Overcoming the Safety Challenges of Aldose Reductase Inhibition: Development of AT-001 for Diabetic Cardiomyopathy

APPLIED THERAPEUTICS

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Disclosures

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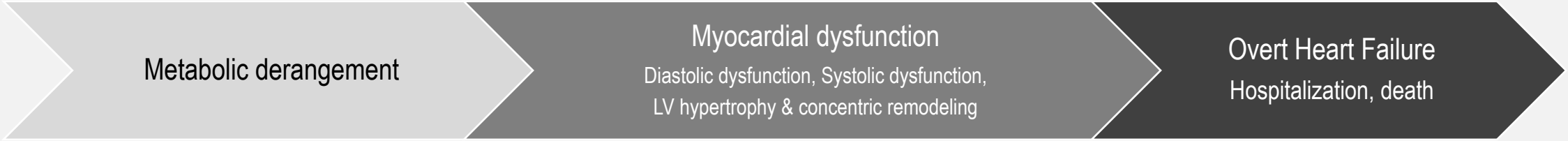
Definition of Diabetic Cardiomyopathy (DbCM)[1]

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



1. Ryden L Eur Heart J. 2013; *34*:3035–3087. 2. Jia G, et al. Circ Res. 2018;122:624-638. 3. Borghetti et al. Frontiers in physiology 2018;9:1514

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Diabetic Cardiomyopathy as a Form of Stage B Heart Failure[1-4]

Stage of Heart Failure		Functional Capacity (Peak VO2)	Cardiac Stress Biomarker (NT-proBNP)
Diabetes Stage A	• Metabolic derangement of the myocardium due to diabetes	~28 ml/kg/min	0-5 pg/ml (normal range)
DbCM Stage B	• Cardiac structural abnormalities • Diastolic dysfunction; LVH • Reduced activity level • Decreased functional capacity	~25% decrease ≤20 ml/kg/min	~ 6-300 pg/ml
Stage C	• Overt Heart Failure • HFpEF or HFrEF • Significant impact on daily activities	>30% decrease 10-15 ml/kg/min	~ 300 – 5,000 pg/ml
Stage D	• Refractory Heart Failure requiring specialized interventions (e.g. LV Assist Device) • Inability to complete daily activities	• ~24% of DbCM patients progress to overt heart failure or death within 1.5 years[3] • 37% within 5 years[4]	> 5,000 pg/ml

LVH left ventricular hypertrophy, DbCM diabetic cardiomyopathy, HFpEF heart failure with preserved ejection fraction, HErEF heart failure with reduced ejection fraction

1. Kosmala et al, J Am Coll Cardiol 2015;65:257–66.; 2. Swank et al. Circ HF 2012; 3. Wang et al. JACC: Cardiovasc Imaging 2018; 4. From et al. JACC 2010

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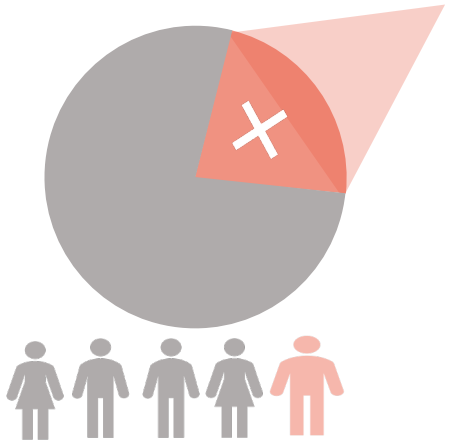
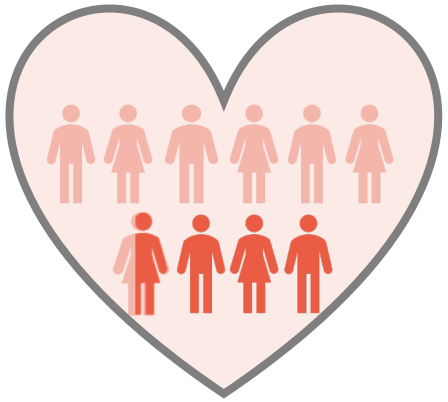
Diabetic Cardiomyopathy: A High Unmet Medical Need



Approximately, **17-24%** of patients with diabetes have DbCM in the absence of other forms of heart disease. [1,2]

~77 M patients worldwide have DbCM[3]

- ~ 8.0M in North America
- ~ 10.0M in Europe



- ~24% of DbCM patients progress to overt heart failure or death within **1.5 years**[4]
- 37% within 5 years[5]

- Patients with diabetes are counseled on HF risk reduction:
  - Lifestyle modification
  - Hypertension
  - Dyslipidemia
  - Hyperglycemia
  - Albuminuria

No Treatment for DbCM

- No therapies target the metabolic derangement responsible for DbCM and subsequent worsening to overt HF
- Heart Failure treatment is only initiated upon onset of clinical symptomatology (stage C heart failure)

1. Dandamudi et al. J Card Fail. 2014;20(5):304-309. 2. Pham et al. Intl J Endocrinology 3. International Diabetes Foundation, 2017,4. Wang et al. JACC: Cardiovasc Imaging 2018; 5. From et al. JACC 2010

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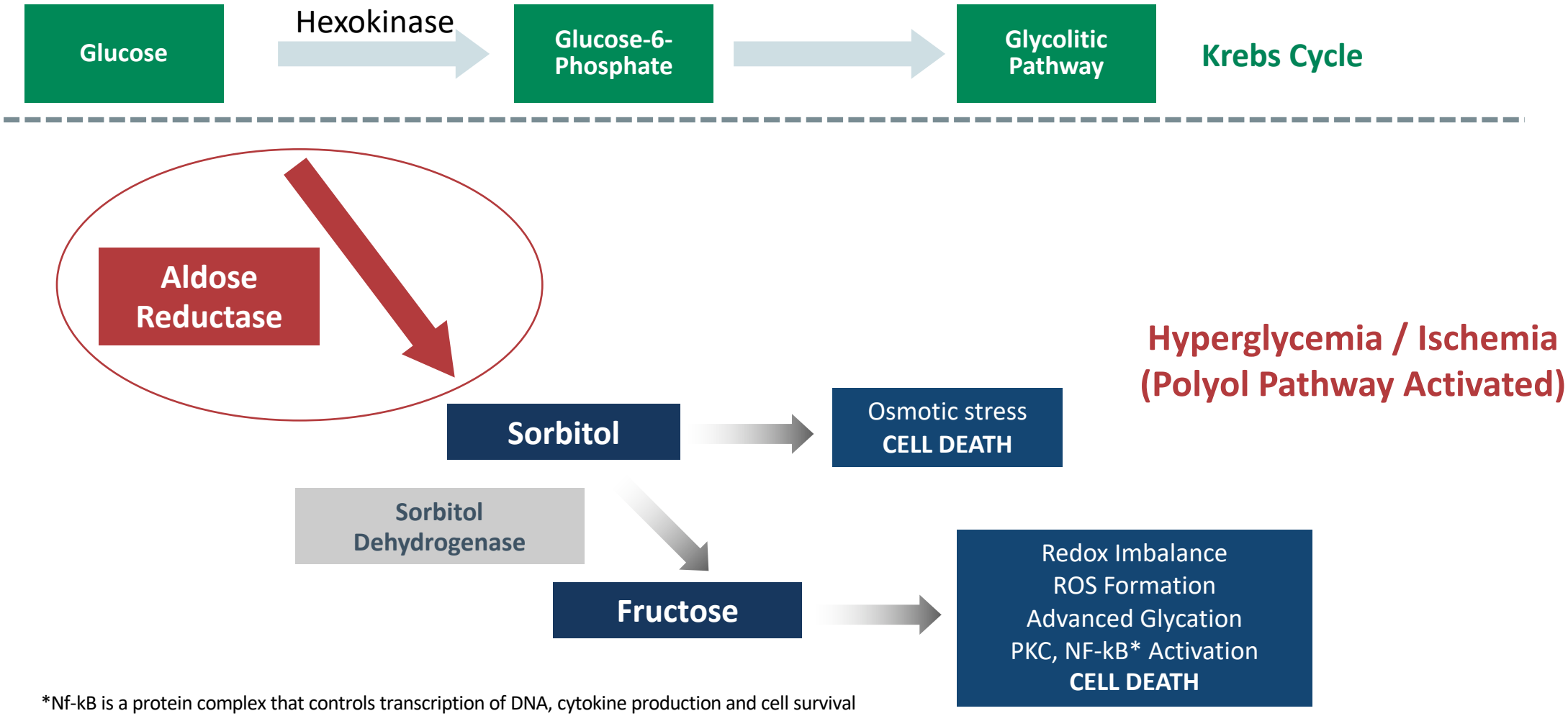
Pathogenesis of DbCM & Hyperactivation of Polyol Pathway[1,2]



*Nf-kB is a protein complex that controls transcription of DNA, cytokine production and cell survival

1. Brownlee M. Diabetes Care. 2005;54(6):1615-1625. 2. Miki T, et al. Heart Fail Rev. 2013;18(2):149-166.

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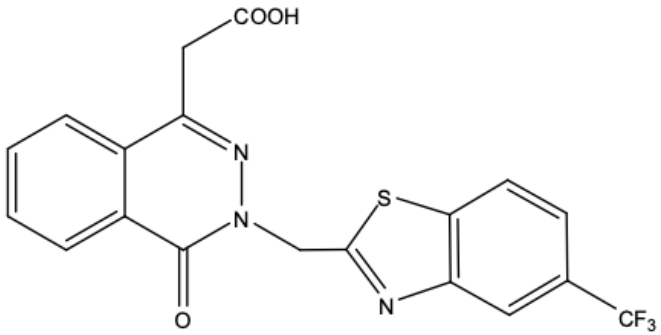
First Generation Aldose Reductase Inhibitor Zopolrestat (Pfizer)

zopolrestat



Inhibition of Aldose Reductase → **Clinical Efficacy**

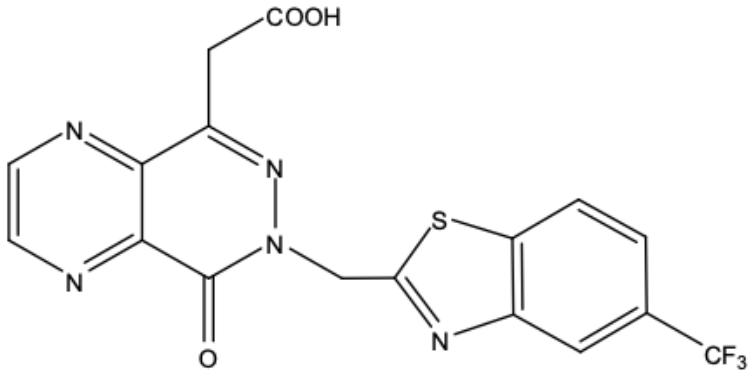
Competitive Inhibition of Aldehyde Reductase → **(Off-Target) Hepatotoxicity**

- First generation Aldose Reductase Inhibitor (zopolrestat) demonstrated clinical efficacy in Diabetic Cardiomyopathy[1]
- Hepatotoxicity was observed in the development program (presumably due to off target competitive binding with Aldehyde Reductase in liver)
- Clinical development was discontinued

[1]Johnson, et al. Diabetes Care, 2004 pp 448-454

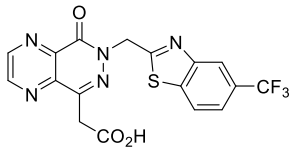
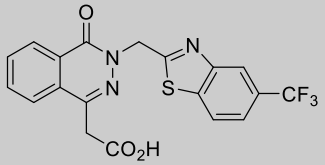
AT-001: A Next Generation Highly Selective Aldose Reductase Inhibitor for Treatment of Diabetic Cardiomyopathy

AT-001



- AT-001 was developed through rational drug design, using the geometric parameters of the active site of the Aldose Reductase enzyme determined via X-ray crystallography.
- Optimal target selectivity for Aldose Reductase and minimization of potential off-target activity with Aldehyde Reductase was achieved.
- Aldehyde Reductase plays an important role in detoxification mechanisms in the liver. Minimization of off-target activity is critical to ensure safety.

AT-001 Increased Affinity for Aldose Reductase vs. Zopolrestat

Compound	Structure	IC_{50}	MTD in animals	Tissue Penetration (in rats)			
				Systemic/ Heart	Nerve	Retina	CNS
AT-001		30pM	>2,000mg/kg	✓	✓	✓	X
zopolrestat		10nM	100mg/kg	✓	✓	X	X

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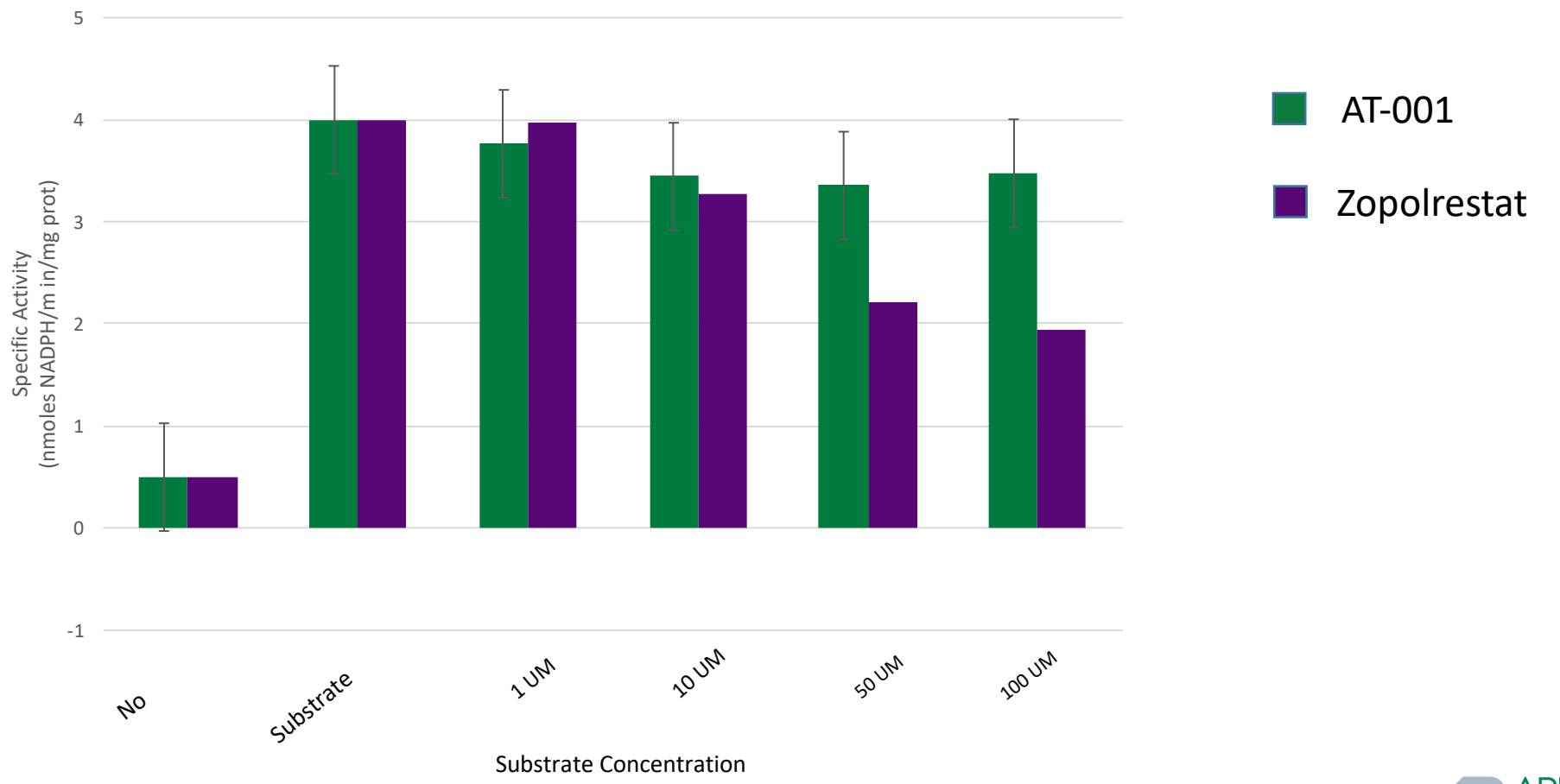
No AT-001 Off-Target Binding

- Eurofins Panlabs Safety Screen Panel (consisting of 87 primary molecular targets including 13 enzyme and 74 binding assays) was used to evaluate potential off target binding activity of AT-001
- No off-target binding activity (defined as ≥50% inhibition or stimulation for biochemical assays) was observed

Zopolrestat (But Not AT-001) Inhibits Aldehyde Reductase



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Conclusions

- AT-001 is logarithmically more potent than zopolrestat in inhibiting Aldose Reductase
- The unique structure and activity of AT-001 provide selectivity for Aldose Reductase and avoid off-target inhibition of Aldehyde Reductase
- 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