Phase 1/2 Safety and Proof of Biological Activity Study of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy

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APPLIED THERAPEUTICS

Abstract

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Hyperactivation of the polyol pathway (PP) contributes to development of diabetic complications. Aldose reductase (AR) is the rate-controlling enzyme in the PP that catalyzes NADPH-dependent reduction of glucose to sorbitol. In hyperglycemic and ischemic conditions, PP activation causes intracellular sorbitol accumulation, leading to osmotic stress, cell death and diabetic complications.
We designed a series of novel AR inhibitors based on characterization of AR structural changes within the active site following enzymatic activation. These compounds display enhanced specificity, affinity and selectivity compared with previous AR inhibitors that were associated with off-target effects and/or lack of efficacy. AT-001 safety, pharmacokinetics (PK) and efficacy were assessed in a phase 1/2 study comprised of single oral ascending doses (SAD) of 5, 10, 20 and 40 mg/kg AT-001 or placebo once daily (QD) and multiple doses (MAD) of 5, 20, 40 mg/kg AT-001 QD or 20 mg/kg twice daily (BID) or placebo for 7 days. Subjects with T2D, age 18-75 and HbA1c 5.0-8.5% were allocated to each dose cohort (n=8 AT-001, n=2 placebo). AT-001 was well-tolerated with no drug-related AEs, no changes in liver or renal function at any dose tested. Mean half-life (T1/2) and time of maximum concentration (Tmax) ranged from 1.7-3h and 1.75-3h, respectively in both SAD and day 1 MAD with no accumulation at day 7. AR inhibition was confirmed by significant dose-dependent reductions in whole blood sorbitol in SAD and MAD up to approximately -50 % change from baseline in SAD and days 1 and 7 of MAD vs a -3% change in Pbo ($p<0.05$ for all doses vs placebo). Maximum inhibition occurred between 2-4 h.

Conclusions: AT-001 improved selectivity and affinity for AR has resulted in potent AR inhibition within a favorable safe dosing range. These findings support further investigation of the therapeutic potential of AT-001 in subjects with Diabetic Cardiomyopathy.

Introduction

Diabetic Cardiomyopathy (DbCM) affects 18-24% of people with type 2 diabetes (T2D)[1,2] and currently lacks any approved therapies. Hyperactivation of the polyol pathway is a key underlying mechanism in DbCM and other diabetic complications. In hyperglycemic and ischemic conditions, polyol pathway activation causes intracellular sorbitol accumulation leading to osmotic stress, cell death and diabetic complications.[3-4] Previous clinical investigations of AR inhibitors for diabetic complications were associated with off-target toxic effects and/or lack of efficacy due to lack of selectivity and specificity.[4] Elevation of liver enzymes and/or abnormal renal function were often observed with previous AR inhibitors. We designed a series of novel AR inhibitors based on characterization of AR structural changes within the active site following enzymatic activation. These compounds display enhanced specificity, affinity and selectivity compared with previous AR inhibitors that were associated with off-target effects and/or lack of efficacy. Here, we describe the safety, PK and efficacy of AT-001, in clinical development for DbCM.

Study Objectives and Overview of Protocol and Procedures

Study Objectives

- Evaluate the safety and tolerability of single and multiple doses of AT-001 in adults with type 2 diabetes (T2D)
- Assess the pharmacokinetics (PK) of a range of AT-001 doses
- Confirm potency of AT-001 by assessing reduction in sorbitol levels, a pharmacodynamic biomarker of aldose reductase inhibition
- Determine relationship between AT-001 exposure and pharmacodynamic effects

Overview

- Two-part phase 1-2 study comprised of sequential, escalating single doses of AT-001 5, 10, 20 and 40 mg/kg with safety review prior to advancing to each higher dose and 7-day multiple ascending doses (MAD) of AT-001 5, 20, 40 mg/kg once daily (QD) or 20 mg/kg twice daily (BID)

Subjects

- Adult subjects age 18-70 years, HbA1c ≥5.5 and <8.5%

Key Features of Study Design and Assessments

- SAD
  - Single ascending doses of AT-001 5, 10, 20 and 40 mg/kg or placebo administered orally in 4 sequential dose cohorts of n=8 active : n=2 placebo
  - Safety review prior to escalation to each higher dose
- MAD
  - Multiple doses of AT-001 5, 20, 40 mg/kg QD, 20 mg/kg BID or placebo administered orally for 7 days in 4 sequential dose cohorts of n=8 active : n=2 placebo
- Assessments (SAD and MAD)
  - Safety: Adverse events, clinical labs, ECG, vital signs
  - Pharmacokinetics (PK)
  - Pharmacodynamic/efficacy: whole blood sorbitol to assess aldose reductase inhibition

Subject Disposition

- SAD: 40 subjects enrolled and completed
- MAD: 40 subjects enrolled and 39* completed

* Non-completer withdrew from the study for a non-drug related reason

Demographics

Table 1A. Baseline Characteristics: SAD

		Placebo (N=8)	5 mg/kg (N=8)	10 mg/kg (N=8)	20 mg/kg (N=8)	40 mg/kg (N=8)	Total (N=40)
Age, years*		52.0 (3.5)	52.1 (2.0)	48.3 (5.9)	47.8 (4.3)	48.1 (6.5)	49.7 (4.9)
Sex, n (%)	Male	5 (62.5)	2 (25.0)	7 (87.5)	4 (50.0)	5 (62.5)	23 (57.5)
	Female	3 (37.5)	6 (75.0)	1 (12.5)	4 (50.0)	3 (37.5)	17 (42.5)
Race, n (%)	African American	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	1 (12.5)	9 (22.5)
	White	6 (75.0)	7 (87.5)	4 (50.0)	7 (87.5)	7 (87.5)	31 (77.5)
Weight (kg)		82.8 (10.7)	75.5 (11.2)	92.0 (14.1)	78.5(12.0)	85 (12.2)	82.8 (12.8)
BMI (kg/m^2)		29.9 (2.3)	28.6 (1.4)	29.2 (2.6)	29.6 (2.6)	30.2 (2.7)	29.5 (2.3)
HbA1c (%)		7.3 (0.5)	7.7 (0.7)	7.2 (0.8)	7.3 (1.0)	6.3 (1.2)	7.2 (0.9)

*Mean (SD) unless otherwise noted

Table 1B. Baseline Characteristics: MAD

		Placebo (N=8)	5 mg/kg (N=8)	20 mg/kg (N=8)	40 mg/kg (N=8)	20 mg/kg BID (N=8)	Total (N=40)
Age, Years*		52.9 (5.4)	48.9 (5.0)	51.5 (13.2)	51.4 (8.9)	61.8 (6.6)	53.3 (9.1)
Sex, n (%)	Male	6 (75.0)	4 (50.0)	4 (50.0)	1 (12.5)	4 (50.0)	19 (47.5)
	Female	2 (25.0)	4 (50.0)	4 (50.0)	7 (87.5)	4 (50.0)	21 (52.5)
Race, n (%)	African American	4 (50.0)	3 (37.5)	2 (25.0)	4 (50.0)	3 (37.5)	16 (40.0)
	White	4 (50.0)	5 (62.5)	6 (75.0)	4 (50.0)	5 (62.5)	24 (60.0)
Weight (kg)		76.7 (15.9)	85.2 (17.4)	79.2 (15.0)	93.2 (11.1)	76.9 (14.5)	82.3 (15.5)
BMI (kg/m^2)		28.4 (3.2)	29.1 (3.4)	29.2 (3.3)	29.9 (3.9)	29.2 (4.1)	29.2 (3.4)
HbA1c (%)		6.6 (0.9)	6.6 (1.2)	6.1 (0.7)	7.1 (0.8)	7.4 (0.7)	6.8 (1.0)

*Mean (SD) unless otherwise noted

Safety

Overall, AT-001 was well tolerated in both SAD and MAD: No treatment emergent AEs or SAEs were observed. No treatment-related discontinuations occurred. No abnormalities in liver or kidney function were observed. Safety summary for SAD is shown in **Table 2A** and for MAD in **Table 2B**.

Table 2A Treatment-emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population (SAD)

System Organ Class Preferred Term	Placebo N=8	5mg/kg N=8	10mg/kg N=8	20mg/kg N=8	40mg/kg N=8	Overall N=40
Any Adverse Event	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	2 (5.0)
Any SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.5)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.5)
Impaired gastric emptying*	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.5)
Nervous system disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Headache	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)

*AE of impaired gastric emptying was reported as an SAE, moderate intensity

Safety (Continued)

Table 2B Treatment-emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Population (MAD)

System Organ Class Preferred Term	Placebo QD/BID N=8	5mg/kg QD N=8	20mg/kg QD N=8	40mg/kg QD N=8	20mg/kg BID N=8	Overall N=40
Any Adverse Event	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	2 (12.5)	4 (7.5)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.5)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.5)
Musculoskeletal and Connective Tissue Disorders	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Back Pain	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (12.5)	2 (5.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.5)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0) 0	1 (2.5)

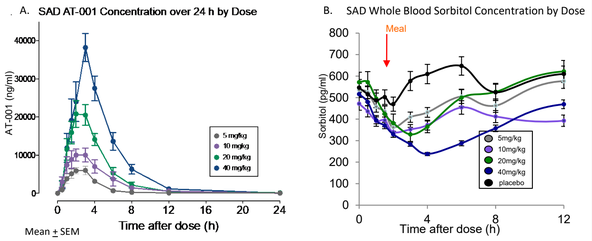
BID=twice per day; QD=daily

Summary of Pharmacokinetic & Pharmacodynamic Findings

- Median time of the maximum concentration (Tmax) was between 1.75 to 3 hours in both SAD and MAD and $T_{1/2}$ ranged between 1.74-3.38 hours across all SAD and MAD cohorts
- Maximal systemic exposure determined from individual concentration-time data (Cmax) and the area under the curve from time time-zero to infinity (AUC0-inf) increased in a dose proportional manner in SAD and MAD
- There was no evidence of accumulation over 7 days in MAD
- Pharmacodynamic effects on sorbitol reduction lasted 10-12 hours post dose, demonstrating extended effect of the drug beyond the half-life of the drug; suggested to be due to reversible covalent binding of AT-001 within the active site of the enzyme

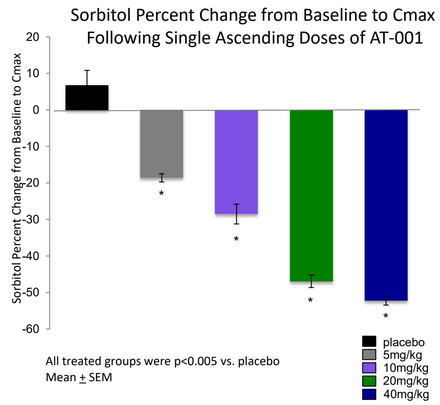
Pharmacokinetic/Pharmacodynamic Results: SAD

Figure 1. A. AT-001 Concentration over 24 h in SAD
B. Sorbitol levels over 12 h post -dose



Note rise in sorbitol in placebo group at ~2h (red arrow) reflects the effect of food intake (AR activation in response to post prandial glucose elevations) and it is blunted by AT-001 in patients

Figure 2. Whole blood sorbitol percent change from baseline at the time of maximum AT-001 exposure (Cmax)



Pharmacokinetic/Pharmacodynamic Results: MAD

Figure 3. AT-001 concentration and sorbitol levels over 24 h on Day 1 (A&B) and Day 7 (C&D) of MAD

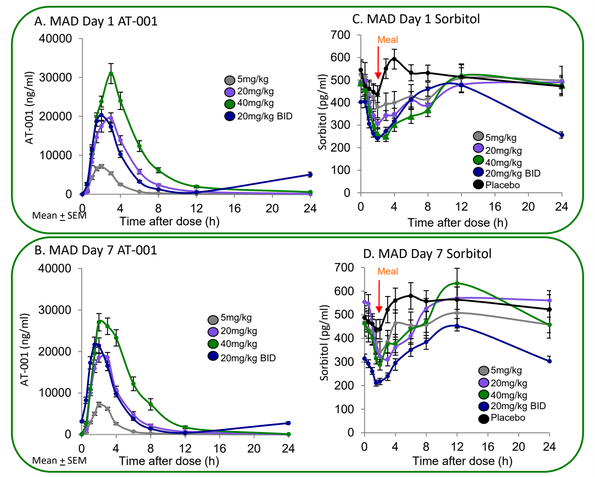
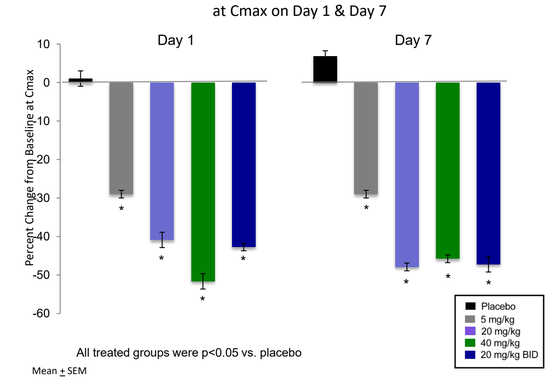


Figure 4. Sorbitol percent change from baseline at individual time of maximum exposure (Cmax) on Day 1 and Day 7 of MAD



Summary

- Single and multiple ascending doses were well-tolerated with no safety concerns identified
- AT-001 produced robust, dose-dependent reductions in sorbitol, demonstrating potent enzyme inhibition
- Sorbitol inhibition lasted approximately 10-12 hours from dosing
- AT-001 prevented post-prandial increase in sorbitol due to transient glucose elevations at meal time in all treated patients

Conclusions

- AT-001 improved selectivity and affinity for AR has resulted in potent AR inhibition within a favorable safe dosing range
- These findings support further investigation of the therapeutic potential of AT-001 in subjects with DbCM

References

1. Dandamundi S, et al. . J Card Fail. 2014;20(5):304-9
2. Miki T, et al. Hear Failure Rev 2013;18:149-166
3. Parim B, et al Heart Failure Rev 2019:24:279-299
4. Grewal AS, et al. Min Rev Med Chem 2016; 16:120-62