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Safety, Pharmacokinetics, and Pharmacodynamics of the New Aldose Reductase Inhibitor Govorestat (AT-007) After a Single and Multiple Doses in Participants in a Phase 1/2 Study

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Abstract

In classic galactosemia (CG) patients, aldose reductase (AR) converts galactose to galactitol. In a phase 1/2, placebo-controlled study (NCT04117711), safety, pharmacokinetics (PK), and pharmacodynamics (PD) of govorestat were evaluated after single and multiple ascending doses (0.5-40 mg/kg) in healthy adults (n = 81) and CG patients (n = 14). Levels of govorestat in plasma and cerebrospinal fluid (CSF) and blood levels of galactitol, galactose, and galactose-1-phosphate (Gal-1p) were measured for population PK and PK/PD analyses. Govorestat was well tolerated. Adverse event frequency was comparable between placebo and govorestat. Govorestat PK displayed a 2-compartment model with sequential zero- and first-order absorption, and no effect of demographic factors. Multiple-dose PK of govorestat was linear in the 0.5-40 mg/kg range, and CSF levels increased dose dependently. Elimination half-life was ~10 h. PK/PD modeling supported once-daily dosing. Change from baseline in galactitol was −15% ± 9% with placebo and −19% ± 10%, −46% ± 4%, and −51% ± 5% with govorestat 5, 20, and 40 mg/kg, respectively, thus was similar for 20 and 40 mg/kg. Govorestat did not affect galactose or Gal-1p levels. In conclusion, govorestat displayed a favorable safety, PK, and PD profile in humans, and reduced galactitol levels in the same magnitude (~50%) as in a rat model of CG that demonstrated an efficacy benefit on neurological, behavioral, and ocular outcomes.

Keywords

galactitol, galactose, galactosemia, govorestat, pharmacodynamics, pharmacokinetics, safety

Introduction

Aldose reductase (AR), an enzyme that belongs to the aldo-keto reductase superfamily, is a key component of the polyol pathway. AR reversibly binds to nicotinamide adenine dinucleotide phosphate (NADPH), whereupon it reduces aldehydic substrates to their corresponding alcohol, including glucose to sorbitol and galactose to galactitol. Metabolic flux through the AR pathway is associated with micro- and macrovascular complications of diabetes, and AR inhibitors (ARIs) have been investigated as potential treatments for diabetic complications.[1,2]

Classic galactosemia (CG, also classified as type I), is the most common form of galactosemia and is caused by severe deficiency of the enzyme galactose-1-phosphate uridylyl transferase (GALT). Patients with CG display severe long-term complications, including behavioral and neurological deficits, ovarian insufficiency, low bone mineral density, and cataracts. Patients with CG have elevated levels of galactose as well as of its metabolites, namely galactose-1-phosphate (Gal-1p) and galactitol in blood and tissues.[3–5]

In patients with CG, elevated galactose is converted by AR to the aberrant metabolite galactitol. Galactitol is not detectable in the plasma of healthy persons, but in patients with CG, galactitol levels typically reach 10-12 µmol/L in plasma and urinary galactitol may be ≥10-fold higher than that in normal individuals.[6] In both preclinical and clinical studies of CG, galactitol elevations were associated with adverse outcomes.[3,7–9] Magnetic resonance imaging (MRI) studies have shown

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that galactitol levels are elevated in the brains of patients with CG.[10] 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.[9] Thus, galactitol represents a metabolite that is clinically relevant for determining adverse outcomes in CG and could serve as a clinically relevant pharmacodynamic (PD) biomarker for the evaluation of ARIs in CG.

Currently, no therapies are available to treat CG or prevent its long-term complications. Govorestat (AT-007) is a potent, highly selective and specific, orally bioavailable ARI, with an [IC_{50}] (50% inhibitory concentration) of 0.10 nM. In comparison, zopolrestat, a first-generation ARI, which is typically viewed as a prior best in class molecule and is used as a positive control in experimental studies, has an IC_{50} of 10 nM. In terms of selectivity, govorestat demonstrated no off-target pharmacological effects in a study of 44 primary molecular targets, including 7 enzyme and 37 binding assays evaluated utilizing the Eurofins Panlabs Safety Screen Panel (Eurofins, NY). Reference standards were run as an integral part of each assay to ensure the validity of the results obtained (Applied Therapeutics, data on file). The novelty of govorestat versus first-generation ARIs is supported by the US patent #10,150,779, B2. Thus, govorestat represents a large improvement regarding potency and selectivity over prior ARIs.

The objective of the present study was to investigate the safety, pharmacokinetics (PK), and PD (galactose and its metabolites) of govorestat in healthy adults and patients with CG.

Methods

Study Design

This first-in-human, phase 1/2, multicenter, randomized, placebo-controlled, single and multiple ascending dose (MAD) study (NCT04117711) was conducted to evaluate the safety and PK of govorestat in healthy individuals and patients with CG and the PD effects of govorestat on galactitol levels in patients with CG (Figure S1). This research was conducted in accordance with International Council for Harmonisation Guideline for Good Clinical Practice and applicable regulatory requirements consistent with the Declaration of Helsinki. Institutional Review Boards and Independent Ethics Committees at each study center approved the protocol. All participants and (where appropriate) caregivers provided written, informed consent.

The study consisted of 4 parts. Parts A-C involved healthy individuals, whereas Part D involved patients with CG (Figure S1 and Table S1). Part A was a single ascending dose (SAD) study of govorestat at doses of 0.5, 5, 10, 20, and 40 mg/kg or placebo. Each dose cohort consisted of 6 healthy individuals randomized to govorestat and 2 individuals (n = 40 individuals total) randomized to placebo in double-blind fashion. In Part B, a MAD study, participants received govorestat at doses of 5 (n = 6), 10 (n = 4), 20 (n = 6), and 40 mg/kg (n = 4) or placebo (n = 2 per dose group) once daily for 7 days in double-blind fashion. Part C was a MAD study to evaluate CNS penetration of govorestat. Healthy individuals received govorestat doses of 10 (n = 4), 20 (n = 4), and 40 mg/kg (n = 4) once daily for 7 days. CSF samples were collected by lumbar puncture 4-6 h after the last govorestat dose. Part C did not include a placebo arm.

Part D consisted of an SAD study followed by an MAD study in patients with CG. In the SAD study, 6 patients per dose cohort were randomly assigned to govorestat 5 (n = 4), 20 (n = 4), or 40 mg/kg (n = 4) or placebo (n = 2 per govorestat dose group) on Day 1. After administration of the single dose of study drug (govorestat or placebo), patients underwent a 5-day washout followed by 27 days of treatment with the same study drug and dose as received in the SAD (Figure S1 and Table S1). Because limited numbers of patients with CG are available to participate in clinical trials, the protocol allowed for patients to take part in more than 1 cohort after completion of treatment in their originally assigned cohort (Table S1). All patients remained blinded to study drug throughout the study, and those who participated in more than 1 dose cohort underwent a washout for ≥5 days prior to joining a new cohort. Biomarkers (galactitol, galactose, and Gal-1p) were assessed before and after dosing (timepoints provided under procedures, below) in each cohort using validated assays.

Study Participants

Eligible healthy adult participants were males or nonpregnant, nonlactating females aged 18-65 years with a body mass index (BMI) between 17.5 and 35 kg/m^2 at screening. Patients with CG were eligible if the diagnosis was confirmed by genotyping (GAL14: Galactosemia Gene Analysis, 14 Mutation Panel, Mayo Clinic Laboratories, Rochester, MN) and a significantly decreased GALT activity (<1%) in red blood cells. Eligible patients were required to have a history of following a galactosemia-specific diet and to continue with this diet during the study. All female participants of childbearing potential or nonsterile male participants were required to use birth control. Complete inclusion and exclusion criteria for both healthy and CG study populations can be found in the Supplementary Information.

Procedures

In the SAD studies (Part A and the first portion of Part D), all participants were admitted to the clinical research unit (CRU) 24 h before their first dose (Day −1) and on Day 1 they were randomized and received a single dose of study drug. All SAD study participants remained at the CRU for at least 48 h after the single dose (Table S1). Healthy participants in the MAD studies (Parts B and C) remained in the CRU for observation from Day −1 through Day 9 (at least 48 h after the last dose; Table S1). At the completion of the SAD portion of Part D on Day 1, patients with CG underwent a 5-day washout after discharge from the CRU. The MAD portion began on Day 6, whereupon patients took the dose of study drug assigned during the SAD portion for 27 days at home (Table S1). Doses administered in the CRU were supervised by study staff. All doses in all settings were to be taken in the morning after a 10-h fast, and food was not to be consumed for at least 2 h after taking the study drug. Patients taking the drug at home were given diary cards to fill out the time each dose was taken.

Safety assessments included the collection of treatment-emergent adverse events (AEs), laboratory evaluations (hematology, chemistry, and urinalysis), physical examination findings, vital signs, and 12-lead electrocardiograms (ECG) (see Table S1 for timing of assessments). Blood samples were taken for PK analyses of govorestat on Days 1-3 in Part A; Days 1, 2, and 7-9 in Parts B and C; and Days 1-3, 12, 13, and 32-34 in Part D (Table S1). Healthy participants enrolled in Part C underwent lumbar puncture to enable evaluation of govorestat in CSF on Day 7. Blood was collected for PD analyses of galactitol, galactose, and Gal-1p on Days 1, 2, 3, 12, 13, 32, 33, and 34 in Part D (Table S1). In Part A, urine samples were collected, and volume recorded from healthy participants in the 20 and 40 mg/kg groups every 4 h over the first 24 h and every 12 h over the following 2 days for an exploratory PK analysis (Table S1).

Bioanalytic Assays

Govorestat was analyzed in human plasma, urine, and cerebrospinal fluid (CSF) using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) methods. The plasma and CSF assays were validated, and the urine assay was qualified. Galactitol was analyzed in human plasma using a validated LC-MS/MS method, and galactose was analyzed in human plasma using a qualified LC-MS/MS method. Gal-1p was analyzed in human whole blood using a qualified LC-MS/MS method. Technical details on how the assays were developed and the investigational samples evaluated are provided in the Supplementary Information.

Objectives

The primary objective of the study was to assess the safety of govorestat based on safety variables outlined above. The secondary objective was to evaluate PK in healthy participants and in those with CG and to assess changes in the PD markers galactitol, galactose, and Gal-1p. The PD objectives also aimed to determine the magnitude of reduction in galactitol, and whether galactose and Gal-1p levels would be affected by govorestat. Key PK endpoints for govorestat included peak maximum concentration (C_{max}), time to maximum concentration (T_{max}), elimination half-life ($t_{\frac{1}{2}}$), and area under the curve (AUC) for the evaluation of the drug concentration over time. PK parameters and analytic methods are detailed in Table S2. Levels of govorestat in CSF were also measured.

Statistical Analysis Methods

No formal sample size calculations were conducted. The number of participants enrolled in the study is typical for studies of this type and is adequate to meet study objectives. Descriptive statistics (number, mean, standard deviation [SD], median, minimum, maximum, percent coefficient of variation [CV%]) were used for PK and PD analyses.

Pharmacokinetic Analysis Methods

PK calculations were performed using Phoenix WinNonlin (Version 6.3 or higher, Pharsight Corporation) and/or SAS (Version 9.4 or higher, SAS Institute Inc.) using a noncompartmental method.

The population PK and PK/PD analyses were performed using Nonlinear Mixed Effects Modeling (NONMEM) program version 7.4.3 (ICON, Dublin, Ireland) with Monte Carlo Importance Sampling (IMP) for estimation. NONMEM executable files were compiled using the Intel Visual FORTRAN Compiler Professional (Intel, Santa Clara, CA). All estimation methods used the interaction option on the $EST record. "Mu Referencing" was used to improve efficiency of computations.

The selected population PK model was a 2-compartment model with sequential zero- and first-order absorption, absorption lag time, and first-order elimination and was fitted using IMP estimation. Employing just first-order absorption and absorption lag time resulted in an underestimation of the higher initial govorestat concentration. Including sequential zero- and first-order absorption into the model resulted in a greatly improved fit and large drop in objective function value. Concentrations below the lower limit of quantitation were treated as zero from the time of the first quantifiable concentration; embedded and terminal concentrations below the lower limit of normal were treated as "missing." Dose proportionality was

assessed using a power model with a fixed-effect term for log-transformed dose. The population PK model estimated interindividual variability (IIV) in 5 parameters (apparent clearance [CL/F], peripheral volumes of distribution [V2/F and V3/F], intercompartmental clearance [Q/F], and first-order absorption [K_a]) and used a 5 ω block to estimate the covariance between these parameters. Estimation of the IIV for absorption lag time (A_{LAG}) and zero-order input (D1) were not supported by the model, and consequently, these were fixed at 15% CV.[11] The model included a separate bioavailability (F1) term for patients with CG. The continuous covariate effects of the demographic variables of body weight, age, BMI, renal function, hepatic function, and baseline galactitol values, and the categorical covariates of gender, race/ethnicity, health status, and dose were evaluated in the population PK model.

Maximum galactitol reduction in patients with CG was defined as the galactitol value in each patient on Day 32 (considering a 27-day dosing period in the MAD portion and a 5-day washout period from the prior single dose in the SAD portion that was given on Day 1) and expressed as change from baseline. The baseline galactitol level was calculated as the mean of 2 predose measurements before the initiation of the SAD portion of the study. The duration of the washout was selected as greater than 5 times the half-life of govorestat. Absolute and percent changes from baseline in plasma galactitol were calculated at each timepoint on Days 1, 12, and 32. Changes in whole blood Gal-1p were evaluated Day 32 versus baseline. Using model-predicted govorestat concentrations, the relationship between govorestat and galactitol concentrations was evaluated using an indirect PK/PD model (see Supplementary Information for details on the modeling analyses). The models were used to simulate the predicted govorestat PK and galactitol PD profiles for selected dosing regimens of govorestat in a CG population. Each dosing scenario was simulated 500 times within NONMEM using parameter estimates from the chosen models including the variability from interindividual errors and may have also included the uncertainty in fixed-effect parameters (θ). No residual variability was included in the predictions. The 95% confidence interval (CI) of the geometric mean and 5th and 95th percentiles for govorestat concentrations and galactitol levels were summarized.

Results

Study Population

A total of 81 healthy adult participants participated in Parts A, B, and C, and 14 patients with CG were enrolled in Part D (Table S3). The number of patients evaluated in Part D totaled 18, with 4 patients participating in 2 separate cohorts after a washout period of ≥5 days. Of the 4 patients who participated to more than 1 cohort, 1 patient in the 20 mg/kg group had previously participated in the placebo cohort, and 3 patients in the 40 mg/kg cohort had previously participated in the placebo cohort (n = 1), 5 mg/kg cohort (n = 1), and 20 mg/kg cohort (n = 1).

The majority of healthy participants were white and female, and slightly more than half were Hispanic or Latino. All patients with CG were white, none were Hispanic or Latino, and the majority were male. The average age was ~40 years for healthy participants and ~31 years for patients with CG (Table S3).

Eight patients with CG were homozygous for the Q188R pathogenic variant; 3 were compound heterozygous for Q188 R; and compound heterozygosity for other pathogenic genes related to galactosemia was found in 3 patients. GALT activity was absent, and urine and plasma galactitol levels were elevated at baseline in all patients (Table S3). Neurological, psychiatric, and endocrine disorders were common in patients with CG, consistent with the phenotypic abnormalities associated with CG (Table S3). Only 2 of these adult patients had completed secondary education, and all 14 lived with family members or in close proximity to a caregiver. Seven were employed, primarily as manual laborers.

Govorestat Safety

Govorestat was generally safe and well tolerated at all dose levels studied. There were no serious AEs, treatment-related discontinuations, or deaths in healthy participants and those with CG in Parts A-D (Table 1). Across Parts A-D, no clinically significant changes in vital signs or ECG findings were reported, and no clinically significant changes in physical examination were considered related to govorestat. Among healthy participants, 11/63 (17.5%) participants from all govorestat dose groups reported a total of 15 AEs. In the pooled placebo group, 4/18 (22.2%) healthy participants reported 7 AEs (Table S4).

Among patients with CG, 6/12 (50%) of those who received govorestat reported 10 AEs, with no dose-related increase in the incidence of AEs. Among those receiving placebo, 2/6 (33.3%) reported 6 AEs. Adverse events occurred in 2/6, 3/4, 1/4, and 2/4 patients with CG receiving placebo and govorestat 5, 20, and 40 mg/kg, respectively. All AEs were mild in severity, and no significant organ-specific abnormalities were reported from baseline through Day 32 in patients with CG (Table 1).

Population PK and PK/PD Results

Govorestat PK After Single and Multiple Ascending Doses. In healthy participants, after a single dose of govorestat

Table 1. Treatment-Emergent AEs with Govorestat (0.5-40 mg/kg) and Placebo in Healthy Participants (Parts A-C) and Patients With CG (Part D)

	Govorestat					
AE, n (%), No. Events Part A	0.5 mg/kg n = 6	5 mg/kg n = 6	10 mg/kg n = 6	20 mg/kg n = 6	40 mg/kg n = 6	Placebo n = 10
Any AE	1 (16.7), 1	0	0	2 (33.3), 4	1 (16.7), 2	2 (20.0), 4
Any related AE	0	0	0	1 (16.7), 2		1 (10.0), 2
Any severe AE	0	0	0	0	0	0
SAE, AE leading to discontinuation, or death	0	0	0	0	0	0
Parts B and C	—	n = 6	n = 8	n = 10	n = 9	n = 8
Any AE		1 (16.7), 1	2 (25.0), 2	3 (30.0), 4	1 (11.1), 1	2 (25.0), 3
Any related AE		0	2 (25.0), 2	1 (10.0), 2	0	1 (12.5), 2
Any severe AE		0	0	0	0	0
SAE, AE leading to discontinuation, or death		0	0	0	0	0
Part D	—	n = 4	—	n = 4	n = 4	n = 6
Any AE		3 (75.0), 6		1 (25.0), 2	2 (50.0), 2	2 (33.3), 6
Any related AE		0		0	0	1 (16.7), 2
Any severe AE		0		0	0	0
SAE, AE leading to discontinuation, or death		0		0	0	0
AEs by preferred term						
Tachycardia		0		0	0	1 (16.7), 1
Ear discomfort		1 (25.0), 1		0	0	0
Abdominal discomfort		1 (25.0), 1		0	0	0
Dyspepsia		0		0	0	1 (16.7), 1
Feeling hot		0		0	0	1 (16.7), 1
Upper respiratory tract infection		2 (50.0) 2		0	0	0
Urinary tract infection		0		0	1 (25.0), 1	0
Contusion		1 (25.0), 1		0	0	0
Weight decreased		0		0	1 (25.0), 1	0
Mobility decreased		0		1 (25.0), 1	0	0
Pain in jaw		0		0	0	1 (16.7), 1
Headache		0		0	0	1 (16.7), 1
Seizure		0		1 (25.0), 1	0	0
Anxiety		0		0	0	1 (16.7), 1
Pruritus		1 (25.0), 1		0	0	0

AE, adverse event; CG, classic galactosemia; SAE, serious adverse event.

in Part A, mean plasma concentrations, C_{max}, and AUC of govorestat increased in a slightly less than dose-proportional manner over the dose range of 0.5-40 mg/kg (Figure 1a and Table S5). The elimination half-life ranged from 8 to 22 h and was longest for the 5 mg/kg dose (22 h). For the 10-40 mg/kg dose levels, the half-life was 8-10 h (Table S5). In the 7-day MAD studies (Parts B and C), exposure increased in a dose-proportional manner on Day 7 (Figure 1b and Table S5). The govorestat half-life ranged from 9.76 to 13.7 h after 7 days of once-daily dosing (Table S5). A high variability in $t_{1/2}$ estimations for some dose groups in Part A of the study was likely related to a combination of inherent variability in volume of distribution and clearance.

In patients with CG, in both the SAD and MAD portions of Part D, C_{max} and AUC increased with increasing doses of govorestat (Table S5). After a single dose on Day 1 (SAD portion), the median T_{max} was between 3.00 and 5.00 h. On Day 32, after 27 days in the MAD portion, the T_{max} remained within this range. The elimination half-life ranged from 10 to 11 h on Day 1 and from 14 to 17 h on Day 32 (Table S5).

Govorestat in Urine. In Part A, the amount of govorestat excreted in urine increased with increasing dose (402 and 829 mg for 20 and 40 mg/kg, respectively). The fraction of drug excreted over 48 h for the 20 and 40 mg/kg dose levels was similar (25.9% and 30.6%, respectively). Urine pharmacokinetic data are provided in Table S6.

Govorestat in CSF. In the 12 healthy participants who underwent lumbar puncture in Part C, the concentration of govorestat in CSF postdose was 15.2-31.8 and 20.9-71.9 ng/mL with the 20 and 40 mg/kg doses, respectively. For the 10 mg/kg dose, govorestat CSF concentrations were below the lower

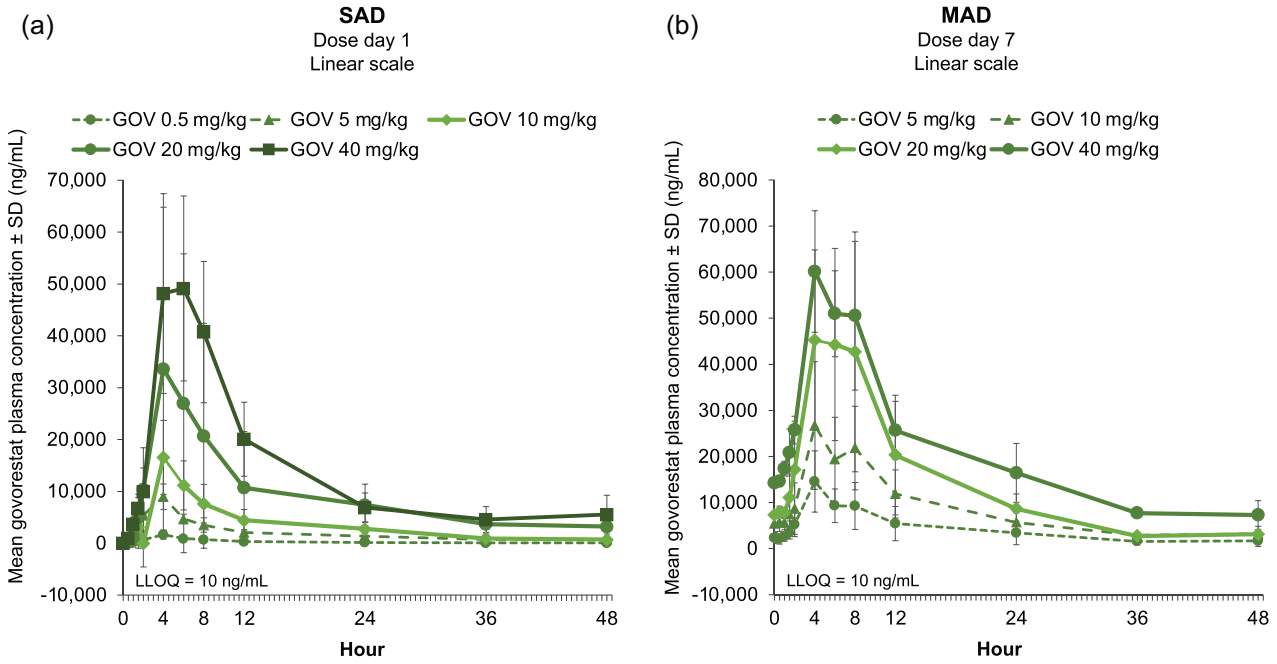

Figure 1. Mean ± standard deviation (SD) plasma concentrations of govorestat (GOV) in healthy participants on (a) Day 1 in the single ascending dose (SAD) study and (b) on Day 7 in the multiple ascending dose (MAD) study.

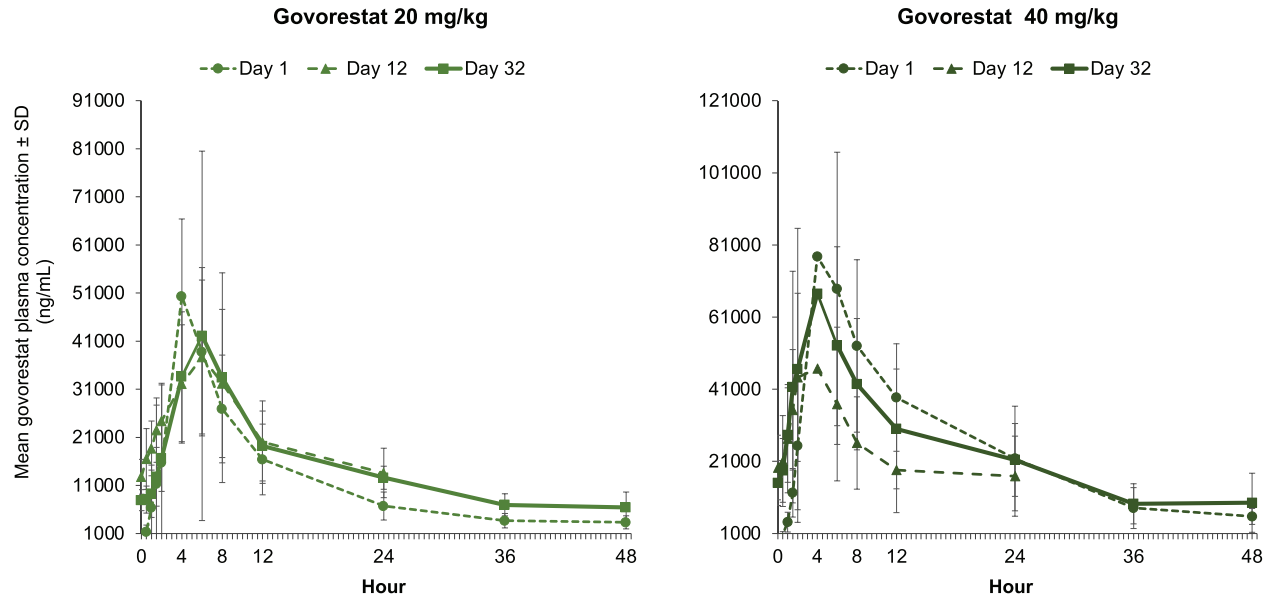

Figure 2. Mean ± standard deviation (SD) plasma concentrations of govorestat 20 and 40 mg/kg on Days 1, 12, and 32 in patients with classic galactosemia (CG).

limit of quantitation (<10.0 ng/mL) and the estimated values ranged from 3.71 to 8.21 ng/mL.

Population PK in CG. Overall, govorestat PK findings in patients with CG were similar to those in healthy participants (Table S5). No significant demographic factors were found to influence the PK of govorestat. The multiple-dose PK of govorestat was linear across the dose range (5-40 mg/kg). Drug half-life and overall pharmacokinetics supported once-daily dosing (Figure 2). Data from the individual patients in each govorestat treatment group appear in Figure S2.

Galactitol and Other Biomarkers. In patients with CG who received govorestat, galactitol plasma levels decreased over time in a dose-dependent manner while remaining stable in the placebo group (Figure 3a). On Day 32, govorestat 20 and 40 mg/kg significantly

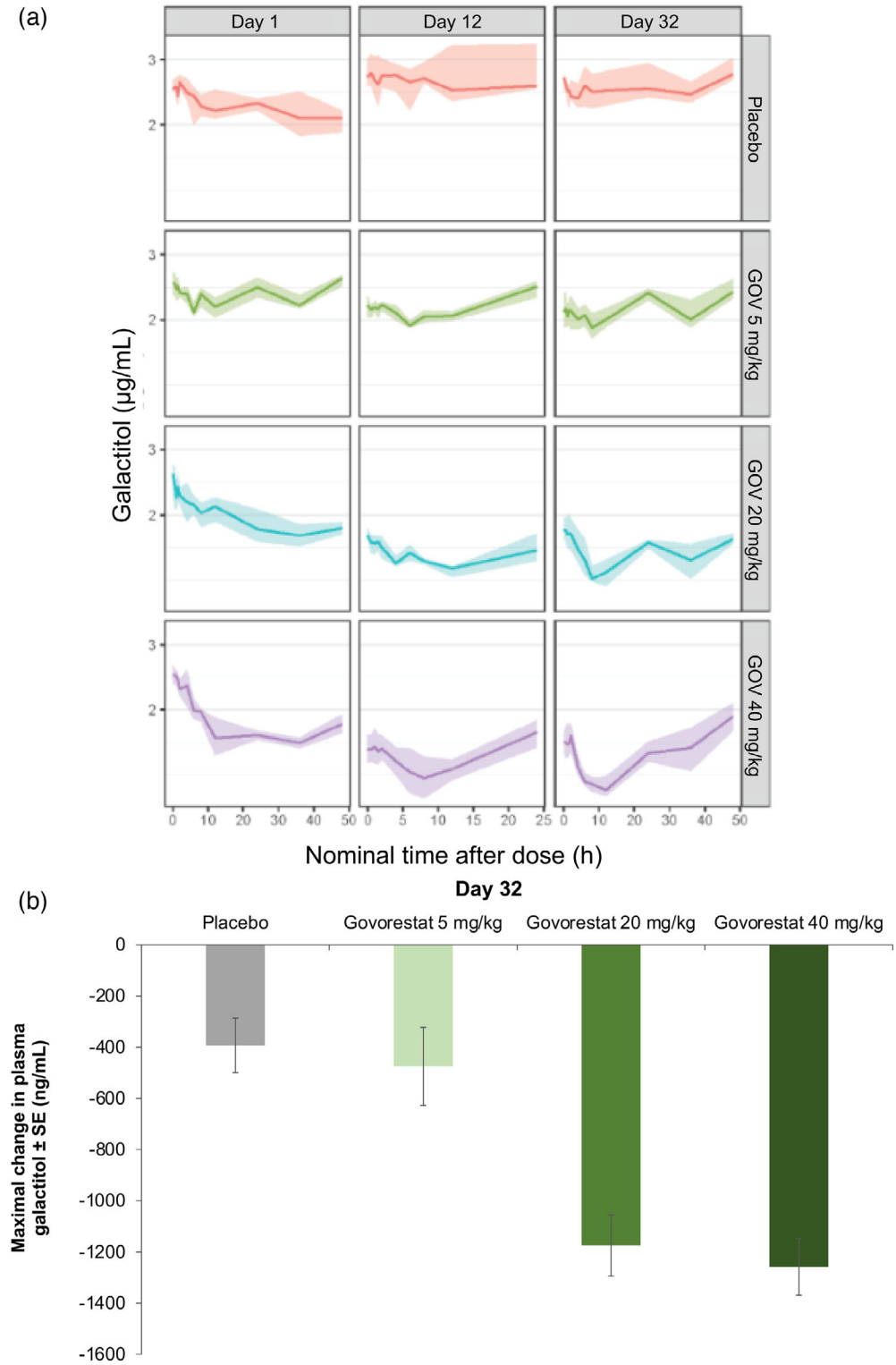

Figure 3. (a) Median (solid line with interquartile range [IQR; shaded areas]) concentrations of galactitol, in patients with classic galactosemia (CG; Part D) on Days 1 (after the first dose), 12, and 32. (b) Maximum ± standard error (SE) change from baseline in plasma galactitol in each treatment group as measured on Day 32. GOV, govorestat.

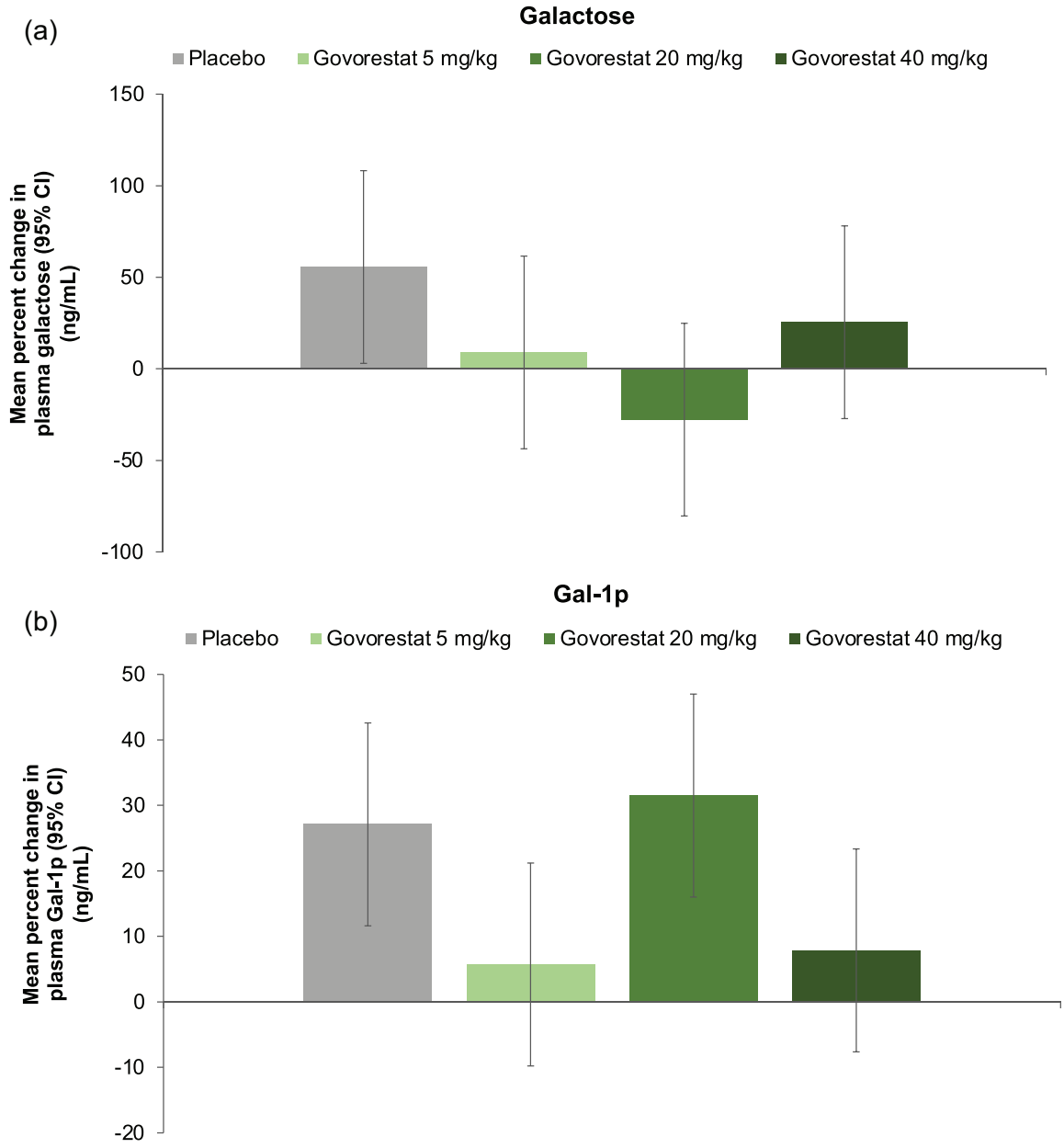

Figure 4. Percent (95% confidence interval [CI]) change from baseline in (a) galactose and (b) galactose-1-phosphate (Gal-1p) in each treatment group on Day 32.

reduced plasma galactitol, and in a similar magnitude, relative to placebo (Figure 3b). Maximal percentage changes (±SD) in galactitol from baseline were −14.9% ± 9.30% in the placebo group and −19.2% ± 10.3%, −46.2% ± 3.62%, and −50.9% ± 4.49% in patients treated with 4, 20, and 40 mg/kg, respectively. Treatment group differences were −4.3% (95% CI, −19.8% to 11.2%; $P = .5294$) with govorestat 5 mg/kg, −31.4% (95% CI, −49.1% to −19.6%; $P = .0004$) with govorestat 20 mg/kg, and −36.0% (95% CI, −48.1% to −23.9%; $P = .0002$) with govorestat 40 mg/kg versus placebo. Considering the SD of the changes from baseline and 95% CI of treatment group differences, the effects of govorestat on plasma galactitol levels were similar for the 20 and 40 mg/kg govorestat doses.

Blood levels of galactose and Gal-1p showed no obvious trend between different govorestat doses and placebo (Figure 4). There was no increase in the blood levels of galactose or Gal-1p after treatment with govorestat.

In terms of galactitol decrease, the PK/PD simulations with once- and twice-daily dosing regimens supported a once-daily dosing regimen. Simulations indicated a reduction in galactitol concentrations of

90% and 97% using a simulated 20 and 30 mg/kg govorestat dose in comparison to a 40 mg/kg govorestat dose (Tables S7-S10 and Figures S3-S10).

Discussion

CG is a rare hereditary disease characterized by severe GALT deficiency in which the accumulation of galactose metabolites Gal-1p and galactitol has been associated with neurologic deficits, ovarian insufficiency, and cataracts. Currently, there is an unmet need for pharmacologic therapies for CG, as the only available treatment option is a galactose-free diet that permits survival but does not prevent disease complications.[3–5]

Galactitol (like other reduced sugar alcohols) is highly toxic, and its intracellular accumulation is associated with osmotic dysregulation, oxidative damage, and disturbances in redox potential in neurons.[12–15] Galactitol has been shown to be associated with long-term complications in patients with galactokinase deficiency, another condition that leads to excess galactose and galactitol levels but which does not involve accumulation of Gal-1p.[7] Thus, galactitol is a clinically relevant biomarker for patients with CG.

In this phase 1/2 study govorestat was safe and well tolerated in healthy adults and in adult patients with CG. AEs were mostly mild, and occurred at rates that were balanced across treatment groups with no discernable patterns. No severe or serious AEs or deaths were reported, and no discontinuations occurred due to AEs.

In MAD studies involving healthy participants and patients with CG, a linear, dose-dependent increase in plasma levels of govorestat was observed. Penetration of govorestat into CSF was documented in healthy participants following 7 days of dosing.

A 2-compartment model with sequential zero- and first-order absorption provided a good description of govorestat concentrations in both healthy participants and those with CG. The PK of govorestat appeared to be similar between the 2 study populations. No demographic factors were found to influence the PK of govorestat. In patients with CG, C_{max}, and AUC_{tau} increased with increasing doses of govorestat, and the plasma half-life was ~10 h at therapeutic dose levels of 20 and 40 mg/kg. These findings were associated with dose-dependent decreases in galactitol blood concentrations but had no measurable effect on galactose or Gal-1p blood concentrations. A GALT-null rat model of classic galactosemia was recently characterized, which displayed the biochemical properties relevant to humans with classic galactosemia, including elevated galactose, galactitol, and Gal-1p levels, as well as a similar neurobehavioral phenotype to humans, including cognitive, learning, and memory deficiencies.[9]

The PK/PD simulations, taking into account govorestat PK and associated levels of galactitol reduction, support a once-daily dosing regimen for galactitol reduction.

AE rates were numerically lower in patients with CG who received govorestat 20 or 40 mg/kg compared with patients treated with placebo or the 5 mg/kg dose. The effects of govorestat on disease outcomes will be further evaluated in ongoing studies involving patients with CG.

A potential limitation of this study is represented by the number of patients with CG enrolled in the study. However, the size of the patient population should be considered in the context of the rarity of the disease and its clinical characteristics.[16] There are currently only 3000 patients with CG in the United States and approximately 40% are adults. Additional CG results in developmental and cognitive issues that render patients enable to live independently, as a result they are often not capable of traveling independently and this renders the possibility of participating to a clinical study more difficult. Finally, the study was conducted during the COVID-19 pandemic which represented an additional challenge for recruitment in clinical studies.

In conclusion, this study demonstrated that govorestat has a favorable safety, PK, and PD profile, and that induced rapid and sustained reductions in plasma galactitol in adult patients with CG. The PK/PD findings support a once-daily dosing regimen. The reduction in plasma galactitol levels with 20 mg/kg was similar to that of the 40 mg/kg dose, resulting in ~50% reduction in plasma galactitol at both doses. The impact of govorestat on long-term complications of galactosemia will be evaluated in future studies in patients with CG.

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Author Contributions

Riccardo Perfetti, Evan Bailey, Stella Wang, and Shoshana Shendelman designed and performed the study and analyzed the data respectively. Richard Mills, performed the pharmacokinetic and modeling analyses. Ramon Mohanlal, analyzed the data and wrote the manuscript. All authors critically reviewed the manuscript and approved the final version for publication.

Conflicts of Interest

Riccardo Perfetti, Evan Bailey, Stella Wang, and Shoshana Shendelman, are employees and shareholders of Applied Therapeutics Inc. Ramon Mohanlal, is a consultant for

Applied Therapeutics Inc. Richard. Mills, is an employee of ICON plc.

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Data Availability Statement

The pharmacokinetic and pharmacodynamic source data used in this study were made available to the Department of Quantitative Pharmacology and Pharmacometrics at ICON plc for an third party data analysis. The data that support the findings of this study are not available due to legal restrictions.

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