage of assessment. Major objection is raised.

Analytical procedures and reference standards

Descriptions of the analytical methods are provided and have been described in detail. Methods include the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula, and an adequate System Suitability Test. The applied methods are in accordance with current technical and scientific requirements.

Validation reports of analytical methods used for determination of identification, assay and related substances (by HPLC) of Govorestat, identification and assay of preservatives, (Methylparaben and Potassium Sorbate), dissolution, viscosity and microbiological examination tests have been performed in accordance with ICH Q2 (R1) guideline, appropriate data are provided. Provided validation reports are acceptable. However, question is raised by assessor regarding to missing forced degradation studies.

Reference to 3.2.S module is provided for further information on reference standards since the same standards are used for testing of the drug product. However, CoA of reference standards used for testing for preservatives should be presented.

Batch analysis

Batch data of several batches is provided. Results corresponds to the proposed specification. No fluctuation of results has been noticed between different batches. However, it has been noticed that not all parameters included in the specification of the finished product have been tested, e.g., results of dissolution test, uniformity of mass of delivered doses and content uniformity are missing. Therefore, batch data provided by the Applicant could not be considered as representative. The Applicant should provide batch data where all specification’s parameters have been tested and the finished product is packed in proposed commercial packaging (bottles of 100 mL). Considering that a lot of relevant information currently is missing in the marketing authorisation dossier confirming that the process leads to a product that complies with the proposed and required specification limits the question is raised as major objection.

Elemental risk assessment

Risk assessment on elemental impurities is performed according to ICH Q3D requirements. Option 2b is used. Class 1 and 2A elements were considered during the assessment. Summary of potential contributions is provided in tabular form and contains quantitative comparison of predicted level of the impurities and established control threshold (30% of the established PDE). Maximum daily dose of 12 ml considered in risk assessment as worst case. According to the product assessment, there is no level of elemental impurities above control thresholds. No screening of elemental impurities was performed in the drug product.

Nitrosamines risk assessment

The Applicant has performed nitrosamines impurities risk assessment in the drug product which is based on active substance, excipients and primary packaging materials suppliers' declarations. Additionally, the Applicant has evaluated drug product manufacturing process, processing aids and cleaning procedures. The active substance may contain traces of residual solvents (sources of secondary and tertiary amines) and excipient microcrystalline cellulose contains nitrite. The historical level of previously mentioned residual solvents in the active substance were NMT 1 ppm, the level of nitrites in the microcrystalline cellulose. The level of nitrites in the purified water is controlled according to Ph.Eur requirements. The secondary and tertiary amines in the active substance may react with nitrites in the microcrystalline cellulose and form nitrosamines impurities. Nevertheless, the Applicant concluded on theoretical assumptions that there is no risk for formation of nitrosamines impurities. The nitrosamines risk assessment provided by the Applicant is not acceptable at this stage of assessment as information on starting materials synthesis of the active substance is missing, different information on active substance batches used in confirmatory testing is provided. The Applicant is required to address the potential formation of nitrosamine impurities with structures derived from the active substance impurities that may form as a result of reaction of vulnerable amine structures in API impurities with nitrosating agents present in the excipients. Taking into account that active substance may contain residual solvents and excipient microcrystalline cellulose contains nitrite at ppm levels, formation of nitrosamines impurities cannot be excluded. It should be taken into account that the maximum daily dose of the active substance is more than 2 g, therefore acceptable limits of potential nitrosamines impurities would be very low (in ppb). Therefore, the Applicant should consider to perform confirmatory testing of nitrosamines impurities with suitable method according to EMA Q&A document (EMA/409815/2020 Rev 20) unless otherwise justified. Major objection.

Container closure system

Govorestat oral suspension is packed in amber polyethylene terephthalate (PET) bottles of 100 ml. The bottles are sealed with a white a child resistant HDPE screw cap.

Push in bottle LDPE syringe adapter 24 mm and graduated disposable PP oral syringes of 2.5 ml, 5 mL and 10 mL are provided to dose the oral suspension. The material of construction of the oral dose syringe is polypropylene.

Oral syringes are classified as Class IIa medical device. The manufacturer is Medicina Ltd, Units 2-4 Rivington View Business Park, Station Road, Blackrod, BL6 5BN, UK. The EU Authorised representative is HMC Premedical S.p.A., Via Bosco 1/3, 41037, Mirandola (MO), Italy. It is certified by Notified Body SGS Belgium NV. The certificate and declaration of conformity are provided in the section 3.2.R.

Press-in-bottle adaptor is classified as Class I medical device without measuring function. The EU Authorised representative is Medical Device Safety Service MDD GmbH, Schiffgraben 41, 30175 Hannover, Germany. The declaration of conformity is provided in the section 3.2.R.

3.1.3.4. Stability of the product

The Applicant has performed stability studies according to ICH guideline at long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions. Three primary stability batches have been used for this purpose. Batches are manufactured according to manufacturing method described in the Module 3, however, different size of bottles (500 mL instead of 100 mL) have been used for packaging of the medicinal product. The material of the bottle and child resistant screw cap are identical for both pack sizes. Generally, results correspond to the proposed specification (excepts viscosity), however, as all parameters (e.g., dissolution etc) have not been tested during stability studies, no conclusion on acceptable shelf-life of the medicinal product cand be made at this stage of assessment.

The Applicant should provide drug product packed in 100 mL bottles stability data at both conditions. Stability studies of primary batches packed in 500 mL bottles provided in the section 3.2.P.8 cannot be considered as representative for commercial batches as not all parameters included in the specification were tested. Additionally, bracketing approach described in ICH Q1D guideline is not possible to apply in this case as 100 mL bottle size corresponds to the smallest container size (i.e., extreme), therefore, full stability data according to proposed specification is necessary to establish the shelf life and storage conditions of the medicinal product. Major objection.

The in-use stability studies of the medicinal product packed in 100 mL bottles performed according to *NfG on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)* should be provided. The claimed in use shelf-life should be justified in relation to the worst-case duration of use of the container. The in-use stability study of one primary batch packed in 500 ml bottles cannot considered as representative as not all specification's parameters were tested. A minimum of two at least pilot scale batches packed in the proposed commercial packaging (i.e., 100 ml bottles) should be subjected to the test. Major objection.

Potential effect of low temperatures on the drug product has been investigated. The stability data generated showed no significant change in any physical, chemical quality attribute. Not all parameters are tested during freeze-thaw study and no stability of the particle size of the drug substance has been demonstrated. Therefore, the conclusion of freeze - thaw study is not supported at this stage of assessment.

Photostability testing should be conducted on at least one primary batch of the drug product according to ICH Q1B. Results should be provided.

3.1.3.5. Post approval change management protocol(s)

Not applicable

3.1.3.6. Adventitious agents

Not applicable.

3.1.3.7. GMO

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation in relation to the proposed product is not of sufficient high quality in view of the present European regulatory requirements.

Drug substance

Further information is required before the control strategy applied to the drug substance is acceptable. There are several issues related manufacture of the drug substance including the supporting information request relating to the definition of starting materials (major objection), control of genotoxic impurities (major objection). Additional information should be provided on characterisation of active substance, manufacturing process controls, carry-over of impurities, drug substance specification, discussion on impurities carry-over, description and validation of analytical methods.

Drug product

It is acknowledged that the product will reach patients with an unmet medical need, however, the marketing authorisation documentation regarding drug product is of non-acceptable quality at this stage of assessment. Further information is required regarding formulation development, dissolution method development and acceptance criteria (major objections), pharmaceutical equivalence of different govorestat oral suspension formulations (major objection), justification of antimicrobial preservatives concentration (major objection), nitrosamines impurities risk assessment (major objection), batch data and stability (including in-use stability) of the drug product (major objections). Additional information should be provided on physicochemical and biological properties of the drug substance and excipients, functionality related characteristics of excipients, viscosity of the formulation, manufacturing process, quality of excipients, justification of specification and stability of the drug product.

3.2. Non-clinical aspects

3.2.1. Introduction

Nugalviq is intended for the treatment of Classic Galactosemia (CG), a rare, debilitating, and progressive long-term disease caused by genetic defects that leads to central nervous system (CNS) complications and cataracts. The drug product, Nugalviq, contains 200 mg/ml govorestat (AT007) as the active pharmaceutical ingredient, and is used a an oral daily treatment. The rationale for administration of govorestat in patients with Classic Galactosemia is to inhibit the function of aldose reductase and reduce the levels of the toxic metabolite galactitol. The non-clinical program of govorestat includes *in vitro* and *in vivo* pharmacology (efficacy and safety), pharmacokinetic (ADME) and rat, rabbit and dog toxicology studies.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

The Applicant has performed an *in vitro* microplate assay to assess inhibition of aldose reductase by govorestat. The results are presented as a high level report/lab journal report, with only very limited details. Govorestat was used in an inhibition assay for aldose reductase inhibition. Concentrations used ranged from 0.1 nM to 10 µM. A govorestat IC_{50} value of 0.100 nM for inhibition of aldose reductase is reported. This finding appeared to support a proposed mechanism of action by govorestat as aldose reductase inhibitor, however additional information is required to fully support this proposed mechanism of action.

The Applicant presented three *in vivo* studies (studies 1, 2 and 3) where govorestat was dosed at 0, 200 (study 3 only), 500 (study 3 only) and 1000 mg/kg to GALT-null (M3/M3) rat pups from day 1 after birth for 10 days (study 1) or 21 days (studies 2 and 3). In all three studies, decreased cataract scores were reported in the govorestat treated groups compared to placebo-treated rats. In general, treatment with govorestat resulted in decreased plasma, brain and eye levels of galactitol, although not as low in wild-type rats. Study 3 showed a trend for decreasing galactitol levels in plasma, brain and eye with increasing govorestat dose, whereas cataract scores appeared to decrease with increasing govorestat dose. Mean plasma concentrations of govorestat were determined at t=4 hours after final dosing in study 3, displaying very high variation between animals and more or less dose dependent increases with increasing govorestat dose. In general, for all three studies a beneficial effect of the use of govorestat in prevention of galactosemia induced cataracts may be present. However, treatment of already established cataracts is not supported by the presented studies. In addition, it appears that only the study summaries are presented and the results can only be considered as indicative of a preventive effect rather than a treatment effect and therefore do not support the current indication.

Another study (study 5) was designed to test the effect of govorestat treatment on rotarod and Morris water maze performance after 5 months of daily doses of 0 (placebo) or 1000 mg govorestat/kg in GALT-null (M3/M3) pups. Historical control data from wild type rats were used for comparison. Unfortunately, statistical analysis of the results was not performed and the overall report presented is very short and of low quality. Placebo treated rats showed decreases in latency, distance and speed with rotarod testing when compared to wild type data, whereas govorestat appeared to reverse this effect. With regard to the Morris water maze, govorestat appeared to reverse the effects observed for placebo treated rats with regard to latency, distance and speed. As the results are presented in a poorly prepared report and only one dose level was tested, only a indicative effect with regard to the beneficial effect of govorestat on behavioral testing can be concluded.

In conclusion, the presented studies do not show a proof of concept with regard to the current indication (treatment starting at 2 years and older), but rather indicate a preventive effect of govorestat dosing on cataract formation and central nervous system outcomes when dosing is initiated right after birth.

3.2.2.2. Secondary pharmacodynamic studies

In a secondary PD screen, govorestat up to 10 µM showed no inhibition or activation of binding higher than 37% for any of the 87 primary molecular targets, including 13 enzyme and 74 binding assays. Therefore, no effects may be expected in humans, as the used concentration of 10 µM (~4.3 µg/ml) exceeds the ~0.11-0.45 µg/mL C_{max} corrected for protein plasma binding at MRHD at least 9-fold (total concentrations 27-49 µg/mL in healthy adults and 15.5-64.4 µg/mL for paediatric population). Therefore, the risk for off-target activity is expected to be limited for govorestat.

3.2.2.3. Safety pharmacology programme

The concentration-response relationship of the effect of govorestat on the hERG potassium channel current was evaluated at near-physiological temperature in stably transfected mammalian cells that express the hERG gene. In this GLP-compliant study, govorestat inhibited hERG current by 2.1 ± 0.2% at 30 µM and 10.3 ± 0.2% at 300 µM versus 2.6 ± 0.3% in control. The IC_{50} for the inhibitory effect of govorestat on hERG potassium current was not calculated but was estimated to be greater than 300 µM (~128 µg/mL), while C_{max} at MRHD for the paediatric population was 15.5-64.4 µg/mL (~0.11-0.45 µg/mL when corrected for protein plasma binding). This translates into a >284-fold difference between human free C_{max} at MRHD and IC_{50} value in hERG assay, indicating that no effects on the cardiovascular system with regard to ventricular repolarization and proarrhythmic risk are to be expected in humans.

An *in vivo* GLP-compliant study was performed to determine the potential acute effects of govorestat, when administered orally by gavage on arterial blood pressure, heart rate, body temperature, and lead II electrocardiogram (ECG) in conscious radiotelemetry-instrumented male Beagle dogs. The following parameters and end points were evaluated in this study: clinical signs, arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, heart rate, body temperature, and ECG waveforms (from which the ECG intervals PR, QRS, QT, and heart rate-corrected QT [QTcV] were derived). There were no effects of 50 or 200 mg/kg govorestat on heart rate, arterial blood pressure, or ECG parameters. A dose level of 1000 mg/kg resulted in an increased heart rate and decreased PR and QT interval durations. Due to the onset, transient nature and magnitude of this change compared to the control group, the increase in heart rate was considered to be test article-related. There was no effect of govorestat, at any dose, to delay ventricular repolarization as represented by QTcV. The ratio of free fraction C_{max} at 200 mg/kg on day 1 in the 13-weeks repeated-dose toxicity study (total concentration 21.1 µg/mL, free fraction calculated at 0.70 µg/mL) to the paediatric C_{max} at the MRHD

(15.5-64.4 µg/mL, free fraction 0.11-0.45 µg/mL) was >1.5-fold, indicating that the effects on the cardiovascular system may be clinically relevant in humans. Alternatively, using the 200 mg/kg C_{max} values from the 28-days and 39-weeks studies (81.9 and 83.1 µg/mL, respectively) resulted in exposure multiples of 6-fold when compared to the MRHD, indicating a lower clinical relevance for the observed findings.

A GLP-compliant respiratory study was performed to evaluate the acute respiratory effects of govorestat when administered orally by gavage to male Sprague Dawley rats. Respiratory parameters were measured continuously for a 5-hour post-dose period in rats dosed with 50, 200 or 1000 mg govorestat/kg via oral gavage. The following parameters and end points were evaluated in this study: respiratory data (respiratory frequency, tidal volume, and calculated minute volume). Based on the results of this study, a single oral administration of govorestat to male Crl:CD(SD) rats dosed with 50, 200, or 1000 mg/kg resulted in absence of effects on respiratory parameters. The ratio of free fraction C_{max} at 1000 mg/kg on day 1 in the 28-days repeated-dose toxicity study (total concentration 254 µg/mL, free fraction calculated at 3.0 µg/mL) to the paediatric C_{max} at the MRHD (15.5-64.4 µg/mL, free fraction 0.11-0.45 µg/mL) was >6 to 27-fold, indicating that no effects on the respiratory system are to be expected in humans.

A GLP-compliant study was performed to evaluate the effects of govorestat when administered orally by gavage on the gross behavioural, physiological, and neurological state of male Sprague Dawley rats using a modification of a primary observation test, specifically the Irwin test. Animals were dosed once via oral gavage with 50, 200 or 1000 mg govorestat/kg. The following parameters and end points were evaluated in this study up to 5 hours post-dosing: observations for the Irwin test and body temperatures. Based on this study, a single oral administration of govorestat to male Crl:CD(SD) rats at dose levels of 50, 200, and 1000 mg/kg resulted in no effects on gross behavioural, physiological, and neurological function, and no effect on body temperatures. The ratio of free fraction C_{max} at 1000 mg/kg on day 1 in the 28-days repeated-dose toxicity study (total concentration 254 µg/mL, free fraction calculated at 3.0 µg/mL) to the paediatric C_{max} at the MRHD (15.5-64.4 µg/mL, free fraction 0.11-0.45 µg/mL) was >6 to 27-fold, indicating that no effects on the CNS system are to be expected in humans.

Overall, except for a potential effect on heart rate, no govorestat-related effects on the cardiovascular system, respiratory system and central nervous system are expected at clinically relevant exposures.

3.2.2.4. Pharmacodynamic drug interactions

No studies were performed to evaluate potential pharmacodynamic drug interactions, this is agreed.

3.2.3. Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) of AT-007 was evaluated in *in vitro* systems and *in vivo* in the rat. Liquid chromatography (LC) with tandem mass spectrometric detection (LC-MS/MS) bioanalytical methods were developed for quantitation of AT-007 in rat, rabbit, and dog plasma to support pharmacokinetic (PK) and toxicokinetic (TK) analyses. Single dose PK was only performed with labelled ^{14}C-AT007 or determined on Day 1 of the multiple dose studies. The *in vivo* multiple-dose TK of AT007 was conducted via oral administration, which is the intended route of administration in humans, to Sprague-Dawley rats, pregnant New Zealand White rabbits and Beagle dogs, which were used as part of the non-clinical safety program.

3.2.3.1. Analytical methods

The bioanalytical methods were developed to support TK analyses of AT007 in rat, rabbit and dog plasma. Liquid chromatography with tandem mass spectrometry (LCMS/MS) methods were employed to analyse plasma samples from both GLP and nonGLP nonclinical toxicology studies in rat, rabbit and dog. In general, EDTA plasma was deproteinized using acetonitrile, centrifuged and subsequently, in the supernatant, AT007 and an internal standard were analysed with an SCIEX API 5000 (rat, dog) or API 5500 (rabbit) LC-MS-MS system equipped with an UPLC column. The analytical range (LLOQ – ULOQ) for plasma samples was 100 to 100,000 ng/mL. The bioanalytical methods for rat and dog plasma met all validation criteria with respect to intra- and inter-day accuracy, precision, sensitivity, linearity, reproducibility, matrix effect and stability (up to 67d).
The rabbit plasma analytical method was partially validated and hampered by carryover effects, for which the analyses were adapted to reduce impact. Therefore, this assay was considered fit for purpose.
Incurred sample reproducibility (ISR) for nonclinical sample analysis was conducted once per method per species.

3.2.3.2. Absorption

Single dose

After a single oral dose of labelled [^{14}C]-AT007 (200 mg/kg, 52 µCi/kg) to male Sprague Dawley rats (n=3 per time point), absorption was fast yielding a Tmax at 1 - 2 h, whereafter it declined quickly in a bidirectional fashion leaving ~17% at 6 hours after dosing. The radioactivity was eliminated quickly displaying an elimination half-life (T½) of 2.5 - 3 hrs leaving less than 0.4% of Cmax at 24 hrs postdosing.

Multiple dose

The TK of AT007 was studied using adult male and female Sprague Dawley (SD) rats (n=3/time point, n=6/sex) following oral gavage daily dosing (PO, QD), in four multiple dose safety studies, including a non-GLP 10 day study (200, 600 and 2000 mg/kg), a non-GLP 4 week and GLP 13 week study (50, 200 and 1000 mg/kg) and a 26 week GLP study (200, 500 and 1000 mg/kg). The single dose PK of AT007 was only studied on day 1 of multiple dose TK studies.
Following oral administration in rats, AT007 was quickly absorbed reaching almost maximal plasma concentration (C_{max}) at 1 - 2 hrs post-dose, but mostly a delayed/extended absorption was seen reaching C_{max} after 2 – 6 hrs. Thereafter, AT007 concentration declined quickly leaving less than 5% in plasma at 18 hours after dosing (200 mg/kg). Terminal elimination half-life ($t_{1/2}$) values were ~2.4 h, when it could be determined. At the higher dose (600 mg/kg), however, the decline was attenuated and with the highest dose (2000 mg/kg) even an increase in AT007 plasma concentration was seen after 12 h up to 24 hours post-dose. It cannot be established whether enterohepatic circulation plays a role, since no bile studies were performed, or that other processes play a role. Generally, plasma exposure increased sub-proportional with increasing dose, i.e. a 2- and 4-fold increase in C_{max} and AUC_{0-24}, respectively, at a 10-fold increase in dose. Upon multiple dosing for 4, 13 or 26 weeks in the rat safety studies, no apparent accumulation of AT007 was found but instead, at the higher doses, with increasing time (weeks) of dosing an up to 0.4-fold lower exposure was found (AUC_{0-24}) as compared to day 1. In general, no clear sex differences were observed although after 26 weeks of dosing male exposure was ~0.4-fold the female exposure. Distribution volume (V) and clearance (CL) were not established as no intravenous dosing was performed. In addition, the fraction absorbed (Fpo) was also not investigated in rats but the excretion study (see 3.5) suggests that the oral absorption in the rat is at least 5%.

The TK of AT007 was studied using adult male and female Beagle dogs (n=3-5/sex) following oral gavage daily dosing (PO, QD), in four multiple dose safety studies, including a non-GLP 9/10 day study (20, 100, 200, 600 and 2000 mg/kg, n=1), a 4 week GLP (20, 50 and 200 mg/kg), a 13 and a 39 week GLP study (50, 200 and 400 mg/kg). The single dose PK was only studied on day 1 of multiple dose TK studies. Although it is stated that in the dog study 00576533 (n=1) single dose PK was determined, this is not agreed given the short (24 h) postdosing period in relation to the extended time to Tmax for the high doses and the PK profile from 12 to 24 h for the lower doses.
Following an oral administration (20, 100, 200, 600, or 2000 mg/kg) to beagle dogs, AT007 was quickly absorbed reaching maximal plasma concentrations after 2 hour (20, 100), 2 to 6 (200), 2 to 12 (600) and 12 to 18 hours (2000 mg/kg) post-dose. Due to the poor condition of the dogs in the 2000 mg/kg group, dosing was stopped after five days QD dosing and for multiple dose GLP safety studies doses up to a maximum of 400 mg/kg were used.
After Tmax, AT007 plasma concentrations decreased in a multidirectional fashion. Terminal elimination half-life ($t_{1/2}$) values were only determined up to 24h (if possible) and were found to be around 4-5 hours in the multiple dose safety studies. AT007 plasma exposure (AUC0-24) was found to increase subproportional from 200 to 2000 mg/kg, i.e. 5-fold less than the increase in dose, and suprapropportional from 20 to 100/200 mg/kg, i.e. ~2-fold more than the increase in dose, in the 9-day study. For the 4 or 13 week dog safety studies, however, C_{max} and AUC_{0-24} values increased dose proportional with increasing dose, while in the 39 week study a subproportional increase (0.6-fold) was seen. Upon multiple dosing, no apparent accumulation of AT007 (0.6x -1.5x) was found yielding similar C_{max} and AUC_{0-24} values as on day 1. Although variable, in general also no clear sex differences were observed. Distribution volume and clearance were not determined as no intravenous dosing was performed.

3.2.3.3. Distribution

In Vitro

Protein binding studies with AT007 were performed *in vitro* with plasma from dog, rat and human using an equilibrium dialysis method and extracted and analysed by LC-MS/MS. Plasma protein binding of AT007 was high across species and the mean percentage bound was found to be 96.5% to 96.7% in dog, 99.2% to 98.8% in rat and 99.5% to 99.3% in human plasma at 2, 10 and 100 µM AT007. AT007 had a similar binding to human serum albumin (99.5%) but did not bind to human alpha1acid glycoprotein (AAG). At 100 µM, which is close to the human Cmax, the unbound AT007 (% Fu) were 3.3%, 1.2% and 0.7% in dog, rat and human, respectively, indicating that the free AT007 concentration is about 4.7- and 1.7-fold higher in dog and rat than in human plasma.

In Vivo

The blood/plasma (B/P) ratio was only studied *in vivo*, in the rat after ^{14}CAT007 administration (200 mg/kg), and found to be 0.63 after 15 min and 0.61 at 2 hours after dosing, indicating ^{14}CAT007 is mainly distributed in plasma and at low levels in the blood cells (<~15%). It is noted that at 24 and 48 hrs after dosing the B/P increased to 1.9 and 4.1, respectively. Although this may suggest that at that time some [^{14}C]-AT007-derived radioactivity was mainly confined to the blood cells (70-85%), this represents only 0.6% of maximum blood ^{14}C-level.

The *in vivo* tissue distribution of ^{14}CAT007 was investigated using quantitative whole body autoradiography (QWBA) at 0.25h up to 168 hrs post dosing in the male albino Sprague Dawley rat (n=8, 1 animal/time point) after an oral (gavage) dose of 200 mg/kg (166 µCi/kg). Following oral administration, radioactivity was quickly distributed to most tissues studied but was completely absent in eye (lens) and very low (<0.05) in brain, eye (choroid/retina) and yellow fat. The highest ^{14}C-related radioactivity in tissues was found at 1 to 2 hours post dose. Except in the excretory organs

(liver, kidney and small intestinal wall), Tissue to Plasma ratio (T/P) was generally found to be <1 for all tissues during the first 6 hours post-dose, meaning that tissue exposure levels were below plasma levels. Thereafter, radioactivity decreased quickly (T½ <4h) and was BQL (below lower limit of quantitation) in most tissues at 24 hrs after administration, except in the pancreas and the excretory organs (liver, kidney and large intestinal wall). At 48 hours after administration, radioactivity was present in plasma and blood but BLQ in all 27 investigated tissues. Except for the excretory organs, total exposure (^{14}C-AUC) in tissue was less than 30% of plasma exposure for most tissues and in brain even less than 1%.
Information on melanin binding of AT007 is not present as pigmented tissues were not studied but a possible risk for phototoxicity is considered low (see toxicology section 4.9.6). In addition, no information on placental transfer, foetal exposure or milk transfer was investigated but this is expected to occur given the nature of the compound and the extended tissue distribution.

3.2.3.4. Metabolism

In Vitro

The *in vitro* metabolite profile of AT007 was assessed following incubation with hepatocytes from Sprague-Dawley rat, beagle dog, and human. Suspensions of hepatocytes (n=2) containing 10 µM AT007 were incubated at 37°C for 0-360 minutes and thereafter analysed by LC-MS/MS. After a 4-hour incubation, the percentage of AT007 slightly decreased in all samples to 93%, 92% and 94% remaining for rat, dog and human, respectively, but increased thereafter in five of the six samples after 6-hour incubation. Therefore, it is concluded that AT007 was essentially stable in rat, dog, and human hepatocytes, and the half-life for AT 007 could not be reliably determined. Due to the low degree of metabolism of AT007 in hepatocyte incubations, metabolite profiling bioanalysis was not performed.

In vitro metabolism studies using human liver microsomes and in supersomes, i.e. recombinant human cytochrome P450 (CYP) enzymes expressed in insect microsomes, showed no indication of metabolism of AT007 (1 µM) by the major human cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) upon a 240 min incubation, while control compound were in the expected metabolism range.

In Vivo

Following a single oral dose of 200 mg/kg (166 µCi/kg) ^{14}C- AT007 to male Sprague-Dawley rats unchanged AT007 was the only source of radioactivity (100%) in plasma at 1, 2 and 6 hrs post-dose (n=1 animal/time point). However, given that no additional time points were assessed after 6h or reported as BLQ (24h), it cannot be established whether any metabolites are formed in rat plasma.
In faeces (0-48h, n=3), containing ~95% of the total radioactive dose, mainly unchanged AT007 was present (80% of the total recovered dose) and most of the additionally recovered radioactivity was associated with nine metabolites. The only metabolite present at >5% of dose was M8 (6%, AT007+S+CH2). The others were present at 1% - 2% (2% M3, AT007+O;1.8% M4, AT007+O; 1.6% M1, AT007+S+C5H8O4; 1.2% M2, AT007+S+glutamine; 1% M7, unknown) or below 1% (0.9% M6, AT007+S+C2H4O; 0.9% M9, AT007+C4H8; 0.7% M5, AT007+H2O). These faecal metabolites suggests that the metabolic pathways for AT007 involved oxidation (M3, M4), hydrolysis (M5), alkylation (M9), and thiolation. The thiolated metabolite underwent further transformation via methylation (M8), acetylation (M6), and conjugation with glutamine (M2) and a pentose sugar (M1). Urine was not analysed for metabolites due to the low amount of label recovered (~4%). Bile samples were not collected.

From clinical studies, no information on the possible presence of human metabolites is available, which makes interspecies comparison impossible. Therefore, given the results from preclinical studies, i.e. the presumed absence of metabolites in rat plasma, it is noted that, if any human (major) metabolites are identified, these will have to be considered human specific and not being toxicologically assessed.

3.2.3.5. Excretion

The excretion of [^{14}C]-AT007-related radioactivity was investigated in male Sprague Dawley rats (n=3) after an oral dose of 200 mg/kg (166 µCi/kg) and followed for up to 7 days (168 hrs). Following oral administration to the rat, [^{14}C]-AT007-related radioactivity was quickly excreted, predominantly through the faecal route, which accounted for 93% of the radioactivity dose after 24 hrs. The total recovery of radioactivity was high (107%) in the rat and was reached already at three days after dosing. The urinary route (including case wash) contributed 4.8%. Excretion to expired air was not studied in the rat but this is expected to be low given the high ^{14}C-recovery.
No study in BDC (Bile Duct Cannulated) rats has been supplied. Therefore, the contribution of biliary clearance cannot be established.

Excretion in dogs is unknown as no dog mass balance study has been supplied.

3.2.3.6. Pharmacokinetic drug interactions

The results of the pharmacokinetic Drug-Drug Interactions (DDI) studies with AT-007 will be evaluated in the clinical assessment report.

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

The maximum tolerated dose was determined in a non-GLP study (Study 576533) in Beagle dogs receiving 200, 600 and 2000 mg/kg govorestat as a single oral dose in an escalating dose design with a 24-hour washout period between dosing. Both animals lost bodyweight over the study period, correlating with decreased food intake. No other relevant findings were observed, and the MTD was considered 2000 mg/kg (AUC: 9765000 ng/ml/h).

3.2.4.2. Repeat dose toxicity

Repeat-dose toxicity studies with oral administration of govorestat were conducted in Sprague Dawley rats (up to 26 weeks) and in Beagle dogs (up to 39 weeks).

<u>Studies in rat</u>
In a non-GLP dose-range finding study (Study 576532), rats were orally administered 0, 200, 600 or 2000 mg/kg/day govorestat for 10 days. Three 2000 mg/kg/day animals were found dead on day 4 and 9. Although the cause of death remained undetermined, these deaths were considered treatment-related. Slight decreased body weight gain was observed at 2000 mg/kg/day. At doses of ≥200 mg/kg/day (AUC: 1090000 ng.h/ml, margin of exposure based on AUC (MoE): 1.9-fold), animals displayed dose-dependent increases in creatinine levels, without changes in urea nitrogen or microscopic correlates. Additionally, animals displayed dose-dependent increases in extramedullary haematopoiesis in the liver, accompanied by increases in total bilirubin. Male animals also had dose-dependent increases in haematopoiesis in the spleen and erythropoiesis in the bone marrow, accompanied by increased reticulocyte count and increased spleen weight. This was also observed in females, but only in females dosed with 2000 mg/kg/day (AUC: 4490000 ng/ml/h, MoE: 8-fold). This is likely correlated to the decreased red blood cells parameters (e.g. red blood cell count, haemoglobin,

haematocrit) observed at 2000 mg/kg/day. In absence of inflammation signs, the changes in white blood cell parameters (increased white blood cell count, neutrophils, lymphocytes, basophils) in male animals dosed with 2000 mg/kg/day were not considered adverse. Similar findings in the spleen, liver and bone marrow were not observed in other repeat-dose toxicity studies in rat or dogs. Due to the observed deaths at 2000 mg/kg/day, the NOAEL was considered 600 mg/kg/day (AUC: 2330000 ng.h/ml, MoE: 4.2-fold).

In a GLP-compliant study (Study 576534), rats were orally administered 0, 50, 200 or 1000 mg/kg/day govorestat for 4 weeks, followed by a 2-week recovery period. At doses of ≥200 mg/kg/day (AUC: 530000 ng.h/ml, MoE: 0.9-fold), animals displayed dose-dependent increases in creatinine levels, without changes in urea nitrogen or microscopic correlates. At doses of ≥200 mg/kg/day, male animals displayed dose-dependent increases in total bilirubin levels, without microscopic correlates. Decreases in red blood cell parameters were observed in female rats dosed with 1000 mg/kg/day (AUC 1290000 ng.h/ml, MoE: 2.3-fold), accompanied by increased reticulocyte count (latter also observed in recovery animals). Females dosed with 1000 mg/kg/day had increased liver weight, but without microscopic correlates. Additionally, both males and females had increased kidney weight at 1000 mg/kg/day, but also without microscopic correlates with the exception of 1 male demonstrating minimal tubular regeneration. Ventricular dilation in the brain was observed in 2 1000 mg/kg/day females, but since these findings were limited to 1 sex, not in observed in the recovery animals nor in other repeat-dose toxicity studies, these findings were considered incidental. In absence of clear adverse findings, the NOAEL was considered 1000 mg/kg/day (AUC: 1290000 ng.h/ml, MoE: 2.3-fold).

In a GLP-compliant study (Study 20198261), rats were orally administered 0, 50, 200 or 1000 mg/kg/day govorestat for 13 weeks, followed by a 4-week recovery period. At doses of ≥200 mg/kg/day (AUC: 688000 ng.h/ml, MoE: 1.2-fold), male animals had increased kidney weights. Increased kidney weights were also observed for female animals at 1000 mg/kg/kg (AUC: 2200000 ng.h/ml, MoE: 3.9-fold), although in both sexes this was without microscopic correlates. Additionally, high dose animals had increased creatinine levels, without changes in urea nitrogen. Females dosed with 1000 mg/kg/day had decreased red blood cell parameters (haemoglobin, haematocrit). In absence of clear adverse findings, the NOAEL was considered 1000 mg/kg/day (AUC: 2200000 ng.h/ml, MoE: 3.9-fold).

In a final GLP-compliant study (Study 576564), rats were orally administered 0, 200, 500 or 1000 mg/kg/day govorestat for 26 weeks, followed by a 4-week recovery period. At doses of ≥200 mg/kg/day (AUC: 674500 ng.h/ml, MoE: 1.2-fold), male animals had increased creatinine levels. This was also observed for female animals dosed with ≥500 mg/kg/day (AUC: 1374500 ng.h/ml, MoE: 2.4-fold). Males dosed with ≥500 mg/kg/day had decreased red blood cell parameters (haemoglobin, haematocrit). At doses of ≥500 mg/kg/day, male animals had increased kidney and liver weights. Increased kidney and liver weights were also observed for female animals at 1000 mg/kg/kg (AUC: 2295000 ng.h/ml, MoE: 4.1-fold), although in both sexes this was without microscopic correlates. Pars distalis hyperplasia of the pituitary gland was observed, leading to gland enlargement and one incidence of a pars distalis adenoma in females dosed with ≥500 mg/kg/day and in 1000 mg/kg/day recovery female animals. The human relevance of this finding is unknown and requires additional discussion, see Section 4.4 on carcinogenicity. Finally, one 1000 mg/kg/day female had a malignant nephroblastoma with lung metastasis. The Applicant's claim that the NOAEL was 1000 mg/kg/day is currently not accepted because of findings in the pituitary gland that need to be elaborated. In lieu of this discussion, the NOAEL is provisionally set at 200 mg/kg/day (AUC: 674500 ng.h/ml, MoE: 1.2-fold) in this assessment.

Studies in dogs:

In the first phase of a non-GLP study (Study 576533), dogs were orally administered 600 or 2000 mg/kg/day govorestat for 10 days. Toxicokinetic parameters were not included. On day 5, the 2000

mg/kg/day male was euthanized in extremis (treatment-related; decreased activity, tachycardia, decreased body weight, decreased body temperature) and dosing stopped for the female animal dosed with 2000 mg/kg/day. Animals dosed with ≥600 mg/kg/day had decreased body weight, accompanied by decreased food intake and soft/liquid faeces. Additionally, decreased in red blood cell parameters (red blood cell count, haemoglobin, haematocrit, reticulocyte count) were observed. Liver weight was also increased in all animals, without gross necropsy findings. Finally, slight increases in urea nitrogen and creatinine were observed. No NOAEL could be established for this study phase. In the second phase of this study, dogs were orally administered 20, 100 or 200 mg/kg/day govorestat for 9 days, and toxicokinetic parameters were measured. Findings were limited to slightly decreased food intake in all animals dosed with ≥20 mg/kg/day, and decreased red blood cell parameters (red blood cell count, haemoglobin, haematocrit, reticulocyte count) in animals dosed with 200 mg/kg/day (AUC: 1190000 ng.h/ml, MoE: 2.1-fold). In absence of clear adverse findings, the NOAEL was considered 200 mg/kg/day (AUC: 1190000 ng.h/ml, MoE: 2.1-fold).

In a GLP-compliant study (Study 576535), dogs were orally administered 0, 20 50 or 200 mg/kg/day govorestat for 4 weeks, followed by a 2-week recovery period. There were no treatment-related effects on body weight, food consumption, ECG, haematology, coagulation, serum chemistry, urinalysis, or organ weights and there were no ophthalmic, macroscopic, or microscopic findings. The NOEL was considered 200 mg/kg/day (AUC: 646000 ng.h/ml, MoE: 1.2-fold).

In a GLP-compliant study (Study 20198263), dogs were orally administered 0, 50, 200 or 400 mg/kg/day govorestat for 13 weeks, followed by a 4-week recovery period. One 400 mg/kg/day male was euthanized on day 85 and the declining condition was likely due to immunosuppression associated with moderate decrease in hematopoietic cellularity in the bone marrow. This death was not considered treatment related since there were no similar findings in other animals. Animals dosed with ≥200 mg/kg/day (AUC: 603000 ng.h/ml, MoE: 1.1-fold) showed red/purple staining of the paws (without correlating microscopic changes), and minimal to mild mixed cell inflammation of adnexa (surrounding and infiltrating hair follicles and sebaceous glands) accompanied by mucinous edema in the periadnexal region and rare presence of arthropods (mites) in the follicular lumen. These findings were also observed in the recovery animals, but since no effects on the skin are observed in humans, the relevance of this finding is likely low. At doses of 400 mg/kg/day (AUC: 1150000 ng.h/ml, MoE: 2-fold), slight decreases in body weight gain and food intake were observed in the first week of dosing, but recovered shortly thereafter. Additionally, slightly increased creatinine levels were observed, although without microscopic correlates. Since the early death of one animal was not considered treatment-related, the NOAEL was considered 400 mg/kg/day (AUC: 1150000 ng.h/ml, MoE: 2-fold).

In a final GLP-compliant study (Study 20198263), dogs were orally administered 0, 50, 200 or 400 mg/kg/day govorestat for 39 weeks, followed by a 4-week recovery period. One 400 mg/kg/day female was euthanized on day 3, but a clear cause of the poor condition was not determined; neutrophils in the heart were suggestive of septicaemia and this death was not considered treatment related since there were no similar findings in other animals. Male animals dosed with ≥50 mg/kg/day (AUC: 175000 ng.h/ml, MoE: 0.3-fold) showed decreased lymphoid cellularity which resulted in decreased thymus weight at ≥200 mg/kg/day (AUC: 456000 ng.h/ml, MoE: 0.8-fold). This was also observed in 400 mg/kg/day male recovery animals. The relation to govorestat administration is not clear, as these type of findings are common in dogs and could be secondary to stress according to the Applicant (see question below). At doses of ≥200 mg/kg/day, female animals had increased liver weights. Increased liver weights were also observed for male animals at 400 mg/kg/kg (AUC: 769000 ng.h/ml, MoE: 1.4-fold), although in both sexes this was without microscopic correlates. Decreased red blood cells parameters (haemoglobin, haematocrit, reticulocyte counts) were observed in 400 mg/kg/day females, also after the 4-week recovery period. Finally, red/purple staining of the paws was observed between day 48-64 in animals dosed with ≥200 mg/kg/day, but without correlating

microscopic changes and it was not observed in the recovery animals. Since the early death of one animal was not considered treatment-related, the NOAEL was considered 400 mg/kg/day (AUC: 769000 ng.h/ml, MoE: 1.4-fold).

3.2.4.3. Genotoxicity

Govorestat was evaluated in an Ames assay, an in vitro micronucleus assay in human TK6 cells, and in an in vivo micronucleus study in rats. Govorestat demonstrated no mutagenic, clastogenic or auneugenic potential in these assays. No toxicokinetic parameters were measured in the in vivo micronucleus study in rats, although when compared to exposure levels achieved in general repeat-dose toxicity studies in rats at similar dose levels, it is likely that sufficient exposure levels were reached in the in vivo genotoxicity study.

3.2.4.4. Carcinogenicity

To assess the carcinogenic potential of govorestat, the Applicant performed a Weight-of-evidence approach to determine the added value of a 2-year rat carcinogenicity study (see discussion on non-clinical aspects).

3.2.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development:
In a GLP-compliant fertility and early embryonic development study (Study 20436207), rats were orally administered 0, 100, 300 or 1000 mg/kg/day govorestat. Males were dosed 4 weeks prior to mating until day 51-52, and female animals were dosed 2 weeks prior to mating until gestational day (GD) 7. No toxicokinetic parameters were measured. Findings were limited to slightly decreased body weight gain and food intake in males dosed with ≥300 mg/kg/day. Govorestat administration did not impact the reproductive function or fertility at any dose level. Therefore, the NOAEL was considered 1000 mg/kg/day. In the 13-week repeat-dose toxicity study this dose resulted in a AUC: 2200000 ng.h/ml and a MoE: 3.9-fold.

Embryofetal development:
In a GLP-compliant embryofetal development study (Study 576557), female rats were orally administered 0, 200, 400 or 1000 mg/kg/day govorestat from GD 6-17. One 400 mg/kg/day female and four 1000 mg/kg/day females were found dead or euthanized prematurely. These deaths were not considered treatment-related (e.g. oral gavage errors or masses with very early onset). Findings were limited to slightly decreased body weight gain and food intake on GD6-7 in females dosed with 1000 mg/kg/day (AUC: 1840000 ng.h/ml, MoE: 3.3-fold). Govorestat administration did not impact the embryofetal growth and survival and fetal morphology at any dose level. Therefore, the NOAEL was considered 1000 mg/kg/day (AUC: 1840000 ng.h/ml, MoE: 3.3-fold).

In a non-GLP embryofetal development dose-range finding study (Study 576558), female rabbits were orally administered 0, 50, 200, 400 or 1000 mg/kg/day govorestat from GD 7-20. No toxicokinetic parameters were measured. All 400 mg/kg/day and 1000 mg/kg/day females were found dead, euthanized or aborted between GD 11-25. These animals displayed decreased body weight and food intake, decreased fecal output, and 100% post-implantation loss, and these deaths were considered treatment-related. One 50 mg/kg/day female was found dead on GD12 and one 50 mg/kg/day female was euthanized on GD 16, and both animals did not display any remarkable findings at necropsy. These deaths were not attributed to the treatment. Furthermore, findings were limited to animals dosed with 200 mg/kg/day and consisted of slight, but not significant, decreased body weight gain and food intake. Therefore, the NOAEL was considered 200 mg/kg/day.

In a definitive GLP-compliant embryofetal development study (Study 576559), female rabbits were orally administered 0, 20, 50 or 200 1000 mg/kg/day govorestat from GD 7-20. One 50 mg/kg/day female and one 200 mg/kg/day female were found dead on GD 26 and 22, respectively, but the cause of deaths remained undetermined. Other findings were limited to animals dosed with 200 mg/kg/day (AUC: 3030000 ng.h/ml, MoE: 5.4-fold) and consisted of slight decreased body weight gain and food intake. Therefore, the death of the 200 mg/kg/day female was attributed to govorestat, and because of the absence of any relevant findings in the 50 mg/kg/day (AUC: 93300 ng.h/ml, MoE: 0.2-fold) animals, the death of the 50 mg/kg/day female was not considered treatment-related. Govorestat administration did not impact the embryofetal growth and survival nor fetal morphology at any dose level. Therefore, the NOAEL for developmental toxicity was considered 200 mg/kg/day (AUC: 3030000 ng.h/ml, MoE: 5.4-fold), and the NOAEL for maternal toxicity was 50 mg/kg/day (AUC: 93300 ng.h/ml, MoE: 0.2-fold). It should be noted that there was high variety in exposure in the 200 mg/kg/day animals (e.g. 3030000±4390000 ng/h/ml), and the MoE is likely an overrepresentation.

Pre- and postnatal development:

In a GLP-compliant pre- and postnatal development study (Study 20436206), female rats were orally administered 0, 100, 300 or 1000 mg/kg/day govorestat from GD 6 to postnatal day (PND) 20. Toxicokinetic parameters were not measured, nor were govorestat concentrations measured in milk. One 300 mg/kg/day female and one 1000 mg/kg/day female were found dead on GD 7 and 8, respectively. These deaths were attributed to oral gavage errors and were not treatment-related. Findings in surviving animals were limited to slightly decreased body weight gain and food intake on GD6-21 in females dosed with 1000 mg/kg/day. Govorestat administration did not impact the F0 pregnancy, parturition or lactation. There were no adverse effects on F1 pup growth or survival, development or behavioural evaluations, reproductive performance or fertility. Therefore, the NOAEL was considered 1000 mg/kg/day. In the embryofetal development study this dose resulted in an AUC: 1840000 ng.h/ml and a MoE: 3.3-fold.

Juvenile toxicity

In a GLP-compliant juvenile repeat-dose toxicity study (Study 576566), juvenile rats were orally administered 0, 50, 400 or 1000 mg/kg/day govorestat from PND 7-56, followed by a 4-week recovery period. 11 males and 9 females dosed with 1000 mg/kg/day were found dead between PND 8-10. These animals displayed a swollen abdomen, decreased respiration, and decreased bodyweight. Exposure levels were 7010000 ng.h/ml on PND 7 (MoE: 12.5-fold). Due to this high mortality, dosing of 1000 mg/kg/day stopped on PND 9, and new group was formed and dosed with 150 mg/kg/day starting from PND 7. Additionally, 13 males and 12 females dosed with 400 mg/kg/day were found dead between PND 11-22. Exposure levels were 4880000 ng.h/ml on PND 7 (MoE: 8.7-fold).

Surviving animals dosed with ≥150 mg/kg/day (AUC: 463000 ng.h/ml, MoE: 0.8-fold) had decreased body weight gains between PND 7-16, and for animals dosed with 400 mg/kg/day (AUC: 657000 ng.h/mg, MoE: 1.2-fold) this effect sustained untill the end of the dosing period. Kidney weight was increased in female animals dosed with 400 mg/kg/day. In male animals dosed with 400 mg/kg/day, both main and recovery animals, cytoplasmic alteration of renal tubular epithelial cells was observed. Interestingly, in contrast with premature decedents, there were no observations of renal tubular necrosis or other adverse findings in the kidney or urinary bladder in surviving animals at 400 mg/kg/day. Since exposures were significantly higher on PND 7 compared to PND 28 and 56, this could be due to the lower exposures in the older animals.

There were no test article-related effects on developmental landmarks, neurobehaviour or ocular exams at any dosage level tested. Therefore, the NOAEL for juvenile toxicity was 150 mg/kg/day (AUC: 463000 ng.h/ml, MoE: 0.8-fold).

3.2.4.6. Toxicokinetic data

The *in vivo* PK/TK studies with AT007 were conducted via oral administration, which is the intended route of administration in humans, to Sprague-Dawley rats, pregnant New Zealand White rabbits and Beagle dogs, which were used as part of the non-clinical safety program.

Exposure margins in the non-clinical studies were based on AUC, and the following exposure values in humans were used for the calculation: adults dosed with 20 mg/kg/day, AUC= 561 µg.hr/mL, Cmax= 48.6 µg/mL (upper limit values).

3.2.4.7. Tolerance

No dedicated local tolerance studies were conducted with govorestat. This is acceptable.

3.2.4.8. Other toxicity studies

Govorestat demonstrated no phototoxic potential in a neural red uptake (NRU) cell viability assay in Balb/c mouse 3T3 fibroblasts with a mean photo effect (MPE) < 0.1 (MPE govorestat: 0.03).

No adequate discussion on the impurity profile of drug substance and drug product was provided (see discussion on non-clinical aspects).

3.2.5. Ecotoxicity/environmental risk assessment

The PBT assessment could not be finalised since a study determining log Kow was not available.

PECsurfacewater for govorestat was stated to be 0.0053 µg/L, which is calculated by the Applicant based on an Fpen refinement reflecting only the younger proportion of the population currently carrying the disease. However, in the SPC also treatment of adults is indicated. Therefore, an F_{pen} refinement is only accepted based on the prevalence of 1:25 000. This results in a PEC_{sw} of 0.028 µg/L, which exceeds the action limit of 0.01 ug/L for a phase II assessment. The Applicant is, therefore, requested to submit a revised ERA according to guideline EMA/CHMP/SWP/4447/00 containing a full phase II assessment and to submit the study reports of all required studies.

Table 1: Summary of main study results

Substance (INN/Invented Name): govorestat			
CAS-number (if available): 2170729-29-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	TBD	Potential PBT: Y/N
PBT-assessment			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined	0.028	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)	not investigated		
Phase II			
Required but not available			

TBD = to be determined.

3.2.6. Discussion on non-clinical aspects

Pharmacology

The presented results of the *in vitro* microplate assay are insufficiently detailed for a full assessment. The Applicant should provide (1) results of negative and positive control compounds and re-calculations of the IC_{50} based on background correction, (2) test govorestat concentrations <100 pM to identify the minimal inhibition by govorestat, (3) mention which species was tested, (4) include other species in order to allow comparison between human and toxicology species, (5) adapt figure 1, since the lowest concentration tested appears to be 100 pM instead of 10 pM, and (6) provide extensive description of the methods used, *e.g.* including concentrations of NADPH and D-glyceraldehyde and background correction .

In the presented *in vivo* studies, GALT-null (M3/M3) pups were dosed with govorestat from birth. The Applicant is asked to discuss the relevance of the presented studies with regard to the clinical indication, as the results appear to indicate an effect of the use of govorestat on early symptoms rather than prevention of long-term complications including cataracts. Specific attention should be given to the relative immaturity of the pharmacological target organs (kidney, liver, CNS and eye) in newborn rats as compared to adults and children of 2 years and older. Also, the Applicant should discuss the relevance of galactitol reduction in terms of severity of clinical disease and progression in terms of age and tissue involvement, in light of the absence of a beneficial effect in the clinical trial AT-007-1002 (see clinical efficacy, where the result of the change in Z-score does not indicate a nominal statistically significant treatment effect and it is uncertain if there is a clinically relevant effect. In the presented in vivo studies, GALT-null (M3/M3) pups were dosed with govorestat from birth. However, the current indication is aimed at children of at least 2 years old. The Applicant is asked to discuss the relevance of the presented studies with regard to the clinical indication, as the results appear to indicate a preventive effect by the use of govorestat after early treatment rather than a reversal or reduced progression of already established GALT-associated symptoms. Also, the Applicant should discuss the relevance of galactitol reduction in terms of severity of clinical disease and progression in terms of age and tissue involvement, in light of the absence of a beneficial effect in the clinical trial AT-007-1002 (see clinical efficacy), where the result of the change in Z-score does not indicate a nominal statistically significant treatment effect and it is uncertain if there is a clinically relevant effect .

Study 1 appears to be presented as a summary report. The Applicant is requested to provide the full study report, or at least present an extensive description of the methods used, HPLC methods, describe toxicity scoring extensively, present tables describing all data presented in the figures, perform statistical analyses to identify statistically significant differences, and update figures 2, 3 and 5.

Study 2 appears to be presented as a summary report. The Applicant is requested to provide the full study report, or at least present an extensive description of the methods used, HPLC methods, describe toxicity scoring extensively, present tables describing all data presented in the figures, perform statistical analyses to identify statistically significant differences, and update figure 1.

Study 3 appears to be presented as a short report rather than a full report. The Applicant is requested to provide additional information regarding this study, including tables with mean and SD values for galactitol concentrations, cataract scores and govorestat concentrations with statistical analysis for significant differences between dosing groups. Also, the Applicant should justify the selection of t=4 hours for blood sampling for govorestat, as the reported tmax values in the toxicology summaries vary between 1 and 6 hours .

Study 5 appears to be presented as a summary rather than a full report. The Applicant is requested to provide the full study report, or any additional information regarding this study, including tables with mean and SD values for all observed parameters with statistical analysis for significant differences between groups. Also, it appears that statistical analysis has been performed on data presented in figure 2 (Morris water maze testing), whereas this analysis has not been described.

Pharmacokinetics

Following oral administration in rats, AT007 was quickly absorbed reaching almost maximal plasma concentration (C_{max}) at 1 - 2 hrs post-dose, but mostly a delayed/extended absorption was seen reaching C_{max} after 2 – 6 hrs. Thereafter, AT007 concentration declined quickly leaving less than 5% in plasma at 18 hours after dosing (200 mg/kg). Terminal elimination half-life ($t_{1/2}$) values were 2-3h. At the higher dose (600 mg/kg), however, the decline was attenuated and with the highest dose (2000 mg/kg) even an increase in AT007 plasma concentration was seen after 12 h up to 24 hours post-dose. It cannot be established whether enterohepatic circulation plays a role, since no bile studies were performed, or that other processes play a role (transporter / enzymes, inhibition / saturation). Therefore, the Applicant is requested to explain the mechanism behind these high plasma concentrations and discuss the clinical relevance .

Given the presumed absence of metabolites in rat plasma, it is noted that, if any human (major) metabolites are identified, these will have to be considered human specific and not being toxicologically assessed. Therefore, the Applicant is asked to discuss why it can be concluded that all relevant human metabolites are toxicologically assessed).

Based on the excretion data, it can be concluded that there are possible interspecies differences in absorption pathways between rat and human. The oral absorption in the rat is at least 5% and in humans is at least 30% of dose. The applicant is therefore asked to propose major transporter pathways responsible for AT-007 absorption and compare the interspecies expression variability for these transporters in rat, dog and human **.**

Toxicology

Repeat-dose toxicity studies with oral administration of govorestat were conducted in Sprague Dawley rats (up to 26 weeks) and in Beagle dogs (up to 39 weeks). Treatment-related findings were limited to decreases in red blood cell parameters and increases in liver and kidney weight. Decreases in red blood cell parameters were consistently observed in all repeat-dose toxicity studies in rats and dogs, although not always in both sexes, and were considered reversible. There were no clinical or microscopic correlates to these changes, therefore the toxicological relevance for humans is considered limited. Increases in liver and kidney weights were consistently observed in all repeat-dose toxicity studies in rats, and were considered reversible. Increases in liver weight were also observed in dogs, although not always consistent in both sexes. In both species, there were no clinical or microscopic correlates, therefore the toxicological relevance for humans is considered limited. The relevance of hyperplasia findings in the pituitary gland in the rat require additional discussion (see Section on Carcinogenicity), as do the findings in the thymus in the 39-week study in dogs (see question below). Increases in creatinine levels were observed in rats, without changes in urea nitrogen or microscopic correlates. The Applicant states that govorestat interferes in the assessment of creatinine in rat serum, but did not submit a report containing relevant information or provide adequate justification of this observation (see question below). In dogs, incidental increases in creatinine levels were observed, without microscopic correlates.

The NOAEL in rats in the 26-week study is now considered 200 mg/kg/day (AUC: 674500 ng.h/ml, MoE: 1.2-fold), due to the unknown relevance of the findings in the pituitary gland, but a NOAEL of 1000 mg/kg/day (AUC: 2200000 ng.h/ml, MoE: 3.9-fold) was obtained in the 13-week rat study. For dogs, the NOAEL was considered 400 mg/kg/day (AUC: 769000 ng.h/ml, MoE: 1.4-fold) in the 39-week study. It should be noted that exposure margins compared to clinical exposure are relatively low.

In some study reports, the Applicant states that govorestat interferes in the assessment of creatinine in rat serum, and refers to the following reference: "Coash J. A non-GLP Interference Check of Rat Clinical Chemistry Laboratory Tests in the Presence of Test Article AT-007 (Study No. 2764-013). MPI

Research, Mattawan, MI, 2019". However, this report cannot be found and should be submitted. Additionally, the Applicant should clarify whether this interference is applicable to all studies conducted in rats (incl. juvenile toxicity studies), since it is not consistently present in all studies and does not appear to demonstrate a dose/exposure-dependent relation .

To assess the carcinogenic potential of govorestat, the Applicant performed a Weight-of-evidence approach to determine the added value of a 2-year rat carcinogenicity study. In general, it can be agreed that the target biology and secondary pharmacology of govorestat do not indicate a carcinogenic potential. In addition, govorestat is not genotoxic, and no hormonal effects or immune modulation was observed. However, since the pharmacokinetic profile of govorestat is insufficiently studied in humans (see clinical assessment), it cannot be determined whether the non-clinical studies conducted to date are sufficient (see Section 3.2.3 on Pharmacokinetics). No neoplastic or preneoplastic microscopic changes were observed in repeat-dose toxicity studies in rats, excluding a single occurrence of nephroblastoma reported in a 1000 mg/kg/day group female in the 26-week study (Study 00576564). However, the Applicant claims that historical incidence of nephroblastoma at the Charles River laboratory where the study was performed was acquired by "personal communication". Considering that nephroblastoma (Wilms tumour) is a rare type of kidney cancer and that the target organ is identical with data from the juvenile animal study showing inflammation, necrosis, and mortality, it is requested from the Applicant to further substantiate the mentioned historical control data . Of note is that Wilms tumour, or nephroblastoma, is the most common renal cancer in the paediatric age with median age at diagnosis approximately 3.5 years. Additionally, the Applicant did not discuss the relevance of the findings in the pituitary gland. Pars distalis hyperplasia of the pituitary gland was observed, leading to gland enlargement and one incidence of a pars distalis adenoma in females dosed with ≥500 mg/kg/day and in 1000 mg/kg/day recovery female animals. The relevance of this finding is unknown, and the Applicant should provide additional discussion .

The Applicant considered that a WoE sufficiently characterized the carcinogenic potential of goverostat and did not perform either a 6-month TG mouse study nor a 2-year rat study. While a WoE approach in line with S1B(R1) is acceptable, there are concerns surrounding observed hyperplasia that should be discussed (see OC above). The absence of a 6-month TG mouse study is currently not acceptable, since this deviates from the guideline without an adequate justification. This was also mentioned in the previous scientific advice procedure (EMA/SA/0000113524). Therefore, the carcinogenic potential is not adequately addressed. The Applicant should provide an adequate assessment of the carcinogenic potential of govorestat and provide compelling arguments why a 6-month transgenic rasH2 mouse study is not required .

A F-EED study in rats, EFD study in rats and rabbits and a PPND study in rats did not demonstrate adverse effects on reproductive and developmental toxicity. However, there is a notable difference in the maternal toxicity between rabbits and rats in the embryofoetal development studies. The Applicant is requested to compare the affinities to aldose reductase in individual species, pharmacokinetics in individual species and discuss possible consequences for the patient population .

In a GLP-compliant juvenile repeat-dose toxicity study (Study 576566), juvenile rats were orally administered 0, 50, 400 or 1000 mg/kg/day govorestat from PND 7-56, followed by a 4-week recovery period. 11 males and 9 females dosed with 1000 mg/kg/day were found dead between PND 8-10. These animals displayed a swollen abdomen, decreased respiration, and decreased bodyweight. Exposure levels were 7010000 ng.h/ml on PND 7 (MoE: 12.5-fold). Due to this high mortality, dosing of 1000 mg/kg/day stopped on PND 9, and new group was formed and dosed with 150 mg/kg/day starting from PND 7. Additionally, 13 males and 12 females dosed with 400 mg/kg/day were found dead between PND 11-22. Exposure levels were 4880000 ng.h/ml on PND 7 (MoE: 8.7-fold). Findings in these animals consisted of a swollen abdomen, decreased activity, and histopathological findings in the kidney and urinary bladder/urethra. These deaths were considered treatment-related. Most of

these animals displayed renal tubular necrosis which was considered the probable cause of death. Other test article-related renal findings seen in 1 or more premature decedents at 400 mg/kg/day group included tubular mineralization, hyperplasia of the renal pelvic urothelium, inflammation of the renal pelvis, neutrophilic inflammation of the renal papilla, and calculus formation in the renal pelvis. Test article-related effects in the urinary bladder of 400 mg/kg/day premature decedents included hyperplasia, inflammation, dilatation, haemorrhage, and calculus formation. Urothelial hyperplasia with or without associated inflammation was also noted in the urethra (in plane with the vagina) in three females. Dilation of the urinary bladder seen in one male was consistent with urinary tract obstruction and this was also considered a test article-related cause of death. Urinary bladder distention may also have caused the transient swollen abdominal areas noted in multiple animals.

Surviving animals dosed with ≥150 mg/kg/day (AUC: 463000 ng.h/ml, MoE: 0.8-fold) had decreased body weight gains between PND 7-16, and for animals dosed with 400 mg/kg/day (AUC: 657000 ng.h/mg, MoE: 1.2-fold) this effect sustained until the end of the dosing period. Kidney weight was increased in female animals dosed with 400 mg/kg/day. In male animals dosed with 400 mg/kg/day, both main and recovery animals, cytoplasmic alteration of renal tubular epithelial cells was observed. Interestingly, in contrast with premature decedents, there were no observations of renal tubular necrosis or other adverse findings in the kidney or urinary bladder in surviving animals at 400 mg/kg/day. Since exposures were significantly higher on PND 7 compared to PND 28 and 56, this could be due to the lower exposures in the older animals.

There were no test article-related effects on developmental landmarks, neurobehaviour or ocular exams at any dosage level tested. Therefore, the NOAEL for juvenile toxicity was 150 mg/kg/day (AUC: 463000 ng.h/ml, MoE: 0.8-fold).

It is agreed with the Applicant that renal development is delayed in PND 7 rats relative to newborn infant humans. In humans, the main period of nephrogenesis takes place during the third trimester of pregnancy and is complete at birth. In contrast, nephrogenesis in rats does not start until PND 8 and is not completed until PND 11, with maturation of Henle's loop not occurring until PND 21. Therefore, the response in rat pups starting on PND 7 is unlikely to be representative to the current indication for treatment in children > 2 years. To date, no adverse clinical signs indicative of renal toxicity were observed in clinical trials in patients > 2 years. An additional rat juvenile study is ongoing, starting at PND 14, when nephrogenesis in rats reaches a maturation stage comparable to the perinatal days in humans to rule out other mechanisms of kidney toxicity that would be relevant to humans. The Applicant is requested to provide a post-marketing-authorisation commitment to provide data of this study once available to complete the safety assessment for paediatric patients .

Although the Applicant states that aldose reductase does not play a role in the developing human kidney, no adequate discussion or literature is provided to support this statement. The current findings of kidney toxicity in juvenile rats raise concern for the developing human fetus, especially during the third trimester. The Applicant should provide additional discussion on the role of aldose reductase during human development, and potential effects of govorestat on the human fetus during pregnancy. Based on this response, the advice on use of govorestat during pregnancy in SmPC section 4.6 will be adjusted .

In the repeat-dose toxicity studies, increased levels of creatinine were observed. However, the Applicant states that this is due to interference of govorestat in the assessment of creatinine in rat serum. Interestingly, no effects on creatinine are observed in this study, and the Applicant is requested to provide clarification (see repeat-dose toxicity).

No adequate discussion on the impurity profile of the drug substance and drug product was provided in the non-clinical part of documentation. However, with reference to quality assessment and module 3, the limits for specified impurities have been set above the qualification threshold in case of four

impurities and should be qualified. The proposed limits of two impurities could be considered justified. The third impurity can be considered qualified. However, with regard to the fourth impurity, the current non-clinical data is not sufficient to justify the proposed limit. Therefore, the limit has to be tightened in-line with results demonstrated in active substance batches used for preclinical and clinical studies.

Ecotoxicology

The PBT assessment could not be finalised since a study determining log K_{ow} was not available. The applicant is requested to submit a study (including study report) determining an experimentally derived log Kow, preferably using OECD guideline 107. A GLP study is preferred, but a study from peer reviewed, scientific literature is in principle also acceptable, however, the study should be of good quality and contain enough detail to allow for evaluation of study validity .

$PEC_{surfacewater}$ for govorestat of 0.0053 µg/L, calculated by the Applicant, is based on an F_{pen} refinement reflecting the younger proportion of the population currently carrying the disease. However, in the SPC also treatment of adults is indicated. Therefore, an F_{pen} refinement is only accepted based on the prevalence of 1:25 000. This results in a PEC_{sw} of 0.028 µg/L which exceeds the action limit of 0.01 ug/L for a phase II assessment. The applicant is, therefore, requested to submit a revised ERA according to guideline EMA/CHMP/SWP/4447/00 containing a full phase II assessment and to submit the full study reports of all required studies .

3.2.7. Conclusion on non-clinical aspects

Overall, the primary pharmacology studies showed a beneficial effect of govorestat on formation of cataracts and behavioural effects upon dosing with govorestat from day 1 after birth of GALT1 knockout rats. However, a treatment effect was not studied, generating uncertainty with regard to the validity of the animal model used with regard to the current indication. Secondary pharmacology as well as safety pharmacology studies showed no reason for concern associated with govorestat. Several other concerns remain to be answered.

The absorption, distribution, metabolism, and excretion (ADME) of AT-007 was evaluated in *in vitro* systems and *in vivo* in the rat only. In addition, the *in vivo* multiple-dose TK of AT007 was conducted via oral administration in Sprague-Dawley rats, pregnant New Zealand White rabbits and Beagle dogs, which were used as part of the non-clinical safety program. From the pharmacokinetic point of view, several issues have been identified, which have to be addressed before marketing authorization, in particular, whether any human metabolites are formed, given the presumed absence of metabolites in rat plasma.

The toxicology studies identified several issues regarding carcinogenicity and juvenile toxicity which have to be addressed before marketing authorization.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 2: Overview of clinical efficacy studies

Study	Study Design/Objectives	Part	Study Population	Subjects (N)	Dose	Duration/length of exposure	Status
AT-007-1001	Placebo-controlled, dose-escalating SAD/MAD study to evaluate the safety and PK of single and multiple escalating doses of govorestat in healthy volunteers, and safety, PK and galactitol reduction in adult subjects with Classic Galactosemia (CG)	D, Part D Extension	Adults with CG	33 adults with CG	5, 20, 40mg/kg	Up to 3 months	Completed
AT-007-1006	Open-Label Extension for patients who completed govorestat-1001 Part D and/or Part D Extension	N/A	Adults with CG	7 adults with CG	20mg/kg	18 months	Completed
AT-007-1002	Randomized, double-blind, placebo-controlled adaptive sequential study (dose escalation, safety, PK, PD, clinical outcomes)	A, B	Children with CG age 2-17	47 paediatric subjects with CG	Dose escalation, followed by long-term dosing at 15mg/kg (>40kg); 20mg/kg (20-40kg); 30mg/kg (<20kg)	Minimum 18 months (oldest children exposed for 22 months)	Double-blind portion completed; open-label extension ongoing in children randomized to placebo in blinded portion of the study

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Govorestat inhibits the conversion of galactose to galactitol. Govorestat is indicated for the treatment of adults and children aged 2 years and older with a confirmed diagnosis of classic galactosemia, also known as galactose-1-phosphate uridylyltransferase deficiency. The recommended dose is 15 mg/kg in paediatric patients weighing >40 kg, 20 mg/kg in paediatric patients weighing 20 to 40 kg and in adults and 30 mg/kg in paediatric patients weighing <20 kg. Govorestat is available as oral suspension with a strength of 200 mg/mL.
The clinical pharmacology of govorestat was assessed in healthy volunteers (3 studies) and patients with classic galactosemia (3 studies). Dedicated healthy volunteer studies assessed the relative bioavailability of different formulation used in the clinical studies. No clinical studies were conducted regarding the effect of food and the effect of renal and hepatic impairment. In addition, no mass balance and clinical drug-drug interaction studies were conducted.
Several *in vitro* studies were performed investigating the permeability, plasma protein binding, metabolic stability in human liver microsomes and human hepatocytes and if govorestat was a substrate of CYP enzymes and transporters. Furthermore, *in vitro* studies were performed to investigate whether govorestat was an inhibitor of CYP and UGT enzymes or transporters or an inducer via AhR, CAR and PXR.

Physicochemical properties
Govorestat ($C_{17}H_{10}F_3N_3O_3S_2$) has a molecular weight: 425.4 g/mol and a pKa of 3.45. Furthermore, govorestat is very soluble in water and buffer (pH 2 to 8). Govorestat has no chiral centres.

Analytical methods
Govorestat was analysed in human plasma, urine, and cerebrospinal fluid (CSF) using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) methods. The plasma (in K_2EDTA) and CSF assays were validated. The bioanalytical method for measuring govorestat in human urine (in K_2EDTA) was an extension of the bioanalytical method for measurement in plasma and was qualified. Additionally, galactose and galactitol were analysed in human plasma.

Population pharmacokinetics (PopPK) modelling
The Applicant developed a PopPK model with the purpose to explore potential demographic factors that may influence the PK of govorestat, to develop a PK/PD model to describe the time-course of plasma galactitol following administration of govorestat and to conduct model-based simulations to support the dosing regimen for govorestat. The final PopPK model is a two-compartment model with first-order absorption, absorption lag time and first-order elimination. The model included a separate F1 term for patients, with a 42% higher F1 estimated compared to healthy adults. Covariates evaluated were age, body weight, BMI, renal function (Cockcroft-Gault), hepatic function, baseline galactitol (for PK/PD model only) and the following categorical covariates: gender, race/ethnicity, health status (healthy adults and patients) and dose. No significant covariates were identified for ETA versus covariate plots, thus no covariates were included in the PopPK model.

PK/PD model
A PK/PD model was developed. The model is informed with the simulated govorestat PK data from the PopPK model.

Exposure-response modelling

The Applicant did not provide an exposure-efficacy and exposure-safety relationship.

Absorption

An *in vitro* study using MDCK cells was conducted to investigate the permeability of govorestat over a dose range of 0.1 µM to 100 µM. The P_{app} from apical to basolateral ranged between 2.56 and 7.65 × 10^{-6} cm/s and the P_{app} from basolateral to apical ranged between 0.68 and 2.84 × 10^{-6} cm/s. Overall, this indicates that govorestat is a low permeability compound.

The pharmacokinetics of govorestat after a single dose in healthy adult volunteers were investigated in studies 1001 (Part A-C), 1004 and 1007 in the dose range of 0.5 to 40 mg/kg. After a single oral dose, govorestat is absorbed at a moderate rate with a median t_{max} of 4 hours ranging between 2.0 to 12.0 hours at a dose of 20 mg/kg. The intended commercial formulation further demonstrated a mean C_{max} of 45.6 µg/mL, mean $AUC_{0\text{-}tlast}$ of 435 µg*h/mL and mean $AUC_{0\text{-}inf}$ of 471 µg*h/mL. The proposed dose of 30 mg/kg and 15 mg/kg in paediatric patients weighing <20 kg and >40 kg, respectively, were not investigated in healthy adult volunteers. The inter-subject variability in healthy adult volunteers ranged between 19-103% for C_{max} and between 18-75% for AUC. C_{max} and $AUC_{0\text{-}tlast}$ after a single dose increased less than dose-proportionally in the dose range 0.5 to 5 mg/kg. In the dose range 5 to 40 mg/kg both parameters increased dose-proportionally.

Multiple dose pharmacokinetics in healthy adult volunteers were investigated in study 1001 (Part B-C) in the dose range of 5 to 40 mg/kg once daily. The median t_{max} on Day 7 was 4 hours (range: 2-8 hours) and was comparable with the single dose. As samples were taken only at Day 1 and 7, it is not known if steady state was reached at Day 7 in healthy volunteers. However, based on the longest $t_{1/2}$ observed across the studies of 27.2 hours, it is very likely that steady state is reached at or before Day 7. The accumulation ratio ranged between 1.2 to 2.0 for C_{max} and 1.5 to 3.3 and $AUC_{0\text{-}tau}$. The accumulation is dose-dependent as the ratio becomes higher with increasing doses which is in line with the observed decrease in CL over time dependent of dose.

Urinary excretion data only indicates that at least 30% is bioavailable. No absolute oral bioavailability, mass-balance and food-effect studies were conducted.

The majority of the Phase I/II clinical studies were performed with govorestat 200 mg/mL suspended in a vehicle and pure govorestat powder in capsule formulations. The intended commercial formulation is 200 mg/mL govorestat suspended in another vehicle, which was only used in 1 clinical study to demonstrate comparable bioavailability in healthy adult volunteers with the suspension in the first formulation. Bioequivalence could not been shown for the different formulation. However, the systemic exposure of govorestat from all three formulations can be considered sufficiently similar and clinical data generated with these formulations can be bridged.

Distribution

The plasma protein binding of govorestat is >99% using equilibrium dialysis. The blood-to-plasma ratio was not determined for govorestat.

Based on the data derived from clinical studies 1001 (Parts A-C), 1004 and 1007, the apparent volume of distribution (Vd/F) of govorestat is 40.2-113.0 L after a single dose and 52.6–83.6 L after multiple doses. Govorestat crosses the blood-brain barrier. Concentrations in CSF ranged from 15.2 to 31.8 ng/mL for the 20 mg/kg dose and 20.9 to 71.9 ng/mL for the 40 mg dose. Relative to the mean C_{max} observed for these doses at Day 7, this is 0.03–0.07 % for the 20 mg/kg dose and 0.03–0.10% for the 40 mg/kg dose.

Metabolism

The *in vitro* metabolism of govorestat was investigated in human liver microsomes and human hepatocytes. Following a 4 hour incubation with human liver microsomes and a 6 hour incubation with human hepatocytes of govorestat, no to very limited (<2%) metabolism was observed. These results indicate that the *in vitro* metabolism of govorestat via CYP is limited. Govorestat may be metabolised by CYP3A4 to a very limited extent. No other enzymes were investigated, e.g. UGT.
No mass-balance study was conducted. Instead, plasma samples at 2 and 8 hours post-dose were collected from 11 healthy subjects to evaluate the presence of nine metabolites identified in rats. No other metabolites were investigated. The primary component in the circulation was parent compound, which was present at 98% of relative observed intensity.

Transporters

In vitro studies were conducted to investigate if govorestat (0.1-100 µM) is a substrate of the transporters Pglycoprotein (MDR1) and BCRP using transfected MDCKII cells. Govorestat is a substrate of BCRP, but not of P-glycoprotein. No other transporters were investigated.

Excretion

No mass balance study or absolute oral bioavailability study was conducted. Urine was collected pre-dose and in 4 hour intervals for the first 24 hours, followed by 12 hour intervals from 24 to 72 hours post-dose. In healthy volunteers, 26% to 30% of the dose was excreted as govorestat in urine following a dose of 20 mg/kg and 40 mg/kg, respectively.
In the clinical studies, the elimination half-life of govorestat ranged from 7 to 27 hours in healthy volunteers after a single dose and from 10 to 16 hours after multiple doses. Using mean AUC_{last} values and amounts excreted in urine in those groups, renal clearance is estimated to be 1.1 to 1.3 L/h. Furthermore, observed values at Day 1 and Day 7 indicate that bodyweight corrected CL/F decreases in time in a dose-dependent manner in the range of 32-63% with more pronounced decrease observed at higher doses.

Pharmacokinetics in target population

The PK of govorestat was investigated in adult patients at a dose of 5 mg/kg, 20 mg/kg and 40 mg/kg once daily and in paediatric patients aged 2 to 18 years at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg (not for the 2-6 year age group) and 40 mg/kg once . In addition, the PK following repeated dosing in open label studies was investigated in patients with a dose of 30 mg/kg in paediatric patients weighing <20 kg, a dose of 20 mg/kg in paediatric patients weighing 20-40 kg and adult patients and 15 mg/kg in paediatric patients weighing >40 kg.
After a single oral dose, govorestat is absorbed at a moderate rate with a median t_{max} of 4 hours ranging between 2.0 to 12.0 hours. In adults, the mean C_{max} was 48.6 µg/mL, the mean $AUC_{0\text{-}tau}$ was 420 µg*h/mL and mean $t_{½}$ was 9.6 h. Following repeated dosing, no accumulation in C_{max} was observed in patients aged 2-6 years and 7-12 years and adult patients at a dose of 20 mg/kg.
Based on the current provided data, the t_{max} appears to be similar in healthy adults and patients and between the different age groups in patients. Also the C_{max} at a dose of 20 mg/kg appears similar between healthy volunteers and adult patients. However, the AUC appears to be higher in patients compared to healthy volunteers. In addition, PK appears to be different in patients aged 2 to 6 years. C_{max} and AUC following repeated dosing is lower (no accumulation, but decrease in exposure) and CL/F

is higher. The posologies of 15 mg/kg and 30 mg/kg cannot be compared between healthy volunteers and patients, since these dosages have not been investigated in healthy volunteers.
The accumulation following repeated dosing appears to be different in patients versus healthy volunteers. No accumulation in C_{max} was observed in patients aged 2-6 years and 7-12 years and adults at a dose of 20 mg/kg. This seems contradicting with the observed accumulation ratio in healthy adults.
In adult patients the inter-subject %CV for AUC ranged between 19-44% after a single dose and 23-61% after multiple doses of govorestat. The inter-subject %CV for C_{max} ranged between 27-31% after a single dose and 15-71% after multiple doses of govorestat.
In paediatric patients the inter-subject %CV for AUC ranged between 5-90% after a single dose and 12-136% after multiple doses of govorestat. The inter-subject %CV for C_{max} ranged between 14-93% after a single dose and 14-235% after multiple doses of govorestat. The variability for AUC and C_{max} is high and the range of the %CV is wide in healthy volunteers and patients. However, it should be noted that the number of included subjects is low in these studies. Thus, no robust conclusion can be made regarding the variability of govorestat.

Special populations

Impaired renal function/hepatic function
No dedicated clinical studies were conducted to investigate the effect of renal impairment and/or hepatic impairment on the PK of govorestat. Kidney function and liver function were investigated as a covariate in a PopPK model and were not significant.

Body weight, age, gender and ethnic factors
The PopPK model was used to investigate the effect of age, gender, race, body weight, BMI, kidney function (as creatinine clearance) and liver function (number of liver function tests) on the PK of govorestat. No significant covariates were identified.

Pharmacokinetic interaction studies

Govorestat as victim
It is currently unknown if govorestat is metabolised to a significant extent. No clinical DDI studies with govorestat as victim were performed. *In vitro* studies indicated that govorestat is a substrate of BCRP, but not of P-glycoprotein. No other transporters were investigated.

Govorestat as perpetrator
No clinical DDI studies with govorestat as perpetrator were conducted. *In vitro* studies were conducted to investigate the inhibition and induction potential of govorestat towards CYPs, UGTs and transporters. *In vitro* studies indicate that govorestat is not a direct inhibitor of CYPs at maximal systemic concentrations (57.1 µM). Additionally, the time-dependent inhibition potential of govorestat was investigated. Govorestat appears to be a mechanism-based inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2C19. Also, govorestat is an inhibitor of the intestinal UGTs 1A1 and 2B7 at maximal intestinal concentrations, but not of UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15, and 2B17 at maximal systemic concentrations. Govorestat is an inhibitor of BCRP at maximal intestinal concentrations. It is unknown if govorestat is an inhibitor of P-glycoprotein at maximal intestinal concentrations. Govorestat is an inhibitor of OATP1B1 and 1B3 at maximal portal vein concentrations. At maximal systemic concentrations govorestat is an inhibitor of BCRP, OATP1B1, OAT1, OAT3 and BSEP. No clinical DDI studies are warranted towards BSEP. Liver toxicity was observed which may be explained by the inhibition potential of govorestat towards BSEP and potential accumulation of bile salts. Furthermore, govorestat is an

inducer of CAR and PXR at maximal systemic concentrations. At a concentration of 50 µM, mRNA increase of >20% of the positive control was observed for CYP2B6, 2C8, 2C9, 2C19 and 3A4.

3.3.1.2. Pharmacodynamics

Mechanism of action

Govorestat is a potent, selective, CNS penetrant, aldose reductase inhibitor, which inhibits the conversion of galactose to galactitol.

Primary and Secondary pharmacology

In both adults and children with CG, galactitol reduction was rapid, beginning on the first day of treatment, and sustained through 18 months. Galactitol was reduced by 46% compared to baseline in adults with CG to 65.3 µmol/l (1175ng/ml)) and 40% compared to baseline in children 2-17 years old with CG (41.3 µmol/l (743ng/ml)). In adults there appears to be a dose response plateau somewhere between 20 and 30 mg/kg dose. A reduction from baseline with 40 to 50% appears to be the maximal effect.

As already discussed the role of galactitol – especially in concentrations seen in patients on diet -is currently under discussion with other metabolites under investigation.

There was no noteworthy change in pre-dose galactose levels throughout the study compared to baseline.

There was no noteworthy change in pre-dose Gal-1P levels throughout the study compared to baseline.

The effects of effects of age or genetic polymorphism were not studied.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics
Analytical methods
Several issues were identified hampering the validation of the analytical method for govorestat. No information on storage time of the plasma samples was submitted for studies 1004 and 1007. Also, the ISR of the urine samples in study 1001 (part A) was performed after a storage period of 760 days which is outside the established long-term stability period. The Applicant should submit the data regarding the storage period of the plasma samples for studies 1004 and 1007. Furthermore, unless otherwise justified, additional long-term stability data up to 760 days in urine samples should be submitted by the Applicant to substantiate the reliability of the measurements in study 1001 (part A) . During the clinical studies, participants used co-medications. However, the interference of these co-medications with the bioanalytical analysis of govorestat was not validated. If not otherwise justified, the interference with these co-medications should be validated for the bioanalytical methods . Intra-assay and inter-assay performance of the QCs were within ±15% for all QC-levels including the LLOQ QC for the plasma and CSF bioanalytical methods. However, for the bioanalytical method for urine, no LLOQ QC was included for the qualification of the method. Also, no inter-assay QC performance was reported. Lastly the intra-assay %CV for Run 4 was not reported as part of the QC performance. The Applicant should submit this information or justify this by discussing the impact of the lack of this information on the assay performance for urine . Inter-assay accuracy and precision values were within the ±15% criteria for most clinical study analyses. However, no QCs were included in the bioanalytical runs for the samples of studies 1004 and 1007. The Applicant should discuss the reliability of the results and the impact of the lack of QCs for these analyses . No ISR was performed for the measurements in plasma for studies 1004

and 1007 and for study 1001 (part D extension) the ISR is not within the criteria. The ISR results are within the criteria for the analysis of govorestat in urine in study 1001 (part A), but this was performed outside the established long-term stability period. Lastly, no ISR was performed for the measurements of govorestat in CSF in study 1001 (part C). The Applicant should discuss the relevance and impact of the results that did not meet the criteria and/or lacking ISR measurements for the mentioned studies.
Additionally, several issues were identified hampering the validation of the analytical method of galactose and galactitol. Regarding the galactitol analyses, in study 1001 6 freeze/thaw cycles were used during sample analysis, which is more than the validated freeze/thaw cycles of 4. According to bioanalytical study report, the number of validated freeze/thaw cycles was 7, which should be reported in report 188910. However, this data could not be found. The Applicant should submit this data . For the bioanalytical method for galactose analysis, high %bias and %CV were observed during the qualification. During clinical sample analyses, %bias values of -4.08% to 14.8% and %CV up to 37.8% was observed in studies 1001 and 1002. Also, selectivity was not investigated for the method qualification. Furthermore, the storage time of the clinical samples exceeded the established long term stability period in for studies 1002 and 1006. In addition, the number of freeze/thaw cycles during sample storage exceeded the validated number of freeze/thaw cycles in studies 1001, 1002 and 1006. Lastly, no ISR was performed to check the reproducibility. Thus, taking into account the above mentioned points, the Applicant should reflect and comment on the overall performance of the bioanalytical method for galactose analysis and discuss the relevance and impact of the observed mentioned issues during the method qualification and clinical study sample analyses .

Population pharmacokinetics (PopPK) modelling

Several issues were identified regarding the model on the following topics: only study data from study 1001 was included, no paediatric data was included, data in healthy volunteers underpredicted the data in patients (a 42% higher bioavailability for correction was used) and a possible time and dose-dependent inhibition mechanism should be investigated in the model if this can solve the underprediction in patients. Based on these considerations, the model should be updated and model parameters and covariates should be re-estimated. Diagnostics should be provided .

PK/PD model

Since the PopPK model is currently not acceptable and should be updated, the PK/PD relationship is currently also not acceptable. Therefore, the PK/PD-model should be updated accordingly including all informative PK and PD data from the submitted studies of the adults and paediatric population .

Exposure-response modelling

No efficacy was observed. Therefore, no exposure-efficacy relationship can be shown. However. the Applicant is requested to provide the exposure-safety relationship for paediatric and adults .

Absorption

After multiple dosing in healthy volunteers_in the dose range of 5 to 40 mg/kg once daily, the accumulation ratio ranged between 1.2 to 2.0 for C_{max} and 1.5 to 3.3 and $AUC_{0\text{-}tau}$. The accumulation is dose-dependent as the ratio becomes higher with increasing doses which is in line with the observed decrease in CL over time dependent of dose. Thus, the accumulation ratio at dosages of 15 mg/kg and 30 mg/kg (paediatric posology) is different than the accumulation at the clinical dose of 20 mg/kg (paediatric and adult posology). Since there are uncertainties regarding the posology, the Applicant is requested to provide a discussion on the differences in accumulation between the different posologies (15 mg/kg, 20 mg/kg and 30 mg/kg) and the potential clinical consequences for safety .
No absolute oral bioavailability study was conducted. It is therefore unknown how much of the administered dose is absorbed. The Applicant is requested to include investigation of the absolute oral bioavailability in a mass balance study .

No food effect study was conducted by the Applicant. It is therefore unknown if exposure from the commercial formulation (oral suspension) is affected by food. Currently, it is advised to take govorestat approximately at the same time each morning following an overnight fast and 2 hours prior to food consumption. This advice is not acceptable, especially not in paediatric patients, without sound justification. Therefore, the Applicant is requested to perform a food effect PK study .

Distribution

The blood-to-plasma ratio was not determined for govorestat. It is therefore unknown if govorestat does not accumulate in red blood cells The Applicant is requested to provide the blood-to-plasma ratio for govorestat over the clinically relevant concentration range .

Metabolism

Govorestat may be metabolised by other enzymes than CYP. No other enzymes were investigated in *in vitro* studies, e.g. UGT. Since there is no mass balance study, it is unknown if other enzymes need to be investigated.

Regarding the analyses of potential metabolites in plasma samples from 11 human healthy volunteers from clinical studies, the t_{max} of govorestat is around 3 to 5 hours and the $t_{½}$ is 7 to 27 hours. Therefore, the samples collected at 2 and 8 hours are not representative to identify potential metabolites and the biotransformation pathway of govorestat. The Applicant is requested to perform a mass balance study and investigate if govorestat is metabolised or not. The Applicant is advised to take into account that some glucuronide metabolites are not stable and samples need to be acidified in order to be analysed(.

Transporters

Govorestat is distributed to the CNS and is thus able to pass the blood-brain barrier. The Applicant is requested to investigate if govorestat is a substrate of transporters in the blood-brain barrier (e.g. OATP1A2 and OATP2B1) . In addition, the elimination pathway (direct elimination in urine and faeces or as metabolite) is currently unknown since a mass balance and absolute oral bioavailability study are lacking. At least 30% of the administered dose is eliminated as parent compound in urine. Therefore, it should be investigated if govorestat is a substrate of renal transporters (e.g. OAT1 and OCT2) . Based on the outcome of mass balance study, additional transporter studies may be warranted .

Excretion

Only govorestat was analysed in urine and it therefore unknown if govorestat may be eliminated as metabolite (e.g. glucuronide metabolite) or only as parent compound in urine. Furthermore, it is unknown if the observed 30% eliminated in urine is the majority of the absorbed material or that also a significant fraction is eliminated via faeces (either as parent or as metabolite) since the fraction absorbed as parent compound is unknown. The Applicant is requested to perform a mass balance study and determine the absolute oral bioavailability .

In healthy volunteers, observed values at Day 1 and Day 7 indicate that bodyweight corrected CL/F decreases in time in a dose-dependent manner in the range of 32-63% with more pronounced decrease observed at higher doses. This indicates a time and dose dependent inhibition of a clearance mechanism of govorestat. The Applicant should discuss and substantiate which clearance mechanisms of govorestat are involved in this process .

Pharmacokinetics in target population

The blood sampling scheme in study 1002 does not appear suitable to predict the PK of govorestat in paediatric patients accurately. Up to 12 hour samples were collected at Day 5. The elimination half-life is >16 hours following repeated dosing. Furthermore, blood samples for PK assessment were obtained in Part B following a single dose, but PK data following a single dose for the proposed posology in paediatric patients were not provided.

The Applicant is requested to include the obtained concentration data into the PopPK model and determine the PK of govorestat with the updated PopPK model. Furthermore, the Applicant should provide a comparison of the C_{max}, C_{trough} and $AUC_{0\text{-}24h}$ following a single and following repeated dosing in adult healthy volunteers and in paediatric and adult patients for the proposed posology . In order to compare the exposure between healthy volunteers and patients and between different patient age categories.

Special populations

Impaired renal function/hepatic function

No dedicated clinical studies were conducted to investigate the effect of renal impairment and/or hepatic impairment on the PK of govorestat and the PopPK model is currently not suitable to investigate the effect of covariates. It is therefore currently unknown if renal impairment and/or hepatic impairment may have a clinically relevant effect on the PK of govorestat. Based on the outcome of the mass balance and absolute bioavailability study a dedicated renal impairment/hepatic impairment study may be warranted .

Body weight, age, gender and ethnic factors

The PopPK model was used to investigate the effect of age, gender, race, body weight, BMI, kidney function (as creatinine clearance) and liver function (number of liver function tests) on the PK of govorestat. However, the PopPK model is currently not suitable to investigate the effect of covariates on the PK . Furthermore, the Applicant is requested to provide the age table .

Pharmacokinetic interaction studies

Govorestat as victim

Since the absolute oral bioavailability of govorestat is unknown, concomitant administration of govorestat with a BCRP inhibitor may lead to a clinically relevant higher exposure of govorestat. In addition, it is currently unknown if govorestat is metabolised to a significant extent. Based on the outcome of the mass balance and absolute oral bioavailability study and additional *in vitro* transporter substrate studies, clinical DDI studies with govorestat as victim may be needed. The outcome of the requested studies are awaited before it can be assessed if clinical DDI studies with govorestat as victim are warranted or not.

Govorestat as perpetrator

In vitro studies indicate that govorestat is not a direct inhibitor of CYPs at maximal systemic concentrations (57.1 µM). However, the maximal intestinal concentration (1881 µM) is much higher than the maximal investigated concentration of 100 µM. It is therefore unknown if govorestat is an inhibitor of CYP3A4 at maximal intestinal concentrations. The Applicant is requested to investigate the *in vitro* inhibition potential of govorestat towards CYP3A4 at maximal intestinal concentrations .

Govorestat appears to be a mechanism-based inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2C19. No metabolites were formed *in vitro*, but time-dependent inhibition was observed. The Applicant is requested to explain this result and discuss if additional clinical DDI studies are warranted .

Govorestat is an inhibitor of the intestinal UGTs 1A1 and 2B7 at maximal intestinal concentrations, but not of UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B15, and 2B17 at maximal systemic concentrations. The Applicant is requested to conduct a clinical DDI study with govorestat as perpetrator following a single dose towards UGTs or provide reasoning why such a study is not warranted .

It is unknown if govorestat is an inhibitor of P-glycoprotein at maximal intestinal concentrations, since the maximal intestinal concentration (1881 µM) is much higher than the maximal investigated concentration of 100 µM. The Applicant is requested to investigate if govorestat is an inhibitor of P-glycoprotein at maximal intestinal concentrations .

Govorestat is an inhibitor of OATP1B1 and 1B3 at maximal portal vein concentrations. At maximal systemic concentrations govorestat is an inhibitor of BCRP, OATP1B1, OAT1, OAT3. Thus, the Applicant is requested to conducts a clinical DDI study with govorestat as perpetrator following a single dose towards BCRP, OATP1B1, OATP1B3, OAT1, and OAT3 .

As induction potential of govorestat is observed in the *in vitro* studies, the Applicant is requested to conduct a clinical DDI study with govorestat as perpetrator following repeated dosing towards CYP2B6, 2C8, 2C9, 2C19 and 3A4 .

In the clinical studies, patients with classic galacotosemia were co-treated for the management of seizure disorders, ADD/ADHD, anxiety, and depression. Additionally, co-treatment with oestrogen compounds

for primary ovarian insufficiency was commonly employed in female patients. If these medicinal products are metabolised CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UGT1A1 and 2B7, or transported by BCRP, OATP1B1, OATP1B3, OAT1, and OAT3, the exposure of these medicinal products may be decreased, which may lead to decreased efficacy, or increased, which may lead to increase side effects. The results from the requested clinical DDI studies is awaited before dose recommendations with co-medication can be given.

3.3.3. Conclusions on clinical pharmacology

The pharmacokinetics of govorestat were assessed in healthy volunteers (3 studies) and patients with classic galactosemia (3 studies). A number of major objections were raised regarding the lack of a mass balance and absolute bioavailability study, issues regarding the PopPK and PK/PD model, the lack of a food effect study and the pharmacokinetics in special populations. Furthermore, a number of concerns were raised regarding the bioanalytical method, the lack of exposure-safety relationship, the accumulation of govorestat in red blood cells, if govorestat is a substrate for the blood brain barrier transporters or renal transporters, a possible time and dose-dependent inhibition mechanism, uncertainties on the accumulation at 15 mg/kg and 30 mg/kg paediatric doses, comparison of PK differences in healthy subjects versus patients, the age table and various questions requesting *in vitro* and *in vivo* interaction studies.

3.3.4. Clinical efficacy

Table 3: Overview of clinical efficacy studies

Study	Study Design/Objectives	Part	Study Population	Subjects (N)	Dose	Duration/length of exposure	Status
AT-007-1001	Placebo-controlled, dose-escalating SAD/MAD study to evaluate the safety and PK of single and multiple escalating doses of govorestat in healthy volunteers, and safety, PK and galactitol reduction in adult subjects with Classic Galactosemia (CG)	D, Part D Extension	Adults with CG	33 adults with CG 18 patients in part D 15 patients in part D extention	5, 20, 40mg/kg	Up to 3 months	Completed
AT-007-1006	Open-Label Extension for patients who completed govorestat-1001 Part D and/or Part D Extension	N/A	Adults with CG	7 adults with CG	20mg/kg	18 months	Completed
AT-007-1002	Randomized, double-blind, placebo-controlled adaptive sequential study (dose escalation, safety, PK, PD, clinical outcomes)	A, B	Children with CG age 2-17	47 paediatric subjects with CG	Dose escalation, followed by long-term dosing at 15mg/kg (>40kg); 20mg/kg (20-40kg); 30mg/kg (<20kg)	Minimum 18 months (oldest children exposed for 22 months)	Double-blind portion completed; open-label extension ongoing in children randomized to placebo in blinded portion of the study

3.3.4.1. Dose-response studies

Study AT-007-1001 is a first-in-human, randomized, placebo-controlled, 6-part, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy adult subjects and adult subjects with CG. The study assessed the safety and PK of govorestat in these subjects as well as the effect of govorestat on biomarkers of galactose metabolism (galactose, galactitol, and other galactose metabolites) in subjects with CG.

Table 4: Overview of study AT-007-1001

Study Part	Study Population	Design	Planned Number of Cohorts	Planned Subjects Per Cohort	Total # of Planned Subjects
A	Healthy adult subjects	SAD	5 double-blind cohorts (A1 - A5)	8 (6 active and 2 placebo) each	40
B	Healthy adult subjects	MAD (QD for 7 days)	4 double-blind cohorts (B1 - B4)	2 double-blind cohorts of 8 subjects (6 active and 2 placebo) each and 2 double-blind cohorts of 6 subjects (4 active and 2 placebo) each	28
C	Healthy adult subjects	MAD (QD for 7 days)	3 open-label cohorts (C1 - C3)	4 subjects each	12
D	Adult Subjects with CG	SAD, 5-day washout, MAD (QD for 27 days)	3 cohorts (D1 - D3)	6 subjects (4 active and 2 placebo) each (the clinical site staff and the subjects blinded to study treatment)	18

Abbreviations: CG = Classic Galactosemia; MAD = multiple ascending dose; QD = once daily; SAD = single ascending dose

The starting dose in Part A was 0.5 mg/kg as a single dose. Subsequent doses in Part A and all doses in Parts B, C, and D were based on the results of previous cohorts and/or previous parts of the study.

Govorestat (capsules or liquid suspension; single and multiple oral doses) was administered QD under fasting conditions for up to 7 days in healthy subjects and up to 27 days in subjects with CG who tolerated a previous single dose.

Oral doses between 0.5 and 40 mg/kg, were administered in Part A of the study. Dose levels in subsequent parts of the study were based on the safety, PK, and galactitol (Part D only) results of previous cohorts and/or previous parts of the study.

In this study only PK and safety related assessments were made. Therefore this study will not further depicted in this section. For PK assessment see section 3.3.1 above, for safety assessment see section 3.3.8 below.

3.3.4.2. Main study

AT-007-1002: A Sequential, Two-Part Study to Evaluate the Clinical Benefit, Safety, Pharmacokinetics, and Pharmacodynamics of govorestat in Paediatric Patients with Classic Galactosemia (CG)

Methods

This pediatric Phase 3 study is a clinical efficacy study performed in children with galactosemia. As such, the study was designed as a sequential two-part randomized placebo-controlled trial in 47 children ages 2 to 17 with CG; three age groups (≥2 to ≤6-year-old, ≥7 to ≤12-year-old, and ≥13 to <18-year-old) were enrolled. The first part determined the optimal dose of govorestat to achieve the targeted exposure levels in children. The second part evaluated galactitol biomarker reduction at the optimal dose and the impact of govorestat on clinical outcome measures. Part B is followed by a OLE in which the patients on placebo in part B are switched to govorestat and treated for 18 months. Part A will be discussed in the PK section as only PK and PD parameters were studied. The results of the OLE were not submitted.

Study Participants

Children aged ≥ 2 and < 18 years were eligible for enrollment if they had a CG diagnosis confirmed by evidence of absent or significantly decreased (<1%) GALT activity in red blood cells, or a historical record of diagnosis of CG (gene analysis and/or enzyme activity). Patients were to have no significant health problems (other than CG) precluding their participation in the study. Patients were to be on a lactose free and galactose-restricted diet

The exclusion criteria do not allow for severely impaired patients to be included (IQ below 50) as well as patients with a serious renal, hepatic or cardiac co-morbidity. Further patients receiving treatment with any sensitive substrates of BCRP, OAT1 and OAT3, CYP3A4, or CYP2B6, CYP2C19, or CYP1A2 ≤5 half-lives prior to the first dose of study drug through the last dose of study drug were excluded.

Treatments

Based on the results of Part A, the following doses were selected for Part B: 15 mg/kg/day in children aged 13 to 17, 20 mg/kg/day in children aged 7 to 12 years; and 20 mg/kg/day in children aged 2 to 6 years.

Objectives, outcomes and endpoints

To evaluate the clinical benefit a composite sum of change on speech and language skills, behaviour and daily living skills (as measured by Oral and Written Language Scales [OWLS-II] and Behaviour Assessment System for Children 3rd Edition [BASC-3] tests) was defined as primary endpoint.

Secondary endpoints were other measures of cognition, behaviour and motor performance (besides the 4 measurements of the primary endpoint, Archimedes Spiral Drawing Test and 9-Hole Pegboard test, SARA, NIH Toolbox Cognition Battery). Of the other secondary endpoints the evaluation of the ovarian function is of interest.

For the remaining secondary endpoints will be referred to the clinical rapport.

Sample size

Part A: 18 patients (6 per age groups; 2:1)

Part B: 54 patients (18 per age group; 2:1) will provide a power of 80% to detect a treatment effect ranging from 0.66 to 0.89 standard deviation (SD) of the post-treatment change within the age subgroup with **a two-sided type I error rate of 0.05** using a global summary measure under assumption of 4 COAs (Tests of Feel and Function) with a correlation coefficient between changes in two different outcomes in the same individual and a correlation coefficient between outcome level at baseline and after treatment both ranging from 0.25 to 0.75.

Randomisation and blinding (masking)

Randomisation

Part A subjects were randomized in a 2:1 ratio to receive active study drug (govorestat) or placebo.

Part B subjects transitioning from Part A retained the same treatment allocation. The novo subjects were randomised in a 2:1 ratio to receive active study drug (govorestat) or placebo. All efforts were made by Applied Therapeutics to ensure that 3 "similar" subjects, with respect to 4 variables (GALT activity, Gender, Age and Gene defect) were assigned to one block.

Blinding

Part A: the clinical site staff (except for unblinded pharmacist) and patients were blind. The Sponsor and the CRO were also blind except for the unblinded pharmacokineticist who provided blinded PK and PD data to the Sponsor and the unblinded statistician who provided unblinded data to the DMC for Part A dose escalation and Part A to Part B transition discussions.

Part B: The CRO also remain blinded except for the unblinded pharmacokineticist who provided blinded PK and PD data to the Sponsor, the unblinded statistician who provided unblinded data to the DMC for the Part B scheduled analyses at Month 6 and Q6M, and the members of the fire-walled team.

Members of the CRC (neurologists with specialized expertise in movement disorders) were blind and also biomarker data evaluating galactitol reduction were reviewed blind at 30, 60 and 90 days on treatment.

Statistical methods

Analysis sets

The biomarker efficacy population consists of all subjects who entered Part B, had a baseline galactitol level (prior to first dose) greater than 500 ng/ml and had been fully compliant (based on the subject's diary) with the study treatment and the galactose-restricted diet for at least 5 consecutive days prior to the biomarker assessment.

The clinical efficacy population consists of all subjects who entered Part B and had a baseline galactitol level (prior to first dose) greater than 500 ng/ml.

The safety population consists of all subjects who received at least 1 dose of study drug in any part of the study.

Primary efficacy endpoint

Changes in the following 4 domains from baseline to Month 6 and every 6 months thereafter (i.e., changes from baseline to Month 12, Month 18, etc.)

- Speech and Language (OWLS-II, both Expressive Language (also termed Oral Expression test) and Receptive Language (also termed Listening Comprehension) domains)

- BASC-3 Behavioural Symptoms index (includes atypicality, withdrawal, attention) and BASC-3 Daily Living domain

Standard scores (adjusted for age) were used in the primary endpoint analysis. Subjects who transitioned from one BASC age group to the next (as an age-specific test is administered based on the age of the child at the time of testing), BASC scores were not included in the primary endpoint analysis.

The baseline time point is defined as the time point prior to randomisation in the study.

Part B Day 1 is defined as the first day of dosing at the optimum dose level, regardless of whether that occurred in Part A or in Part B.

Primary efficacy analysis

For each feel and function outcome assessment, a two-sample t-test based on the observed change from baseline data was performed at each time point. Because the units/scale of the tests/questionnaires are test-specific, the estimated group difference was standardised using a Z score (the estimated difference divided by the standard error estimate). A positive, large Z score indicates that the treatment is better than the control.

The mean of the four Z scores was calculated as a global summary measure to quantify the treatment effect. Under the null hypothesis that there is no difference between two arms, the chance of the observed mean Z score or beyond was determined based on permutations as presented in Li et al. (2020). The one-sided p-value for this global test is the area under the histogram beyond the observed mean Z score.

The totality of evidence of treatment effect was assessed by the Wei-Lachin global test (Wei et al. 1984).

Missing data

No imputations were performed on missing data; all analyses were planned to be based on observed data only.

Sensitivity analysis

Three sensitivity analyses were planned:

1. An analysis on raw scores.
2. If significant imbalance between groups was detected at baseline, an analysis accounting for covariance (ANCOVA-type analysis) was considered with the observed data at each time point corrected for a baseline risk score.
3. O'Brien rank-sum method: a global test based on the sum of the rank of individual patients' outcomes on the four primary feel and function test scores (OWLS-II Oral Expression and Listening Comprehension standard scores and BASC-3 Behavioral Symptoms Index and Activities of Daily Living T scores) will be calculated. The means of the rank sums for each treatment group will be compared using a two-sample t-test.

Supplemental analyses

Four supplemental analyses were planned:

1. Global Statistical Test for each individual age group (3-6; 7-12; 13-17 for active vs. placebo).
2. Inclusion of Dexterity (9 -Hole Pegboard Test)

3. Inclusion of Cognition.
4. The primary analysis including covariates for baseline galactitol level, calculated compliance with study treatment and the galactose-restricted diet.

Interims and adjustment for multiplicity

No formal interims were specified although testing of superiority was planned and tested after 6 months and every 6 months. Results were presented to the unblinded DMC, which informs the Sponsor in case statistical superiority of govorestat is established.

No multiplicity adjustment: A penalty for multiple testing was not considered due to sample size limitations since CG is a low-prevalence, rare paediatric disease.

Secondary efficacy endpoints

- Changes in each of the individual domains/tests noted above as components of the primary endpoint
    - Expressive Language domain of OWLS-II
    - Receptive Language domain of OWLS-II
    - Behavioural Symptoms Index of BASC-3
    - Activities Daily Living of BASC-3
- Changes in NIH Toolbox Cognition Battery (NIH-CB)
- Changes in NIH Toolbox Motor Battery (NIH-MB) -Manual Dexterity aka 9-Hole Pegboard Test [9HPT]
- Archimedes Spiral Drawing Test
- Changes in gross motor skills, as measured by NIH Toolbox Motor Battery Standing Balance test
- Changes in gross and fine motor function as assessed by SARA (age 5+)
- Changes in onset and severity/progression of cataracts using the Lens Opacities Classification System III (LOCS III)
- Changes in sexual maturation and ovarian function in female patients (based on follicle stimulating hormone [FSH], luteinizing hormone [LH], oestradiol, Tanner stage milestones, and clinical endocrinology examination)
- Changes in plasma galactitol from baseline

Secondary efficacy analyses:

All results of secondary efficacy endpoints were summarised and/or analysed as for the primary endpoint.

Results

Participant flow

The study was performed at three study sites: 2005-Rare disease research, LLC (42 subjects); 2006-Children’s hospital Colorado (1 subject) and 2007-Michigan medicine university of Michigan (4 subjects). The results are mainly determined by one site with 42 subjects.

In the study a total of 47 subjects were randomized, 17 were randomized in part A and transitioned to part B and 29 were randomized in part B.

In part B a total of 16 patients were on placebo whereas 31 were on govorestat. Of the patients in the placebo group 6 were treated for one month in part A (were they also received placebo) and in the govorestat group 11 patients received treatment for one month in part A.

Day 1 in Part B is defined as the first day of dosing at the optimum dose level. Therefore, for patients who participated in Part A, there is partial overlap between Parts A and B because Part B Day 1 will be set retrospectively to be the same as Part A Optimum Dose Level Day 1.

There were 7 patients who discontinued treatment in part B.

The primary reasons for discontinuation were AE's (2 patients [6.5%] in the total govorestat group vs 1 patient [6.3%] in the placebo group) and withdrawal by patient or parent/LAR(s) (3 patients [9.7%] in the total govorestat group vs 1 patient [6.3%] in the placebo group).

Conduct of the study

The percentages of patients with major protocol deviations were generally balanced across age groups (range: 3 to 7 patients [50.0% to 66.7%]), with the exception of patients who received govorestat in the ≥2 to ≤6-year age group (9 patients [81.8%]), which was driven by major protocol deviations related to blood collection for laboratory tests (8 patients [72.7%] vs ≤2 patients [≤40.0%]) and protocol procedures (4 patients [36.4%] vs ≤2 patients [≤16.7%]), which were higher in younger children due to difficulties obtaining blood at all time points during pre-specified windows and performance of some tests which required patient cooperation.

No GCP inspection was done.

Baseline data

The demographics and baseline characteristics are only presented for the safety population.

The patients were diagnosed with CG according to the current guidelines. The mean GALT activity was 0.02 nmol/h/mg in the placebo group and 0.01 nmol/h/mg in the govorestat group. The results of the individual patients were not reported.

Further the baseline data in terms of sex, weight and hight were consistent with healthy peers. The included patients were all Caucasian. Further, most of the patients were from the higher socio-economic classes [most of the parents (77.8%) had a College, technical college, university degree or a Graduate degree (PhD, MD, etc.)].

The medical history is as expected for patients suffering from CG except for the rhinitis which was reported in the medical history for 1 patient only.

Numbers analysed

All 47 randomised patients were included in part B of study AT-007-1002 the deposition of these patient is summarised in the table below

Age ≥2 to ≤6 years		Age ≥7 to ≤12 years		Age ≥13 to <18 years		Total	
Placebo	govorestat	Placebo	govorestat	Placebo	govorestat	Placebo	govorestat
N=5	N=11	N=6	N=12	N=5	N=8	N=16	N=31

Outcomes and estimation

Primary endpoint

No summary statistics of the baseline values was submitted.

The estimated Mean Z Score of the composite endpoint (OWLS-II (OE, LC), BASC-3 (ADL, BSI)) is 0.8683 (95% CI -0.204, 2.087; one-sided p-value of 0.1030). The study was not type I error controlled due to the unplanned interims.

The pre-planned sensitivity analysis based on the raw scores showed a difference in mean Z-score of -0.28 in favour of the placebo. The O'Brien Rank-sum method did also not show a nominal statistical significant treatment effect.

The results of the four domains used in the primary composite endpoint are presented in Table 6.

Table 5: Primary Clinical Efficacy Analysis and sensitivity analyses: Composite Primary Endpoint by Age Group at Month 18; Efficacy Population; Part B – Age ⩾ 2 to < 18. Adapted by the CHMP

	Statistic	Age ≥ 2 to ≤ 6 (N=16)	Age ≥ 7 to ≤ 12 (N=16)	Age ≥ 13 to < 18 (N=12)	Total (N=44)
Composite Primary Endpoint (*OWLS-II (OE, LC) and BASC-3 (ADL, BSI)*)	n	14	14	10	38
	Mean Z Score (govorestat - Placebo)[1] 95% Confidence interval [2]	0.5983	1.1922	-0.3595	0.8683 (-0.204, 2.087)
	P-value[3]				0.1030
Composite Primary Endpoint Using Raw Scores	n	14	14	10	38
	Mean Z Score (govorestat - Placebo)[1]	-0.3314	0.5242	-0.6363	-0.2800
	P-value[3]				0.6621
Composite Primary Endpoint Using the O'Brien Rank-Sum Method	n	14	16	12	44
	Difference in mean CFB rank sum score (govorestat - Placebo) [4](SE)	2.8 (5.02)	6.1 (5.31)	-3.6 (4.41)	9.1 (9.49)
	P-value[5]				0.3492

Abbreviations: BASC-3 = Behavior Assessment System for Children 3rd Edition; CFB = change from baseline; OWLS-II = Oral and Written Language Scales
Notes:

- The n counts are the number of subjects who had at least one non-missing result out of the four primary feel and function test scores. The N counts are the number of subjects in the efficacy population.
- Baseline is defined as the last available measurement taken prior to the first dose of study drug.
- Higher Z scores represent better performance. Lower Z scores represent worse performance.
- BASC-3 Behavioral Symptoms Index (BASC-BSI) T scores move in the opposite direction compared to the OWLS-II Oral Expression, OWLS-II Listening Comprehension, and BASC-3 Activities of Daily Living scores. As such, higher T scores of BASC-BSI indicate worse outcomes. For this reason, in the global Z score calculation, the BASC-BSI is adjusted by multiplying the T score by -1.
- Month 18 BASC-3 results that were obtained from a test version that is different from the version used at baseline are excluded from this analysis.

[1] The Mean Z Score is the mean of the calculated Z scores for the mean CFB differences (govorestat – Placebo) at Month 18 for each of the four primary feel and function test scores: OWLS-II Oral Expression and Listening Comprehension standard scores and BASC-3 Behavioral Symptoms Index and Activities of Daily Living T scores.

[2] The 95% CI is taken from Table 14.2.1.1 Global least squared mean summary
[3] The one-sided p-value at a 5% level of significance is calculated using the Wei-Lachin global test.
[4] The Mean CFB Rank Sum Diff (SE) and two-sided p-value at a 5% level of significance are calculated using a two-sample t-test.
[5] Using O'Brien's Rank-Sum method, individual subjects' CFB results for the four primary feel and function test scores (OWLS-II Oral Expression and Listening Comprehension standard scores and BASC-3 Behavioral Symptoms Index and Activities of Daily Living T scores) were ranked and summed. The means of the rank sums for each treatment group were compared using a two-sample t-test.
Reference: Tables 14.2.1.1.1, 14.2.1.1, 14.2.1.7.1, and 14.2.1.6.1

Table 6: Primary clinical efficacy analysis: individual domain scores by age group at month 18; Efficacy population; Part B

	Age ≥ 2 to ≤ 6		Age ≥ 7 to ≤ 12		Age ≥ 13 to < 18		Total	
	Placebo (N=5)	govorestat (N=11)	Placebo (N=4)	govorestat (N=12)	Placebo (N=4)	govorestat (N=8)	Placebo (N=13)	govorestat (N=31)
OWLS-II Oral Expression Standard Score								
n	5	7	4	10	3	7	12	24
Mean CFB	6.0	7.9	12.8	10.0	14.0	10.3	10.3	9.5
Mean CFB Diff (SE)		1.9 (7.60)		-2.8 (6.08)		-3.7 (8.12)		-0.8 (4.25)
Z Score		0.2443		-0.4523		-0.4576		-0.1864
OWLS-II Listening Comprehension Standard Score								
n	5	7	4	10	3	7	12	24
Mean CFB	3.2	-2.1	-1.3	1.4	5.7	4.7	2.3	1.3
Mean CFB Diff (SE)		-5.3 (8.25)		2.7 (7.37)		-1.0 (6.17)		-1.0 (4.27)
Z Score		-0.6479		0.3595		-0.1543		-0.2344
BASC-3 Behavioral Symptoms Index T Score								
n	2	7	3	7	3	7	8	21
Mean CFB	5.5	-2.7	10.3	-2.4	-0.7	2.0	5.0	-1.0
Mean CFB Diff (SE)		-8.2 (4.75)		-12.8 (4.49)		2.7 (2.85)		-6.0 (2.88)
Z Score		1.7290		2.8429		-0.9363		2.1016
BASC-3 Activities of Daily Living T Score								
n	2	7	3	7	3	7	8	21
Mean CFB	1.0	3.7	-6.7	7.3	0.3	1.0	-2.1	4.0
Mean CFB Diff (SE)		2.7 (2.54)		14.0 (6.91)		0.7 (6.06)		6.1 (3.42)
Z Score		1.0677		2.0188		0.1101		1.7926

Abbreviations: BASC-3 = Behavior Assessment System for Children 3rd Edition; CFB = change from baseline; Diff = Difference (govorestat - Placebo); OWLS-II = Oral and Written Language Scales
Notes:
• Baseline is defined as the last available measurement taken prior to the first dose of study drug.
• Mean CFB Diff (SE) is calculated using a two-sample t-test.
• The Z score is calculated as the mean CFB difference (govorestat – placebo) divided by the SE.
• Higher Z scores represent better performance. Lower Z scores represent worse performance.
• The OWLS-II is used only for subjects aged 3 and older.
• BASC-3 Behavioral Symptoms Index (BASC-BSI) T scores move in the opposite direction compared to the OWLS-II Oral Expression, OWLS-II Listening Comprehension, and BASC-3 Activities of Daily Living scores. As such, higher T scores of BASC-BSI indicate worse outcomes. For this reason, in the Z score calculation, the BASC-BSI is adjusted by multiplying the T score by -1.
• Month 18 BASC-3 results that were obtained from a test version that is different from the version used at baseline are excluded from this analysis.

Secondary and explorative endpoints

OWLS Oral Expression

At baseline for the OWLS Oral Expression (OWLS-OE) in the placebo arm the standard score was 72.4 (95%CI 61.4, 83.3) in the active treated group this was 74.3 (95% CI 67.7, 80.9). After 18 months treatment the scores were 80.3 (95% CI 64.7, 95.9) and 79.8 (95% CI 73.0, 86.5), respectively.

Estimated change over time in OWLS Oral Expression (OWLS-OE) from baseline to 18 months was 10.3 (95%CI 3.0, 17.5) in the placebo treated patients and 9.5 (95% CI 3.9, 15.0) in the govorestat treated patients.

The estimated difference (govorestat - placebo) in change over time (baseline to 18 months treatment) in OWLS Oral Expression was -0.8 (95% CI -9.5, 7.9).

OWLS Listening Comprehension

At baseline in the placebo arm the standard score was 76.9 (95% CI 66.6, 87.2) in the active treated group this was 82.8 (95% CI 76.0, 89.6). After 18 months treatment the scores were 77.9 (95% CI 64.2, 91.6) and 81.1 (95% CI 73.9, 88.3), respectively.

Estimated change over time in OWLS Listening Comprehension (OWLS-LC) from baseline to 18 months was 2.3 (95%CI -5.5, 10.1) in the placebo treated patients and 1.3 (95% CI -3.6, 6.3) in the govorestat treated patients.

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in OWLS Listening Comprehension was -1.0 (95% CI -9.9, 7.9).

BASC-3 Behavioural Symptoms Index

At baseline in the placebo arm the t-score was 47.9 (95%CI 43.6, 52.2) in the active treated group this was 56.4 (95% CI 53.7, 59.1). After 18 months treatment the scores were 52.4 (95% CI 45.6, 59.2) and 57.2 (95% CI 52.7, 61.7), respectively

Estimated change over time in BASC-3 Behavioural Symptoms Index from baseline to 18 months was 5.0 (95%CI -0.4, 10.4) in the placebo treated patients and -1.0 (95% CI -4.7, 2.6) in the govorestat treated patients.

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in BASC-3 Behavioral Symptoms index was -6.0 (95% CI -12.2, 0.1). (Cave; lower scores indicate a better result).

BASC-3 Activities of Daily Living

No information of the t-scores at baseline or after 18 months treatment were submitted.

Estimated change over time in BASC-3 Activities of Daily Living from baseline to 18 months was -2.1 in the placebo treated patients and 4.0 in the govorestat treated patients.

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in BASC-3 Activities of Daily Living was 6.1 (SD 18.1). (Cave; lower scores indicate a better result).

NIH Toolbox Cognition Battery (NIH-CB)

At baseline the mean standard score in the placebo group was 73.1 (95% CI 59.2, 86.9) in the govorestat group this was 75.1 (95% CI 67.9, 82.3). After 18 months of treatment the score in the placebo group was 74.3 (95% CI 62.9, 85.6) and in the govorestat treatment group 80.9 (95% CI 71.4, 90.4).

Month 18 estimated mean change from baseline in the NIH-CB composite standard score was 8.62 (95% CI 2.9, 14.4) in the govorestat group and 4.5 (95% CI -0.6, 9.6) in the placebo group.

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Cognition Battery was 4.1 (95% CI -3.2, 11.5).

NIH Toolbox Motor Battery (NIH-MB) – Standing Balance

At baseline the mean standard score in the placebo group was 37.8 (95% CI 31.5, 44.0) in the govorestat group this was 41.7 (95% CI 37.0, 46.5). After 18 months of treatment the score in the placebo group was 42.5 (95% CI 34.5, 50.4) and in the govorestat treatment group 45.4 (95% CI 39.5, 51.3).

Month 18 estimated change from baseline for the NIH-MB standing balance T scores in patients receiving govorestat was 4.3 (95% CI 0.0, 8.6) and for the placebo treated patients this was 5.2 (95% CI -1.7, 12.0).

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Motor Battery – Standing Balance was -0.9 (95% CI -8.6, 6.8).

NIH Toolbox Motor Battery (NIH-MB) -Manual Dexterity

At baseline the mean standard score in the placebo group was 41.4 (95% CI 35.1, 47.7) in the govorestat group this was 39.0 (95% CI 34.9, 43.0). After 18 months of treatment the score in the placebo group was 38.9 (95% CI 32.6, 45.3) and in the govorestat treatment group 37.0 (95% CI 31.4, 42.6).

Month 18 estimated change from baseline in the NIH-MB 9HPT dexterity (dominant hand) T scores were -0.2 (95% CI -4.4, 4.0), in those receiving placebo this was -2.8 (95% CI -7.9, 2.3).

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Motor Battery - Manual Dexterity was 2.6 (95% CI -3.7, 9.0).

Scale for Assessment & Rating of Ataxia (SARA)

At baseline the mean standard score in the placebo group was 5.00 (95% CI 1.50, 8.50) in the govorestat group this was 4.03 (95% CI 1.95, 6.11). After 18 months of treatment the score in the placebo group was 5.07 (95% CI 0.26, 9.88) and in the govorestat treatment group 5.36 (95% CI 2.31, 8.40).

Month 18 estimated change from baseline value SARA total scores in patients receiving govorestat were -0.71 (95% CI -0.33, 1.76) and in the placebo group this was 0.36 (95% CI -2.74, 2.03).

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in Scale for Assessment & Rating of Ataxia (SARA) was 1.07 (95% CI -1.39, 3.53).

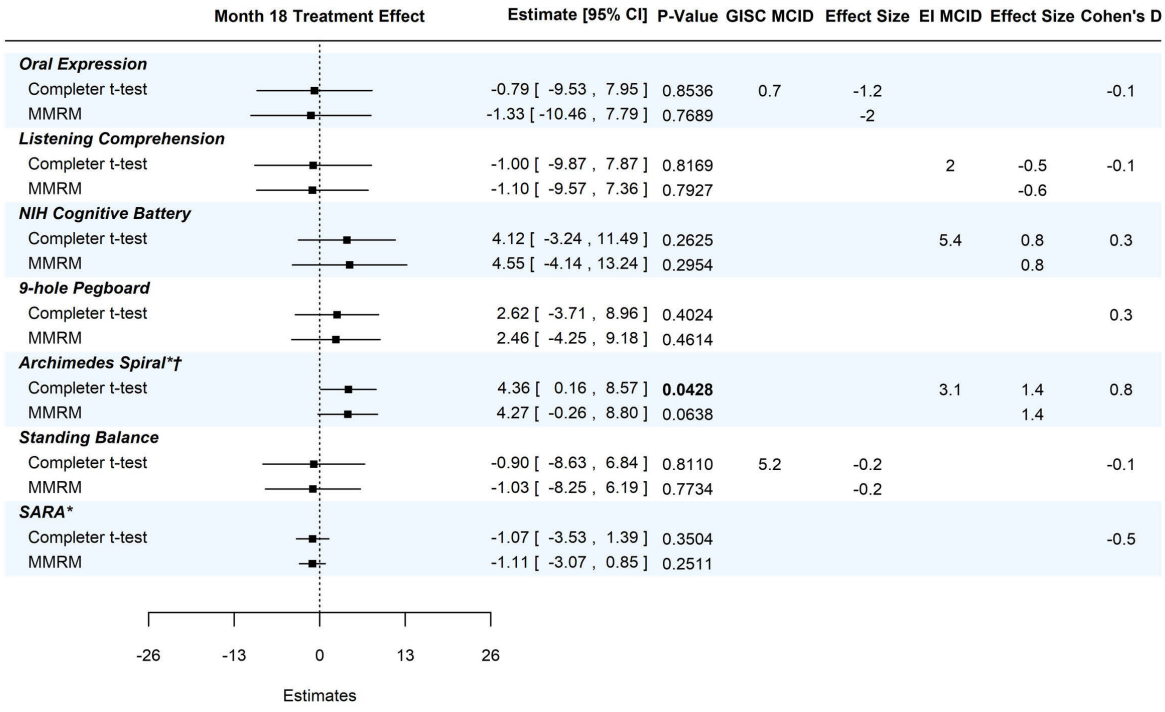
Spiral Drawing Test

For Archimedes spiral drawing at baseline the mean standard score in the placebo group was 1.45 (95% CI 1. 0.83, 2.07) in the govorestat group this was 1.78 (95% CI 1.40, 2.16). After 18 months of treatment the score in the placebo group was 1.56 (95% CI 0.96, 2.15) and in the govorestat treatment group 1.48 (95% CI 1.09, 1.87).

Month 18 estimated change from baseline for the Archimedes spiral drawing scores in patients receiving govorestat was -0.38 (95% CI -0.65, -0.11) and in the placebo group Month 18 change from baseline value was -0.06 (95% CI -0.30, 0.41).

The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in Spiral Drawing Test was -0.44 (95% CI -0.86, -0.02). (Cave; lower scores indicate a better result).

Figure 2: Global Forest Plots with Effect Sizes at 18 Months Clinical Efficacy Population



* Variables were reversed so that higher scores represented improvement
† Archimedes Spiral was multiplied by 10 and GSTs were multiplied by 5 to match scales
EI = Exit Interview, GISC = Global Impression of Severity - Caregiver, MCID = Minimum Clinically Important Difference, Effect Size = Estimate / MCID MCIDs and corresponding effect sizes were only included if the underlying improved, no effect, and worsened group means were in the proper order
See Table 14.2.1.1, Table 14.2.1.2 and Tables 14.2.X.X.6.X
P:/Clients/Applied Therapeutics/govorestat-1002/Programs/Production/Figures/f14_2_1_2.R

Clinician Global Impression of Severity (GIS) & Global Impression of Change (GIC) each domain & overall

The Clinician GIS was instituted during Part A. As such, investigators did not perform baseline assessments for multiple subjects (28/47 or 59.6% missing baseline).

Caregiver Global Impression of Severity (GIS) & Global Impression of Change (GIC) each domain & overall

Considering the GIS score at baseline in the placebo group 3 (23.1%) patients scored "normal", 6 (46.2%) mildly impaired and 4 (30.8%) moderate or markedly impaired. In the govorestat group 10 (32.3%) patients scored "normal" at baseline, 6 (19.4%) was mildly impaired with 15 (48.4%) moderate or markedly impaired. At Month 18, the placebo group 3 (25.0%) patients scored "normal", 4 (33.3%) mildly impaired and 5 (31.7%) moderate or markedly impaired. In the govorestat group 10 (32.3%) patients scored "normal" at baseline, 6 (19.4%) was mildly impaired with 15 (48.4%) moderate or markedly impaired after 18 months treatment.

Overall caregiver GIC scale scores at Month 18, most patients in the total govorestat group had overall caregiver GIC scale scores of 'much better' or 'a little better' (10 patents [38.5%] and 9 patients [34.6%], respectively), whereas most patients in the placebo group had overall caregiver GIC scale scores that did not change or were 'a little better' (6 patents [50.0%] and 4 patients [33.3%], respectively).

3.3.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7: Summary of efficacy for trial AT-007-1002

Title: A Sequential, Two-Part Study to Evaluate the Clinical Benefit, Safety, Pharmacokinetics, and Pharmacodynamics of govorestat in Paediatric Patients with Classic Galactosemia (CG)			
Study identifier	AT-007-1002		
Design	This pediatric Phase 3 study is the first clinical efficacy study ever performed in children with Galactosemia. As such, the study was designed as a sequential two-part randomized placebo-controlled trial in 47 children ages 2 to 17 with CG; three age groups (≥2 to ≤6-year-old, ≥7 to ≤12-year-old, and ≥13 to <18-year-old) were enrolled. The first part (part A) determined the optimal dose of govorestat to achieve the targeted exposure levels in children. The second part (part B) evaluated galactitol biomarker reduction at the optimal dose and the impact of govorestat on clinical outcome measures, including ability to perform activities of daily living, behavioral symptoms, two measures of expressive speech/ language (receptive and expressive language), cognition, fine motor skills, gross motor skills and tremor.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18 months 1 months (i.e. part A) 18 months (not submitted) 3
Hypothesis	Superiority		
Treatments groups	Govorestat group		30 mg/kg/day in children aged 2 to 6 years. 20 mg/kg/day in children aged 7 to 12 years; 15 mg/kg/day in children aged 13 to 17, Treatment duration 1 month in part A Treatment duration 18 months in part B number randomized N=31
	Placebo group		placebo. 18 months, N=17
Endpoints and definitions	primary composite endpoint	Primary endpoint	a within-patient multi-component endpoint with 4 domains: OWLS-II OE, OWLS-II LC, BASC-3 BSI and BASC-3 ADL
	Secondary endpoint	NIH-CB	NIH Toolbox Cognition Battery

	Secondary endpoint	NIH-MB-standing balance	NIH Toolbox Motor Battery (NIH-MB) – Standing Balance
	Secondary endpoint	NIH-MB-manual dexterity	NIH Toolbox Motor Battery (NIH-MB) -Manual Dexterity, aka peg hole test
	Secondary endpoint	SARA	Scale for Assessment & Rating of Ataxia (SARA)
	Secondary endpoint	spiral drawing test	Archimedes spiral drawing test
	Secondary endpoint	GIS-I and GIC-I	Clinician Global Impression of Severity (GIS) & Global Impression of Change (GIC)
	Secondary endpoint	GIS-C and GIC-C	Caregiver Global Impression of Severity (GIS) & Global Impression of Change (GIC)
Database lock	24 Mar 2023 last patient completed the study. The double placebo-controlled core study was unblinded 10 May 2023		
Results and Analysis			
Analysis description	**Primary Analysis** The statistical test for each outcome is based on a conventional two-sample t-statistic based on the observed change from baseline to month 18. For the primary composite endpoint, based on four domains, the mean of the four Z scores (estimated difference divided by the standard error) was estimated and the p-value was calculated by using permutations..		
Analysis population and time point description	Clinical efficacy population Change from baseline to 18 months		
Descriptive statistics and estimate variability	Treatment group	Placebo group	Govorestat group
	Number of subjects	16 (different for the various endpoints)	31 (different for the various endpoints)
	Primary composite endpoint Mean difference between baseline to 18 months i.e. estimated mean Z-score.	Not submitted	Not submitted
	95% CI	Not submitted	Not submitted
	Estimated mean NIH-CB T-score	4.5	8.6
	95% CI	-0.6, 9.6	2.9, 14.4
	Estimated mean NIH-MB-standing balance T-score	5.2	4.3
	95% CI	-1.7, 12.0	0.0, 8.6
	Estimated mean NIH-MB-manual dexterity T-score	-2.8	-0.2
	95% CI	-7.9, 2.3	-4.4, 4.0
	Estimated mean SARA T-score	-0.36	0.71
	95% CI	-2.74, 2.03	-0.33, 1.76
	Estimated mean spiral drawing test T-score	0.06	-0.38
	95% CI	-0.30, 0.41	-0.65, -0.11

	Mean GIS-I and GIC-I	Not reliable	Not reliable	
	95% CI	Not reliable	Not reliable	
	GIS-C			
	Score Worsened	4 (33.3%)	4 (15.4%)	
	No Change in Score	5 (41.7%)	14 (53.8%)	
	Score Improved	3 (25.0%)	8 (30.8%)	
	GIC-C	Not submitted	Not submitted	
Effect estimate per comparison	Composite Primary Endpoint (OWLS-II (OE, LC) and BASC-3 (ADL, BSI)	Comparison groups		Govorestat- placebo
		Estimated mean z-score		0.8683
		95% CI		-0.204, 2.087
		One-sided P-value based on permutations		0.1030
	NIH-CB	Comparison groups		govorestat-placebo
		Estimated T-score		4.1
		95% CI		-3.2, 11.5
	NIH-MB-standing balance	Comparison groups		govorestat-placebo
		Estimated T-score		-0.9
		95% CI		(-8.6, 6.8)
	NIH-MB- manual dexterity	Comparison groups		govorestat-placebo
		Estimated T-score		2.6
		95% CI		-3.7, 9.0
	SARA	Comparison groups		govorestat-placebo
		Estimated T-score		1.07
		95% CI		-1.39, 3.53
	spiral drawing test	Comparison groups		govorestat-placebo
		Estimated T-score		-0.44
		95% CI		-0.86, -0.02
	GIS-I and GIC-I	Comparison groups		govorestat-placebo
		Not analysed		Not applicable
	GIS-C	Comparison groups		govorestat-placebo
		Not analysed		Not applicable
	GIC-C	Comparison groups		govorestat-placebo
		Not analysed		Not applicable
Notes				

3.3.4.4. Clinical studies in special populations

No patients below the age of 2 years were treated. No patients over the age of 50 were treated.

No studies in patients with hepatic, renal or cardiac insufficiency were performed.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

No analysis across studies was performed

3.3.4.7. Supportive study

Study AT-007-1006 was a 24-month open-label extension (OLE) study of govorestat in adult subjects with CG who previously participated in Study AT-007-1001 Part D and/or Part D Extension.

The study was designed to assess the long-term safety of govorestat in patients with CG as well as the pharmacodynamics (PD) (inhibition of galactitol) and PK of govorestat. The effect of 12-month treatment on the levels of galactose and other galactose metabolites in patients with CG were evaluated. There was an exploratory evaluation of baseline burden of illness (BOI) of the subjects via interview with the subjects and their caregivers (only if it had not been completed for Study AT-007-1001) as well as chart review, detailed medical history, physical examination including a detailed neurologic exam, National Institute of Health (NIH) Toolbox Motor Battery for assessment of balance and dexterity, and Archimedes Spiral Test for assessment of tremor. Balance, dexterity, and tremor were evaluated at Month 12. QOL measures of adult patients with CG were assessed at baseline and Month 12 using validated Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires.

Seven (7) patients were enrolled in the study. No patients completed the full 24 months of the study due to early termination of the study at 18 months. Four patients completed the study through the Month 18 visit (this was the last possible visit before the study was prematurely terminated by the applicant). No conclusions could be drawn for either baseline BOI or effect of govorestat treatment because of the small number of patients. In addition, 2 patients entered this study directly from antecedent Study AT-007-1001 (and no baseline value were measure in 1001 for these endpoints) and one of the patients had been on govorestat for over 90 days at baseline for the current study and another patient had been on govorestat as recently as 2 days before baseline for the current study.

3.3.5. Discussion on clinical efficacy

Study AT-007-1001 was a first-in-human, randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study. The study was structured in 6 parts: Part A (SAD in healthy volunteers, Part B (MAD in healthy volunteers), Part C [MAD with CSF measurement of govorestat (AT-007) level], Part D (SAD/MAD in patients with galactosemia), Part D extension (3-month extension in patients with CG). The originally planned Part-E aiming at recruiting patients with GALK deficiency, a very rare enzymatic defect affecting an enzyme in the galactose metabolism pathway, was not activated as the selected clinical sites were closed at the time of the COVID epidemic. No clinically relevant endpoints were evaluated in this study.

Study **AT-007-1002** is a pediatric Phase 3 study and was designed as a sequential two-part randomized placebo-controlled trial in 47 children ages 2 to 17 with CG; three age groups (≥2 to ≤6-year-old, ≥7 to ≤12-year-old, and ≥13 to <18-year-old) were enrolled. The first part determined the optimal dose of govorestat to achieve the targeted exposure levels in children and is discussed above. The second part B evaluated the impact of govorestat on clinical outcome measures, including ability to perform activities of daily living, behavioral symptoms, two measures of expressive speech/ language (receptive and expressive language), cognition, fine motor skills, gross motor skills and tremor.

Patients enrolled in study 1002 were children aged ≥2 to <18 years with a CG diagnosis and have no significant health problems (other than CG) precluding their participation in the study. All children were on strict lactose-free and galactose limited diet. The exclusion criteria do not allow for severely impaired patients (IQ below 50) as well as patients with a serious renal, hepatic or cardiac co-morbidity. Further patients were not permitted specific co-medication (BCRP substrates and inhibitors, OAT1 and OAT3 substrates, CYP3A4 substrates, CYP2B6 substrates, CYP2C19 substrates, CYP1A2 substrates) and some foods interacting with the CYP's mentioned above. With this the group of

patients included is not completely representative for the population intended for treatment . Further the fact that govorestat is given on top of a diet should be reflected in the indication. Considering the diet, no information on the adherence to the diet could be found in the MAA. The applicant is requested to clarify if and how the adherence to the diet is measured.

The primary endpoint is a composite endpoint of the sum of change on speech and language skills, behaviour and daily living skills (as measured by Oral and Written Language Scales [OWLS-II] and parts of the Behaviour Assessment System for Children 3rd Edition [BASC-3] tests (BSI and ADL).

The primary endpoint changed during the study a couple of times, so selection bias cannot be ruled out. No justification for any of the changes of the primary endpoint was provided. Just before de-blinding the applicant changed the composite endpoint. Changing the primary endpoint during a confirmatory trial without proper planning will **render the trial to be considered exploratory**. The applicant is requested to justify this change to the selected parts of the OWLS-II and BASC-3 and justify why only these parts of the measures were included, rather than the validated total scale. Further, the applicant is requested to clarify by whom and at what time point these changes have been made. Also discuss the possible effect on the B/R.

Reading the DMC minutes it is clear that the DMC informed the sponsor that no statistically significant superiority of govorestat versus placebo was demonstrated.

At this point, the Sponsor unblinded the study and crossed the placebo group to active treatment. The results of the blinded portion of the trial through 18 months of treatment are reported. No discussion or justification for the applicants decision not to proceed another 6 months is lacking. As it is assumed that the decision of the applicant is justified and documented (according to the applicant CGP rules are followed) the document (s) containing the justification of the decision to stop the study should be submitted.

Per age group, blocks of 3 'similar' subjects (based on GALT activity, Gender, Age and Gene defect) will be assigned by the applicant before randomisation. A justification is requested why the subjects within a block selected based on galt activity, gender, age and gene defect can be considered clinically similar.

The randomisation date and time as well as the values for GALT activity, gender, age and gene defect are lacking in the randomisation list. The applicant is requested to present a randomisation list including the columns study part, stratification factor age range, randomisation date, randomisation time, randomisation number, subject ID, block number, galt activity, gender, age, gene defect and randomised treatment group and sorted by stratification factor age range, randomisation date, randomisation time.

The blinding in part B should be clearly described for all the subjects participating in part B and also how the sponsor was kept blinded, especially during the interims at month 6, 12 and 18. Also the role of the members of the fire-walled team and their communication/relation to the sponsor should be discussed and how blinding was kept.

The applicant is requested to submit an analysis in those patients with GALT enzyme activity > 1% and compare the results with patients GALT enzyme activity ≤ 1%.

The selection of the components of the BASC-3 score are poorly understood. On the one hand the composite score of the BSI is chosen, on the other hand the very basic measurement of the ADL is selected over the composite "adaptive skills". The applicant is invited to justify the chosen endpoints .

According to the SAP 5.0, as primary efficacy analysis the mean Z-score will be calculated and the one-sided p-value of the global test will be the area under the histogram and beyond the observed mean Z-score, which is based on 100,000 permutations with a reference to Li et al. (2020). While it is also

mentioned that for the totality of evidence of treatment the Wei-Lachin global test with a reference to Wei et al. (1984) will be used. The applicant is requested which global test was pre-planned to be used for the primary analysis.

In the article Wei-Lachin (1984) the authors wrote about their test which was developed for time-to-event endpoints. However, primary composite endpoint is not composed from time-to-event endpoints but from scores. The Applicant is asked to explain how Wei-Lachin test is adapted to primary composite endpoint.

For the Wei-Lachin global test and for the permutation test based on Li et al (2020), the applicant is requested to present the null and the alternative hypotheses that were used.

No formal interims are described in the protocol and SAP, however, the study was planned to perform analyses at 6 months and every 6 months. The results of these analyses were presented to the unblinded DMC. The applicant is asked to present all the feedback from the DMC to the sponsor for each performed interim and how this could have impacted the study (e.g. unblinding, performing assessments, …).

The analysis of the secondary endpoints (changes in OWLS-II (OE, LC), BASC-3 (ADL, BSI), NIH Toolbox Cognition Battery (NIH-CB) and NIH Toolbox Motor Battery (NIH-MB) -Manual Dexterity aka 9-Hole Pegboard Test [9HPT]). Other secondary endpoints were the individual measurements of the analysis above (OWLS-II (OE, LC), BASC-3 (ADL, BSI), NIH Toolbox Cognition Battery (NIH-CB) and NIH Toolbox Motor Battery (NIH-MB) -Manual Dexterity aka 9-Hole Pegboard Test [9HPT]). Additional measurements were Archimedes Spiral Drawing Test, Scale for the Assessment and Rating of Ataxia (SARA), the Vineland-3, Bayley Scales of Infant and Toddler Development (Bayley-4) and Clinician- and Caregiver-Assessment of Global Impression of Severity (GIS), and Global Impression of Change (GIC).

The SARA can only be performed (is validated) for patient over 8 years of age. For the spiral drawing the lower age limit is 5 years.

Further the effect on ovarian function and cataract is evaluated along with morphological brain phenotype and quantitate galactitol deposition in the brain.

The effect of govorestat on plasma galactitol levels, other metabolites, blood biomarkers of neurologic disease as neurofilament light (Nf-L) and antimullerian hormone (AMH) was measured as secondary endpoints.

Type I error was not controlled for the primary endpoint.

There is no pre-planned time point for the primary efficacy analysis. Repeated testing for statistical significance introduces a multiplicity issue which **inflates the type I error**. Even though no statistical significance was observed for the primary outcome, the applicant is requested to discuss the impact of inflation of the type I error on the totality of evidence and on the B/R and justify the absence of a pre-planned time point for the primary efficacy analysis.

During the study, the dosing was adjusted based on weight instead of age. No scientific justification for the dose change (from age to weight based dosing) has been provided. The applicant is requested to provide the rationale for the change to weight based dosing instead of age based dosing. In addition the Applicant is asked to discuss the potential impact of using the start of the optimal dose as Day 1 for part B rather than first day of their planned dose. Any data driven changes during the course of the study reduce the confirmatory nature of the study.

Both efficacy populations (biomarker and clinical) consist of all subjects who had a baseline galactitol level (prior to first dose) greater than 500 ng/ml, which was not an in/exclusion criteria of the study.

This **may lead to bias** as it is a selection after randomisation. The applicant needs to reflect on the chosen threshold of 500 ng/ml, clarify why it was not listed as an eligibility criterion and clarify when it was introduced as a criterion for selection of the analysis population. The applicant is also asked to discuss the possible bias for the primary endpoint and the effect on the B/R. A listing of the individual galactitol levels should be presented as this is lacking.

According to SAP version 5.0 an anchor-based sensitivity analyses should be performed on the GIS and GIC scales to include the clinical relevance of changes in the primary endpoint. The GIS based analysis is not found for the primary endpoint in the MAA, at least not in the CSR, summary of efficacy or overview submitted by the applicant. This analysis and a discussion considering the interpretation thereof should be submitted . The relevance of the parent GIS and GIC is questioned as the parent may have insufficient experience with "normal" and variation thereof to fully comprehend the activities of the child in the context of a bigger group of normal and impaired children. The lack of a validation report for this measure further hampers the assessment of the results. The applicant is invited to discuss the relevance of the measure in the light of the experience of the care-givers. Further a validation report of the measure should be submitted . As the results of analyses with the GIC as an anchor are of interest for the assessment of the value at which the parents notice a change a discussion considering the interpretation thereof should be submitted.

The value of the anchor based calculation using the GIS form the caregivers results in a value for each endpoint at which the parents become aware of a change. The relation between this awareness of a change and a MICD is not evident, this should be discussed taking in mind the conclusions of the exit interviews were it is stated that every improvement is considered important by the care-givers.

The study was formally performed at three sites with 42 subjects, 1 subject and 4 subjects respectively. The results, however, are mainly determined by one site (Rare disease research, LLC) with 42 subjects. This is also surprising, given that the rarity of the disease was used to substantiate the absence of type I error control. As stated in Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/QWP/2330/99), section III.2, Prerequisites for one pivotal study applications, "None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect". In light of other phase 3 studies, study AT-007-1002 can be considered as the only pivotal study where potential treatment effect is dominated by one centre. This results rather in exploratory status of study. The applicant is requested to elaborate how the results can be regarded as robustly established as the results were mainly based on one site.

Originally, the study was designed to include up to 3 sites in Europe; however, due to the covid-19 pandemic, the EU sites were not activated.

Part B consist of 47 subjects with 17 subjects entered from part A and 30 are newly included subjects.

The efficacy population consists of 44 subjects with 13 subjects in the placebo group and 31 subjects in the govorestat treatment group. The patients included patients were all Caucasian and most of the care-givers (77.8%) had a College, technical college, university degree or a Graduate degree (PhD, MD, etc.). This questions the representability of the included population as this condition is not limited to the Caucasian race. Further there is no indication that this condition has a higher frequency in the higher socio-economic classes. The applicant is requested to discuss the differences between the included population and the expected population based on the frequencies reported in literature. Further the applicant is requested to discuss the existence of potentially relevant effect-modifiers (among others adherence to diet), and discuss the representativeness of the population included in the study with regard to this effect modifiers, i.e. the applicant should demonstrated that the results obtained can be extrapolated to the population intended to be treated (all patients with CG above the age of 2 years). Further As disease management may differ between the US and the EU, the difference in treatment strategy should be properly discussed.

The demographics and baseline characteristics should be presented for the efficacy population.

The applicant should report the GALT activity per patient indicating if the GALT activity is below or over 1%.

For the OWLS-II score in the placebo arm the baseline standard score for "Oral Expression" was 72.4 (95%CI 61.4, 83.3) in the active treated group this was 74.3 (95% CI 67.7, 80.9). In the placebo arm the baseline standard score for "Listening Comprehension" was 76.9 (95% CI 66.6, 87.2) in the active treated group this was 82.8 (95% CI 76.0, 89.6). For the BASC-3 BSI in the placebo arm the baseline t-score was 47.9 (95%CI 43.6, 52.2) in the active treated group this was 56.4 (95% CI 53.7, 59.1). For the BASC-3 ADL no detailed information was found. The baseline results of the OWLS-II indicate that the children were "below average" but not deficient. The results of the BASC-3BSI indicates that at baseline the children both in the placebo and the govorestat group were within the normal score. For the other secondary endpoints the same picture arise i.e. patients are low normal or just below normal. As a considerable group of patient had scores within the normal range the need for treatment is not evident. The applicant is requested to justify any treatment in those patients who are within the normal range. It is well known that, in addition to diet, speech and physical therapy are an integral part of the care of patients with galactosemia. Speech and physical therapy have a positive effect on the patient's clinical condition. This non-pharmacological treatment was not standardized, nor was it required to be stable before the study initiation. This may also affect the assessment of the study endpoints. Patient's baseline characteristics (speech, listening, behavioral patients baseline characteristics etc.) were not well balances between treatment groups.

Based on the results of Part A, the following doses were selected for Part B: 15 mg/kg/day in children aged 13 to 17, 20 mg/kg/day in children aged 7 to 12 years; and 20 mg/kg/day in children aged 2 to 6 years. (for a discussion on the posology reference is made to section 3.3.2 and relevant sections of the PK assessment)

The estimated Mean Z Score of the composite endpoint (OWLS-II (OE, LC), BASC-3 (ADL, BSI)) is 0.8683 (95% CI -0.204, 2.087; one-sided p-value 0.1030). The study was not type I error controlled, and the totality of the evidence will be assessed. The result of the change in Z-score does not indicate a nominal statistically significant treatment effect and it is not known if this effect is a clinically relevant effect..

Regarding statistical significance in overall, as stated in Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/QWP/2330/99), section III.2, Prerequisites for one pivotal study applications, "*Statistical evidence considerably stronger than p<0.05 is usually required (…)*". However, such p-value was not observed for primary composite endpoint and almost in no sensitivity analysis for primary composite endpoint.

The pre-planned sensitivity analysis based on the raw scores showed a difference in mean Z-score of -0.28 in favour of the placebo. The corresponding confidence interval is missing. The O'Brien Rank-sum method did also not show a nominal statistical significant treatment effect.

The subjects who transitioned from part A to part B may be different from the subjects who are directly randomised in part B as they are treated for a longer period and are more familiar to fill in the COA's due to the several drug doses before the final dose. Therefore two separate primary efficacy analysis are requested, one based on only the subjects who are directly randomised in part B and one based on the subjects who are also treated in part A are of interest and are requested.

A justification is needed why month 18 was chosen for presentation of the primary efficacy analysis result in the CSR. The applicant is requested to submit for each of the domains included in the primary efficacy composite endpoint, the baseline data as well the scores after 6, 12 and 18 months of treatment.

The p-value is considered a one-sided p-value at a 5% level of significance, while the sample size calculation was based on a two-sided alpha of 0.05. The applicant is requested to comment and explain this difference.

The applicant is requested to present all relevant intercurrent events (e.g. change of diet, initiation of speech therapy, use of concomitant medication) and how they have been handled in the primary analysis.

The results of the 4 COA's which are part of the primary composite endpoint are presented. The 95% confidence intervals are missing in Table 36 and are requested. Furthermore the clinical relevance of the observed differences should be discussed.

The applicant is requested to submit the detailed results of the primary efficacy analysis. The results should include for each of the four parameters, the number of subjects, the mean value, median value, minimum value, maximum value and the corresponding 95%CI for the adjusted scores at baseline, after 6, 12 and 18 months of treatment and the changes compared to baseline. Also the difference compared to placebo should be presented. This should be performed for the total clinical efficacy population and the various age groups. The parts of the OWLS-II score showed favourable effects for the placebo treated patients. The BASC-3 behavioural symptoms index T score and the BASC-3 activities of daily living T score resulted in an estimated mean Z-score, which is in favour of the treatment with govorestat. However, the clinical relevance is unknown. The 95% confidence intervals are missing and requested.

The results of the OWLS-II should be interpreted with caution as a baseline imbalance in patients receiving speech therapy existed, with more patients in the placebo group receiving speech therapy vs. the active treatment arm. This disbalance is considered a result of the disbalance in speech between treatment groups (see discussion on OWLS oral expression below). Further, many patients initiated speech therapy during the study such that nearly all patients in the placebo group were receiving speech therapy as the trial progressed, while several patients in the active treatment arm decreased or discontinued speech therapy. Unfortunately no detailed information of which and how many patients receiving speech therapy, how many patients decreased or discontinued speech therapy and the reason why therapy was initiated or stopped was submitted.

There appears to be differences between the information mentioned in the final study report and the information provided in the appendix but also between the various tables in the appendix. For example the treatment difference in mean z-score for the primary composite endpoint found in table 14.2.1.1. and mentioned in the final study report is both 0.868. The corresponding p value in the final study report or in Table 14.2.1.1.1 is 0.1030 while in table 14.2.1.1 and Figure (forest plot) 0.0920 is reported. The applicant is requested to explain the differences observed in the final study report and the various appendices for the primary composite endpoint and the accompanied sensitivity analysis.

The detailed discussion of the results and analysis of the secondary composite endpoint [consisting of OWLS-II (OE, LC), BASC-3 (ADL, BSI), NIH Cognition Composite and 9-Hole Pegboard Dexterity (Dominant)] are not readily found in the overview or final study report. The applicant is requested to submit the detailed results of these analyses. The results should include for the composite as well as for each of the parameters, the number of subjects, the mean value, median value, minimum value, maximum value and the corresponding 95% CI both for the adjusted scores at baseline, and after 18 months of treatment and the changes compared to baseline. Also the difference compared to placebo should be presented. This should be performed for the whole clinical efficacy population and the various age groups.

For the remaining endpoints (NIH toolbox, SARA, Archimedes spiral drawing, and Vinland score) the same conclusions can be drawn and questions raised.

No effect on existing cataract or the development thereof was observed.

Most children did not indicate signs of ovarian maturation which is to be expected given their age. In those who are over 7 years of age most (7/11) did not show any sign ovarian maturation. The remaining 4 patients (1 on placebo and 3 on govorestat) reported some signs of ovarian maturation. This maturation already stated before the inclusion in the study in 3 patients (1 on placebo and 2 on govorestat). Of these 3 patients one reported an spontaneous menarche while on govorestat treatment.

The results of changes in neurofilament light (Nf-L), MRI/MRS or the Bayley-4 were not discussed in the overview or CSR.

Results of the Clinician GIS and GIC were not interpretable as a considerable part of the baseline values was missing.

The results of the parent GIS and GIC are somewhat confusing as based on the GIS score there is some impression of worsening while the GIC score clearly mentions both improvement and worsening. The applicant is requested to explain the apparent differences.

Analysis in severely impaired patients (in the context of this study as the most impaired patients are already excluded) were inconclusive.

For none of the parameters included in the primary endpoint a clear relation with the plasma galactitol concentration or the change thereof could be demonstrated (i.e. R was below 0.3).

Reading the DMC minutes it is clear that the DMC informed the sponsor that no statistically significant superiority of govorestat versus placebo was demonstrated.

At this point, the Sponsor unblinded the study and crossed the placebo group to active treatment. The results of the blinded portion of the trial through 18 months of treatment are reported. No discussion or justification for the applicants decision not to proceed another 6 months is lacking. As it is assumed that the decision of the applicant is justified and documented (according to the applicant CGP rules are followed) the document(s) containing the justification of the decision to stop the study should be submitted.

Study AT-007-1006 was designed to assess the long-term safety of govorestat in patients with CG as well as the pharmacodynamics (PD) (inhibition of galactitol) and PK of govorestat. The effect of 12-month treatment with govorestat on the levels of galactose and other galactose metabolites in patients with CG were evaluated. There results are discussed in the dose-finding section of the report.

Seven (7) patients were enrolled in the study. No conclusions could be drawn for either baseline BOI or effect of govorestat treatment because of the small number of patients. In addition, 2 patients entered this study directly from antecedent Study AT-007-1001 (and no baseline value were measured in AT-007-1001 for these endpoints) further 1 of the patients had been on AT-007 for over 90 days at baseline for the current study and another patient had been on AT-007 as recently as 2 days before baseline for the current study. Further, the applicant halted the study after the last patient 18 month visit for administrative reasons and transitioned the patients who wished to continue receiving the study drug onto an Expanded Access Protocol

As the results of study 1006 are not useful for the benefit risk assessment in adults, no information on the clinical efficacy in adults is available. The applicant should discuss the use of govorestat in adult patients. First of all the applicant should discuss the clinical need for treatment in the light of the postulated mode of action (stop or slow down the neurodegenerative effect), i.e. the applicant should demonstrate any disease progression in untreated adults during adult life in one of the important domains (for example cognition, behaviour, social skills or motor disabilities), the applicant should

justify the need for treatment (i.e. should demonstrate an existing baseline deviation from normal in the important domains), the applicant should convincingly discuss the to be expected clinical benefits based on the information obtained in children (the lack of a firmly established relation between changes in galactitol level and the clinical outcomes prohibits an extrapolation on this PD parameter, see also the scientific advise provided (see part 2.3)). In this discussion all available knowledge should be taken onboard including the less favourable.

Additional expert consultation

None

Assessment of paediatric data on clinical efficacy

See pivotal study

Additional efficacy data needed in the context of a conditional MA

The request for CMA is currently not acceptable and the applicant is invited to further justify their request in light of the provided data package and taking into account available guideline[10]. For the CMA proposal the following major issues have been identified:

a. There is a major doubt whether govorestat is able to address the unmet medical need for classic galactosemia patients. This should be thoroughly discussed by the applicant, based on the following aspects:

    i. Placebo treated patients did not show a clear and consistent deterioration and no progression of the disease appears to be measurable over a period of 18 months using the chosen endpoints. Natural history of the disease, updated literature, and feedback from healthcare professionals and patient organisation indicate that a deterioration in cognitive function is not expected in the short run (i.e. few years). In this context, the applicant should discuss if and how this endpoint (or possibly alternatives) can provide evidence of efficacy in this condition.

    ii. Although galactitol is widely considered a disease biomarker, doubts exist on its use as a surrogate endpoint to establish efficacy. Thus, the value of lowering galactitol levels is questioned. For none of the parameters included in the primary endpoint, a clear relation with the plasma galactitol concentration or the change thereof could be demonstrated. The applicant should address the value of galactitol as a relevant surrogate, preferably based on evidence of its causal role in the pathophysiology of classic galactosemia, and the applicant should discuss the clinical relevance of the observed effects on galactitol.

    iii. The unmet need and its fulfilment should be further defined, by describing the specific symptoms patients experience and how these are changed by treatment.

b. The proposed clinical SOBS are unlikely to confirm the benefit risk balance in the claimed indication. The applicant should further discuss how these additional studies

[10] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf

will be comprehensive and confirm the efficacy and safety of the medicinal product in the claimed indication (above 2 years old) taking into account the following:

i. - the paediatric study is in children below the age of 2 years and not related to the claimed indication

ii. - the study in adults is not sufficiently detailed and an outline of the proposed protocol should be provided to assess its feasibility and adequacy.

iii. - the additional long term follow-up data on the children who participated in the placebo-controlled AT-007-1002 clinical study are not considered sufficient to confirm the efficacy and safety of govorestat in the claimed indication

iv. - The study on food effect is required to support the initial marketing authorisation application. Currently, the recommendation is to administer the daily dose at the same time in the morning after an overnight fast and 2 hours prior to a meal. However, this is not acceptable is paediatric patients. Therefore, the effect of food on the PK of govorestat should be investigated.

c. The benefit risk balance of the product is currently negative.

d. The applicant should further discuss whether, in light of the points above, the benefits of immediate availability outweigh the risk inherent in the fact that additional data are still required.

3.3.6. Conclusions on clinical efficacy

The totality of the information does not indicate a clear and consistent favourable effect. The uncertainties and limitations about the primary composite endpoint make it impossible to draw conclusions on the efficacy of govorestat. The primary composite endpoint as presented in this report, did not show a statistical significant effect. Although a difference was reported by the caregivers, no clinical relevant and consistent effect was seen in any of the endpoints studied. From this perspective the study can be considered a failed study.

In addition, there is not clear role of galactitol as a predictor for evaluation of clinical effect of therapy with aldose reductase inhibitor govorestat.

3.3.7. Clinical safety

3.3.7.1. Patient exposure

The primary evidence of the safety of treatment with govorestat is based on 2 pivotal studies conducted in subjects with CG. AT-007-1002 is a phase 3 study in paediatric subjects with CG, with an OLE currently ongoing. AT-007-1001 is a phase 1/2 study divided in 5 parts (A, B, C, D, D-extension). Parts A, B, C were in healthy subjects and part D and D extension (3 months) were in adults with CG. Administered doses of govorestat in part D and part D extension varied from 5-20-40 mg/kg. The open label extension study AT-007-1006 (20 mg/kg govorestat) is a completed open-label long-term study (18 months) with seven CG adults who participated in AT-007-001.

Other supportive data from completed studies with healthy subjects is from studies AT-007-1004 (20 mg/kg govorestat) and AT-007-1007 (20 mg/kg govorestat), two phase 1 studies of bioavailability and bioequivalence.

Data from the sorbitol dehydrogenase (SORD) deficiency development program is also provided by the Applicant. Ongoing study AT-007-1005 (20mg/kg govorestat) assessed data from 56 subjects, data

from the study AT-001-AT-007-1001 (part A, B) with 7+9 subjects is also provided. These studies are considered supportive.All studies concerning galactosemia patients included patients with a CG diagnosis with absent or significantly decreased (<1%) GALT activity in RBCs.

Safety data are available for 31 paediatric patients and 30 adult patients with classic galactosemia. In AT-007-1002, a total of 47 patients with CG between age 2 and 18 years were enrolled (18 months). 31 patients received at least 1 dose of active treatment. The patients were distributed over three age groups (2-6 years old; 7-12 years old and adolescents 13-18 years old). 26 patients completed the whole study (Part B, 18 month). 14 additional patients crossed from placebo to active treatment in AT-007-1002 OLE. Full safety data from this study are not yet available.

In the adult population, several subjects have participated several times in the same study (AT-007-1001) and/or participated in several studies. 14 unique adult patients with CG were enrolled in study AT-007-1001 Part D. 12 patients received at least 1 dose of active treatment (used dose 5, 20 and 40 mg/kg). In part D extension 9 patients from Part D and another 6 unique patients were enrolled. The dose used in this extension was 20 and 40 mg/kg. Not all patients completed the study, 2 subjects in the 20 mg/kg group discontinued the study due to TEAEs of AST increased and hepatic enzyme increased and 2 subjects in the 40 mg/kg group discontinued due to the sponsor closing the dosing cohort. Therefore, only 11 patients are considered to be exposed to the drug treatment for whole duration of the study (90 days treatment). 7 patients who participated in study AT-007-1001 were enrolled to study AT-007-1006 for evaluation of the long-term safety (18 months, dose 20 mg/kg). 2 subjects entered the study immediately and other 5 subjects after approximately 12 months govorestat treatment gap. 3 patients discontinued the study prematurely – 2 subjects due to withdrawal of a consent and 1 subject due to an AE (LFT increased).

It is unclear how many unique adult CG patients have been exposed to govorestat in the proposed dose. 20 unique subjects have been included for the treatment groups (all doses) and the placebo groups combined.

In the studies concerning adult CG patients, all included patients were 18 – 50 years old.

Additionally, 119 healthy volunteers and 46 SORD patients have been exposed to govorestat.

Maximum duration of exposure to govorestat was 18 months (AT-007-1002, 31 paediatric patients included, and AT-007-1006, 7 adult patients included).

In- and exclusion criteria and other characteristics of the study population are described in the sections on clinical efficacy.

3.3.7.2. Adverse events

Paediatric CG patients

In AT-007-1002, nearly all patients in the govorestat group reported at least 1 adverse event (96.8%) and all placebo patients reported at least 1 event (100%). A total of 412 TEAEs was reported. None of the AEs were considered serious or severe and all resolved. The most frequently reported TEAEs were of the System Organ Class of gastrointestinal disorders: in 74.2% of subjects in the govorestat group, and 68.8% of subjects in the placebo group. The number of gastro-intestinal events in the govorestat treated group exceeded the number in placebo treated patients (76 events in 31 patients and 21 events in 16 patients, respectively). Changes in ALT and/or AST and in renal function were reported (see section 3.3.8.3). Renal disorders occurred more frequently in the placebo treated subjects. Of note, among the most common TEAEs, the TEAEs of abdominal pain, constipation, and oropharyngeal pain were reported only in patients who received govorestat.

By age group, the percentage of patients who received govorestat reporting pyrexia and vomiting decreased with increasing age; a similar trend for pyrexia was observed in patients who received placebo across age groups.

TEAEs that were judged as drug related were reported in 7 (43,8%) patients in the placebo arm and 16 (51,6%) patients in the govorestat arm. A higher number of related TEAEs was reported in the govorestat group compared with the placebo group – 35 vs 11. The most frequently reported TEAEs considered to be related to govorestat were hepatic enzyme increase (7 subjects, 22.6%), diarrhea (4 subjects, 12.9%), and urine albumin/creatinine ratio increase (3 subjects, 9.7%). Vomiting, abdominal pain and acute kidney injury were each reported in 2 (6.5%) of subjects.

Table 8: Summary of Treatment-Emergent Adverse Events in ≥10% of subjects in AT-007-1002 by System Organ Class and Preferred Term

System organ class Preferred term	**Placebo (n=16)** **(age 2-17 Combined)** **Number (%) of subjects [events]**	**AT-007 (n=31)** **(age 2-17 combined)** **Number (%) of subjects [events]**
Subjects reporting ≥1 TEAE	16 (100%) [148]	30 (96.8%) [264]
Gastrointestinal disorders	11 (68.8%) [21]	23 (74.2%) [76]
Vomiting	5 (31.3%) [9]	15 (48.4%) [28]
Diarrhoea	2 (12.5%) [3]	8 (25.8%) [15]
Abdominal pain	0	7 (22.6%) [12]
Toothache	4 (25.0%) [6]	3 (9.7%) [6]
Constipation	0	4 (12.9%) [5]
Hepatobiliairy disorders	2 (12.5%) [2]	8 (25.8%) [9]
Hepatic enzyme increased	2 (12.5%) [2]	8 (25.8%) [9]
Renal & Urinary Disorders		
Urine albumin/creatinine ratio increased	7 (43.8%) [8]	5 (16.1%) [5]
Urine protein/creatinine ratio increased	3 (18.8%) [3]	2 (6.5%) [2]
General disorders	10 (62.5%) [24]	19 (61.3%) [31]
Pyrexia	9 (56.3%) [19]	17 (54.8%) [23]
Infections and infestations	10 (62.5%) [26]	18 (58.1%) [55]
Viral upper respiratory tract infection	3 (18.8%) [6]	14 (45.2%) [27]
Nervous system disorders	6 (37.5%) [8]	12 (38.7%) [20]
Headache	4 (25.0%) [5]	8 (25.8%) [14]

Adult CG patients

TEAEs observed in the Part D of study AT-007-1001 were mild in severity and no TEAEs reported by patients who received govorestat was considered as drug related.

TEAEs observed in Part D extension were mostly mild or moderate in severity and not related to the study treatment. 2 patients who received govorestat (20 mg/kg) reported a single AE considered as severe: liver injury and hepatic enzyme increase. 6 (54,5%) patients (5 of them dosed with 20 mg/kg) experienced 12 TEAEs (10 TEAEs in the 20 mg/kg group) considered related to the drug treatment. In the 20 mg/kg group, as possibly related to study treatment were judged ALT increased, AST increased, bowel movement irregularity and menstruation delayed; as probably related were judged diarrhoea, LFT abnormal, GGT increased, hepatic enzyme increased and blood lactate dehydrogenase increased. In the 40 mg/kg group, as possibly related were judged TEAEs ALT increased and AST increased.

In the study AT-007-1006, 6 (85,7%) patients reported a total of 22 TEAEs. All 6 patients reported some TEAE considered related to the drug treatment (10 of 22 TEAEs) – constipation, liver function increase (3 patients, therefrom 3 occurrences in 1 patient), blood creatinine increase (2 patients).

The occurrence of the most reported TEAEs were comparable across the investigated groups (adult vs paediatric, single age groups).

3.3.7.3. Serious adverse events, deaths, and other significant events

Adverse events of special interest

Hepatic and renal adverse events are considered of special interest, based on the safety profile of previously studied aldose reductase inhibitors.

Hepatic adverse events

Pediatric CG patients

In AT-007-1002, laboratory abnormalities of hepatic function occurred in 11 (23,4%) patients overall. Eight patients receiving govorestat showed abnormal liver enzymes on at least one measurement (8/31, 25.8%). These subjects had mild to moderate elevations of the transaminases (ALT and/or AST), none had elevations in other liver enzymes or bilirubin. In three of these patients, govorestat was interrupted and subsequently resumed due to liver enzyme abnormalities, possibly related to govorestat use. Concurrently, urinary tract infections/bacteriuria were detected.

In two patients elevation of ALT and AST lead to discontinuation of govorestat. In both patients govorestat was initially interrupted followed by a decrease of transaminases. However, upon rechallenge transaminases increased to >5x ULN and govorestat was halted. Follow-up laboratory studies after discontinuation returned to normal.

Adult CG patients

In adult patients, 9 subjects showed liver enzyme elevations: 5/11 patients (45.5%) in AT-007-1001 part D extension, and 4/7 patients (57.1%) in AT-007-1006. In 6/9 subjects these were considered possibly or probably related to govorestat. In four of these patients, treatment was repeatedly interrupted or permanently discontinued due to these hepatic abnormalities. In two patients, severe elevations of hepatic transaminases occurred. In one of these patients, a SAE of liver injury was reported.

Renal adverse events

Pediatric CG patients

5/47 (11%) included patients had lower than expected eGFR based on serum creatinine at the end of the study. However, there was no imbalance between the active and placebo group. Increased urine albumin/creatinine ratio or protein creatinine ratio was reported more frequently in placebo treated patients than in govorestat treated subjects. In 3/31 govorestat-treated patients, significant increases in creatinine concerning for possible acute kidney injury occurred. However, in all three cases the creatinine immediately normalized on repeat testing. The renal abnormalities were considered not related to govorestat by the investigator, but were interpreted as spurious results, or attributed to transient dehydration and/or urinary tract infection (UTI).

Adult CG patients

In the studies concerning adults with galactosemia, one subject in study AT-001-1001 part D extension showed renal events (mild blood creatinine increase, moderate glomerular filtration decrease,

moderate acute kidney injury), not considered related to govorestat. In AT 007-1006, three TEAEs of blood creatinine increase were reported in 3 patients. One event was mild in severity, two were moderate. 2 events of blood creatinine increase were considered possibly or probably related to govorestat. In one event, govorestat was interrupted. All events resolved.

Serious adverse events

One SEA of liver injury was reported in an adult patient in AT-007-1001 part D extension. The patient's history contained galactosemia, anxiety, depression, Gilbert's syndrome and Epstein-Barr virus infection. At day 37 of exposure to govorestat 20 mg/kg/day, the study drug was withdrawn due to TEAE's of AST and ALT increase (3.8X ULN and 3.5X ULN respectively), possibly related to the study drug. Severe liver injury was reported at day 76. At this time, transaminases had increased up to 349 U/l (10x ULN) for AST and 614 U/l (11x ULN) for ALT, associated with symptoms of decreased appetite, weight loss, fatigue, increased anxiety, increased insomnia and light-headedness. A liver biopsy showed remote confluent pericentral necrosis of unknown etiology and mild perisinusoidal fibrosis. The pathologist commented that the differential diagnosis included drug induced injury. During follow-up, the biochemical abnormalities resolved. The investigator considered the SAE of liver injury possibly drug-related. In the Hepatic Safety Adjudication Committee decision form, the causal relationship of the hepatic abnormalities to the study drug is described as possible (25-49%). However, a comment is included that the long delay of the study drug makes a causal relationship unlikely. No serious TEAE was reported in paediatric patients.

Deaths

No AEs led to death during any of the studies.

3.3.7.4. Laboratory findings

Laboratory abnormalities in hepatic and/or renal parameters were reported in several subjects. In paediatric CG patients, the most frequently observed TEAEs were urine albumin/creatinine ratio increased (placebo, 43.8%; govorestat, 16.1%), hepatic enzyme increased (placebo, 12.5%; govorestat 25.8%), and urine protein/creatinine ratio increased (placebo, 18.8%; govorestat, 6.5%). No patient experienced a severe or serious TEAE. The most frequently reported laboratory-related TEAEs considered to be related to govorestat by the investigator were hepatic enzyme (ALT/AST only) increased (7 patients [22.6%] and urine albumin/creatinine ratio increased (3 patients [9.7%]).

In CG adults, in study AT-007-1001 part D and part D extension, 5 subjects in the govorestat 20 mg/kg and 1 subject in the govorestat 40 mg/kg groups had clinically significant changes in laboratory values that were reported as TEAEs. In 5 patients, elevated liver enzymes were reported: AST/ALT increase in all, accompanied by GGT and LDH increase in 1 patient. 4/5 were considered possibly/probably related. One patient had renal events (blood creatinine increased -mild, glomerular filtration rate decreased -moderate, and acute kidney injury -moderate); all considered not related to the study drug. In study AT-007-1006, a total of 10 laboratory related TEAEs were reported in 5 subjects. In 4 patients, elevations of hepatic enzymes (AST/ALT) occurred. In 3 patients, creatinine elevations were reported. All laboratory related TEAEs were mild or moderate and either resolved or resolving by the end of the study.

In healthy adults, two AEs of increased hepatic enzymes (ALT/GGT) were reported; one was considered related.

No other notable differences in hematology, chemistry, and coagulation results were observed over time in any age group, and no consistent or clinically relevant changes from baseline in results were observed.

3.3.7.5. In vitro biomarker test for patient selection for safety

Not applicable

3.3.7.6. Safety in special populations

Safety data in paediatric patients have been described in previous sections. No studies have evaluated the safety of govorestat in paediatric patients <2 years of age. The proposed indication includes children 2 years and older.

No safety data are available on elderly patients. All studies included CG patients <50 years of age.

To date, no study has been conducted to characterize safety and efficacy of govorestat in pregnant or lactating women with classic galactosemia. It is not known whether govorestat is secreted in human milk.

To date, no study has been conducted to characterize safety and efficacy of govorestat in CG patients with hepatic or renal impairment. Patients with a history or presence of hepatic or renal disorders were excluded from the clinical studies.

3.3.7.7. Immunological events

Not applicable

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

Pharmacokinetic interaction studies are assessed in section 3.2.

No in vivo human drug-drug interaction (DDI) studies were performed.

No cases of safety concerns due to DDI have been reported in the clinical studies.

3.3.7.9. Interruption and discontinuation due to adverse events

Paediatric CG patients

In study AT-007-1002, in 6 patients (19.4%) who received govorestat and 2 patients (12.5%) who received placebo, non-serious and non-severe TEAEs resulted in study drug interruption. For the govorestat group these TEAEs were elevated hepatic enzymes in 4 patients (possibly/probably related), elevated creatinine in one patient (possibly related) and vomiting and diarrhoea in one patient (unlikely and possibly related, respectively). In the placebo group drug interruption was because of a urinary tract infection with haematuria in one patient and an elevated urine albumin/creatinine ratio in one patient.

Two (6.5% of subjects) adverse events led to permanent discontinuation in the govorestat group and one (6.3%) in the placebo treatment group. All permanent discontinuations were related to moderate ALT and/or AST liver enzyme elevation. All events leading to permanent discontinuation were asymptomatic and resolved upon study drug discontinuation. The first subject in the govorestat-treated group (15mg/kg govorestat) experienced elevation of ALT just under 3 x ULN on Day 30. AST and INR were also mildly increased at this time. Intercurrent abdominal pain and diarrhoea were also observed. It was decided to interrupt study drug as the elevation was close to the threshold of 3x ULN. Follow-up labs demonstrated decreasing ALT. Study drug was restarted when ALT was approximately 2x ULN with planned repeat labs approximately 2 weeks afterwards. The repeated labs demonstrated ALT elevation > 5x ULN. The DILI committee evaluated this to be probably related to the study drug and stated that the case did not meet Hy's Law. The other subject (20 mg/kg govorestat) experienced

elevation of ALT >3x ULN (day 30) and the study drug was interrupted. Subsequent follow-up showed ALT return to normal and study drug was restarted. ALT and AST increased on follow-up with ALT >3 x ULN and <5 x ULN. Approximately 10 weeks after restarting study drug, labs demonstrated ALT and AST elevations >5 x ULN. Study drug was discontinued. The DILI committee reviewed the case as probably related to the study drug and not meeting Hy's Law.

Adult CG patients

In adult patients, in study AT-007-1006 7 TEAEs in 2 subjects led to dose interruptions. The TEAEs that led to dose interruptions were single events of moderate constipation and mild alopecia considered possibly related to study drug in one subject and an event of moderate elevated creatinine considered not related to study drug and 4 events of mild or moderate LFT increase considered probably related to study drug in the other subject. In AT-007-1001, in 2 subjects dosing was interrupted. One subject experienced renal events (blood creatinine increased -mild, GFR decreased -moderate, and acute kidney injury -moderate), considered not related. The other subject experienced liver enzyme elevations (ALT increased and AST increased -both mild, considered possibly related to study drug, resolved).

3 subjects experienced liver enzyme elevations that led to discontinuation of govorestat. These were increases in AST, ALT, GGT and/or LDH. In the first subject, a SAE of liver injury was reported. This patient is described in section 3.3.8.3. Other subject (20mg/kg govorestat) experienced GGT increased, hepatic enzyme increased, blood LDH increased (each considered mild and probably related but did not meet Hy's Law). The comment of the committee states that the case presents probable DILI based on the time to onset, height of the ALT, rapid dechallenge and complete workup. The event resolved after discontinuation of the product. Other subject (20mg/kg govorestat) experienced LFT increased (increased ALT, AST - Hy's criteria was not met). The DILI committee evaluated the case as probably related to study drug. Patient's history contained galactosemia, tremor,. The patient was referred to hepatologist which revealed possible liver injury.

3.3.7.10. Post marketing experience

Not applicable

3.3.8. Discussion on clinical safety

Safety database

The safety of treatment with govorestat in the proposed indication is based on study AT-007-1002 in which children are studied and AT-007-1001 part D/D extension and AT-007-1006 in which adult patients were included. Additionally, the safety of govorestat has been evaluated in healthy subjects in two Phase 1 studies (AT 007-1004 and AT-007-1007) and in the first parts (A-C) of AT-007-1001. Further, safety of govorestat was also evaluated in 2 studies in adult subjects with sorbitol dehydrogenase deficiency (SORD) (AT-001-AT-007-1001 and AT-007-1005). This is provided as supportive data. The two pivotal studies (AT-007-1001 and AT-007-1002) are randomised controlled trials and data collection is considered standardised.

Patient exposure

Only 31 paediatric and 7 adult patients with CG were treated with govorestat for 18 months. This is considered very limited for expected chronic, long-term administration of a medicinal product and the provided data should be interpreted with caution. The uncertainties concerning the representativeness of the study population for the target population as a whole are discussed in the discussion on clinical efficacy.

Since classic galactosemia is a rare disease, the number of paediatric patients (31) exposed to govorestat in AT-007-1002 can beconsidered acceptable at this moment. Although the adult safety population consist of 30 subjects in total, the long term safety evaluation in adults is based on merely 7 patients in an open design study, of whom 4 completed the study. This is considered too limited to establish long-term safety. Furthermore, for the adult safety population, the provided data are inconsistent on how many unique CG patients have been exposed to govorestat. A discrepancy exists between the number of 30 patients as stated by the applicant in the overview of exposed patients, and the number of 20 unique patients specified in the description of the study populations (for govorestat and placebo combined). This hampers the interpretation of safety data, mainly in the determination of the frequency of adverse events, and should be further elucidated. From a GCP perspective, discussion is required on the potential consequences of including patients several times in the same study (AT-007-1001).

Safety data on long term exposure to govorestat are crucial considering the chronic nature of classic galactosemia and the intended long term use of this medication. Maximum duration of exposure in AT-007-1002 and AT-007-1006 is 18 months. The duration of follow-up allows for an initial assessment of long-term safety, however it is desirable to have access to more extensive follow-up data. This is especially relevant since clinical experts on galactosemia have expressed concerns on the consequences of altering a single metabolite (in this case galactitol) without full comprehension of the effects on other metabolites in galactose metabolism.

The applicant is invited to discuss the sufficiency of the submitted long-term data in adults and to summarise any additional available data on the long-term safety of govorestat treatment (literature, etc.). The applicant should share additional safety data as they become available. In addition, as the number of adult patients who completed the submitted long-term study is currently considered insufficient to establish a long-term safety profile, a thorough discussion and a detailed proposal for further steps to establish long-term safety should be provided. This should include, but is not restricted to, a proposal for a long term (e.g. 5 years) disease registry to follow-up safety data. This registry should ideally also include CG patients not pharmacologically treated. The applicant is requested to provide an outline and commitment for this registry.

Adverse events

The currently available data do not give cause to assume a different safety profile in the paediatric and the adult population, therefore data can be combined in the discussion of safety and in the SmPC.

No comprehensive overview is available for all adverse drug reactions in CG patients exposed to govorestat in the proposed dose range. The Applicant is requested to provide a clear overview of how many patients have been exposed specifically to the dosage proposed in the SmPC (20mg/kg), duration of the treatment in these cases and brief overview of AEs/ADRs in these patients **.** Furthermore, the applicant is requested to provide a table combining all adverse drug reactions in pediatric and adult CG patients, exposed to govorestat in the proposed dose range. This should serve as a starting point for the display of adverse effects in the SmPC. In paediatric patients, no serious adverse events were reported. In adults, a single SAE (liver injury) was reported (see hepatic enzyme abnormalities). From this point of view, use of govorestat seems to be quite safe in patients with CG. However, as it was already stated above, the long-term data are insufficient and a higher occurrence of possible drug related TEAEs serious in severity cannot be excluded.

Gastro-intestinal disorders

Among the reported TEAEs, gastro-intestinal disorders occurred most frequently. In the paediatric population, this consisted of vomiting (48.8% of subjects), diarrhoea (25.8%), abdominal pain

(22.6%) and constipation (12.9%). Vomiting and diarrhoea are included in the proposed SmPC as adverse reactions, however abdominal pain and constipation are not. The applicant states that these are common occurrences in the general paediatric population. Although this is correct, this does not explain why these AEs were reported in the govorestat population and not in the placebo population. Also, the investigator considered some of these AEs at least possibly related to govorestat. This was also the case in the adult population, although infrequently.

Hepatic enzyme abnormalities

Abnormalities in hepatic enzymes are considered adverse events of special interest by the applicant, based on the safety profile of previously studied aldose reductase inhibitors. Elevations of hepatic parameters are reported both in paediatric CG patients (25.8% of subjects) and adult CG patients (5/11 patients in AT-007-1001 [45%] and 4/7 patients in AT-007-1006 [57%]). In almost all cases this consisted of elevations of AST and/or ALT without concurrent abnormalities. Elevations ranged from mild (1,5 – 3 x ULN) to severe (>10x ULN). In several patients this resulted in discontinuation of the study drug.

Positive de-challenge-rechallenge both in children and adult subjects are supportive of a causal relationship to govorestat. No association with the level of drug exposure was found by the applicant. Since disorders of hepatic function are not a characteristic of classic galactosemia after the neonatal period, a causal relationship between the elevated transaminases and the galactosemia itself is considered unlikely, although an increased sensitivity to hepatic abnormalities in this patient population cannot be excluded, as stated by the Applicant. However, hepatic enzyme abnormalities have been identified as adverse events of special interest based on the knowledge of the safety profile of other aldose reductase inhibitors, which have been tested in patients with other diagnoses. Presumably, the transaminase elevations should be viewed as an idiosyncratic reaction to govorestat.

In one adult patient (AT-007-1001 part D extension), a serious adverse event related to transaminase elevations was reported. In this patient, govorestat was discontinued due to AST and ALT increase (3.8X ULN and 3.5X ULN respectively), possibly related to the study drug. 40 Days after discontinuation of govorestat, transaminases increased again up to 349 U/l (10x ULN) for AST and 614 U/l (11x ULN) for ALT, associated with symptoms of decreased appetite, weight loss, fatigue, increased anxiety, increased insomnia and light-headedness. The investigator considered this liver injury probably related. In the HSAC decision form a possible causal relationship is assigned. In the voting form of one of the committee members, a comment is included that the long delay off the study drug makes it very unlikely. An in-depth discussion on the causality by the applicant is required, especially considering the hepatic enzyme elevations occurring in other subjects and the safety profile of other aldose reductase inhibitors.

Considering the transaminase elevations, these are described as 'mild' in the SmPC, while moderate and severe events have been reported in the study population, and in several patients interruption and/or discontinuation of treatment was necessary. This is not accepted. Furthermore, no warning is included in section 4.4 of the SmPC. Since several patients discontinued the study treatment due to the hepatic abnormalities, this could also be expected in use of govorestat in clinical practice. Therefore, monitoring of hepatic function is considered obligatory during treatment with govorestat and needs to be dealt with in the product information. The SmPC section 4.4 should include a warning on the possibility of liver function abnormalities, and guidance on the extent and frequency of the monitoring of hepatic parameters. A warning should be included in the SmPC not to restart treatment in case of liver function abnormalities, unless the applicant can justify that restarting of the treatment can be performed safely.

Renal abnormalities

Renal adverse events were reported more frequently in the placebo treated paediatric patients than in the govorestat treated children. These events were mild and mostly transient. An alternative explanation, of transient dehydration and/or urinary tract infection, is provided. However, in adults two of the reported instances of creatinine increase were considered related to govorestat. Also, in AT-007-1002 the following statement is included in the discussion on renal function: 'Given the small numbers of subjects, the abnormalities in both treatment and placebo patients, and the unclear natural history of galactosemia and kidney disease, the available data doesn't seem to support that this drug's potential for renal injury is significant enough to outweigh the potential benefit of this drug on multiple other organ systems. Renal testing should however be a routine part of monitoring for patients who receive this medication. However, this is not included in the SmPC.

Considering the limited data available, the causality of creatinine elevations cannot be definitively determined. Furthermore, the frequency, severity and clinical relevance of possible creatinine elevations are unclear. The applicant should justify not including monitoring of renal function in the SmPC. Otherwise, recommendations concerning monitoring of renal function should be included in SmPC section 4.4.

Other adverse events

Headache was reported in all subject categories (CG paediatric and adult patient, and healthy volunteers). In paediatric patients, the number of subject reporting headache was similar in placebo and govorestat treated patients (4/16 [25.0%] and 8/31 [25.8%] respectively), but the number of events was higher in the govorestat treated group (5 vs 14 events). These events were considered to be not related by the investigator. In adult CG patients, headache was reported in 2 subjects and considered not related. In healthy volunteers, headache was reported in 4 events in 2 subjects and considered possibly related. Headache is not included in the SmPC as a possible adverse effect.

No clinically meaningful trend was observed for any other chemistry, hematology, or other laboratory parameters over time in any of the studies. No clinically meaningful observations were noted for other safety assessments (vital signs, ECGs, and C-SSRS).

Safety in special populations

No safety data are available on elderly patients. In fact, all included CG patients were <50 years of age. The applicant should justify that use of govorestat in the elderly population is safe based on the disease mechanisms, mode of action of the product, the experience in adults and changes due to aging. This justification should include potential restrictions for use, and/or special warnings and precautions for use in the elderly. Otherwise, the SmPC should state that safe use in the elderly is not established and use in the elderly population cannot be recommended.

No safety data are available in patient with hepatic or renal impairment. Subjects with a history or presence of hepatic or renal impairment were excluded from the studies according to the approved study protocols. Both subgroups can be considered vulnerable due to the expected risks, therefore, the use in these subgroups cannot be recommended. The risks and lack of data should be reflected in the proposed SmPC**.**

Drug-drug interaction

The Applicant states that based on nonclinical in vitro data, govorestat may increase exposure of CYP1A2 substrates, interact with CYP 3A substrates, increase the systemic exposure to sensitive substrates of CYP2B6, CYP2C19, breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3. Govorestat was a substrate for BCRP.

The Applicant states that based on the observed data from in vitro DDI studies, patients with concomitant treatment with sensitive substrates of BCRP, OAT1/3, CYP 3A4, CYP 2B6, CYP2C19, CYP

1A2 and potent inhibitors of BCRP were excluded from studies. No information on expected magnitude of clinical relevancy and further practical recommendation on the management of concomitant administration in clinical practice is provided. This should be amended .

Additional expert consultation

None

Assessment of paediatric data on clinical safety

Not applicable

Additional safety data needed in the context of a conditional MA

Considering the limited number of patients included in the safety database and the limited duration of follow-up, additional long-term data in both children and adults are necessary.

The applicant is requested to follow-up safety data in a long term (5 years) patient registry. Long term follow-up data on hepatic and renal function are considered especially relevant. This registry should ideally also include CG patients not pharmacologically treated. The applicant is requested to provide a detailed proposal and commitment for this registry.

3.3.9. Conclusions on clinical safety

Govorestat is intended for use in adult, adolescent and paediatric patients above 2 years of age with classic galactosemia. The evaluation of safety is limited by both the size of the safety database and the duration of exposure to govorestat. Although in a rare disease the size of the safety database is expected to be smaller, in this application the long-term safety cannot yet be established especially in adults because of the very low number of patients who completed the long-term study.

The occurrence of the mostly reported TEAEs was comparable across the investigated groups (adult vs paediatric, single age groups in paediatric patients). Most frequently reported adverse events are gastro-intestinal disorders (diarrhoea, vomiting, abdominal pain, constipation) and elevation of transaminases. The latter varies from mild to severe and has been the cause to interrupt and/or discontinue treatment in several patients in the clinical development programme. Presumably, this concerns an idiosyncratic reaction. Abnormalities in renal function have been reported as well, although a causal relationship to govorestat seems less straightforward.

Some of the observed TEAEs are already listed in the proposed SmPC (diarrhoea, vomiting and elevation of hepatic transaminases (ALT/AST), addition of some others should be discussed further.

In the majority of patients who interrupted or discontinued treatment this was due to increases in laboratory findings e.g., increases in ALT/AST, creatinine, GGT, LDH. Further discussion on these risks is considered needed and a description of the population at risk and the management of these risks should be provided within the Product Information.

No safety data are available for elderly patients, pregnant and lactating women, and patients with hepatic or renal impairment.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 9: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Elevation of hepatic transaminases
Important potential risks	• None
Missing information	• Use in patients with renal impairment • Use in patients with hepatic impairment • Long-term safety • Use in children less than 2 years of age • Use in pregnancy and breast-feeding

3.4.1.1. Discussion on safety specification

Important identified risk:

- 'Elevation of hepatic transaminases':

We propose to rename this safety concern as "Hepatotoxicity", as this term more adequately describes the important risk of liver toxicity, as compared to transaminase increases.

Missing information:

- 'Use in patients with renal impairment' and 'Use in patients with hepatic impairment':

Patients with hepatic impairment and renal impairment were not included in the clinical development programme. The MAH is requested to delete these missing information topics, or justify why these have been included in the RMP summary of safety concerns.

As described in GVP Module V (Rev 2) on missing information:

"The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP."

- 'Long term safety':

We agree to include long term safety as missing information safety concern.

- 'Use in children less than 2 years of age':

The missing information topic "Use in children less than 2 years of age" should be deleted. The proposed treatment population (indication) does not include patients less than 2 years of age, and is therefore not considered missing information in the current application.

- 'Use in pregnancy and breast-feeding':

We consider that "Use during pregnancy or breast-feeding" should be removed as safety concern in the RMP. Although the Applicant did not propose any additional pharmacovigilance activity to further study this patient population, we also do not consider such studies feasible due to anticipated difficulties to include sufficient pregnant women to draw robust conclusions:

- Classic galactosaemia is a rare disease
- Classic galactosaemia is associated with reduced fertility in females
- The proposed product information describes that govorestat therapy is not recommended during pregnancy.

Finally, based on the clinical and non-clinical data provided, developmental/reproductive toxicity is not expected.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification,

It is considered that the following issues should be addressed:

- The MAH is requested to rename "Elevation of hepatic transaminases" to "Hepatotoxicity"
- The MAH is requested to justify including the safety concerns "Use in patients with renal impairment" and "Use in patients with hepatic impairment"

It is considered that the following should not be safety concerns: "Use in children less than 2 years of age" and "Use in pregnancy and breast-feeding".

3.4.2. Pharmacovigilance plan

Please refer to the PRAC Rapp RMP AR.

3.4.3. Risk minimisation measures

Please refer to the PRAC Rapp RMP AR.

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.0 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 7.5.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the EBD or IBD to determine the forthcoming Data Lock Points.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication for govorestat is: "*Nugalviq is indicated for the treatment of adults and children aged 2 years and older with a confirmed diagnosis of classic galactosemia, also known as galactose-1-phosphate uridylyltransferase deficiency*".

The proposed dosing schedule is:

Adults (≥18 years)

The recommended dosing regimen is 20 mg/kg of body weight once daily for adults aged 18 years and over.

The once daily recommended dosing regimen in children and adolescents aged 2 to 17 years depends on the weight range as shown in below tables.

Paediatric dosing	
Body weight range (kg)	Recommended dose (mg/kg/day)
< 20	30
20 – 40	20
> 40	15

GALT deficiency can be classified into three categories based on the residual enzyme activity: Classic Galactosemia (CG) (<1% enzyme activity), Clinical Variant Galactosemia (1%-10% enzyme activity), and Duarte Galactosemia (15-35% enzyme activity).

Classic Galactosemia (CG) is a rare disease (1:16,000-1:44,000 in Europe) (Murphy et al., 1999; Bosch et al., 2005; Honeyman et al., 1993; Schweitzer-Krantz, 2003). Patients have autosomal mutations in the gene encoding for galactose-1-phosphate uridylyltransferase (GALT). The lack of GALT enzyme activity in GC patients leads to accumulation of galactose which is metabolized by aldose reductase (AR) to its metabolite galactitol and by galactokinase (GALK) to galactose-1-phosphate (Gal-1P). In untreated CG patients the galactitol in plasma (120–500 µmol/l) is markedly elevated (controls 0.08–0.86 µmol/l); under dietary treatment, the galactitol concentrations (4.7–20 µmol/l) remain above the control range.

Galactosemia is reported among all races and ethnicities. The distribution of the various races and ethnicities is comparable.

If untreated from birth, onset of severe metabolic symptoms occurs within a few weeks, followed by death during infancy (Berry, Updated 2021; Demirbas et al., 2018). Early implementation of a

galactose-restricted diet, within the first 10 to 14 days of life, typically resolves the acute neonatal complications, and infants appear normal until 1 to 2 years of age. Long-term complications become visible when cognition and fine motor function become of more importance (Berry 1997, Demirbas 2018) despite early detection and life-long dietary restriction of galactose. This long-term neurological damage includes speech/voice/language and cognitive impairment, behavioural symptoms (withdrawal, depression, ADHD, anxiety), tremor, and seizures. As a result, a considerable part of the patients are unable to perform activities of daily living, to have gainful employment, to form social or emotional relationships with others, or to live independent, and as a result require lifelong care (Rubio-Gozalbo et al, 2019; Randall et al. 2022).

In a GALT- null rat model of CG, galactitol accumulation was associated with cognitive and neurobehavioral deficits, similar to the defects observed in humans with CG (Rasmussen, 2020).

5.1.2. Available therapies and unmet medical need

There are currently no pharmacological treatments approved for CG, patients are currently treated with a diet.

5.1.3. Main clinical studies

The only clinical evidence of efficacy submitted is a single, sequential, Two-Part Study (study 1002) to Evaluate the Clinical Benefit, Safety, Pharmacokinetics, and Pharmacodynamics of govorestat in Paediatric Patients with Classic Galactosemia (CG).

A total of 47 paediatric patients (age 2 to 18) were included (16 in the placebo arm and 31 in the govorestat arm). The diagnosis of CG was state of the art. All patients were on diet. Patients with an IQ below 50, with severe renal or liver impairment or cardiac conditions were excluded.

The primary endpoint was a composite of the OWLS-II and a selection of the BASC-3 score. The OWLS-II addressed the expressive language and receptive language. From the BASC-3 the behaviour symptom index - obtained from caregivers only - addresses the behavioural problems (atypicality, withdrawal, attention, etc) while the BASC-3 ADL addresses the ADL. Secondary endpoints addressed behaviour (elements of the BASC-3, NIH Toolbox Cognition Battery), motor function (OWLS-II oral expression, elements of the NIH Toolbox Motor Battery, Archimedes Spiral Drawing Test, Scale for the Assessment and Rating of Ataxia (SARA), and Caregiver-Assessment of Global Impression of Severity/change.

Follow up time was 18 months.

Study AT-007-1001 was a phase 1-2 study evaluating the dosing in healthy volunteers and adult CG patients in this study only pharmacological endpoints (i.e. PK and galactitol) were measured.

Study AT-007-1006 included 7 adult patients with a maximal follow-up of 18 months. In this study the burden of illness and quality of life was measured.

5.2. Favourable effects

Clinical efficacy data were available for 47 children and 7 adults.

The population included in the study are Caucasian US residents from the higher socio-economic classes. The exclusion criteria do not allow for severely impaired patients to be included (IQ score < 50). All patients with a serious renal, hepatic or cardiac co-morbidity are excluded.

Based on the results obtained in the phase 1-2 study AT-007-1001 it was established that there is a maximal reduction of galactitol in adult patients at a dose of 20 - 30mg/kg.

Based on the results obtained in Part A of study AT-007-1002 combined with the optimal dose established in study AT-007-1001, the following posology was investigated in Part B of study AT-007-1002: 15 mg/kg/day in children aged 13 to 17, 20 mg/kg/day in children aged 7 to 12 years; and 20 mg/kg/day in children aged 2 to 6 years. Later this was changed in 15 mg/kg in paediatric patients weighing >40 kg, 20 mg/kg in paediatric patients weighing 20 to 40 kg and 30 mg/kg in paediatric patients weighing <20 kg.

The presented primary composite endpoint consists of changes from baseline to Month 18 for the four domains OWLS-II Expressive Language, OWLS-II Receptive Language, BASC-3 Behavioural Symptoms index and BASC-3 Daily Living domain The estimated mean z-score (govorestat - placebo) for the primary composite endpoint is 0.8683 (95% CI -0.204, 2.087; one-sided p-value 0.10). Two sensitivity analyses were performed, one where the estimated mean Z score is based on the raw scores instead of the adjusted scores (z-score -0.28; one-sided p-value 0.66) and one where the O'Brien rank-sum method is used and based on the adjusted scores (estimated difference in mean CFB rank sum score (govorestat – placebo = 9.1 (SD 63.0); p-value 0.35)).

Inclusion of cognition and motor skills in the composite endpoint analysis resulted in an estimated mean z-score of 0.917 (95% CI -0.051, 1.989).

At baseline in the placebo arm the standard score for the **OWLS Oral Expression** was 72.4 (95%CI 61.4, 83.3). In the active treated group this was 74.3 (95% CI 67.7, 80.9). The estimated difference from baseline to 18 months in the placebo group was 10.3 (95% CI 1.2, 19.4) in the govorestat treated group this difference was 9.5 (95% CI 3.9, 15.0). The estimated difference (govorestat - placebo) in change over time (baseline to 18 months treatment) in OWLS Oral Expression was -0.8 (95% CI -9.5, 7.9).

At baseline in the placebo arm the standard score for the **OWLS Listening Comprehension** was 76.9 (95% CI 66.6, 87.2) in the active treated group this was 82.8 (95% CI 76.0, 89.6). The estimated difference from baseline to 18 months in the placebo group was 2.3 (95% CI -5.5, 10.1) in the govorestat treated group this difference was 1.3 (95% CI -3.6, 6.3). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in OWLS Listening Comprehension was -1.0 (95% CI -9.9, 7.9).

At baseline in the placebo arm the t-score for **the BASC-3 Behavioral Symptoms index** was 47.9 (95%CI 43.6, 52.2). In the active treated group this was 56.4 (95% CI 53.7, 59.1). The estimated difference from baseline to 18 months in the placebo group was 5.0 (95% CI -0.4, 10.4) in the govorestat treated group this difference was -1.0 (95% CI -4.7, 2.6). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in BASC-3 Behavioral Symptoms index was -6.0 (95% CI -12.2, 0.1). (Cave; lower scores indicate a better result).

No information of the t-scores for **BASC-3 Activities of Daily Living** at baseline was submitted. The estimated difference from baseline to 18 months in the placebo group was -2.1 (95% CI Not submitted) in the govorestat treated group this difference was 4.0 (95% CI not submitted). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in BASC-3 Activities of Daily Living was 6.1 (SD 18.1).

At baseline the mean standard score for the **NIH Toolbox Cognition Battery** in the placebo group was 73.1 (95% CI 59.2, 86.9) in the govorestat group this was 75.1 (95% CI 67.9, 82.3). The estimated difference from baseline to 18 months in the placebo group was 4.5 (95% CI -0.6, 9.6) in the govorestat treated group this difference was 8.62 (95% CI 2.9, 14.4). The estimated difference

(govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Cognition Battery was 4.1 (95% CI -3.2, 11.5).

At baseline the mean standard score for **NIH Toolbox Motor Battery – Standing Balance** in the placebo group was 37.8 (95% CI 31.5, 44.0) in the govorestat group this was 41.7 (95% CI 37.0, 46.5). The estimated difference from baseline to 18 months in the placebo group was 5.2 (95% CI -1.7, 12.0) in the govorestat treated group this difference was 4.3 (95% CI 0.0, 8.6). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Motor Battery – Standing Balance was -0.9 (95% CI -8.6, 6.8).

At baseline the mean standard score for the **NIH Toolbox Motor Battery - Manual Dexterity** in the placebo group was 41.4 (95% CI 35.1, 47.7) in the govorestat group this was 39.0 (95% CI 34.9, 43.0). The estimated difference from baseline to 18 months in the placebo group was -2.8 (95% CI -7.9, 2.3) in the govorestat treated group this difference was -0.2 (95% CI -4.4, 4.0). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in NIH Toolbox Motor Battery - Manual Dexterity was 2.6 (95% CI -3.7, 9.0).

At baseline the mean standard score for the **SARA** in the placebo group was 5.00 (95% CI 1.50, 8.50). In the govorestat group this was 4.03 (95% CI 1.95, 6.11). The estimated difference from baseline to 18 months in the placebo group was 0.36 (95% CI -2.74, 2.03) in the govorestat treated group this difference was -0.71 (95% CI -0.33, 1.76). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in Scale for Assessment & Rating of Ataxia (SARA) was 1.07 (95% CI -1.39, 3.53).

For **Archimedes spiral drawing** at baseline the mean standard score in the placebo group was 1.45 (95% CI 1. 0.83, 2.07), in the govorestat group this was 1.78 (95% CI 1.40, 2.16). The estimated difference from baseline to 18 months in the placebo group was -0.06 (95% CI -0.30, 0.41) in the govorestat treated group this difference was -0.38 (95% CI -0.65, -0.11). The estimated difference (govorestat - Placebo) in change over time (baseline to 18 months treatment) in Spiral Drawing Test was -0.44 (95% CI -0.86, -0.02). (Cave; lower scores indicate a better result).

At Month 18, most children in the total govorestat group had overall caregiver Global Impression of Change (GIC) scale scores of 'much better' or 'a little better' (10/26 patients [38.5%] and 9/26 patients [34.6%], respectively), whereas most patients in the placebo group had overall caregiver GIC scale scores that did not change or were 'a little better' (6/12 patients [50.0%] and 4/12 patients [33.3%], respectively).

For the Global Impression of Severity at baseline, 3/13 patients (23.1%) of the placebo group scored "normal", 6/13 (46.2%) mildly impaired and 4/13 (30.8%) moderate or markedly impaired. In the govorestat group, 10/31 (32.3%) patients scored "normal" at baseline, 6/31 (19.4%) was mildly impaired and 15/31 (48.4%) moderate or markedly impaired. At Month 18 in the placebo group, 3/12 (25.0%) patients scored "normal", 4/12 (33.3%) mildly impaired and 5/12 (31.7%) moderate or markedly impaired. In the govorestat group 10/26 (32.3%) patients scored "normal" at baseline, 6/26 (19.4%) was mildly impaired with 15/26 (48.4%) moderate or markedly impaired after 18 months treatment.

No effect on existing cataract or the development thereof was observed.

Most children did not indicate signs of ovarian maturation which is to be expected given their age. Among those patients who are over 7 years of age, most (7/11) did not show any sign ovarian maturation. The remaining 4 patients (1 on placebo and 3 on govorestat) reported some signs of ovarian maturation. Based on FSH, LH and AMH this maturation was already started before the inclusion in the study in 3 patients (1 on placebo and 2 on govorestat). Of these 3 patients one reported an spontaneous menarche while on govorestat treatment.

The results of changes in neurofilament light (Nf-L), MRI/MRS or the Bayley-4 were not discussed in the overview or CSR.

Analysis in severely impaired patients (in the context of this study as the most impaired patients are already excluded) were inconclusive.

There was no clear relation between the parameters included in the primary endpoint and the plasma galactitol concentration nor with the change thereof could be demonstrated (i.e. R was below 0.3).In the most impaired patients(i.e. those with a score below normal for any of the composites of the primary endpoint) the baseline values the for the Oral and Written Language Scales (OWLS-II) in the placebo group (n=4) were almost 1SD worse compared to the govorestat group (n=12). For the placebo group the Oral Expression was deficient and remained, despite a small improvement, deficient (i.e. t-score <70). In the active treated group the average t-score for Oral Expression was just below "below average" and improved to "below average" after 18 months of treatment. The mean treatment difference was 10.1 (95% CI -8.8, 28.9). For the Listening Comprehension both the placebo and the govorestat group were deficient as they were after 18 months of treatment. For the BASC-3 At baseline the t-scores were within the normal range as they are after 18 months of treatment.

5.3. Uncertainties and limitations about favourable effects

It is acknowledged that CG represents a unmet medical need. However, The benefit-risk balance of govorestat is negative in the claimed indication. This should be thoroughly discussed by the applicant, based on the following aspects:

a. In this study, placebo treated patients did not show a clear and consistent deterioration and no progression of the disease appears to be measurable over a period of 18 months using the chosen endpoints. Natural history of the disease, updated literature, and feedback from healthcare professionals and patient organisation indicate that a deterioration in cognitive function is not expected in the short run (i.e. few years). In this context, the applicant should discuss if and how this endpoint (or possibly alternatives) can provide evidence of efficacy in this condition.

b. Overall, the data collected so far apparently do not substantiate a favourable effect of govorestat. The applicant is requested to discuss and justify the clinical relevance of the observed clinical effects based on the totality of the results.

c. Although galactitol is widely considered a disease biomarker, doubts exist on its use as a surrogate endpoint to establish efficacy. Thus, the value of lowering galactitol levels is questioned. For none of the parameters included in the primary endpoint, a clear relation with the plasma galactitol concentration or the change thereof could be demonstrated. The applicant should address the value of galactitol as a relevant surrogate, preferably based on evidence of its causal role in the pathophysiology of classic galactosemia, and the applicant should discuss the clinical relevance of the observed effects on galactitol.

d. Very limited information is available in adults (n=7) to support an indication in this age group. Furthermore, no information in patients over 50 years of age was submitted. The applicant should substantiate the use in adults or otherwise exclude the adult patients.

e. The indication should be revised to reflect that govorestat is used in addition to the galactose-free diet

Reading the DMC minutes it is clear that the DMC informed the sponsor that no statistically significant superiority of govorestat versus placebo was demonstrated.

At this point, the Sponsor unblinded the study and switched the placebo group to active treatment. No discussion or justification was provided for the applicants decision to not proceed another 6 months. As it is assumed that the decision of the applicant is justified and documented (GCP rules were followed according to the applicant) the document(s) containing the justification of the decision to stop the study should be submitted.

The exact role of galactitol in the pathophysiology of the disease has not yet been established and a clear association between galactitol levels and long-term complications of galactosemia is lacking. Furthermore, galactitol levels do not reflect disease severity. Its value depends on age. The selection of a plasma galactitol level of 500 ng/ml as a criterion for the severity of the disease is therefore not entirely clear. Further, none of the parameters included in the primary composite endpoint a clear relation with the plasma galactitol concentration or the change thereof could be demonstrated.

Posology

For children the posology was based on the C_{max} and AUC seen in adults and resulted in 15 mg/kg/day in children age 13 to 17, 20 mg/kg/day in children age 7 to 12 years; and 20 mg/kg/day in children age 2 to 6 years. For unknown reasons this was later changed from age depended dosing to weight dependent dosing. The resulting posology is not well understood, impractical and prone to medication errors. Furthermore, as this dose adjustment was not pre-defined in the sequential design, this may inflate the type I error.

Children (pivotal study AT-007-1002)

General

The totality of the information does not indicate a favourable effect. For some endpoints the change from baseline to 18 month showed an improvement (this applies to both placebo and govorestat) for others there is a deterioration. Sometimes the difference between govorestat and placebo at 18 months is in favour of govorestat sometimes in favour of placebo with the clinical relevance of the effects needs to be demonstrated.

Methodology

The primary endpoint was changed a couple of times, so selection bias cannot be ruled out. No justification for any of the changes of the primary endpoint was provided. Just before de-blinding the applicant changed the composite endpoint to the sum of change on speech and language skills, behaviour and daily living skills (as measured by Oral and Written Language Scales [OWLS-II] and Behaviour Assessment System for Children 3rd Edition [BASC-3] tests). Changing the primary endpoint during a confirmatory trial without proper planning will **render the trial to be considered exploratory**. The applicant is requested to justify this change to the selected parts of the OWLS-II and BASC-3. Further, the implication of using only the parent part of the assessment and the validation of the sub-scores warrants further justification. Additionally, the applicant is requested by whom and at what time point the changes in the primary efficacy endpoint have been made. Also discuss the possible effect on the B/R. This further is a concern in terms of GCP.

The imputation of the BASC-3 test by extrapolation of the previous results was not pre-planned and therefore the analyses with this imputation are considered as post-hoc analyses. This extrapolation is not common standard practice. After a certain age, not the parents/care givers fill out the questionnaires but this is done by the adolescent him- or herself. As t-scores are used in this analysis it is poorly understood why these results are not used. Therefore the applicant is requested to fully explain the used methodology, the assumptions that were made on which this practice is based, the validation of the analysis and a confirmation that this was considered before blinding was lifted.

During the study, the dosing was adjusted based on weights instead of age. This resulted that for some subjects Day 1 was not the first day of the planned age adjusted dosing, but the first day of their weight adjusted (optimal) dosing, which could be different. Any data driven changes during the course of the study reduce the confirmatory nature of the study. Furthermore, there is no pre-planned time point for the primary efficacy endpoint. Repeated testing for statistical significance introduces a multiplicity issue which inflates the type I error.

Both efficacy populations (biomarker and clinical) consist of all subjects who had a baseline galactitol level (prior to first dose) greater than 500 ng/ml, which was not an in/exclusion criteria of the study. This may lead to bias as it is a selection after randomisation. The applicant needs to reflect on the chosen threshold of 500 ng/ml and the possible bias for the primary endpoint and the effect on the B/R and a listing of the individual galactitol levels should be presented as this is lacking.

The study was formally performed at three sites with 42 subjects, 1 subject and 4 subjects respectively. The results, however, are mainly determined by one site (Rare disease research, LLC) with 42 subjects and are not robustly established. This is also surprising, given that the rarity of the disease was used to substantiate the absence of type I error control. The applicant is requested to elaborate how the results can be regarded as robustly established as the results were mainly based on one site.

A considerable part of the analysed secondary endpoints are sub-scores of established and validated measures, as such these sub-scores should be validated. No validation reports were found in the MAA.

The demographics and baseline characteristics are only presented for the safety population. The results for the efficacy population are missing.

Included patients

The number of patient is very limited (N=47), therefore, the results should be interpreted with caution.

The population included in the study are Caucasian US residents from the higher socio-economic classes, therefore, the results might be biased. The exclusion criteria do not allow for severe impaired patients to be included (IQ score < 50), which are the ones with the highest need for treatment. All patients with a serious renal, hepatic or cardiac co-morbidity were excluded. The included population does not represent the population intended for treatment according to the proposed indication with govorestat.

The medical history is as expected except for the rhinitis in 1 patient which is surprisingly low. Further, also surprisingly, no patent with an e-coli septicemia was reported. The applicant should explain the low frequency of the rhinitis in these children and the lack of expected issues such as e-coli septicemia, neonatal icterus or feeding problems.

All patients were on a diet, this should be reflected in the proposed indication.

Dietary intake was not standardized, which could have biased the study, since galactose intake in the diet significantly affects the levels of galactitol and other metabolites and thus the course of the disease.

Speech and physical therapy have a positive effect on the patient's clinical condition. However, this non-pharmacological treatment was not standardized, nor was it required to be stable before the study initiation. This may also affect the assessment of the study endpoints.

A discussion of potentially relevant effect-modifiers (among others adherence to diet), and the representativeness of the population included in the study with regard to these effect modifiers is lacking, i.e. the applicant should demonstrate that the results obtained can be extrapolated to the population intended to be treated (all patients with CG above the age of 2 years).

The mean and median GALT activity at baseline is reported not the GALT activity per patient. To assess whether patients were accurately diagnosed, the GALT activity per patient should be reported and it should be indicated whether the GALT activity is below or over 1% .

Further some co-medication (BCRP substrates and inhibitors, OAT1 and OAT3 substrates, CYP3A4 substrates, CYP2B6 substrates, CYP2C19 substrates, CYP1A2 substrates) and some foods interacting with the CYP's mentioned above were not permitted. It is not clear how the adherence to this restriction was controlled by the applicant (OC?).

The subjects who transitioned from part A to part B (these patients stayed after the switch on the assigned treatment, i.e. placebo or govorestat), may be different from the subjects who are directly randomised in part B as they were treated for a longer period and are more familiar to fill in the Clinical Outcome Assessments due to the several drug doses before the final dose. Therefore a primary efficacy analysis based on only the subjects who are directly randomised in part B and a primary efficacy analysis based on only the subjects who are also treated in part A are of interest and are requested.

Results general

A considerable group of patients scored within the normal range for most endpoints, therefore, the need for treatment is not evident for every patient. The applicant is requested to justify any treatment in those patients who are within the normal range for the various endpoints. In case a need for treatment is considered the applicant should indicated the most favourable treatment for the observed abnormal finding(s).

Results primary endpoint

For the primary composite endpoint consisting of OWLS-II (OE, LC) and BASC-3 (ADL, BSI) no baseline t-scores were presented nor information on t-scores after 18 months of treatment. This information should be submitted for an adequate assessment of the effect. The result of the change in Z-score does not indicate a nominal statistically significant treatment effect and it is uncertain if there is a clinically relevant effect.

Results secondary endpoints

The detailed results of the analysis of the secondary composite endpoint [consisting of OWLS-II (OE, LC), BASC-3 (ADL, BSI), NIH Cognition Composite and 9-Hole Pegboard Dexterity (Dominant)] are not readily found in the overview or final study report. The applicant is requested to submit the detailed results of the analyses. The results should include for each of the parameters, the number of subjects, the mean value, median value, minimum value, maximum value and the corresponding 95% CI both for the adjusted scores at baseline, and after 18 months of treatment and the changes compared to baseline. Also the difference compared to placebo should be presented. This should be performed for the whole clinical efficacy population and the various age groups.

For the spiral drawing the lower age limit is 5 years. Therefore the results for the youngest age group should be interpreted with caution.

SARA is a tool for assessing ataxia (more specific spinocerebellar ataxia, ataxic Stroke and Friedreich's ataxia) and only validated for patient over 8 years of age. The applicant is requested to explain how the fine and gross motor function can be assessed using SARA. This explanation should include a discussion on the validation of the motor tests for patients with CG and if possible a discussion on the MICD (not the noticeable difference as calculated by the applicant using the caregiver GIS as an anchor). The applicant is explicitly not requested to give any explanation/discussion of the use of SARA as a tool for assessing ataxia. This is well known by theCHMP and the information readily available on the internet.

According to the SAP version 5 an anchor-based sensitivity analyses should be performed on the GIS and GIC scales to include the clinical relevance of changes in the primary endpoint. For the primary composite endpoint this analysis is not submitted by the applicant. Further, the analyses using the GIC are lacking for all endpoints. The results of these analyses (especially those relaying on the GIC) are of interest for the assessment of the clinical relevance. Therefore, the results and a discussion considering the interpretation of the results should be submitted.

The relevance of the parent GIS and GIC is questioned as the parent has insufficient experience with "normal" and variation thereof to fully comprehend the activities of the child in the context of a bigger group of normal and impaired children. The lack of a validation report for this measure further hampers the assessment of the results. The applicant is invited to discuss the relevance of the measure in the light of the lesser experience of the care-givers. Further a validation report of the measure should be submitted .

Based on the results of this study the applicant calculated the value of the various endpoints at which a difference became noticeable for the parents, this cannot be considered a minimally clinically importance difference (MICD), i.e. it does not indicate a change in the patients' management. As no information on the MICD is found in the MAA the applicant should submit a discussion on the MICD for comparable conditions from literature.

The Vineland interviews were rendered not useful due to inexperience of the interviewers. This further questions proper GCP adherence.

An analysis of the initially preferred primary endpoint the Vineland Adaptive Behaviour Scales Composite Standard Scores is not readily found in the MAA. The applicant is requested to submit the descriptive statistics at baseline and after 18 months of treatment, the differences compared to baseline and the differences between treatment groups. Further a discussion of the observed changes should be submitted.(OC)

Adults

Very limited information considering the clinical endpoints in adults (N=7) is available.

No information in patients over 50 years of age were submitted.

Long term treatment

No interpretable information on treatment for more than 18 months is available.

5.4. Unfavourable effects

Clinical safety data are available for 31 paediatric patients and 30 adult patients with CG (studies AT-007-1001 part D/D extension; AT-007-1002; and AT-007-1006). Of these patients, safety data on long-term exposure (12-18 months) are available for 31 paediatric and 7 adult patients (studies AT-007-1002 and AT-007-1006). All included CG patients were <50 years of age.

In the paediatric population treated with govorestat, the most frequently reported adverse events were gastro-intestinal AEs. This consisted of vomiting (48.8% of subjects), diarrhoea (25.8%), abdominal pain (22.6%) and constipation (12.9%). All events were mild, of short duration and resolved. In adult patients treated with govorestat, diarrhoea, abdominal discomfort, constipation and bowel movement irregularity were reported, each in one patient.

Liver enzyme abnormalities occurred in 25.8% of paediatric patients exposed to govorestat (8/31 patients). These subjects had mild to moderate elevations of transaminases (ALT and/or AST), none had elevations in other liver enzymes or bilirubin. In three of these patients, govorestat was

interrupted and subsequently resumed. Two patients permanently discontinued govorestat due to elevation of ALT and AST. Follow-up laboratory studies showed that transaminases returned to normal in all patients.

In adult patients treated with govorestat, transaminase elevations were reported in 45.5% of subjects in AT-007-1001 part D extension (5/11 patients), and 57.1% of subjects in AT-007-1006 (4/7 patients). In four of these patients, treatment was repeatedly interrupted or permanently discontinued due to these hepatic abnormalities. Most events were mild or moderate, however in two patients severe elevations of hepatic transaminases occurred. In one of these patients, a SAE of liver injury was reported consisting of elevations of ALT and AST up to 11 x ULN and 10 x ULN, respectively. All events resolved.

Renal adverse events (mainly creatinine increase) occurred in both paediatric and adult CG patients when treated with govorestat. In paediatric patients, the renal abnormalities were considered not related to govorestat by the investigator but were interpreted as spurious results, or attributed to transient dehydration and/or urinary tract infection (UTI). In AT-007-1006, mild-moderate creatinine increase was reported in three patients (42.9%). In one event, govorestat was interrupted. All events resolved.

5.5. Uncertainties and limitations about unfavourable effects

Safety population

The uncertainties concerning the representativeness of the study population for the target population as a whole are discussed in the section on clinical efficacy.

It is unclear how many unique adult CG patients have been exposed to govorestat. A discrepancy exists between the number of 30 patients as stated by the applicant in the overview of exposed patients, and the number of 20 unique patients specified in the description of the study populations (for govorestat and placebo combined). This hampers the interpretation of safety data, mainly in the determination of the frequency of adverse events. From a GCP perspective, discussion is required on the potential consequences of including patients several times in the same study (AT-007-1001).

The long term (12-18 months) safety database consist of 38 CG patients. The duration of follow-up in combination with the number of patients, especially adult patients, is considered too limited for a full evaluation of the long term safety profile. Long term safety cannot be established based on 4 adult patients who completed study AT-007-1006, a study without a control group. The applicant is invited to discuss the sufficiency of the submitted long-term data in adults and to summarise any additional available data on the long-term safety of govorestat treatment (literature, etc.). The applicant should share additional safety data as they become available. In addition, as the number of adult patients who completed the submitted long-term study is currently considered insufficient to establish a long-term safety profile, a thorough discussion and a detailed proposal for further steps to establish long-term safety should be provided. This should include, but is not restricted to, a proposal for a long term (e.g. 5 years) disease registry to follow-up safety data. This registry should ideally also include CG patients not pharmacologically treated. The applicant is requested to provide an outline and commitment for this registry.

Adverse events

No comprehensive overview is available for all adverse drug reactions in CG patients exposed to govorestat in the proposed dose range. The Applicant should provide a clear overview of how many patients have been exposed specifically to the dosage proposed in the SmPC (20mg/kg), duration of the treatment in these cases and brief overview of AEs/ADRs in these patients . Furthermore, the

applicant is requested to provide a table combining all adverse drug reactions in paediatric and adult CG patients exposed to govorestat in the proposed dose range, to serve as a starting point for the display of adverse effects in the SmPC. The table of adverse reactions in section 4.8 of the proposed SmPC is considered to not adequately reflect the safety information derived from the clinical studies. For example, the gastro-intestinal events of vomiting and diarrhoea are included in the proposed SmPC as adverse reactions, while abdominal pain and constipation are not.

Liver enzyme abnormalities were reported in both paediatric and adult CG patients exposed to govorestat. The occurrence of transaminase elevations is in line with adverse effects previously reported in other aldose reductase inhibitors. Positive de-challenge-rechallenge both in children and adult subjects are supportive of a causal relationship to govorestat. No association with the level of drug exposure was found by the applicant. Disorders of hepatic function are not a characteristic of CG after the neonatal period. Therefore, a causal relationship between the elevated transaminases and the galactosemia itself is considered unlikely. However, an increased sensitivity to hepatic abnormalities in this patient population cannot be excluded. Presumably, the transaminase elevations should be viewed as an idiosyncratic reaction to govorestat.

The transaminase elevations are described as 'mild' in the proposed SmPC, while moderate and severe events have been reported in the study population, and in several patients interruption and/or discontinuation of treatment was necessary. This is not accepted. Furthermore, based on the data in the clinical studies, monitoring of hepatic function is considered obligatory during treatment with govorestat. Currently, no recommendations on the clinical management of these risks within clinical practice is proposed by the Applicant. The SmPC section 4.4 should include a warning on the possibility of liver function abnormalities, and guidance on the extent and frequency of the monitoring of hepatic parameters. A warning should be included in the SmPC in section 4.4 not to restart treatment in case of liver function abnormalities, unless the applicant can justify that treatment can be restarted safely in case of liver function abnormalities.

Concerning the SAE of liver injury, a discrepancy exists in judgement on causality between the investigator, the HSAC and the applicant. An in-depth discussion on the causality by the applicant is required, taking into consideration the views of the investigator and the HSAC, the hepatic enzyme elevations occurring in other subjects and the safety profile of other aldose reductase inhibitors.

Regarding the renal adverse events, the causality of creatinine elevations cannot be definitively determined due to the limited data available. Furthermore, the frequency, severity and clinical relevance of possible creatinine elevations are unclear. In the study report of AT-007-1002, the investigator states that renal testing should be a routine part of monitoring for patients who receive govorestat. However, this is not included in the SmPC.

Safety in special populations

No safety data are available on elderly patients. In fact, all included CG patients were <50 years of age. No justification for the safety of use of govorestat in the elderly population is available in the MAA.

No submitted data provide information on administration of govorestat in patients with hepatic and renal disorders. Patients with hepatic or renal impairment were excluded from the clinical studies. No justification for the safety of use of govorestat in patients with hepatic or renal impairment is available in the MAA. As abnormalities in laboratory findings in these organ systems were observed, these concerns should be further discussed by the Applicant.

Drug-drug interactions

The Applicant states that based on the observed data from in vitro DDI studies, patients with concomitant treatment with sensitive substrates of BCRP, OAT1/3, CYP 3A4, CYP 2B6, CYP 2C19, CYP

1A2 and potent inhibitors of BCRP were excluded from studies. No information on magnitude of clinical relevancy and further practical recommendation on the management of concomitant administration in clinical practice is provided .

5.6. Effects Table

Table 10: Effects Table for govorestat for the treatment of CG based on Study AT-007-1002.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
Composite Primary Endpoint (*OWLS-II (OE, LC) and BASC-3 (ADL, BSI)*)	Estimated mean Z Score (govorestat - Placebo) 95% Confidence interval One-sided p-value	none	N= 38 Z = 0.8683 (-0.204, 2.087) P=0.1030		**U** as baseline data are not mentioned the need for treatment remains to be established. **U** no statistical significant difference is reported, the clinical relevance remains to be established
Change over time in NIH Toolbox Cognition Battery (NIH-CB)	Estimated change from baseline to 18 months of treatment	None, T-score	N=12 8.6 (2.9, 14.4)	N=24 11.9 (5.2, 18.5)	**U** the clinical relevance remains to be established.
NIH Toolbox Motor Battery (NIH-MB) – Standing Balance	Estimated change from baseline to 18 months of treatment	None, T-score	4.3 (0.0, 8.6)	5.2 (-1.7, 12.0)	**U** the clinical relevance remains to be established. **U** only a few patients in both placebo and govorestat group reached normalisation.
NIH Toolbox Motor Battery (NIH-MB) - Manual Dexterity	Estimated change from baseline to 18 months of treatment	None, T-score	-0.2 (-4.4, 4.0)	-2.8 (-7.9, 2.3)	**U** the clinical relevance remains to be established. **U** in both placebo and govorestat group deteriorated**.**
SARA	Estimated change from baseline to 18 months of treatment	None	0.71 (-0.33, 1.76)	-0.36 (-2.74, 2.03)	**U** the clinical relevance remains to be established. **U** no normal values were found, the need for treatment is to be established **U** this test is not validated for CG tremor
Spiral Drawing Test	Estimated change from baseline to 18 months of treatment	None	-0.38 (-0.65, -0.11)	0.06 (-0.30, 0.41)	**U** the clinical relevance remains to be established. **U** the govorestat treated group detoriated
GIS caregiver	Estimated change from baseline to 18 months of treatment	Score Worsened	4 (15.4%)	4 (33.3%)	**U** is from the caregiver, in the exit interviews is concluded that according to the caregiver any change is an important improvement.
		No Change in Score	14 (53.8%)	5 (41.7%)	
		Score Improved	8 (30.8%)	3 (25.0%)	
Unfavourable Effects					
Transaminase elevations	Incidence of elevated AST and/or ALT	%	25.8	12.5	Transaminase elevations occurred in all age groups. Most were mild-moderate however in adults 2 severe events occurred. **U** Due to limitations to the safety database, frequency in adults is unclear
Vomiting	Incidence of vomiting	%	48.8	31.3	Gastro-intestinal events occurred in all age groups. Events were mostly mild, single events with spontaneous resolution.
Diarrhoea	Incidence of diarrhoea	%	25.8	12.5	
Abdominal pain	Incidence of abdominal pain	%	22.6	0	
Constipation	Incidence of constipation	%	12.9	0	
Creatinin increase	Incidence of increased creatinin	%	42.9	NA	Creatinin elevations occurred in all age groups. **U** The causality, frequency, severity and clinical relevance are unclear. Frequency is based on adult patients. Ref: Study AT-007-1006[1]

Abbreviations: OWLS-II = Oral and Written Language Scales version II; OE = oral expression; LC = Listening Comprehension; BASC-3 = Behavior Assessment System for Children 3rd Edition; ADL = Activities of Daily Living; BSI = Behavioral Symptoms Index
Notes: [1]Data from the clinical studies are not pooled.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

It is acknowledged that there is a unmet medical need for CG patients, i.e. the treatment or prevention of the long-term complications (among others cognitive deficiencies and resulting deviant behaviour, motor disfunction (among others dysarthria, tremor) and ovarian failure). However, the progressive nature of the disease remains to be established and many sources in literature question the progressive nature of CG. As the placebo treated patients in this study did not show a clear, consistent deterioration, the disease progression appears not to be measurable in 18 months.

The MoA of govorestat is to decrease the galactitol levels. However, a clear correlation between galactitol and clinical benefit has not been established and is a point of debate among experts. Galactitol is not a surrogate endpoint and certainly not in the concentrations measured in CG patients on diet. In addition, the relevance of a further galactitol decrease in the patients on a diet is unclear. Taken together, these uncertainties seriously raise doubts about the ability of govorestat to adress the unmet medical need for these patients.

The fact that all included patients were on a stable diet, should be represented in the indication. Govorestat would then serve as an add-on treatment.

Submitted pivotal study is considered to be more exploratory than confirmatory trial. The study endpoints were changed several times during the study.

As a considerable group of patient had scores within the normal range, the need for treatment is not evident. The applicant is requested to justify any treatment in those patients who are within the normal range. This also relates to the concern whether govorestat is able to meet the unmet need for GC patients.

The totality of the information does not indicate a clear and consistent favourable effect. The uncertainties and limitations about the primary endpoint make it impossible to draw conclusions on the efficacy of govorestat. The primary endpoint as presented in this report, did not show a statistical significant effect and from this perspective, the study can be considered a failed study.

For some of the secondary endpoints the change from baseline to 18 month shows a limited improvement (this applies to both placebo and govorestat); for others there is a deterioration. Sometimes the difference between govorestat and placebo at 18 month is in favour of govorestat and sometimes in favour of placebo. For all changes the clinical relevance needs to be demonstrated.

Most children did not show signs of ovarian maturation; in those 4 patients who did show some ovarian maturation, this process was well underway before the administration of govorestat.

Very limited information considering the clinical endpoints in adults (N=7) is available and no information in patients over 50 years of age was submitted. As the improvement of cognition and/or motor disability are the treatment goals for the adult population of CG patients on stable diet and extrapolation from children is not self evident, the lack of this information is of importance.

No interpretable information over more than 18 months is available. This is of importance, as these patients require lifelong management of the disease. Unfortunately, the study was stopped prematurely.

The primary endpoint was adjusted a couple of times and as this was not pre-planned it may render the study to be considered exploratory. No justification for any of the switches of the primary endpoint was provided. This is also a concern in terms of GCP. The Vineland interviews were rendered not useful due to inexperience of the interviewers. The results were already de-blinded at an early stage while other measures could be taken without de-blinding the results. Together, these uncertainties raise serious doubts about GCP adherence and thus, about the reliability of the results.

Regarding safety, the most commonly observed unfavourable effects were gastrointestinal disorders and hepatic disorders. Additionally, abnormalities in the renal organ class were also reported. The drug-drug interaction potential in clinical practice has not been elucidated.

Although the safety profile seems acceptable there are concerns considering the limitations of the safety database and the hepatotoxicity observed in a few patients. This is especially relevant since clinical experts on galactosemia have expressed concerns on the consequences of altering a single metabolite (in this case galactitol) without full comprehension of the effects on other metabolites in galactose metabolism. Further hepatotoxicity is considered a class effect of the aldose reductase inhibitors.

Based on the limited number of included patients, observed safety concerns and an expected long-term use of govorestat, further additional monitoring of the safety profile (via a registry at minimum) is considered necessary for a clear assessment of the importance of the observed unfavourable effects. Additional discussion on this missing information is needed.

5.7.2. Balance of benefits and risks

Overall, the dossier lacks the detail and accuracy that are required for regulatory approval in the EC. Even if the credibility of the data could be significantly improved by an extensive revision, the totality of data may not evidence efficacy. The lack of an observable deterioration in the natural development of the disease, and the observation that most patients are within normal ranges before starting treatment would a prior hamper showing clear benefits. In controlled data, a convincing effect of govorestat was absent. In conclusion, the B/R is negative.

5.7.3. Additional considerations on the benefit-risk balance

Genotyping

Patients were enrolled based on plasma GALT enzyme level (<1%) or on historical record of diagnosis of of GALT deficiency (medical record or gene analysis report or written communication by health care professional). As described in Reichardt, 1992, besides GALT enzyme polymorphism, 3 classes of classic galactosemia-causing mutations have been reported: cross-reacting material (CRM)+ missense mutations (the most common class), CRM− missense mutations, and splicing mutations. Thus, classic galactosemia is heterogeneous at the molecular level, which is noteworthy in light of the well-documented clinical variability observed in this disorder. A prospective GALT genotyping-phenotyping correlation would be desirable also considering the limited sample size (47 subjects randomized) in order to try to isolate the drug effect. The Applicant should comment on this

Conditional marketing authorisation

The request for CMA is currently not acceptable and the applicant is invited to further justify their request in light of the provided data package and taking into account available guideline[11]. For the CMA proposal the following major issues have been identified:

a. There is a major doubt whether govorestat is able to address the unmet medical need for classic galactosemia patients. This should be thoroughly discussed by the applicant, based on the following aspects:

   i. Placebo treated patients did not show a clear and consistent deterioration and no progression of the disease appears to be measurable over a period of 18 months using the chosen endpoints. Natural history of the disease, updated literature, and feedback from healthcare professionals and patient organisation indicate that a deterioration in cognitive function is not expected in the short run (i.e. few years). In this context, the applicant should discuss if and how this endpoint (or possibly alternatives) can provide evidence of efficacy in this condition.

   ii. Although galactitol is widely considered a disease biomarker, doubts exist on its use as a surrogate endpoint to establish efficacy. Thus, the value of lowering galactitol levels is questioned. For none of the parameters included in the primary endpoint, a clear relation with the plasma galactitol concentration or the change thereof could be demonstrated. The applicant should address the value of galactitol as a relevant surrogate, preferably based on evidence of its causal role in the pathophysiology of classic galactosemia, and the applicant should discuss the clinical relevance of the observed effects on galactitol.

   iii. The unmet need and its fulfilment should be further defined, by describing the specific symptoms patients experience and how these are changed by treatment.

b. The proposed clinical SOBS are unlikely to confirm the benefit risk balance in the claimed indication. The applicant should further discuss how these additional studies will be comprehensive and confirm the efficacy and safety of the medicinal product in the claimed indication (above 2 years old) taking into account the following:

   iv. - the paediatric study is in children below the age of 2 years and not related to the claimed indication

   v. - the study in adults is not sufficiently detailed and an outline of the proposed protocol should be provided to assess its feasibility and adequacy.

   vi. - the additional long term follow-up data on the children who participated in the placebo-controlled AT-007-1002 clinical study are not considered sufficient to confirm the efficacy and safety of govorestat in the claimed indication

   vii. - The study on food effect is required to support the initial marketing authorisation application. Currently, the recommendation is to administer the daily dose at the same time in the morning after an overnight fast and 2 hours

[11] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf

prior to a meal. However, this is not acceptable is paediatric patients. Therefore, the effect of food on the PK of govorestat should be investigated.

c. The benefit risk balance of the product is currently negative

d. The applicant should further discuss whether, in light of the points above, the benefits of immediate availability outweigh the risk inherent in the fact that additional data are still required.

Patient and healthcare provider engagement

Responses were received form HCP (N=2) and a patient organisation.

Both the patients and the HCP's are of the opinion that there is an unmet need for treatment of classical galactosemia. While the diet is effective in preventing severe illness or death in the newborn phase, it does not prevent cognitive deficiencies or ovarian failure.

Patients and HCP's both indicate the complications (by apathy, vomiting, haemorrhages, liver failure, jaundice or sepsis) seen shortly after birth as important, troublesome symptoms. The situation can be life-threatening. Among newborn, there is a rare risk of cataract.

The complications encountered later in life (learning disability, cognitive delay, and speech impairment) is considered a troublesome complication by some patients although in most patient this is either none existing or acceptable not leading to restrictions in daily life.

The lactose free and galactose limited diet is currently considered an effective and acceptable treatment. Both patients and HCP's consider the deterioration none existing or very slow provided the diet is followed. Further specific treatments for specific complications are used.

Both HCP's and patients express the need for a treatment preventing or improving cognitive disorders, speech difficulties or trembling.

Both Patients and HCP's highlight the lack of treatment for the ovarian insufficiency seen in most female patients.

GCP issues

According to the applicant all studies were performed under GCP. No inspection of any site was done nor ongoing.

Despite this statement some events might indicate that the adherence to GCP was not optimal. Further there is missing information prohibiting the assessment of the adherence.

Aspects that are worrisome are

<u>Data handling</u>

- Protocol amendments and also amendments to the HSAC charter resulted in retrospectively new defined data, changes to already entered data including a most likely extensive query process. This process Retrospective data entries, queries and delayed QC of the data caused a potential risk for reducing quality of the clinical trial data.
- The DMC meeting minutes mention 1 occasion of hard coding of data during the conduct of the clinical trial. Hard coding is only acceptable in (very) exceptional cases, most of the time after database lock. The (detailed) process and its justification should be extremely well documented (and kept in the TMF). During the conduct of the trial QC of the data via SDV and a query process should have been in place. These type of data should be under the control of the

investigator before data base lock. Changes to the data should be approved by the investigator and documented in a DCF form (in case of a paper CRF) or be captured in the audit trail (in case of an (e)CRF. Both methods are supposed to capture when, what, why and by whom. In addition, this deficiency was not identified and remedied by clinical trial monitoring.

- Furthermore, since the practice of hard coding was introduced, it cannot be excluded that hard coding of data was practised on more then this occasion alone.

Conduct of the study

- On 27 September 2022 the DMC was informed by the sponsor as follows: '*Dr. R. Perfetti informed the members of the DMC that he had assembled a subset of the Applied Therapeutics team to become unblinded and firewalled for the remainder of the study in order for the Sponsor to be able to review the available data.*

This took place 6 months before data cut off (24 March 2023). Moreover, a protocol amendment, changing the (composite) endpoint was issued 05 December 2022 (and consequently an updated SAP (05 March 2023).

- Recommendations of the DMC were not implemented, such as:

a) The duration of the conduct of the study: *the DMC will meet when a sufficient number of children have completed each 6-month milestone and will inform the Sponsor if statistically significant superiority of AT-007 versus placebo, or futility (after at least 2 years of treatment) has been demonstrated for a specific age group (or for all age groups).*

b) The assembly of a firewalled subset of the sponsor team in accordance with the DMC charter: *If, at the Month 6 analysis the nominal p-value of the global test for a specific age group is less than 0.001, or at any subsequent timepoint is less than 0.05, the DMC will inform the Sponsor that a statistically significant difference between AT-007 and placebo has been demonstrated for that specific age group. The Sponsor will then appoint a fire-walled team that will be completely independent of the study team.*

From the DMC meeting minutes 27 September 2022: *The primary efficacy endpoint compared the treatment arm vs. placebo and did not reach statistical significance, yet.*

- Likelihood of the study population reflecting the real population, in terms of economic and educational background, environmental circumstances/living conditions and origin.

CSR

- CSR is missing information/description on several aspects such as hard coding, protocol version 17 and 18, justification on the nonparticipation of the intended 3 EU-sites, (clarification on) change in dosing based on age to dosing based on weight. It cannot be excluded that more information is missing.

CSRs should also include extensive details on the course of treatment for trial participants, the medical information collected from the participants as part of the research, and demographic data, as well as other kinds of information to explain how the trial was conducted and results were analysed.

Of note the FDA has planed inspections to inspect the various aspects of study AT-007-1002.

5.8. Conclusions

The overall benefit /risk balance of Nugalviq is negative.

6. Biosimilarity assessment

Not applicable

7. Recommended conditions for marketing authorisation and product information in case of a positive opinion

In view of the major objections it is premature to recommend any conditions for marketing authorisation and to propose changes in the product information (SmPC, Annex II, labelling, PL). The results of the user consultation or the justification for not having them should however be addressed.

User consultation

The results of user consultation will be provided at Day 121.

Quick Response (QR) code

Not applicable.