Diabetic Cardiomyopathy (DbCM) leading to overt heart failure is a common sequela of both Type 1 and Type 2 Diabetes. Previous attempts to develop treatments for DbCM through inhibition of the enzyme Aldose Reductase (AR) were unsuccessful, due to unfavorable drug-gastring and poor selectivity for Aldose Reductase (AldR). The unique structural and activity of AT-001 provide selectivity for Aldose Reductase and lack of off target activity.

Methods and Results: AT-001 was evaluated for AR binding affinity as compared to zopolrestat, a 1st generation ARI. AT-001 demonstrated a 300-fold greater affinity for AR versus zopolrestat (Kp of 30 pm for AT-001 and 10 nm for zopolrestat). In contrast to zopolrestat, AT-001 showed no inhibition of AR at 50x and 100x IC50 levels in assay medium, while zopolrestat inhibited Aldose Reductase by 50% and 60% respectively (active site of 2.3 and 3.5 nm NADPH/micron/mg protein). In addition to these analyses, AT-001 was evaluated in a standard off target receptor binding analysis of 87 substrates (16 enzymes, 74 binding assays) to characterize pharmacological specificity and selectivity. No significant off-target effects (defined as >50% inhibition activity) were observed in this panel.

Conclusion: The unique structure and activity of AT-001 provide selectivity for Aldose Reductase and lack of off-target effects. The in vivo safety of this agent together with the positive safety data from the phase 1/2 program, supports the ongoing pivotal study in DbCM.

Diabetic Cardiomyopathy (DbCM)1

- Abnormal cardiac structure and/or performance
- Resulting from diabetes-associated metabolic alterations
- In the absence of coronary artery disease (CAD) as well as hypertension, valvular or congenital heart disorder
- Progresses to overt heart failure (HF)2,3

Pathogenesis of DbCM & Hyperactivation of Polyol Pathway1,2

AT-001 - A Next Generation Highly Selective Aldose Reductase Inhibitor for Treatment of Diabetic Cardiomyopathy

AT-001: Increased Affinity for Aldose Reductase vs. Zopolrestat

No AT-001 Off-Target Binding

Zopolrestat (But Not AT-001) Inhibits AldhReductase

AT-001 Pre-clinical and Clinical Profile Summary

- First generation Aldose Reductase inhibitor (zopolrestat) demonstrated clinical efficacy in Diabetic Cardiomyopathy
- Hepatotoxicity was observed in the development program (presumably due to off target competitive binding with AldhReductase in liver)
- Clinical development was discontinued

Conclusions
- AT-001 is logarithmically more potent than zopolrestat in inhibiting AldhReductase
- The unique structure and activity of AT-001 provide selectivity for Aldose Reductase and avoid off-target inhibition of AldhReductase
- The in vitro safety of this agent together with the positive safety data from the phase 1/2 program, support the ongoing pivotal study in DbCM