# Safety and proof of biological activity support clinical development of AT-001 for Diabetic Cardiomyopathy: A phase 1/2 study

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## ABSTRACT

**Background:** Diabetic Cardiomyopathy (DbCM) is a highly prevalent complication of diabetes with no specific approved therapies[1]. Hyperactivation of the polyol pathway contributes to development of diabetic complications.[2] Aldose reductase (AR) is the rate-controlling enzyme in the polyol pathway that catalyzes NADPH-dependent reduction of glucose to sorbitol. In hyperglycemic and ischemic conditions, AR activation causes intracellular sorbitol accumulation, consequent changes in NAD+/NADH, oxidative stress, cell death and diabetic complications.[3-4] We designed a series of novel AR inhibitors, including AT-001, 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.
**Methods and Results:** AT-001 safety, pharmacokinetics (PK) and efficacy were assessed in a phase 1/2 placebo controlled study comprised of single oral ascending doses (SAD, n=8 per group) of 5, 10, 20 and 40 mg/kg once daily (QD) and multiple doses (MAD) of AT-001 5, 20, 40 mg/kg QD or 20 mg/kg twice daily (BID) for 7 days. Subjects with type 2 diabetes, age 18-75 and HbA1c 5.0-8.5% were allocated to each dose cohort (n=8 AT-001, n=2 Pbo). AT-001 was well-tolerated with no drug-related AEs or changes in liver or renal function. Mean half-life (T½) 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% reduction from baseline in SAD and days 1 and 7 of MAD vs. a 3% change in Pbo ($p<0.05$ for all doses vs. Pbo). Maximum inhibition occurred between 2-4 h and lasted for several hours afterword.

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

## OBJECTIVES

- To assess the safety and tolerability of single (SAD) and multiple (MAD) ascending doses of AT-001 in subjects with type 2 diabetes
- To confirm target engagement by assessing the impact of AT-001 sorbitol levels
- To determine the relationship between AT-001 exposure and pharmacodynamic effects

## METHODS

**Design:** Two-part single (SAD) and multiple ascending dose (MAD) controlled trial. In SAD 40 subjects were allocated to receive 5, 10, 20 or 40 mg/kg or placebo oral doses of AT-001 in sequential cohorts of active (n=8) and placebo (n=2). In MAD 40 subjects were allocated to 5, 20 or 40 mg/kg once daily, 20 mg/kg twice daily (BID) or placebo for 7days in sequential ascending cohorts of 8 active:2 placebo. Safety parameters were assessed between each escalating dose in both SAD and MAD.
**Assessments:** Safety, vital signs, ECG, clinical labs, drug exposure and whole blood sorbitol
**Subjects:** Men and non-pregnant, non-lactating women with type 2 diabetes mellitus (T2DM), 18-70 years of age, with glycosylated hemoglobin (HbA1c) levels ≥5% and <8.5%).

## RESULTS

**Table 1. Subject Characteristics (Mean±SD)**

| | Sex (M/F) | Age (y) | Weight (kg) | HbA1c (%) | FPG mg/dL |
|---|---|---|---|---|---|
| **SAD** | 23/17 | 50±5 | 83±13 | 7.2±1.0 | 155±71 |
| **MAD** | 21/19 | 53±9 | 82±16 | 6.8±1.0 | 127±38 |

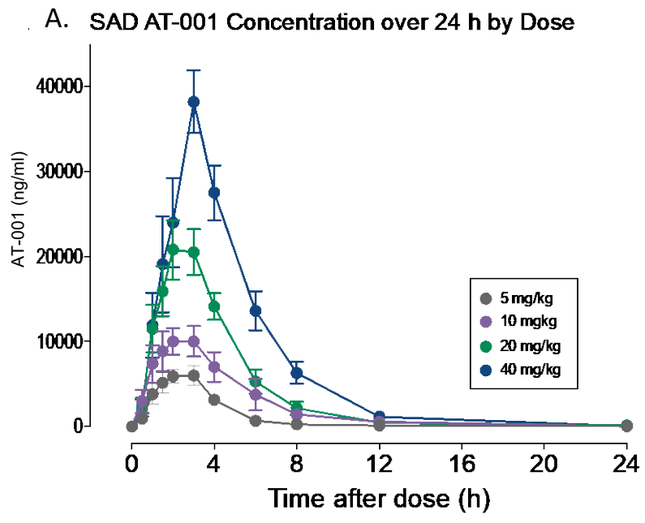
**Safety**
AT-001 was well-tolerated with no drug-related adverse events (AE) or serious AEs (SAE) and no discontinuations due to AEs. In SAD there was one AE headache (5 mg/kg) and one SAE, not drug-related, of impaired gastric emptying (20 mg/kg). In MAD there were no SAEs and a total of 4 AEs in 3 subjects (7.5%) were reported: flatulence and headache in a subject in the 20 mg/kg BID group, one AE of back pain in placebo, and one AE of presyncope in 40 mg/kg. All AEs were mild to moderate severity and resolved without sequelae. No clinically significant changes in vital signs, clinical chemistry, or ECG were observed in SAD or MAD.

**Pharmacokinetics (PK)**
The median time of maximum concentration (Tmax) was between 1.75 to 3 h and half-life ranged between 1.74-3.38 hours in both SAD and MAD. The maximal and systemic exposure increased in a dose proportional manner in SAD, as well as in MAD cohorts on Days 1 and 7. No accumulation of AT-001 in plasma following administration of daily doses for 7 days was noted in MAD.

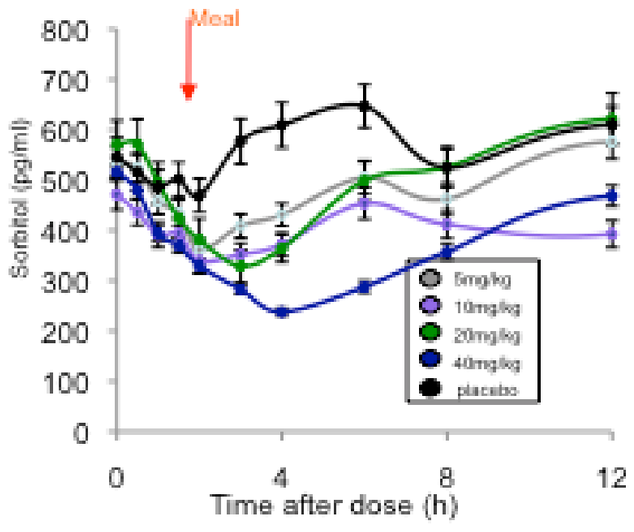
## SINGLE ASCENDING DOSE

**Figure 1: Exposure over 24 hours (A) and dose-dependent reductions in sorbitol (B) over 12 h**

A. SAD AT-001 Concentration over 24 h by Dose




B. SAD Sorbitol Concentration over 12 h by Dose




## MULTIPLE ASCENDING DOSE

**Figure 2: Exposure (A&B) and whole blood sorbitol (C&D) on Day 1 and Day 7 of multiple ascending AT-001 doses**

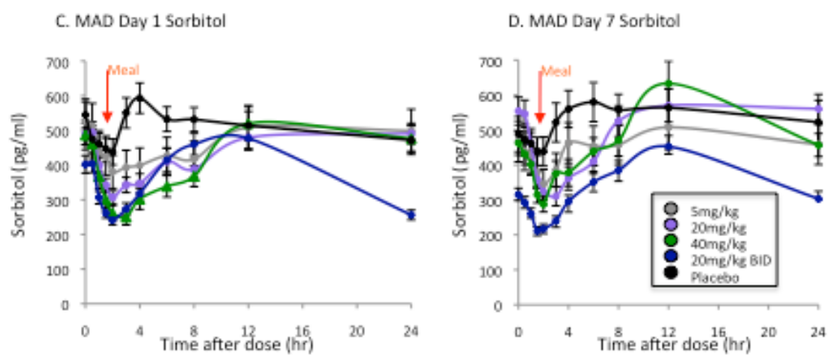
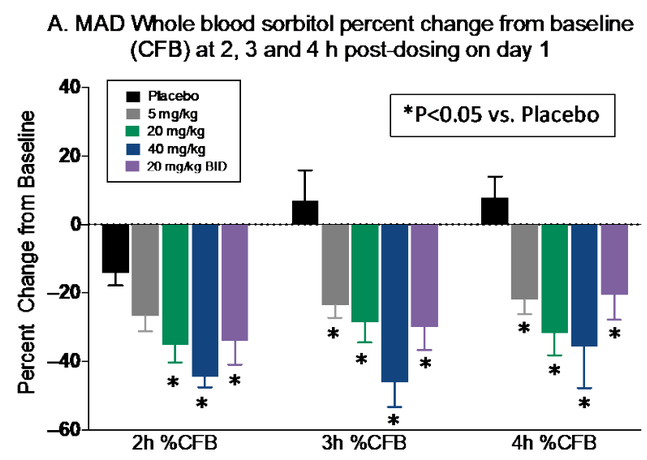
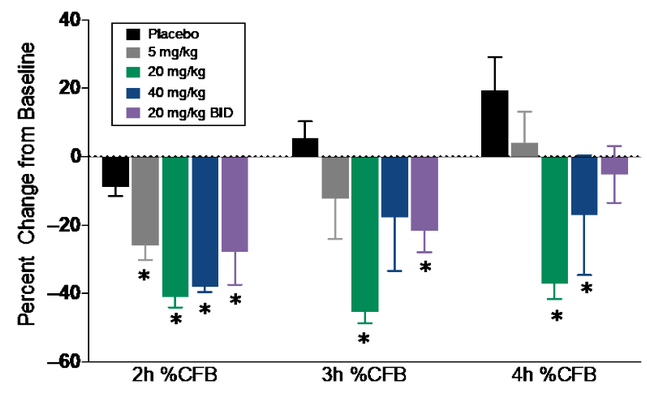



**Figure 3: Dose-dependent reductions in sorbitol at 2, 3 and 4 h post-dose on Days 1 (A) and 7 (B)**
Decreases from baseline in mean (±SEM) sorbitol were observed for AT-001 doses vs. Placebo on Days 1 and 7.

A. MAD Whole blood sorbitol percent change from baseline (CFB) at 2, 3 and 4 h post-dosing on day 1




B. MAD Whole blood sorbitol percent change from baseline (CFB) at 2, 3 and 4 h post-dosing on day 7




## CONCLUSIONS

- AT-001 was safe and well-tolerated at all doses tested
- Target engagement was confirmed by potent AR inhibition as evidenced by significant reductions in sorbitol persisting for several hours post-dose
- These findings support further clinical investigation of AT-001 in DbCM

## REFERENCES

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## DISCLOSURE OF INTEREST

R. Perfetti, P. Rowell and S. Shendelman are employees of Applied Therapeutics. R. Perfetti and S. Shendelman are stockholders in Applied Therapeutics.