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# First-in-Human Study of AG10, a Novel, Oral, Specific, Selective, and Potent Transthyretin Stabilizer for the Treatment of Transthyretin Amyloidosis: A Phase 1 Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Adult Volunteers

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**Abstract**

AG10 is a novel, potent, and selective oral transthyretin (TTR) stabilizer being developed to treat TTR amyloidosis (ATTR). This randomized, double-blind, placebo-controlled study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics (ex vivo stabilization) of orally administered AG10 in healthy adult volunteers. Both mutant and wild-type ATTR are underdiagnosed diseases with limited therapeutic options. As TTR amyloidogenesis is initiated by dissociation of TTR tetramers destabilized due to inherited mutations or aging, AG10 is designed to treat the disease at its source. Four single and three multiple ascending dose levels of AG10 or matching placebo were orally administered. Safety and tolerability were assessed by vital signs, electrocardiogram, adverse events, and clinical laboratory tests. Pharmacokinetics were measured using a validated bioanalytical assay. Pharmacodynamics were assessed via three pharmacodynamic assays of TTR stabilization. AG10 was uniformly well tolerated, and no safety signals of clinical concern were observed. Pharmacokinetic observations included time to maximum concentration $<1$ hour, dose-dependent maximum concentration and area under the plasma concentration–time curve, low intersubject variability, and half-life $\sim$25 hr. Complete ($>$90%) stabilization of TTR was observed across the entire dosing interval at steady state on the highest dose tested. Serum TTR levels, an in vivo reflection of TTR stabilization by AG10, increased from baseline following 12 days of dosing. AG10 appears to be safe and well tolerated in healthy adult volunteers and can completely stabilize TTR across the dosing interval, establishing clinical proof of concept. Based on these data, AG10 has the potential to be a safe and effective treatment for patients with either mutant or wild-type ATTR.

**Keywords**

AG10, amyloidosis, ATTR, cardiomyopathy, transthyretin

Transthyretin (TTR) amyloidosis (ATTR) is a progressive, fatal disease in which deposition of amyloid derived from either mutant or wild-type TTR causes severe organ damage and dysfunction. Clinically, ATTR presents predominantly as either TTR amyloid cardiomyopathy (ATTR-CM) or as a peripheral polyneuropathy (ATTR-PN); some mutant genotypes present with a mixed phenotype.

ATTR-CM is an infiltrative, restrictive cardiomyopathy characterized by right and left heart failure, usually with preserved ejection fraction. Patients with ATTR-CM have a high risk of developing both heart block and atrial fibrillation.[1]

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Familial ATTR (ATTRm, or mutant ATTR) syndromes are driven by pathogenic point mutations in the TTR gene. While a systemic disease process, TTR amyloid deposition displays tissue tropism according to genotype. The V122I mutation carried by 3.4% of African Americans[2] is predominantly cardiomyopathic. Conversely, the V30M mutation endemic in certain regions of Portugal, Sweden, and Japan is predominantly polyneuropathic.[3]

Older individuals may develop ATTR derived from wild-type TTR (ATTRwt). The major clinical manifestation is ATTR-CM, although carpal tunnel syndrome, spinal stenosis, and tendon involvement are also prevalent.[4–6]

As TTR amyloidogenesis is initiated by dissociation of TTR tetramers destabilized due to inherited mutations or aging, AG10 is designed to treat the disease at its source. Subsequent misfolding, aggregation, and deposition of TTR amyloid causes the tissue damage in both ATTRm and ATTRwt diseases. Several small molecules can bind to and stabilize TTR, slowing or preventing the initiating event in amyloidogenesis. The therapeutic hypothesis driving the development of TTR stabilizers is that they will halt or slow ATTR disease progression. Several clinical trials of TTR stabilizers have been published that validate the stabilization hypothesis in the context of both ATTR polyneuropathy[7–9] and cardiomyopathy.[10–12] AG10 is a potent, highly selective, small-molecule TTR stabilizer. It is manufactured by a simple synthetic route, and its pharmaceutical properties include good oral bioavailability, high binding selectivity, and ability to stabilize TTR in vivo following oral dosing to nonhuman mammals. AG10 has been well tolerated in toxicology studies at exposures that are >100-fold the target therapeutic concentration.

Nonclinical pharmacokinetics of AG10 administered by the intravenous and oral routes were studied in male CD-1 mice, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Pharmacokinetic profiles of AG10 were consistent across the 4 species tested. Following intravenous administration, systemic clearance of AG10 was low (0.0613, 0.0270, 0.0219, and 0.0423 L/hr/kg for mouse, rat, dog, and monkey, respectively). Volume of distribution at steady state was low (0.392, 0.488, 0.612, and 0.525 L/kg for mouse, rat, dog, and monkey, respectively). Terminal elimination half-life ($t_{1/2}$) was relatively long (5.32, 12.9, 19.4, and 10.1 hours for mouse, rat, dog, and monkey, respectively).

Following oral administration, maximum plasma concentration ($C_{max}$) was reached rapidly in all species (0.833, 2.67, 0.583, and 0.833 hours for mouse, rat, dog, and monkey, respectively). AG10 was well absorbed and absolute oral bioavailability values were 30.5%, 59.7%, 39.5%, and 49.4% for mouse, rat, dog, and monkey, respectively.

With respect to metabolic routes of biotransformation, when tested in human liver microsomes, there was minimal evidence of cytochrome P450 (CYP) involvement in the metabolism of AG10. AG10 does not inhibit any of the major CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) as assayed in human liver microsomes. In vitro AG10 metabolite identification studies in rat, dog, monkey, and human hepatocyte suspensions consistently indicated that acylglucuronidation is the predominant pathway of AG10 metabolism. In vitro uridine 5′-diphospho-glucuronosyltransferase (UGT) reaction phenotyping of AG10 in both human liver microsomes and recombinant human UGT enzyme preparations indicated that UGT1A9 contributes to AG10 acylglucuronide (AG10-AG) formation in vitro. However, UGT1A1 and UGT2B7 cannot be excluded as contributors to AG10-AG formation. AG10-AG has been shown to have only 24% to 34% activity of that of parent AG10 by a western blot TTR stabilization assay. As the steady-state plasma exposure (area under the plasma concentration–time curve from time zero extrapolated to infinity [$AUC_{0\text{-inf}}$]) of AG10-AG is ~25% that of the parent, the contribution of AG10-AG to overall clinical efficacy is expected to be negligible.

As an initial clinical experience with AG10, the current investigation was a phase 1, first-in-human, safety, tolerability, pharmacokinetic, and pharmacodynamic study conducted in healthy adult volunteers.

## Methods

### Subjects

The study was approved by the Chesapeake (now Advarra) Institutional Review Board (Columbia, Maryland). All participants provided written informed consent. The trial was conducted at a single center (Celerion, Tempe, Arizona) according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and the World Health Organization Declaration of Helsinki. Healthy adult volunteers ages 18 to 55 years were eligible for the study.

### Study Design

The study was a randomized, double-blind, placebo-controlled, single and multiple ascending dose study. The primary objective of the study was to evaluate the safety and tolerability of single and multiple doses of AG10 administered to healthy adult subjects. The secondary objectives were to characterize the pharmacokinetics (PK) of AG10 in healthy adult subjects and to describe the pharmacodynamic (PD) properties of AG10, as well as the PK-PD relationship

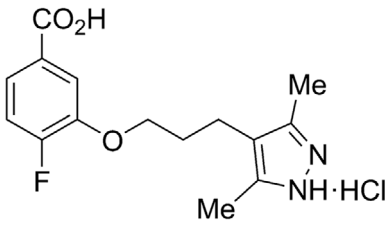


**Figure 1.** Chemical structure of AG10. The molecular formula of AG10 (3-[3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid) is $C_{15}H_{17}FN_2O_3$, and its molecular weight is 292.13; the molecular formula of the hydrochloride salt (drug substance) is $C_{15}H_{18}FClN_2O_3$, and its molecular weight is 328.77.

of AG10 in healthy adult subjects. The study also evaluated the effect of food on the PK of AG10.

### *Investigational Medicinal Product*

AG10 (and matching placebo) was provided in two strengths of film-coated tablets (50 mg and 200 mg), administered orally. AG10's chemical name is 3-(3-(3, 5-dimethyl-1H-pyrazol-4- yl)propoxy)-4-fluorobenzoic acid (the drug substance is the hydrochloride salt). AG10's chemical structure is shown in Figure 1.

### *Safety Evaluation*

Safety evaluations included vital signs (blood pressure, heart rate), physical examination, clinical laboratory tests (hematology, clinical chemistry, urinalysis), electrocardiogram, and assessment of adverse events (AEs).

### *Sample Collection*

*Pharmacokinetic Collection.* In the single ascending dose (SAD) portion of the study, blood samples for determination of AG10 concentrations were collected before dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, and 216 hours after dosing. Urine samples were collected in three 8-hour aliquots for the first 24 hours and 2 additional 24-hour aliquots from 24 to 48 hours and from 48 to 72 hours. In the multiple ascending dose (MAD) portion of the study, blood samples were collected on day 1: before dosing and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing; days 4, 6, 8, 10 and 11: before dosing; day 12 (before dosing and 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours after dosing; and in the morning of days 16, 17, 18, 19, and 21). Urine samples were collected in 8-hour aliquots starting at the time of the last dose administration (ie, 0-8, 8-16, 16-24 hours).

*Pharmacodynamic Collection.* Both serum and plasma samples were collected for PD assays. In the SAD portion of the study, PD samples were collected before dosing, and 1, 2, 4, 12, 24, 48, 72, 120, 168, and 216 hours after dosing. In the MAD portion of the study, PD samples were collected on day 1: before dosing and 1, 2, 4, 12, and 24 hours after dosing; days 4, 6, 8, 10, and 11: before dosing; day 12: before dosing and 1, 2, 4, 12, 24, 48, and 72 hours after dosing; and in the morning of days 16, 17, 18, 19, and 21.

### *Analytical Methods*

Human $K_2$–ethylenediaminetetraacetic acid plasma samples were analyzed for AG10 by a validated method over a range of 10 to 10 000 ng/mL based on the analysis of 0.0500 mL of acidified plasma, and for AG10-AG using a qualified method over a range of 1 to 1000 ng/mL based on the analysis of 0.0500 mL of acidified plasma. Human urine samples were analyzed for AG10 by a qualified method over a range of 10 to 5000 ng/mL for AG10 and 100 to 50 000 ng/mL for AG10-AG based on the analysis of 0.100 mL of acidified urine. All bioanalysis was conducted at Worldwide Clinical Trials (Austin, Texas). Human plasma or urine samples containing AG10, AG10-AG, and internal standards AG10-D6 and AG10-AG-D6 were extracted using protein precipitation and analyzed by a Sciex API 4000 LC-MS-MS (Applied Biosystems, Foster City, California) equipped with a high-performance liquid chromatography column. Samples were chromatographed on a Kinetex C18, 2.6 μm, 2.1 × 50 mm column (Phenomenex, Torrance, California). For AG10 in plasma, samples were eluted using a gradient between water/ammonium acetate solution/formic acid (1000:2:1) and acetonitrile/water/ammonium acetate solution/formic acid (950:50:2:1). For AG10-AG in plasma and AG10 and AG10-AG in urine, samples were eluted using a gradient between water/formic acid (1000:2) and acetonitrile/methanol/formic acid (900:100:2). The peak area of the m/z 293.1 → 139.1 AG10 product ion was measured against the peak area of the m/z 299.1 → 139.1 AG10-D6 internal standard product ion. The peak area of the m/z 469.2 → 293.2 AG10-AG product ion was measured against the peak area of the m/z 475.2 → 299.2 AG10-AG-D6 internal standard product ion. Quantitation was performed using a weighted $1/x^2$ linear least squares regression analysis generated from calibration standards prepared on the day of extraction. For the plasma AG10 assay, intra-assay precision (% coefficient of variation [CV]) and accuracy (% bias) were within 0.5% to 2.7% and –7.5% to 13.4%, respectively, and interassay precision (%CV) and accuracy (% bias) were within 2.4% to 3.5% and –5.0% to 10.4%, respectively. For the plasma AG10-AG assay, intra-assay precision (%CV) and accuracy (% bias) were within 0.6% to 2.8% and –0.5% to 5.3%, respectively, and interassay precision (%CV) and accuracy (% bias) were within 1.2% to 2.6% and –0.1% to 4.0%, respectively. For the urine AG10 assay, intra-assay precision (%CV) and accuracy (% bias) of quality controls were within 0.7% to 3.8% and –6.8%

to 17.0%, respectively, and interassay precision (%CV) and accuracy (% bias) were within 3.3% to 6.4% and –4.5% to 8.7%, respectively. For the urine AG10-AG assay, intra-assay precision (%CV) and accuracy (% bias) were within 1.2% to 5.3% and –3.0% to 16.3%, respectively, and interassay precision (%CV) and accuracy (% bias) were within 3.4% to 8.6% and 4.5% to 6.0%, respectively.

### Pharmacokinetic Analysis

Pharmacokinetic calculations based on AG10 and AG10-AG plasma concentrations were performed by Celerion (Tempe, Arizona) using noncompartmental analysis in Phoenix WinNonlin version 6.3 or higher (Certara, Princeton, New Jersey). Individual plasma concentration data from each subject and the exact time points for blood sampling were used throughout the analysis. Pharmacokinetic parameters calculated from plasma AG10 concentrations included, but were not limited to, $C_{max}$, time of maximum concentration ($t_{max}$), area under the plasma concentration–time curve from time zero to 24 hours ($AUC_{0\text{-}24}$), and $AUC_{0\text{-}inf}$. Calculated PK parameters also included apparent distribution half-life ($t_{1/2,d}$), determined by linear regression of log concentration on the apparent distribution portion of the plasma concentration–time curve and calculated as $\ln(2)/(-\alpha)$, where $\alpha$ is the slope of the distribution portion of log concentration–time curve, and apparent terminal half-life ($t_{1/2,t}$), determined by linear regression of log concentration on the terminal portion of the plasma concentration–time curve and calculated as $\ln(2)/(-\beta)$, where $\beta$ is the slope of the terminal portion of e log concentration–time curve. Dose-normalized values for $C_{max}$ and $AUC_{0\text{-}24}$ were calculated and captured as $C_{max}$/D and AUC/D, respectively. From urine data, cumulative amount excreted from time zero to 72 hours after dosing ($A_e$) and renal clearance ($CL_r$) were determined. For the MAD portion of the study, dose-normalized values for $C_{max}$ and $AUC_{0\text{-}tau}$ were calculated and captured as $C_{max}$/D and AUC/D, respectively. Accumulation ratio based on $C_{max}$ was calculated as $C_{max,}$day 12/$C_{max,}$day 1. From urine data, the cumulative amount excreted from time zero to 24 hours after dosing on day 12 ($A_e$) and $CL_r$ were calculated.

### Pharmacodynamic End Points

PD properties of AG10 were assessed ex vivo in serum or plasma samples obtained before and after administration of AG10 by 3 established assays of TTR stabilization: fluorescent probe exclusion assay (FPE), western blot, and measurement of circulating TTR concentration. FPE is a competitive binding assay measuring occupancy of TTR's T4 binding site; the western blot is a measure of a bound ligand's ability to prevent the accelerated dissociation of tetrameric TTR under denaturing conditions. Serum TTR (prealbumin) concentration reflects an individual balance between overall nutritional status and the intrinsic stability of the TTR tetramer, and thus at a given nutritional state reflects the pharmacological effect of a TTR stabilizer in vivo.

The FPE assay was performed using serum from timed blood samples according to an established method.[13] Briefly, the probe is a small molecule that becomes fluorescent only when covalently bound to the T4 binding site of TTR. The time-dependent development of the fluorescence signal is reduced in direct proportion to the percentage of occupancy of the T4 binding site by a competing ligand. Relative fluorescence units at t = 60 minutes were normalized to t = 60 minutes relative fluorescence units from the predose serum sample from each individual subject to determine the percentage of target occupancy by the competing ligand AG10.

The western blot assay was performed on plasma from timed blood draw samples as previously described.[14] Briefly, plasma samples were acidified to pH 3.8 and incubated for 72 hours prior to crosslinking with glutaraldehyde. "Time zero" replicates from each plasma sample were similarly acidified immediately prior to crosslinking. All replicates were subjected to denaturing gel electrophoresis and immunoblotting using antihuman TTR polyclonal antibody (DAKO-A0002, DAKO, Carpinteria, California). Immunoblots were quantified using a ChemiDoc MP Imaging System (Biorad Laboratories, Richmond, California). Band intensities for tetrameric TTR (either TTR alone or retinol binding protein–bound TTR) were compared between zero- and 72-hour denaturation for each sample to determine the percentage of stabilization.

Serum TTR (prealbumin) concentrations were determined using a qualified enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Prealbumin ELISA kit [human]; Aviva Systems Biology, San Diego, California). Because of differences in methodology compared to a widely available clinical prealbumin assay, the results are not directly comparable to results generated by the clinical assay and should be considered qualitative in nature.

### Statistical Considerations

For the PD data, summary measures were determined and a relationship to increasing dose was explored. The statistical model included the actual dose of AG10 and the baseline value of the measurement.

The PK-PD relationship was analyzed by the logistic $E_{max}$ model. Data were fitted to the equation:

$$E = E_o + \frac{E_{max}}{1 + exp\left(\frac{ED_{50} - d}{\partial}\right)}$$

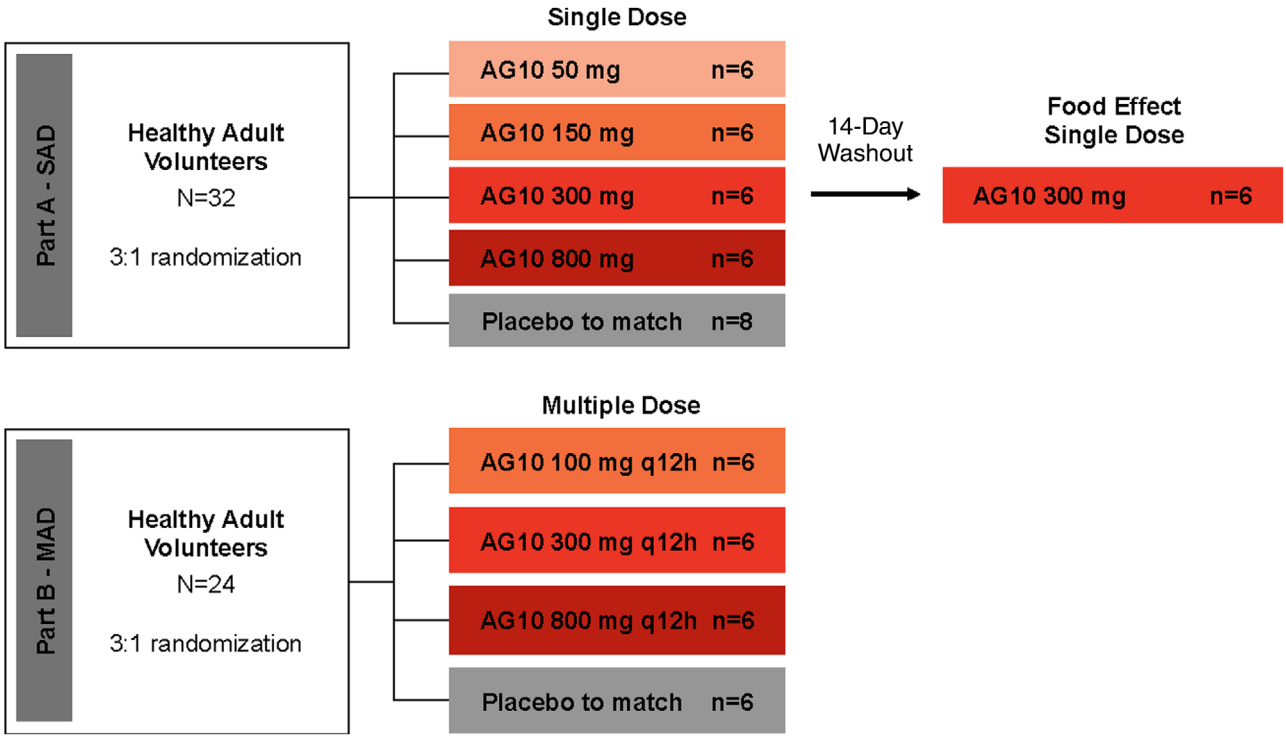


**Figure 2.** AG10-001 study design. Study AG10-001 was a 2-part, randomized, double-blind, placebo-controlled first-in-human study of AG10 in healthy adult volunteers. Part A was a single ascending dose (SAD) design consisting of 4 cohorts of 8 subjects each randomized in a 3:1 ratio (active:placebo). One cohort participated in 2 sequential dose periods to test for a food effect on the pharmacokinetics of AG10. Part B was a multiple ascending dose (MAD) design consisting of 3 cohorts of 8 subjects each randomized in a 3:1 ratio (active:placebo).

Derived parameters with confidence intervals are reported in the Figure 7 legend.

## Results

### *Subject Disposition*

In all, 4 cohorts of 8 healthy subjects each (N = 32; 24 active and 8 placebo) were administered single doses of 50, 150, 300, and 800 mg of AG10 in Part A under fasting conditions. Following a 2-week washout, subjects in the 300-mg cohort were administered a second 300-mg single dose following a high-fat breakfast.[15] Three cohorts of 8 healthy subjects each (N = 24; 18 active and 6 placebo) were administered multiple doses of 100, 300, or 800 mg of AG10 every 12 hours (q12h) for 12 days in the MAD Part B (Figure 2).

The mean (standard deviation [SD]) age of the subjects randomized to AG10 in Part A was 37 (9.29) years (range, 18-55 years); subjects were primarily male (17 of 24 [71%]), white (20 of 24 [83%]), and Hispanic or Latino (17 of 24 [71%]) and had a mean (SD) body mass index of 27.1 (3.29) kg/m$^2$.

The mean (SD) age of the subjects randomized to AG10 in Part B was 41 (8.97) years (range, 25-55 years); subjects were primarily male (13 of 18 [72%]), white (15 of 18 [83%]), and Hispanic or Latino (14 of 18 [78%]) and had a mean (SD) body mass index of 27.8 (2.83) kg/m$^2$.

### *Safety*

No dose-limiting toxicities were observed in the study. In Part A, AEs were reported by 29% of actively treated subjects (7 of 24) and 25% of placebo subjects (2 of 8). In Part B, AEs were reported by 44% of actively treated subjects (8 of 18) and 50% of placebo subjects (3 of 6). No dose-related pattern in AEs was observed. No deaths or serious AEs were reported and none assessed as causally related to the study drug (Table 1), and there were no AEs leading to study drug discontinuation.

Most AEs were reported by single subjects, and all were mild to moderate in intensity. The only AEs that occurred in more than 1 subject were dry mouth, generalized headache, upper respiratory infection, and dizziness, all of which occurred in 2 separate subjects.

Small fluctuations in mean vital sign values were seen in the AG10 dose groups and in the pooled placebo group, which were considered expected and clinically unimportant. There were no clinically important changes or trends observed in safety laboratory tests, nor were there clinically important postdose electrocardiogram findings in the study.

**Table 1.** Treatment-Emergent Adverse Events for Single Ascending Dose and Multiple Ascending Dose

| | Single Ascending Dose | | | | | Multiple Ascending Dose (q12h) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose | Placebo (n = 8) | 50 mg (n = 6) | 150 mg (n = 6) | 300 mg[a] (n = 6) | 800 mg (n = 6) | Placebo (n = 6) | 100 mg (n = 6) | 300 mg (n = 6) | 800 mg (n = 6) |
| SAEs | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| AEs | 2 (25%) | 3 (50%) | 2 (33%) | 1 (17%) | 1 (17%) | 3 (50%) | 2 (33%) | 5 (83%) | 1 (17%) |

All adverse events (AEs) observed in the study are presented as number (%) of AEs observed within each dose cohort. No serious adverse events (SAEs) were observed.

[a]Adverse events in the fed component; no subjects in the fasted component experienced treatment emergent SAEs or AEs.

The lack of any observed safety signals of potential clinical concern is consistent with the AG10 toxicology program that has established a No Observed Adverse Effect Level >100-fold higher than the predicted target therapeutic concentration of 8 μM.

### *Pharmacokinetics of AG10*

Concentration-time profiles and associated PK parameters for all cohorts in the SAD and MAD portions of the study are presented in Figure 3 and Table 2, respectively. After single-dose administration of 50 to 800 mg, median plasma AG10 $t_{max}$ values ranged from 0.75 to 1 hour across dose levels. The $t_{1/2,d}$ was comparable among all doses of AG10 administered and ranged from approximately 2.2 to 5 hours. The $t_{1/2,t}$ was similar across dose levels, ranging from 21.5 to 27.6 hours. The increase in exposure parameters ($AUC_{0\text{-}24}$ and $C_{max}$) was less than dose proportional between the 50-mg and 150-mg and the 150-mg and 300-mg doses, but was approximately dose proportional between the 300-mg and 800-mg doses. Mean cumulative amounts of intact AG10 excreted in urine over 72 hours after dosing ranged from approximately 2.3 to 68 mg and increased with increasing dose of AG10 administered. Mean cumulative amounts of intact AG10 excreted were relatively low, representing at most 9.5% of the dose administered for all dose levels.

The effect of food on the PK of AG10 was studied at a single dose of 300 mg of AG10 in the same cohort of subjects under fasted and fed conditions sequentially with a 2-week washout between periods. Overall exposure to AG10 was higher under fed than under fasted conditions (Figure 4 and Table 2). In addition, $C_{max}$ was lower following administration of food in comparison to fasted conditions. There was a delay in AG10 $t_{max}$ under fed in comparison to fasted conditions (median $t_{max}$ of 1.5 vs 0.75 hours, respectively). The $t_{1/2,d}$ was approximately 5 hours and the $t_{1/2,t}$ was approximately 21.5 hours under both fed and fasted conditions. The findings from the fasted vs fed data in the food effect cohort were not considered clinically meaningful.

Following both the first dose (day 1) and the final repeat dose (day 12) administration of 100, 300, and 800 mg of AG10 q12h, mean AG10 concentrations peaked at 0.5 or 1 hour after dosing and then declined in a multiphasic fashion. Mean accumulation ratios for plasma AG10 $C_{max}$ ranged from 1.3 to 1.6. There was an increase in $C_{trough}$ between days 2 and 4, following which the mean $C_{trough}$ values were generally stable between days 4 and 12. The majority of AG10 urinary excretion occurred from zero to 8 hours after dosing following multiple oral doses of 100 and 300 mg of AG10. Following multiple oral doses of 800 mg of AG10, approximately half of the cumulative amount of intact AG10 was excreted from zero to 8 hours after dosing, and most of the remaining amount was excreted from 8 to 16 hours after dosing. The increase in exposure parameters (AUC and $C_{max}$) was less than dose proportional between the 100-mg and 300-mg and the 300-mg and 800-mg doses on both day 1 and day 12. Following multiple oral doses of AG10, mean cumulative amounts of intact AG10 excreted in urine over 24 hours after dosing ranged from approximately 8.7 to 139.5 mg and increased with increasing dose of AG10 administered.

### *Pharmacokinetics of AG10-AG*

Concentration-time profiles and associated PK parameters for all cohorts in the SAD and MAD portions of the study are presented in Figure 5 and Table 3, respectively. Median plasma AG10-AG $t_{max}$ was 1 hour across all dose levels. The $t_{1/2,d}$ was 1.9, 2.3, 1.8, and 1.3 hours for the 50-, 150-, 300-, and 800-mg doses, respectively. The $t_{1/2,t}$ was 16.9, 28.2, 18.8, and 24.2 hours for the 50-, 150-, 300-, and 800-mg doses, respectively. The intersubject variability for these parameters was generally high. Dose-normalized plasma AG10-AG $AUC_{0\text{-}24}$ and $C_{max}$ values were similar across all dose levels. Mean cumulative amounts of AG10-AG excreted in urine over 72 hours after dosing ranged from approximately 21.27 to 270.9 mg and increased with increasing dose of AG10 administered and represented approximately 19.5% to 23.5% of the dose of AG10 administered following a single dose of 50 to 800 mg AG10. Arithmetic mean $CL_r$ values ranged from approximately 14.2 to 18.6 L/hr.

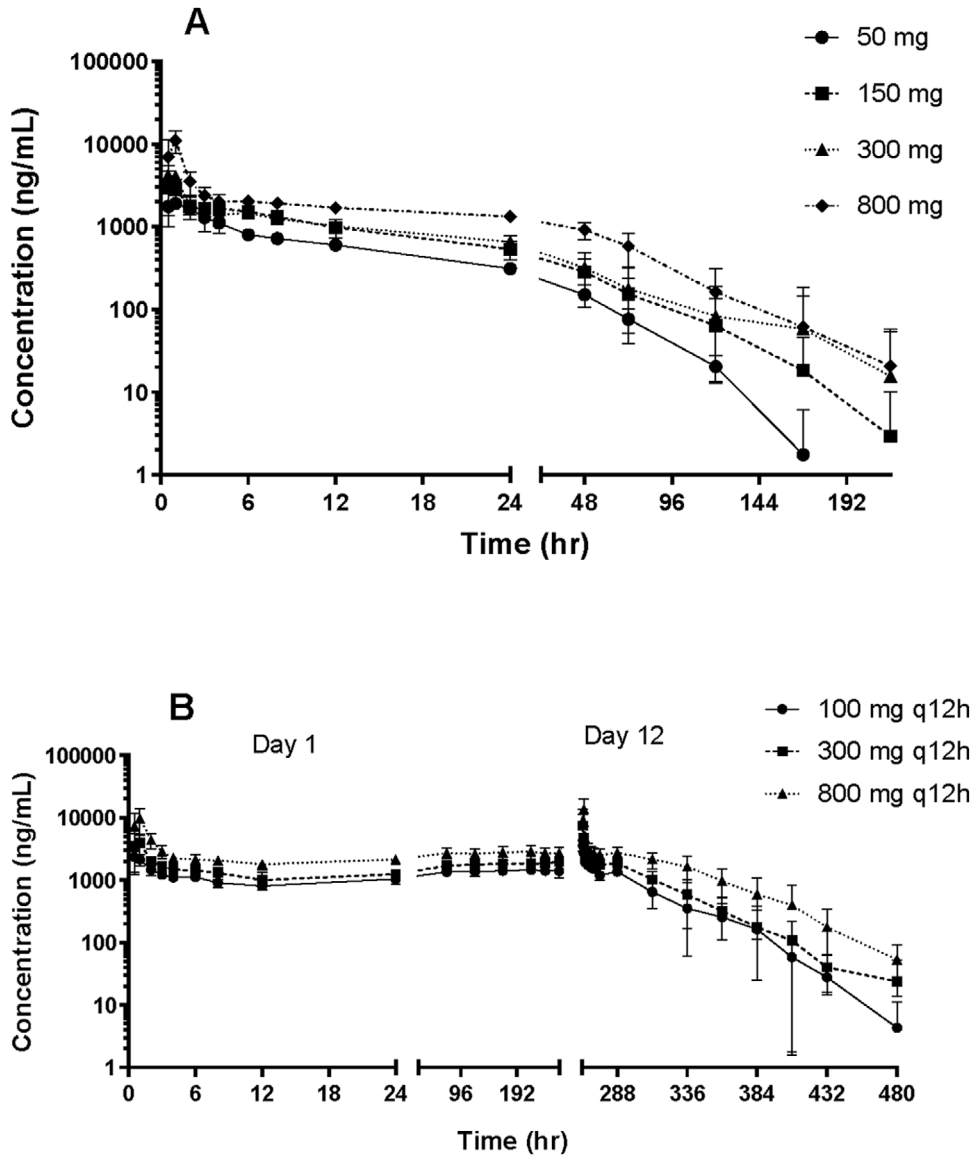


**Figure 3.** AG10 plasma concentration–time profiles following administration of (A) single oral doses of AG10 and (B) multiple oral doses of AG10 every 12 hours for 12 days. Prior to and following the administration of single oral doses of AG10 50, 150, 300, and 800 mg, and multiple oral doses of AG10 100, 300, and 800 mg, serial timed blood samples were analyzed for AG10 plasma concentration as described in Methods. Values represent arithmetic mean ± standard deviation (SD) of 6 subjects at each dose. Values below the lower limit of quantitation are entered as zero and included as such in calculation of the arithmetic means and SDs.

The effect of food on the PK of AG10-AG was studied at a single dose of 300 mg of AG10. Overall exposure to AG10-AG was generally comparable under fed and fasted conditions, while $AUC_{0\text{-inf}}$ was slightly lower under fed conditions. The average $C_{max}$ was approximately 50% lower following administration of food in comparison to fasted conditions. There was a delay in AG10-AG $t_{max}$ under fed in comparison to fasted conditions (median $t_{max}$ of 2.5 vs 1.0 hours, respectively). The $t_{1/2,d}$ was approximately 2 hours under both fed and fasted conditions, and the $t_{1/2,t}$ also appeared relatively similar under both conditions (approximately 18.8 hours under fed conditions and 14.9 hours under fasted conditions). The findings from the fasted vs fed data in the food effect cohort were not considered clinically meaningful.

Following both a single dose (day 1) and q12h dose (day 12) administration of 100, 300, and 800 mg AG10, arithmetic mean AG10-AG concentrations increased in a dose-dependent manner and maintained a similar profile following different doses. Mean AG10-AG concentrations peaked at 1 hour after dosing and then declined in a multiphasic fashion. Mean accumulation ratios for plasma AG10-AG $C_{max}$ ranged from

**Table 2.** Plasma and Urine Pharmacokinetic Parameters of AG10

| Parameters | Fasted | Fasted | Fasted | Fed | Fasted |
|---|---|---|---|---|---|
| SAD | | | | | |
| Dose (mg) | 50 | 150 | 300 | 300 | 800 |
| N | 6 | 6 | 6 | 6 | 6 |
| $C_{max}$ (ng/mL) | 2110 (210) | 3540 (1390) | 4510 (1050) | 3040 (675) | 11 500 (3310) |
| $t_{max}$ (hr) | 0.8 (0.5, 2.0) | 0.8 (0.5, 3.0) | 0.8 (0.5, 1.1) | 1.5 (1.0, 4.0) | 1.0 (0.5, 1.0) |
| $t_{1/2,d}$ (hr) | 3.5 (1.1) | 3.4 (3.0) | 4.9 (5.8) | 5.4 (1.6) | 2.2 (1.1) |
| $t_{1/2,t}$ (hr) | 25.2 (2.9) | 27.6 (7.8) | 21.5 (5.9)[a] | 21.6 (6.4)[a] | 27.5 (9.2) |
| $AUC_{0-24}$ (ng • hr/mL) | 17 200 (1190) | 27 500 (4900) | 29 300 (2870) | 32 600 (3990) | 51 900 (8080) |
| $AUC_{0-inf}$ (ng • hr/mL) | 28 600 (3550) | 50 600 (13 700) | 52 800 (18 700)[a] | 65 100 (21 500)[a] | 123 000 (25 700) |
| AUC/D (ng • hr/mL/mg) | 387 (26.7) | 206 (36.7) | 110 (10.8) | 122 (14.9) | 72.9 (11.3) |
| $C_{max}$/D (ng/mL/mg) | 47.5 (4.73) | 26.5 (10.4) | 16.9 (3.94) | 11.4 (2.53) | 16.1 (4.65) |
| CL/F (L/hr) | 1.58 (0.203) | 2.79 (0.646) | 5.44 (1.40)[a] | 4.37 (1.03)[a] | 5.98 (1.18) |
| RA, $C_{max}$ | N/A | N/A | N/A | N/A | N/A |
| $A_e$ (mg) | 2.30 (0.396) | 6.54 (2.27) | 18.7 (10.9) | 18.0 (5.88) | 68.1 (26.5) |
| $CL_r$ (mL/hr) | 91.4 (19.9) | 154 (41.7) | 382 (179) | 326 (77.7) | 697 (240) |
| MAD | | | | | |
| Dose (mg) | 100 q12h | 300 q12h | 800 q12h | | |
| N | 6 | 6 | 6 | | |
| $C_{max}$ (ng/mL) | 3590 (638) | 7650 (3750) | 13 700 (6090) | | |
| $t_{max}$ (hr) | 0.5 (0.5, 1.0) | 0.5 (0.5, 1.0) | 1.0 (0.5, 1.0) | | |
| $t_{1/2,d}$ (hr) | 10.5 (4.8) | 17.5 (4.0) | 7.0 (3.7) | | |
| $t_{1/2,t}$ (hr) | 23.5 (2.6) | 29.8 (5.7) | 28.8 (5.8) | | |
| $AUC_{tau}$ (ng • hr/mL) | 20 600 (1810) | 28 700 (2650) | 47 200 (10300) | | |
| $AUC_{0-inf}$ (ng • hr/mL) | 89 200 (32 300) | 131 000 (38 700) | 259 000 (93 800) | | |
| AUC/D (ng • hr/mL/mg) | 232 (20.3) | 108 (9.94) | 66.3 (14.5) | | |
| $C_{max}$/D (ng/mL/mg) | 40.4 (7.17) | 28.6 (14.1) | 19.3 (8.56) | | |
| CL/F (L/hr) | 4.35 (0.382) | 9.36 (0.936) | 15.6 (3.16) | | |
| RA, $C_{max}$ | 1.45 (0.374) | 1.84 (1.06) | 1.48 (0.775) | | |
| $A_e$ (mg) | 8.75 (5.06) | 31.8 (14.2) | 139 (67.8) | | |
| $CL_r$ (mL/hr) | 239 (119) | 629 (272) | 1750 (608) | | |

$A_e$, amount of unchanged drug excreted in the urine collection interval, cumulative over the entire 72 hour collection (SAD) or 24-hour collection (MAD); $AUC_{0-24}$, area under the plasma concentration–time curve from time zero to 24 hours; $AUC_{0-inf}$, AUC from time zero extrapolated to infinity; AUC/D, dose-normalized value for AUC; CL/F, apparent clearance; $CL_r$, renal clearance; $C_{max}$, maximum concentration; $C_{max}$/D, dose-normalized value for $C_{max}$; MAD, multiple ascending dose; N/A, not applicable, RA, $C_{max}$, accumulation ratio calculated from $C_{max}$ at steady state (last day of dosing) and $C_{max}$ following a single dose (day 1); SAD, single ascending dose; $t_{1/2,d}$, apparent distribution half-life; $t_{1/2,t}$, apparent terminal half-life; $t_{max}$, time of maximum concentration.

$T_{max}$ values are presented as median (minimum, maximum). Other parameters are presented as arithmetic mean (standard deviation). For MAD, pharmacokinetic parameters listed are for day 12, the last day of dosing.

[a]$N = 5$.

1.2 to 1.6. Following multiple oral doses of AG10, mean cumulative amounts of AG10-AG excreted in urine over 24 hours after dosing ranged from 70.78 to 967 mg and increased with increasing dose of AG10 administered. Arithmetic mean $CL_r$ values ranged from 23.7 to 24.1 L/hr.

### *Pharmacodynamics of AG10*

Percentage of target occupancy was assessed by FPE (which is linearly correlated with more direct measures of stabilization)[13,14] and stabilization confirmed by western blot.

Prior to analyzing clinical study PD samples, we assessed the linearity of the AG10 concentration response in these assays by adding known concentrations of AG10 to pooled healthy donor serum and plasma samples in vitro prior to analysis by the assays (see Figures S1 and S2).

Applied to the clinical study samples, FPE confirmed target engagement at all single doses tested, with complete stabilization of TTR at $C_{max}$ following single doses of 300 or 800 mg and sustained stabilization up to 12 hours ranging from 29% to 62% at 300 mg and from 56% to 82% at 800 mg. Western blot also confirmed complete stabilization of TTR at $C_{max}$ and sustained stabilization up to 12 hours following single doses of 300 or 800 mg of AG10 (data not shown).

Following 12 days of dosing with either 100, 300 or 800 mg q12h, FPE confirmed sustained target engagement at steady state. Mean stabilization of TTR at the

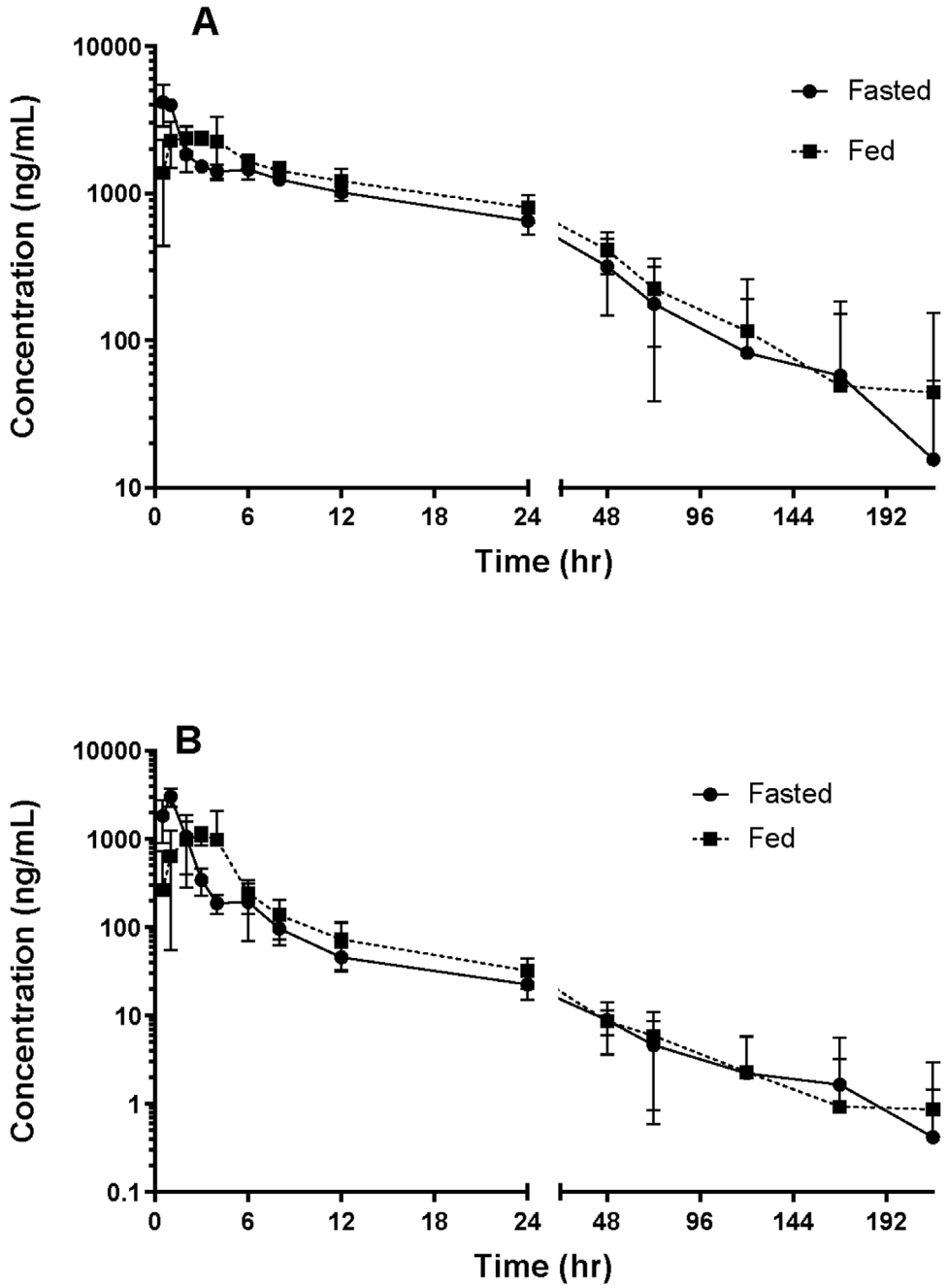


**Figure 4.** Plasma concentration–time profiles of (A) AG10 and (B) AG10-AG following administration of a single oral dose of AG10 in fasted and fed states. Prior to and following the administration of a single oral dose of 300 mg AG10, serial timed blood samples were analyzed for AG10 plasma concentration as described in Methods. Values represent arithmetic mean ± standard deviation (SD) of 6 subjects. Values below the lower limit of quantitation are entered as zero and included as such in calculation of the arithmetic means and SDs.

12-hour postdose (trough) time point on the last day of dosing was 92% in the 800-mg q12h dose cohort (Figure 6). This was confirmed by western blot (see Figure S3). The aggregate PK-PD data from all subjects receiving multiple ascending oral doses of AG10 demonstrated a predictable and dose-responsive PD effect of AG10 as measured by FPE in human subjects dosed with AG10, with near-complete stabilization (average >90%) achieved at plasma concentrations ≥8 μM (Figure 7).

Finally, to explore the in vivo effects of increased TTR stability on its circulating concentration, we measured serum TTR (prealbumin) levels in archived samples from Part B. The rationale for expecting an increase

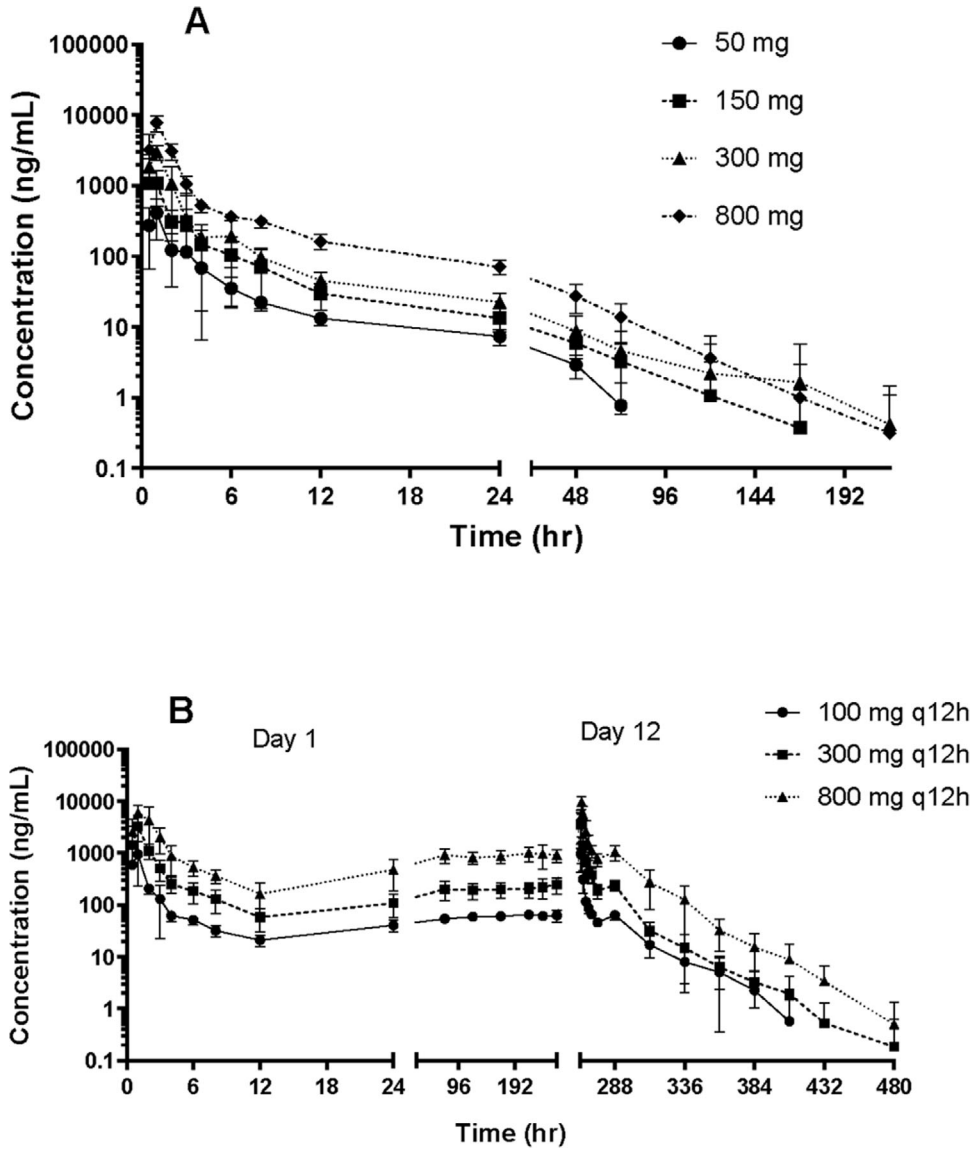


**Figure 5.** AG10-AG plasma concentration–time profiles following administration of (A) single oral doses of AG10 and (B) multiple oral doses of AG10 every 12 hours for 12 days. Prior to and following the administration of single oral doses of AG10 50, 150, 300, and 800 mg, and multiple oral doses of AG10 100, 300, and 800 mg, serial timed blood samples were analyzed for AG10-AG plasma concentration as described in Methods. Values represent arithmetic mean ± standard deviation (SD) of 6 subjects at each dose. Values below the lower limit of quantitation are entered as zero and included as such in calculation of the arithmetic means and SDs.

in TTR levels as an in vivo reflection of increased TTR stability is based on several lines of evidence:

- In healthy adults, serum TTR concentrations range from 3.6 to 7.3 μM (20-40 mg/dL), depending on the reference range of the assay employed, and has a circulating half-life of approximately 2 days. [16]
- Hepatic production in individuals has a fixed "set point" (reflecting nutritional status and lean muscle mass)[17] without an apparent feedback loop of relative stability on hepatic production. The lack of a feedback loop can be inferred from both the increase in TTR concentrations following treatment with a stabilizer,[11,18–20] the increase in average TTR concentrations in heterozygous carriers of the super-stabilizing mutation T119M,[21] and the absence of tachyphylaxis during chronic treatment with a TTR gene silencing agent.[22,23]
- Destabilizing mutations are often associated with below-normal serum TTR concentrations in ATTRm patients[24]; ATTRwt patients tend to have low-normal to below-normal levels as well.[25]

**Table 3.** Plasma and Urine Pharmacokinetic Parameters of AG10 Acylglucuronide

| Parameters | Fasted | Fasted | Fasted | Fed | Fasted |
|---|---|---|---|---|---|
| SAD | | | | | |
| Dose of AG10 (mg) | 50 | 150 | 300 | 300 | 800 |
| N | 6 | 6 | 6 | 6 | 6 |
| $C_{max}$ (ng/mL) | 479 (197) | 1680 (1010) | 3010 (707) | 1620 (873) | 7750 (1920) |
| $T_{max}$ (hr) | 1.0 (0.5, 3.0) | 1.0 (0.5, 3.0) | 1.1 (1.0, 1.1) | 2.5 (1.0, 4.0) | 1.0 (1.0, 1.0) |
| $t_{1/2,d}$ (hr) | 1.9 (1.1) | 2.3 (1.2) | 1.8 (1.3) | 2.1 (1.3) | 1.3 (1.1) |
| $t_{1/2,t}$ (hr) | 16.9 (3.0) | 28.2 (15.8) | 18.8 (9.7)[a] | 14.9 (2.1)[b] | 24.2 (7.3) |
| $AUC_{0\text{-}24}$ (ng • hr/mL) | 1070 (141) | 2880 (969) | 6060 (2210) | 5830 (2100) | 15 700 (2750) |
| $AUC_{0\text{-}inf}$ (ng • hr/mL) | 1270 (174) | 3420 (1240) | 6780 (2960)[a] | 5460 (1440)[b] | 18 000 (2620) |
| AUC/D (ng • hr/mL/mg) | 24.1 (3.18) | 21.6 (7.26) | 22.7 (8.29) | 21.8 (7.86) | 22.1 (3.86) |
| $C_{max}$/D (ng/mL/mg) | 10.8 (4.42) | 12.6 (7.59) | 11.3 (2.65) | 6.08 (3.27) | 10.9 (2.69) |
| RA, $C_{max}$ | N/A | N/A | N/A | N/A | N/A |
| $A_e$ (mg) | 21.3 (6.56) | 56.4 (11.3) | 93.9 (44.9) | 99.8 (28.4) | 271 (80.9) |
| $CL_r$ (mL/hr) | 16 900 (3630) | 18 600 (5240) | 14 200 (3890) | 15 700 (1320) | 16 000 (5550) |
| MAD | | | | | |
| Dose of AG10 (mg) | 100 q12h | 300 q12h | 800 q12h | | |
| N | 6 | 6 | 6 | | |
| $C_{max}$ (ng/mL) | 1260 (545) | 4420 (2250) | 9820 (2690) | | |
| $t_{max}$ (hr) | 0.8 (0.5, 1.0) | 1.0 (0.5, 4.0) | 1.0 (1.0, 2.0) | | |
| $t_{1/2,d}$ (hr) | 3.4 (1.2) | 4.5 (2.0) | 2.9 (0.9) | | |
| $t_{1/2,t}$ (hr) | 21.4 (3.9) | 23.6 (5.4) | 18.4 (3.5) | | |
| $AUC_{tau}$ (ng • hr/mL) | 2480 (631) | 10 500 (3200) | 31 000 (9230) | | |
| $AUC_{0\text{-}inf}$ (ng • hr/mL) | 4730 (454) | 17 400 (3740) | 65 800 (20 300) | | |
| AUC/D (ng • hr/mL/mg) | 27.8 (7.09) | 39.2 (12.0) | 43.5 (13.0) | | |
| $C_{max}$/D (ng/mL/mg) | 14.2 (6.13) | 16.6 (8.42) | 13.8 (3.78) | | |
| RA, $C_{max}$ | 1.77 (1.78) | 1.46 (0.791) | 1.74 (0.843) | | |
| $A_e$ (mg) | 70.8 (29.6) | 282 (86.5) | 967 (123) | | |
| $CL_r$ (mL/hr) | 23 700 (10 300) | 23 700 (10 600) | 24 100 (5720) | | |

$A_e$, amount of unchanged drug excreted in the urine collection interval, cumulative over the entire 72 hour collection (SAD) or 24-hour collection (MAD); $AUC_{0\text{-}24}$, area under the plasma concentration–time curve from time zero to 24 hours; $AUC_{0\text{-}inf}$, AUC from time zero extrapolated to infinity; AUC/D, dose-normalized value for AUC; CL/F, apparent clearance; $CL_r$, renal clearance; $C_{max}$, maximum concentration; $C_{max}$/D, dose-normalized value for $C_{max}$; MAD, multiple ascending dose; N/A, not applicable, RA, $C_{max}$, accumulation ratio calculated from $C_{max}$ at steady state (last day of dosing) and $C_{max}$ following a single dose (day 1); SAD, single ascending dose; $t_{1/2,d}$, apparent distribution half-life; $t_{1/2,t}$, apparent terminal half-life; $t_{max}$, time of maximum concentration.

$T_{max}$ values are presented as median (minimum, maximum). Other parameters are presented as arithmetic mean (SD). For MAD, pharmacokinetic parameters listed are for day 12, the last day of dosing.

[a]N = 5.

[b]N = 4.

- In ATTRwt-CM patients, below-normal TTR levels (<3.2 μM or 18 mg/dL) are associated with a worse prognosis than normal levels.[11]
- Heterozygous T119M (super-stabilizing mutation) carriers have 20% higher TTR concentrations compared to the general healthy adult population.[21]
- Treatment with a TTR stabilizer increases circulating TTR concentrations in patients with ATTR.[11]

Because of the small sample size, all actively dosed subjects' data were pooled, as were the data from placebo subjects (Figure 8). Given this limitation and the fact that an ELISA was used to analyze stored, frozen samples, the increase in TTR levels should be considered a qualitative result. Despite these caveats, the observation of a nearly 60% increase from baseline in the actively dosed subjects seems a robust biomarker of TTR stabilization in this small group of healthy adult volunteers.

## Discussion

This study represents the first clinical experience with AG10, a novel, orally available, potent, and highly selective TTR stabilizer. Oral administration of single and multiple doses (to steady state) of AG10 up to 800 mg were well tolerated and not associated with clinical or laboratory safety signals of potential clinical concern

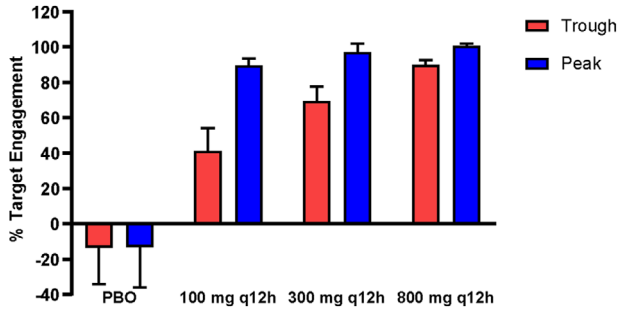


**Figure 6.** TTR stabilization (% target engagement) at steady state by fluorescent probe exclusion (FPE) assay following administration of multiple oral doses of AG10 every 12 hours for 12 days, Serial blood samples from subjects administered oral doses of AG10 100, 300, or 800 mg q12h for 12 days were assayed ex vivo by FPE. Trough and peak values represent arithmetic mean ± standard deviation of triplicate determinations in samples (N = 6) obtained on day 12 at trough (predose) and at peak ($t_{max}$) following the final dose.

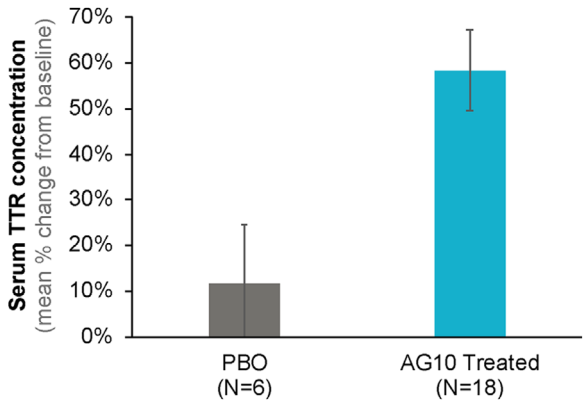


**Figure 8.** Change from baseline in serum transthyretin (TTR) concentration following administration of multiple oral doses of AG10 every 12 hours for 12 days. Blood samples from subjects administered oral doses of AG10 100, 300, or 800 mg q12h for 12 days were assayed for serum TTR concentration by enzyme-linked immunosorbent assay. Values represent mean ± standard deviation of triplicate samples obtained on day 12. Pooled results for all placebo (PBO) subjects, and all actively dosed (AG10 Treated) subjects, are shown.

in healthy adult volunteers. Adverse events were mostly mild and no more than moderate in intensity. The lack of any signals of hepatic stress or injury, electrolyte disturbances, impaired renal filtration, adverse hematologic effects, or electrocardiographic changes associated with AG10 administration are all reassuring at this early stage of clinical development.

Pathogenic loss-of-function (destabilizing) TTR mutations increase the risk of developing ATTR and vary in their penetrance, age of disease onset, and rate of progression leading to a patient's demise. The pathogenicity of individual mutations correlates well with the propensity of the tetramer to dissociate and form monomers.[26] Conversely, the T119M variant demonstrates clearly how a gain-of-function mutation, by increasing the stability of tetrameric TTR, confers protection from V30M-mediated ATTR-PN[27] and, in-

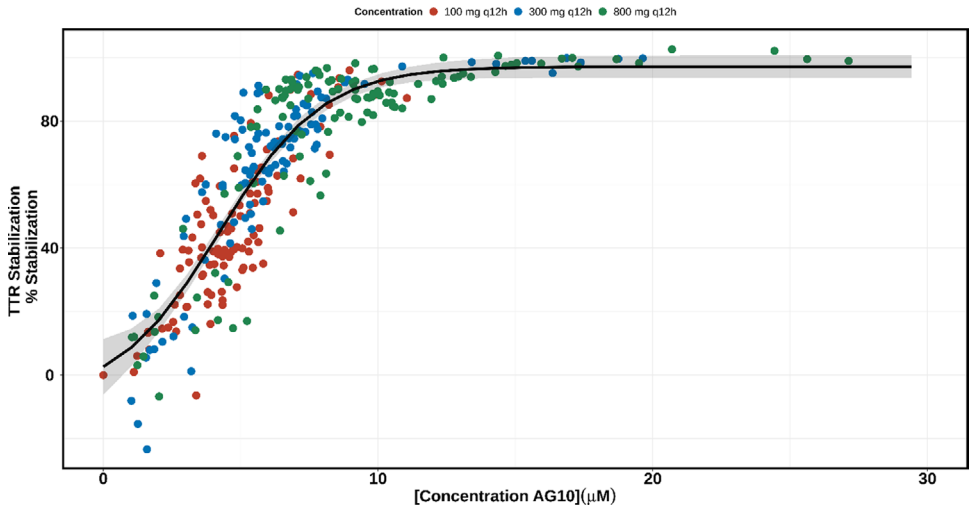


**Figure 7.** Pharmacokinetic-pharmacodynamic relationship between AG10 plasma concentration and TTR stabilization (% occupancy) by fluorescent probe exclusion (FPE). Serial blood samples from subjects administered oral doses of AG10 100, 300, or 800 mg q12h for 12 days were assayed ex vivo by FPE. Individual FPE values obtained from serial samples prior to the first dose, and prior to and following the final dose, are plotted against the corresponding AG10 plasma concentrations determined by bioanalysis as described in Methods. Parameters with 90% confidence intervals following analysis by logistic $E_{max}$ model: $E_o$ = –7.29 (–24.4, 9.8), $E_{max}$ = 104.41 (85.6,123.2) $ED_{50}$ = 4.22 (3.5, 4.9) delta = 1.87 (1.5, 2.3), d = AG10 plasma concentration. Akaike information criteria = 2644.16. Data indicate complete occupancy of available transthyretin binding sites above an AG10 plasma concentration of approximately 8 μM (2.34 μg/mL).

cidentally, also confers protection from cerebrovascular disease and leads to enhanced longevity in healthy adult heterozygotes compared to the general population.[21]

X-ray crystallographic and TTR tetramer dissociation studies have documented what appears to be a rational structural and biophysical basis behind the protective effects of the T119M disease-sparing variant. The X-ray crystallographic structure of the T119M variant reveals the potential to form strong hydrogen bonds between pairs of serine residues, at position 117 of each monomer, at the center of the tetramer. Such hydrogen bonds can potentially explain the observed 40-fold slower dissociation rate of the T119M tetramer as compared to the wild type tetramer.[14,26] When AG10 was co-crystallized with tetrameric TTR, this structure revealed that the two nitrogen atoms of AG10's pyrazole ring are similarly capable of forming hydrogen bonds with adjacent serine 117 residues.[14,28] These data suggest a structural basis to expect superior stabilizing properties of AG10 in vivo. No other stabilizer that binds to the thyroxine binding site, including TTR's natural ligand thyroxine, is structurally capable of similar molecular binding interactions. Together these data highlight the advantages of a molecularly targeted, translational approach to drug development.

The ability of AG10 to uniquely stabilize TTR with a mechanism mimicking the T119M allele has potentially important implications for patients with ATTR. Based on clinically validated ex vivo assays, the degree of stabilization conferred by clinically achieved plasma concentrations of tafamidis and diflunisal appear to be correlated with their clinical efficacy in slowing progression in ATTR-PN.[7,8] If one considers that stabilizers and gene-silencing agents converge on the molecular pathway of amyloidogenesis at the point of limiting the generation of unstable monomers, the degree to which the gene-silencing agents inotersen and patisiran also slow progression in ATTR-PN follows a similar relationship.[22,23] Clinical outcomes with diflunisal (which stabilizes TTR to a numerical extent similar to the level of knockdown with inotersen) appear comparable to those achieved with inotersen. Such cross-study comparisons, while perhaps conceptually illustrative, must, of course, be interpreted with caution and not viewed as evidence on a par with data from a direct comparative trial.

## Conclusion

The invention and development of AG10 represents a rational, structure-based drug design and genetically inspired approach to drug development. The human genetics of TTR have revealed that the intrinsic stability of tetrameric TTR and its dissociation properties are reflected in the clinical consequences of both loss-of-function (destabilized, pathogenic) and gain-of-function (super-stabilized, protective) mutations. The 3-dimensional structure of different TTR tetramers shows the putative basis for both categories of mutations and for distinct binding modes and dissociation behaviors of tetrameric TTR bound to different stabilizers. Clinical studies are now revealing how these molecular properties are related to the clinical consequences of TTR stabilization.

Transthyretin amyloidoses, for many years considered an obscure family of rare genetic diseases, have more recently received a high level of interest. Long understood by experts in the field as a progressive and uniformly fatal disease, the advent of novel therapeutic approaches based on solid, basic scientific discoveries is about to revolutionize the treatment of these syndromes. Helping clinicians increasingly recognize the disease at an earlier clinical stage are both newly developed noninvasive diagnostic algorithms and increased patient, family, and clinician awareness.

The present study represents the initial clinical experience with AG10, characterizing the overall tolerability, PK, and PD of AG10 in healthy adult volunteers. As such, limitations of this study include the fact that this study provides no evidence that AG10 stabilizes TTR-containing mutant TTR monomers, nor does it provide any data on stabilization of TTR in the context of symptomatic ATTR (ie, in patients with active disease). AG10 has been tested for its ability to stabilize TTR when added in vitro to samples obtained from patients with a spectrum of the more prevalent TTR mutations representing diversity in both topographic location of the mutation within the 3-dimensional structure of native, tetrameric TTR and the phenotypic clinical characteristics of those mutations.[29]

In summary, AG10 administration was well tolerated, was not associated with safety signals of potential clinical concern, and resulted in a high degree of TTR stabilization in healthy adult volunteers. A phase 2 study in patients with symptomatic ATTR cardiomyopathy has recently been completed and reported, with consistent findings of good overall tolerability, similar exposures following sustained oral dosing, stabilization of TTR using the same methods reported here, and encouraging results in the ability of AG10 to restore low baseline serum TTR concentrations to the normal reference range.[30] These studies together provide a foundation to investigate the efficacy and safety of AG10 in ATTR with respect to accepted clinical end points, and a phase 3 trial in ATTR-CM has been initiated (clinicaltrials.gov: NCT03860935). AG10 could prove to be an important option among new, disease-modifying treatments, together transforming ATTR from a progressive, fatal disorder into a treatable chronic disease.

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## Declaration of Conflicting Interests

J.C.F., J.L.H., S.R., J.J., and U.S. are employees of Eidos Therapeutics, Inc. T.O. is an employee of Celerion, Inc. R.L. and D.G. are independent consultants who contributed to this work under contract to Eidos Therapeutics, Inc.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.