Clinical Assessment of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy: a 28 day proof of concept study

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Abstract

Clinical Assessment of AT-001, an Aldose Reductase Inhibitor in Development for Diabetic Cardiomyopathy: a 28 day proof of concept study

Diabetes is an independent risk factor for heart disease and Diabetic Cardiomyopathy (DbCM) has been associated with the development of heart failure. Epidemiological studies have demonstrated that even in the absence of ischemia, dyslipidemia, or valvular disease, patients with diabetes may manifest morphological and functional changes of the myocardium. This cardiac dysfunction is often accompanied by low level elevations of N-terminal pro-B-type Natiuretic Peptide (NT-proBNP), a recognized marker of heart disease. While NT-proBNP is a biomarker used at high levels (>300pg/ml) to diagnose overt heart failure, low level elevations (10-300pg/ml) have been shown to precede progression to overt HF and are predictive of long term outcomes in DbCM patients. In a 28-day proof of concept study in patients with T2D, we investigated the ability of AT-001, a novel inhibitor of aldose reductase, to normalize the intracellular utilization of glucose by inhibiting its aberrant metabolism to sorbitol, and to reduce NT-proBNP levels.

Results: T2D adult patients (age 18-75, HbA1c 5.0-8.5%) with early DbCM were treated with AT-001, a novel potent ARI, for 28 days in a Phase 2a study. Patients received AT-001 3000mg/day dosed as 1000mg three times daily capsule (TID) or 1500mg twice daily capsule (BID) vs. placebo (n=8 per group). AT-001 potently inhibited AR, resulting in significant reduction in blood sorbitol levels, sustained over 28 days. AT-001 was well tolerated with no SAEs and no dose limiting AEs reported over 28 days. Treatment with AT-001 at 1000mg TID and 1500mg BID significantly reduced NT-proBNP levels over 28 days vs. placebo. 50% of AT-001 treated patients showed a clinically meaningful reduction in NT-proBNP at 28 days, defined as >25 pg/mL reduction from baseline.

Conclusions: In the present study, AT-001 prevented sorbitol production by AR, a potential pathogenic mechanism in DbCM. The exploratory measurement of changes in NT-proBNP showed that in many patients the normalization of sorbitol was associated with a lowering of NT-proBNP. These findings support further investigation of the therapeutic potential of AT-001 in subjects with DbCM.

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 biological activity 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
- Evaluate changes in NT- proBNP, a biomarker for Heart Failure, in a 28 day 2 dose (BID/TID) study

Overview

- Two-part phase 1-2 study comprised of sequential, escalating single doses of AT-001: 5, 10, 20 and 40 mg/kg. 7-day multiple ascending doses (MAD) of AT-001: 5, 20, 40 mg/kg once daily (QD) or 20 mg/kg twice daily (BID)
- A 28 day safety, tolerability and PK, study comparing AT-001 at 1000 mg TID and 1500 mg BID, with an exploratory assessment of NT-proBNP levels

Subjects

- Adult subjects age 18-75 years, HbA1c ≥5.5% and <8.5%

Key Features of Study Design and Assessments

- Single Ascending Dose Study (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
- Multiple Ascending Dose Study (MAD)
  - Multiple doses of AT-001 5, 20, 40 mg/kg QD, 20 mg/kg BID or placebo (administered QD or BID) orally for 7 days in 4 sequential dose cohorts of n=8 active : n=2 placebo
- Proof Of Concept Study (POC)
  - Placebo vs 1000mg AT-001 TID vs 1500mg AT-001 BID (22 patients total*: 18 active, 4 placebo)
- Assessments Safety: Adverse events, clinical labs, ECG, vital signs
  - Pharmacokinetics (PK)
  - Pharmacodynamic/efficacy: whole blood sorbitol to assess aldose reductase inhibition
  - NT-proBNP change from screening to day 28

* in the POC study more patients were recruited than originally planned (25 actively treated and 5 placebo)

Subject Disposition

- SAD study: 40 subjects enrolled and completed
- MAD study: 40 subjects enrolled and 39* completed
- POC study : 30 subjects treated with two doses AT-001 and placebo

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

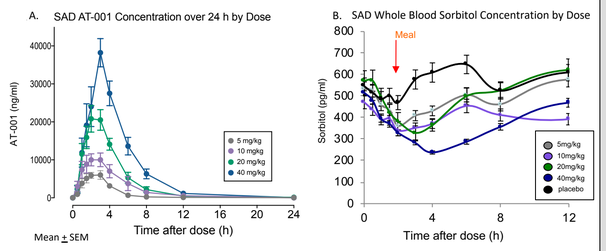
Safety

Overall, AT-001 was well tolerated in all studies conducted to date

- No treatment emergent AEs or SAEs were observed
- No treatment-related discontinuations occurred
- No EKG changes observed
- No abnormalities in liver or kidney function were observed

Pharmacokinetic/Pharmacodynamic Results 1: 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

Pharmacokinetic/Pharmacodynamic Results 2: MAD

Figure 2. **AT-001 concentration and sorbitol levels over 24 h on Day 1 (A&B) and Day 7 (C&D) of MAD**

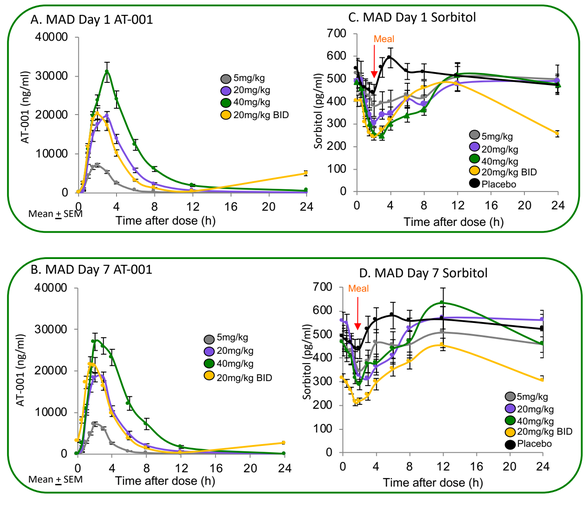
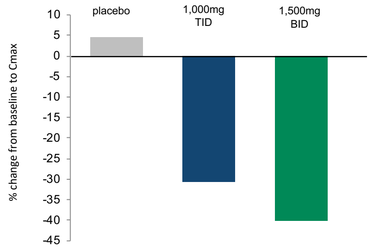


Figure 3. **Plasma sorbitol reductions observed at 28 days treatment with AT-001: 1000mg/TID and 1500mg/BID**



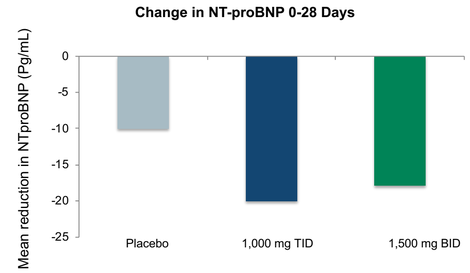
Summary of Pharmacokinetic & Pharmacodynamic Findings

- 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

NT-proBNP Results: POC study

Figure 4. **NT-proBNP Changes Observed Over 28 day treatment with AT-001 – Placebo vs BID vs TID Dosing Study**

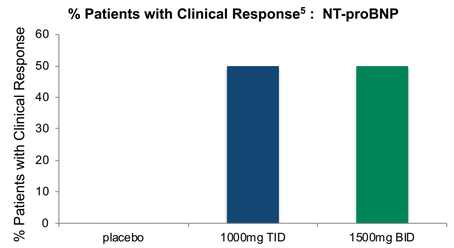
NT-proBNP levels were evaluated at patient screening and at 28 days in patients treated with placebo (N=5), AT-001, 1000mg TID (N=10), 1500mg BID (N=10)



NT-proBNP Results: Responder Analysis:

Figure 5. **Responder Analysis: Study Subjects with > 25pg/ml decrease[5] in plasma NT-proBNP after day 28**

- NT-proBNP baseline range: 30-235pg/ml
- NT-proBNP mean at baseline: 65pg/ml



Clinical response defined as >25 pg/ml reduction in plasma NT-proBNP after day 28[5].

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
- Mean decreased levels of NT-proBNP were observed after 28 days in the two doses of AT-001 evaluated
- Approximately 50% of patients treated with AT-001 showed a response a >25 pg/ml decrease in NT-proBNP after 28 days treatment

Conclusions

- AT-001 improved selectivity and affinity for AR has resulted in potent AR inhibition within a favorable safe dosing range
- Observed reductions in sorbitol and NT-proBNP with AT-001 support further investigation of the therapeutic potential of this novel agent in subjects with DbCM

References

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