CORPORATE OVERVIEW OCTOBER 2019

APPLIED THERAPEUTICS

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Investment Highlights

2 Pivotal programs in high unmet need indications with near-term readouts

- Galactosemia 2019
- Diabetic Cardiomyopathy 2021

Distinct late-stage commercial opportunities

- Galactosemia - easily commercialized orphan indication based on biomarker data
- Diabetic Cardiomyopathy - potential blockbuster indication supported by deep science

Reproducible discovery and development strategy

- Early stage pipeline in orphan oncology indications targeting PI3k

Our mission is to create transformative, life-changing treatments for patients who desperately need them

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Applying Science to Transform Lives

High Unmet Need Indications	Validated Molecular Targets	Verification via Biomarkers
Fatal or debilitating diseases with no approved therapies Abbreviated regulatory pathways decrease development cost and time Limited/ no competition	Targeting pathways with known roles in pathogenesis Building on prior knowledge limits MOA risk Novel compounds with improved potency/selectivity	Clinical efficacy confirmed via biomarkers in first- in-human studies De-risks and lessens burden of clinical development

We develop drugs quickly at a lower cost:
A significant benefit to patients in need of treatment

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Pipeline

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing Route	Target Tissue	Anticipated Milestones
Aldose Reductase Franchise							
AT-001	Diabetic Cardiomyopathy				Oral	Systemic	Ph 3 trial initiated in Q3 2019; data in 2021
AT-001	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	
AT-001	Acute Myocardial Infarction				SC*	Systemic / Peripheral Nerve	
AT-007	Galactosemia				Oral	CNS	Biomarker data in 4Q 2019
AT-003	Diabetic Retinopathy				Oral	Retina	Preclinical data 2019; Initiate Ph 1 2020
PI3 Kinase Franchise							
AT-104	PTCL, CTCL, TALL**				SC / Oral	Selective δ/γ inhibitor	Initiate Ph 1 2020

* Subcutaneous
** Peripheral T-cell lymphoma, cutaneous T-cell lymphoma and T-cell acute lymphoblastic leukemia

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Unlocking the Potential of Aldose Reductase Inhibition

Validated Target Resistant to Therapeutic Development	• AR known to play a key role in diabetic complications and heart disease • Past efforts failed to produce sufficiently potent, selective and tolerable drugs
Recent Advances Enable Improved ARI's	• New understanding of structural changes within the active site of AR following enzymatic activation – Novel structures; all drugs are new chemical entities • Increased potency and selectivity compared to prior compounds with none of the prior off-target safety issues to date
R&D and Regulatory Opportunities	• High unmet need in numerous AR-mediated diseases • Leverage prior ARI programs for streamlined, abbreviated development of our novel compounds • Potential to utilize regulatory pathways designed for accelerated drug development

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AT-007 for Galactosemia

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AT-007 for Galactosemia

Pathogenesis of Disease

- Rare genetic metabolic disease caused by inability to break down galactose
- Galactose is a sugar produced naturally by the body
- **Aldose Reductase converts galactose to galactitol, a toxic metabolite**
- Clinical presentation:
  - Significant CNS complications - motor, speech, cognitive, and psychiatric impairments, tremor, and seizures
  - Cataracts
  - Ovarian insufficiency in females

Standard of Care

- Mandatory newborn screening and initiation of dairy free diet; dietary restriction prevents fatalities, but **does not prevent long term consequences of disease**
- No approved therapies

Galactosemia Commercial Opportunity

- **Easily identifiable patients & substantial population**
- Newborn screening and patient registry
- “Low Prevalence” but not ultra-rare
  - ~2,800 US patients; ~3,500 patients in Europe
  - ~80 new births per year in the US; more in Europe
- **Low burden of development due to biomarker-based program under new FDA guidance**
- **Opportunity to launch quickly with high market penetration**
  - >90% patients seen by ~20 specialists worldwide
  - High prescriber awareness of Applied clinical development program

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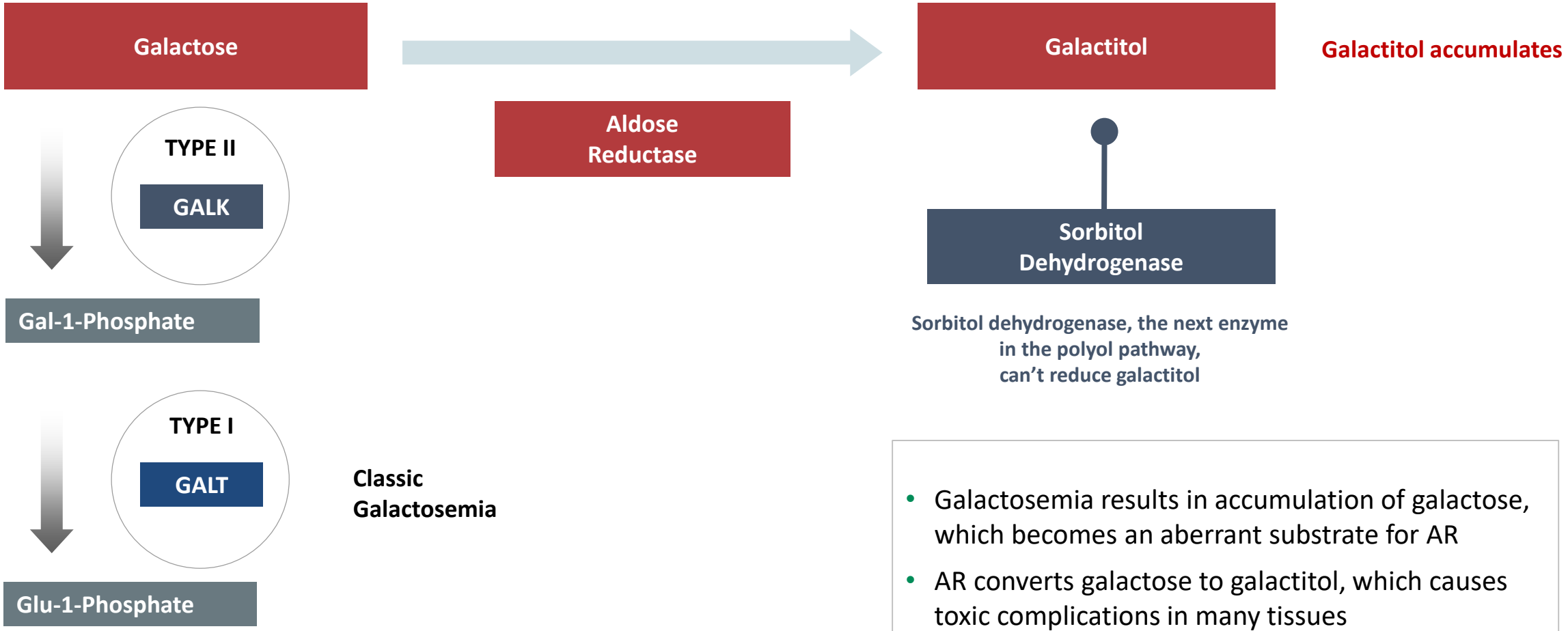
Aldose Reductase Activity Causes Toxic Accumulation of Galactitol in Galactosemia



- Galactosemia results in accumulation of galactose, which becomes an aberrant substrate for AR
- AR converts galactose to galactitol, which causes toxic complications in many tissues

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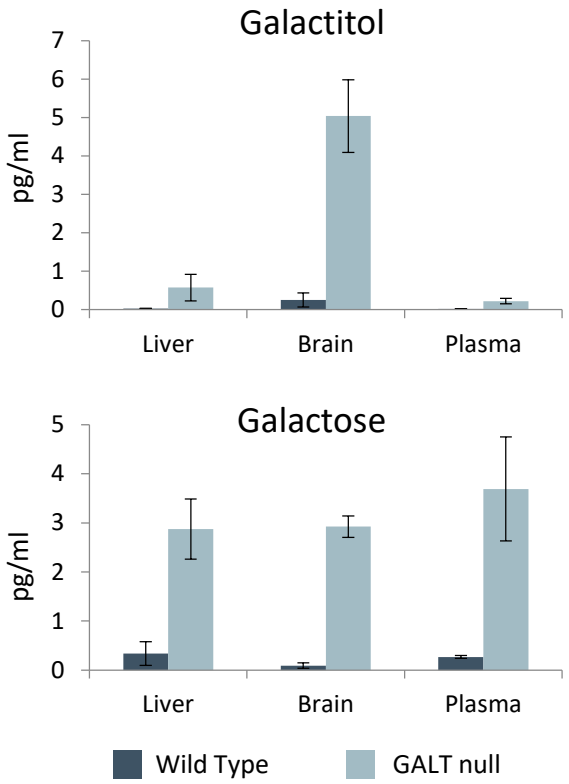
GALT Deficient Rat Model Closely Mirrors Human Disease

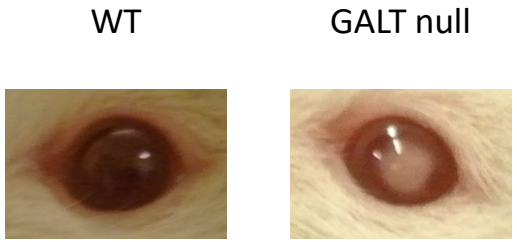
Biochemical Effects

GALT null rats have exponentially higher levels of galactose and galactitol, as well as Gal1p



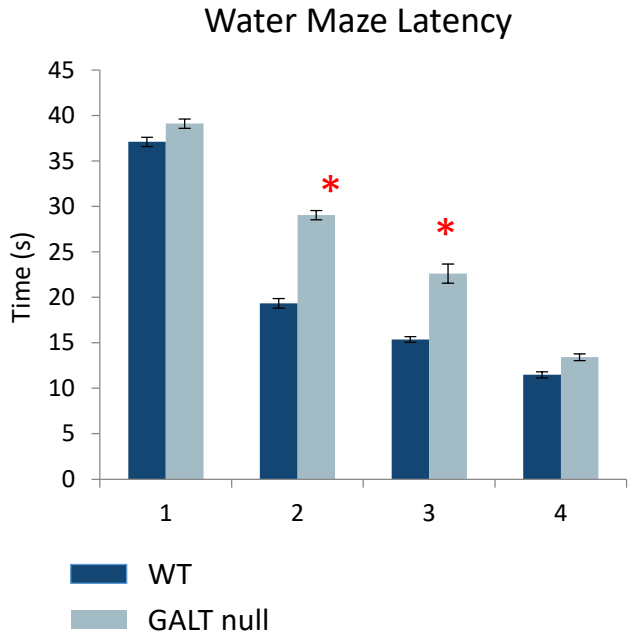
Tissue Deposition of Galactitol

All GALT null rats display cataracts (caused by galactitol deposition in the eye) vs. none of the WT rats



CNS Outcomes

GALT null rats display deficiencies in learning, cognition, and motor skills as measured by rotarod and water maze



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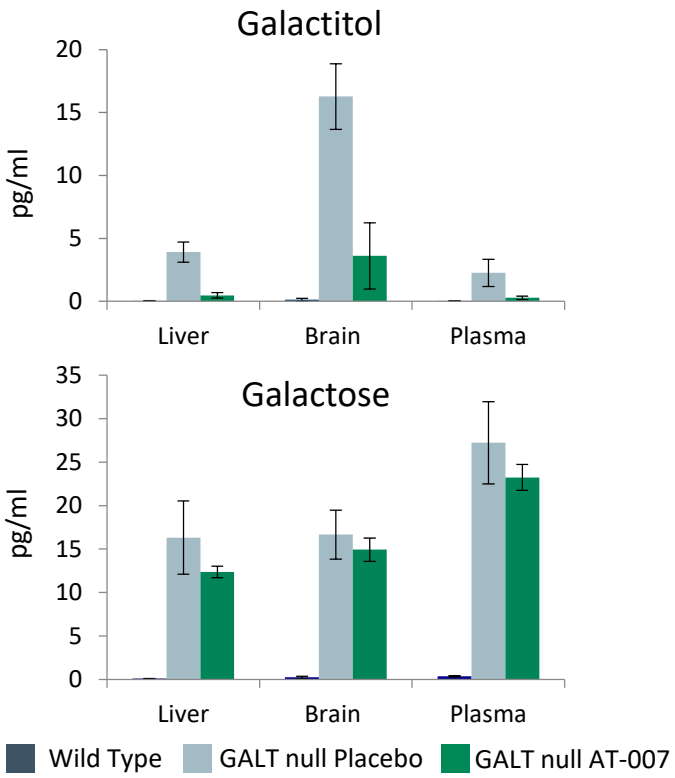
AT-007 Treatment Corrects All 3 Aspects of Disease in the Galactosemia Rat Model

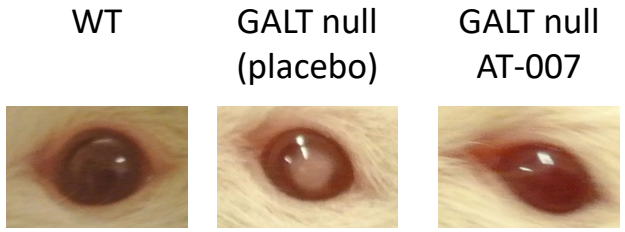
Biochemical Effects

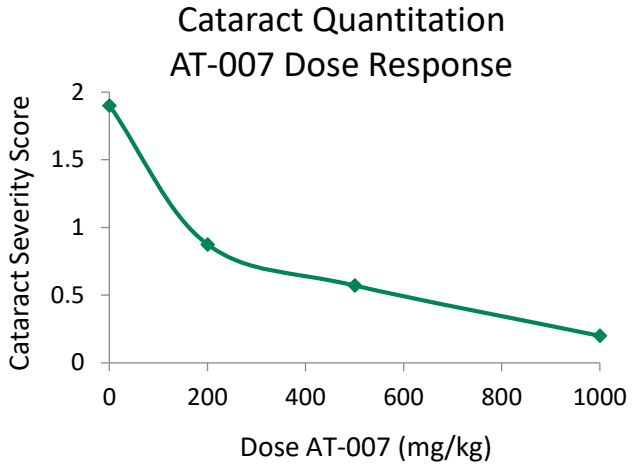
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



Tissue Deposition of Galactitol

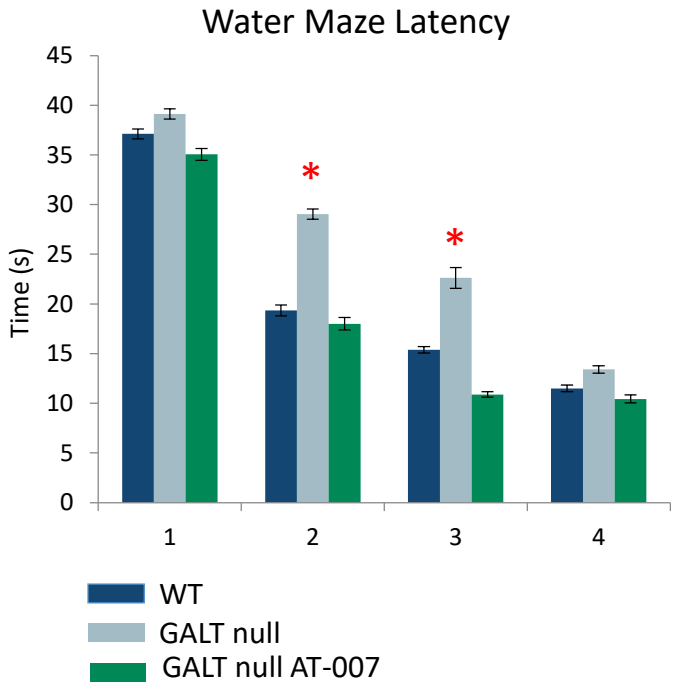
AT-007 treatment prevented galactitol accumulation in tissues, resulting in absence of cataracts





CNS Outcomes

AT-007 treatment normalized CNS outcomes on both water maze and rotarod



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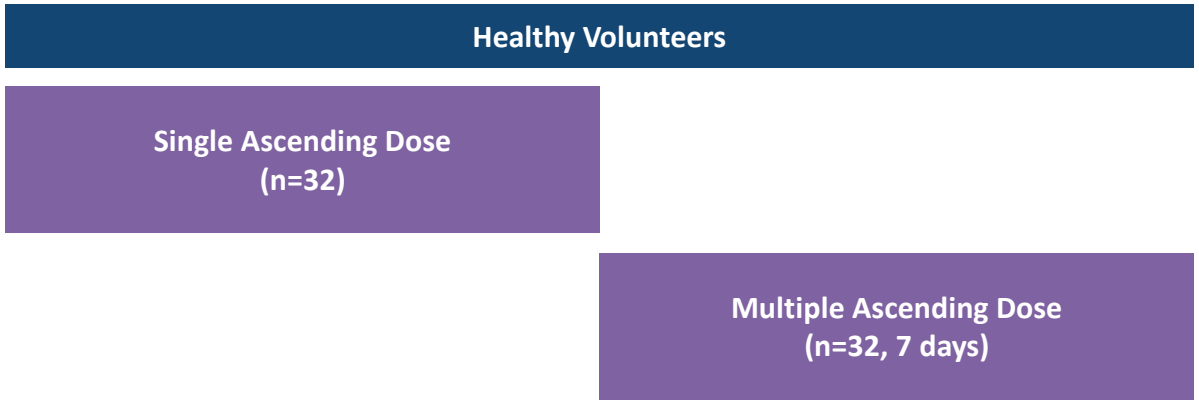
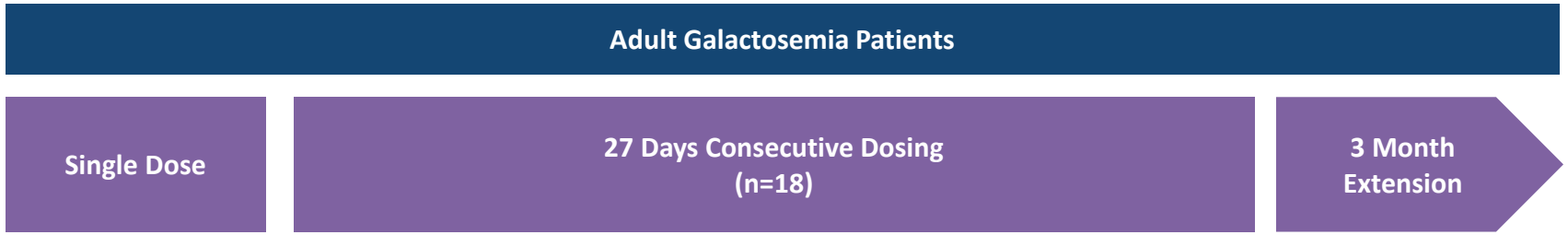
Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients



Healthy Volunteer Endpoints:

- Safety
- Pharmacokinetics
- Pharmacodynamics



Galactosemia Endpoints:

- Safety
- Pharmacokinetics/Pharmacodynamics
- **Efficacy Biomarker - Galactitol**

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Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients

Healthy Volunteers

Single Ascending Dose (n=32)

Multiple Ascending Dose (n=32, 7 days)

Healthy Single Ascending Dose Results:

No drug-related safety issues at any dose tested

Dosing: 0.5, 5.0, 10, 20mg/kg

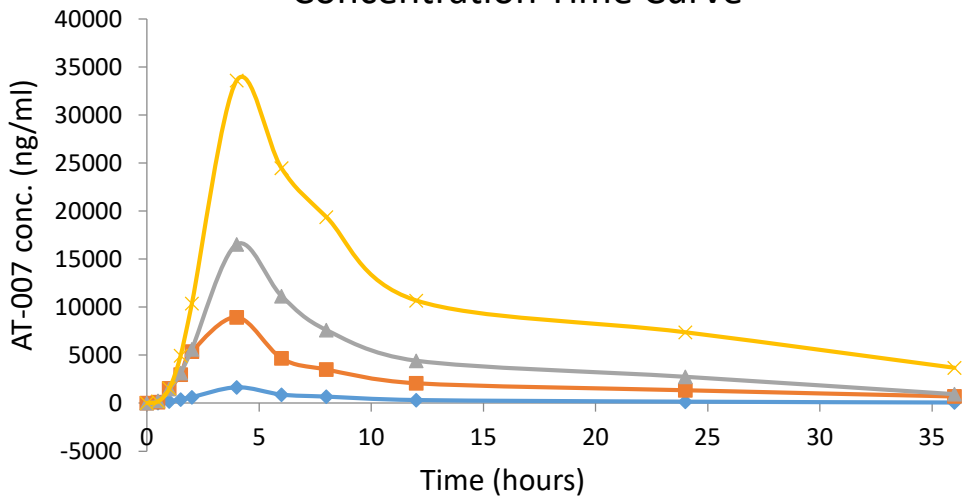
PK consistent with once daily dosing

(half-life ~12 hours)

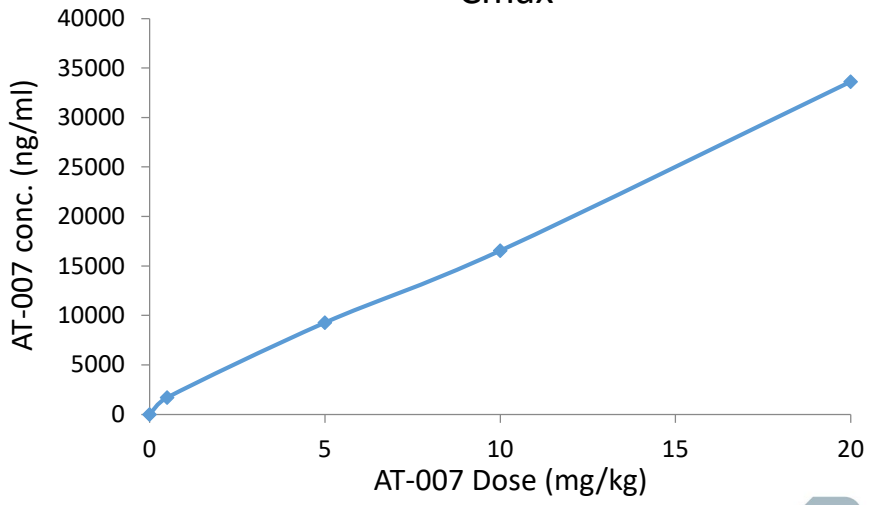
Consistent exposure across patients

Linear dose response

Concentration Time Curve



Cmax



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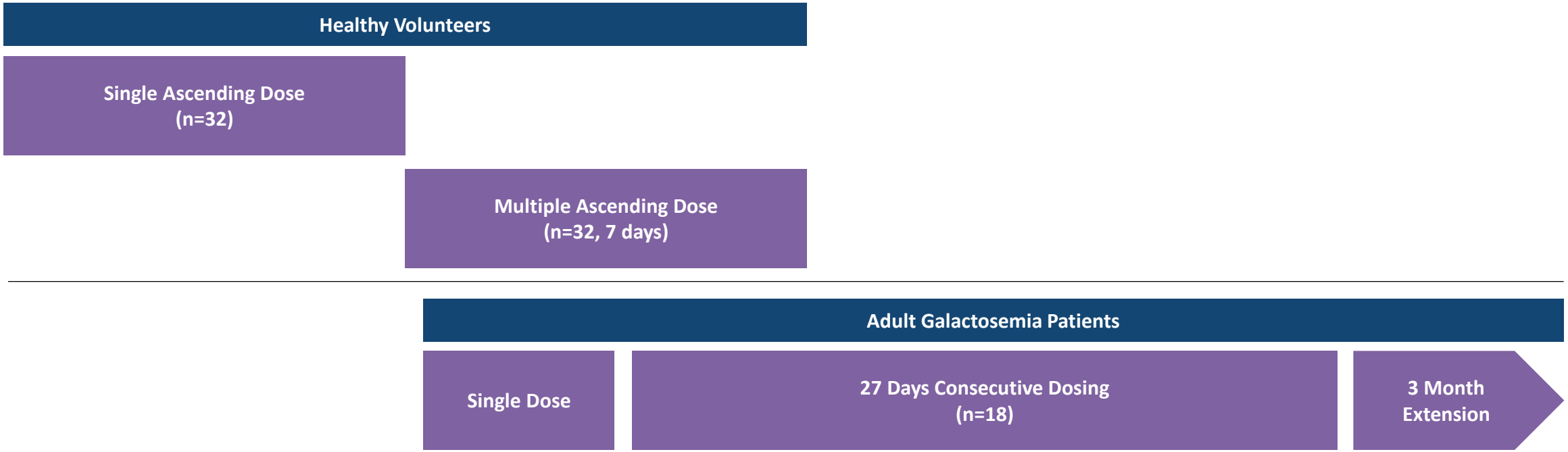
Galactosemia Phase 1/2 Registrational Study (ACTION-Galactosemia)

Multi-Center Placebo-Controlled Study in Healthy Volunteers & Adult Galactosemia Patients



Galactosemia Endpoints:

- Safety
- Pharmacokinetics/Pharmacodynamics
- **Efficacy Biomarker - Galactitol**

*Data from the adult Galactosemia patient portion of the trial expected in **4Q 2019***

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AT-007: Oral CNS Penetrant Aldose Reductase Inhibitor

Drug Profile	• Structurally distinct molecule with potent AR inhibition and unique PK profile • Exposure to all Galactosemia target tissues – CNS, nerve and retina penetrant • Oral once-daily dosing (half life 12-18 hrs)
Safety	• No drug-related safety or tolerability issues in Phase 1 healthy volunteer study (SAD) • No safety issues in newborn rat treatment studies, supporting eventual infant/pediatric use
Path to Registration	• Prevented complications of disease in Galactosemia rat model • Biomarker effects correlate with clinical endpoints • Did not increase galactose levels or levels of other galactose metabolites (Gal1P) • Ongoing biomarker-based study in adults with Classic Galactosemia to read out 4Q 2019 • Pediatric study to follow

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AT-001 for Diabetic Cardiomyopathy

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AT-001 for Diabetic Cardiomyopathy

Pathogenesis of Disease

- Fatal fibrosis of the heart; cardiac tissue “hardens” and limits contractility
- Caused by aberrant metabolism of glucose to sorbitol in cardiomyocytes (by Aldose Reductase)
- Affects 17-24% of diabetics (77M patients worldwide)
- Occurs in both Type 1 and Type 2 diabetes

Standard of Care

- No treatments exist for DbCM
- Patients are counseled on glucose control and lifestyle

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DbCM Commercial Opportunity: Blockbuster Potential with Limited Capital Requirement

Regulatory	Commercial Market	Point of Care
• Clear path to registration based on functional capacity endpoint (exercise tolerance) • Single Phase 3 trial required	• 10M patients in the US; 77M worldwide • Sufficiently narrow heart failure population - can be targeted with limited commercial investment • High disease awareness	• Easily diagnosed and tracked by cardiologists (echo) • Easily identified for referral- endocrinologists/PCPs can identify probable patients through a simple blood test (NTproBNP cardiac stress biomarker)

Strong Rationale for AT-001 Development in Diabetic Cardiomyopathy: First-in-Class Potential

Building on Prior Body of Evidence

- The role of AR in DbCM is well supported by preclinical and clinical evidence
- Proof of mechanism: Pfizer's zopolrestat achieved proof-of-concept on LVEF in Phase 2 Diabetic Cardiomyopathy trial

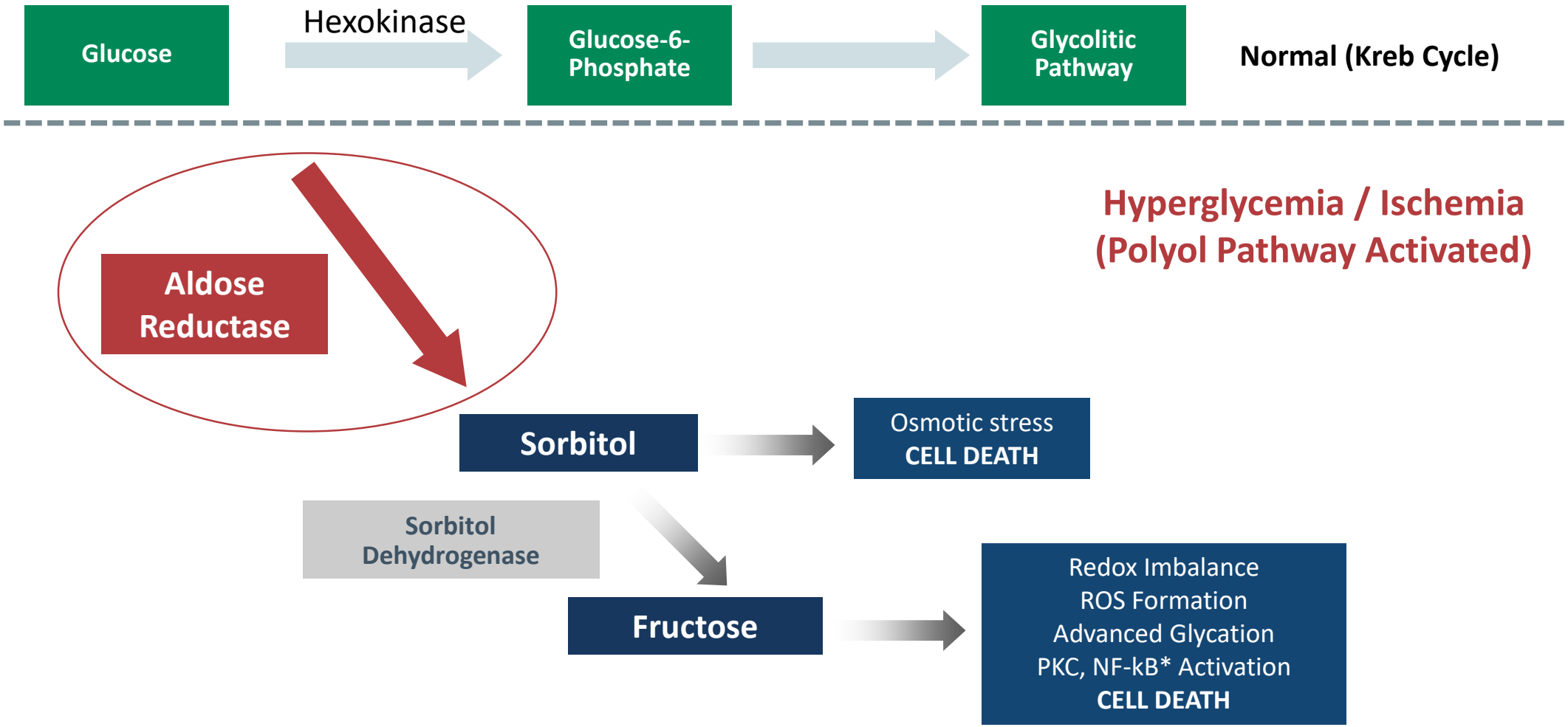
AT-001's Robust Pre-Clinical Profile

- 1,000X more potent than prior best-in-class ARI (zopolrestat), in vitro and in vivo
- Broad exposure: Cardiac and nerve tissue
- Highly favorable preclinical profile: MTD>2,000mg/kg

AT-001's Robust Clinical Profile (Ph 1/2 trial)

- Clinical proof-of-concept via sorbitol biomarker observed in T2D patients
- No drug related AEs observed at any dose; well tolerated
- Heart inflammatory biomarkers in 28 day arm in DbCM patients informed dose selection for pivotal study

Aldose Reductase Causes Damage to Tissues (Including Cardiomyocytes) Under Oxidative Stress



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

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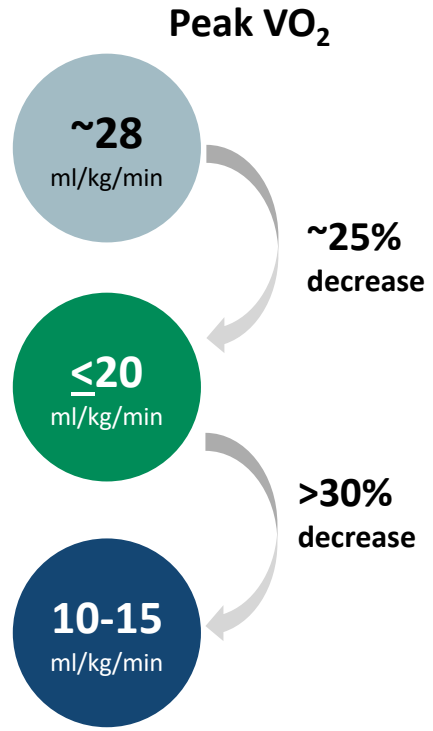
Understanding Diabetic Cardiomyopathy as a Form of Heart Failure

Diabetes **Stage A Heart Failure**	• Metabolic derangement of the myocardium due to diabetes
DbCM **Stage B Heart Failure**	• Cardiac structural abnormalities • Diastolic dysfunction; LVH • Early symptoms of DbCM; noticeable impact on activities • Decreased exercise capacity (~75% normal)
Stage C Heart Failure	• Overt Heart Failure • HFpEF or HFrEF • Significant impact on daily activities
Stage D Heart Failure	• 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
- 37% within 5 years

References: Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: Cardiovasc Imaging 2018; From et al. JACC 2010

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AT-001 Phase 1/2 Trial in Type 2 Diabetic Patients

Parts A & B

Design

- 80 Type 2 Diabetic Patients
- All patients remained on concomitant meds
- 40 patients in SAD – (5, 10, 20, 40mg/kg)
- 40 patients in MAD – (5, 20, 40mg/kg; 20mg/kg BID)
- 8 drug treated & 2 placebo in each cohort

Results

- No drug-related AEs in entire study (up to 7 days treatment)
- No abnormal labs
- Normalization of sorbitol (PD biomarker)

Part C

Design

- 30 DbCM patients
- 10 patients per cohort (8 drug treated, 2 placebo)
  - Placebo
  - 1,500mg BID
  - 1,000mg TID

Results

- No drug-related AEs in entire study (up to 28 days treatment)
- No drug-related lab abnormalities
- Effect on cardiac biomarker NTproBNP

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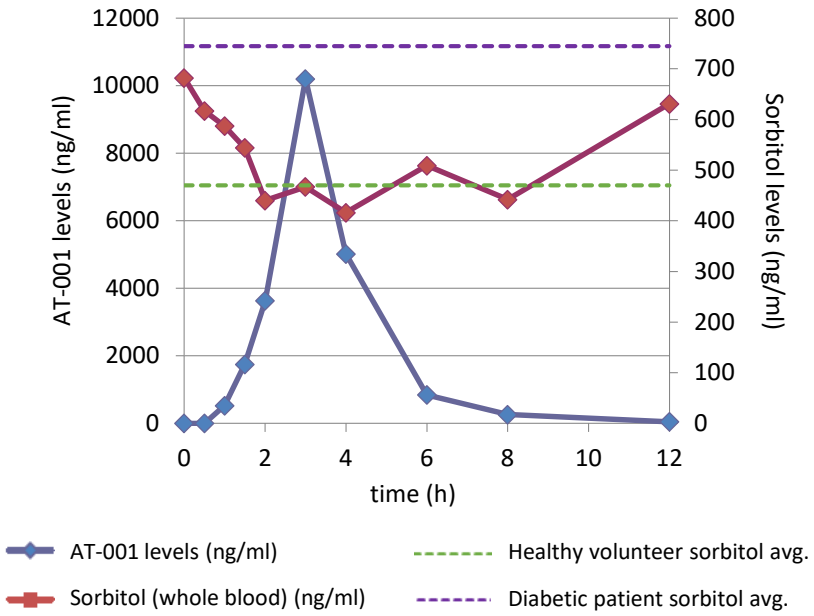
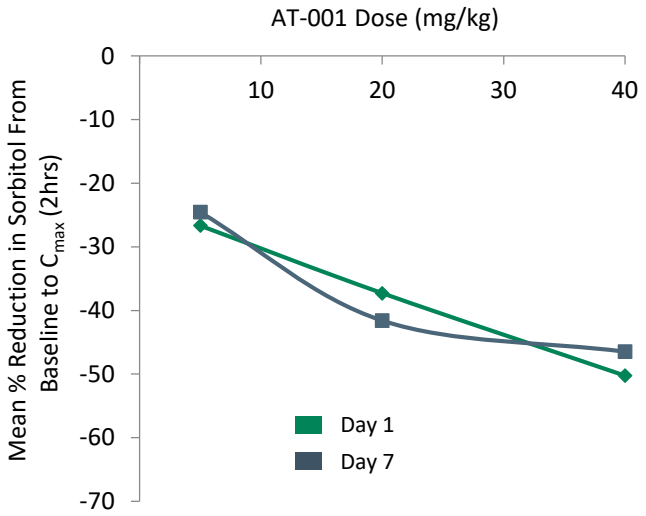
AT-001 Normalizes Sorbitol, a Biomarker of AR Activity, in Diabetic Patients

Proof of Biological Activity



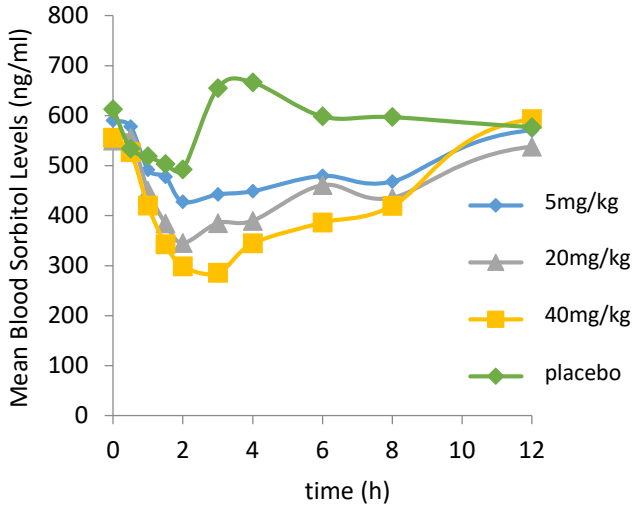
- Drug treatment with AT-001 normalized sorbitol to healthy volunteer levels

Sorbitol Reduction by Dose



- Mean reduction in sorbitol at Day 1 and Day 7: Results are persistent over 1 week of treatment
- At 40mg/kg patients were normalized to healthy volunteer sorbitol levels, demonstrating complete AR inhibition

Sorbitol Normalization Over Time



- Rapid release capsule provides sorbitol normalization effects (PD biomarker) through 10-12hrs post-dose at >10mg/kg
- Includes protection from food-related sorbitol spikes during times of post-prandial hyperglycemia

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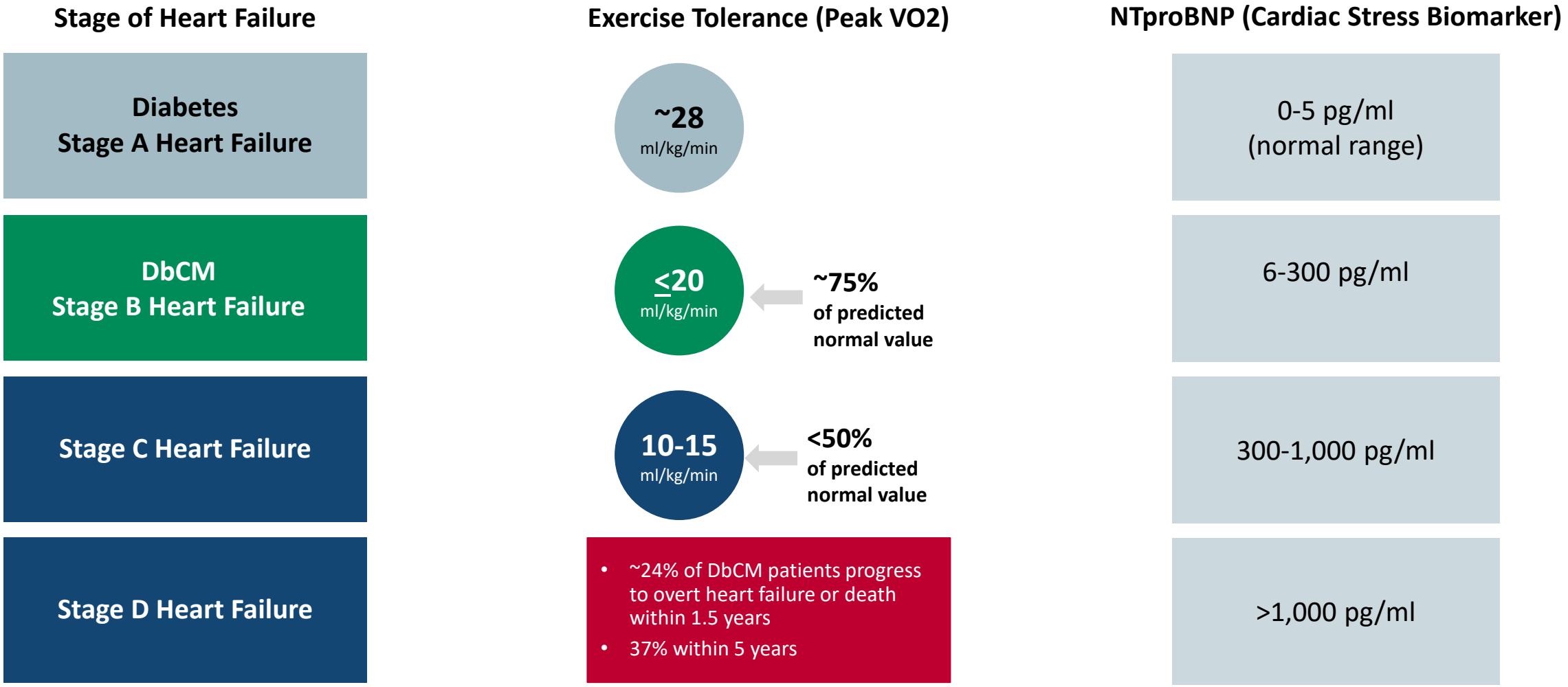
NTproBNP Levels are Elevated in DbCM Patients (Blood-based cardiac stress biomarker)



References: Kosmala et al, JACC V O L . 6 5 , NO . 3 , 20 1 5; Swank et al. Circ HF 2012; Wang et al. JACC: Cardiovasc Imaging 2018; From et al. JACC 2010

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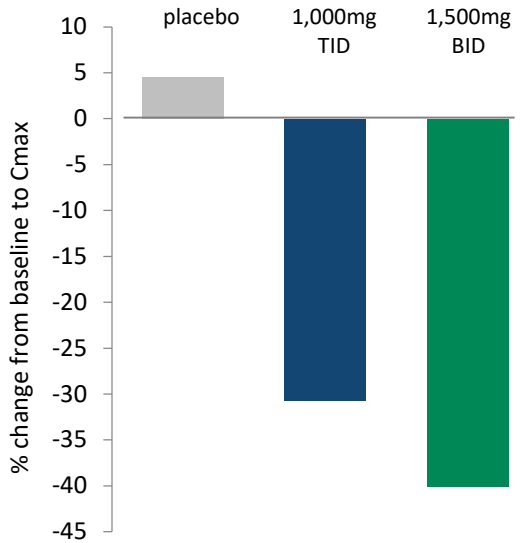
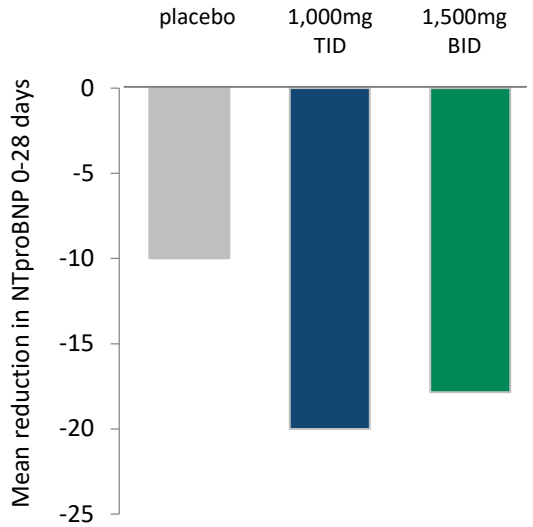
AT-001 Reduced Levels of NTproBNP Cardiac Stress Biomarker Over 28 Days of Treatment

Sorbitol Normalization



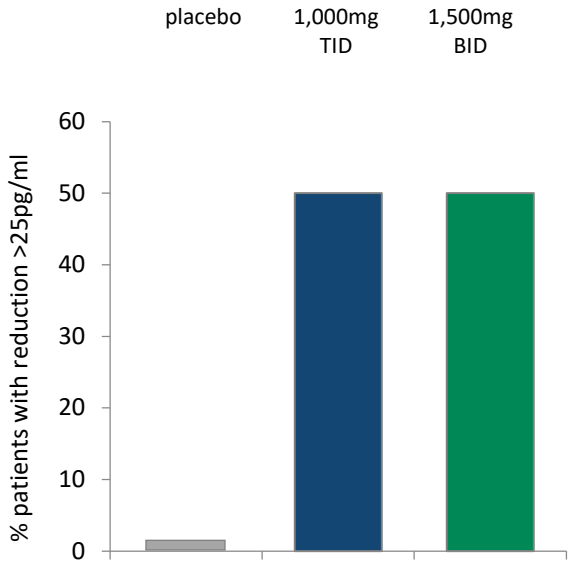
- Significant sorbitol reduction achieved by both 1,000mg TID and 1,500mg BID AT-001
- Higher C_{max} achieved with BID slightly beneficial – normalizes sorbitol to healthy volunteer levels

Mean Reduction in NTproBNP



- Mean reduction in NTproBNP seen over 28 days vs. placebo
  - Mean baseline NTproBNP was 65pg/ml

Clinical Responder Analysis



- ~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days
  - >26pg/ml reduction from baseline

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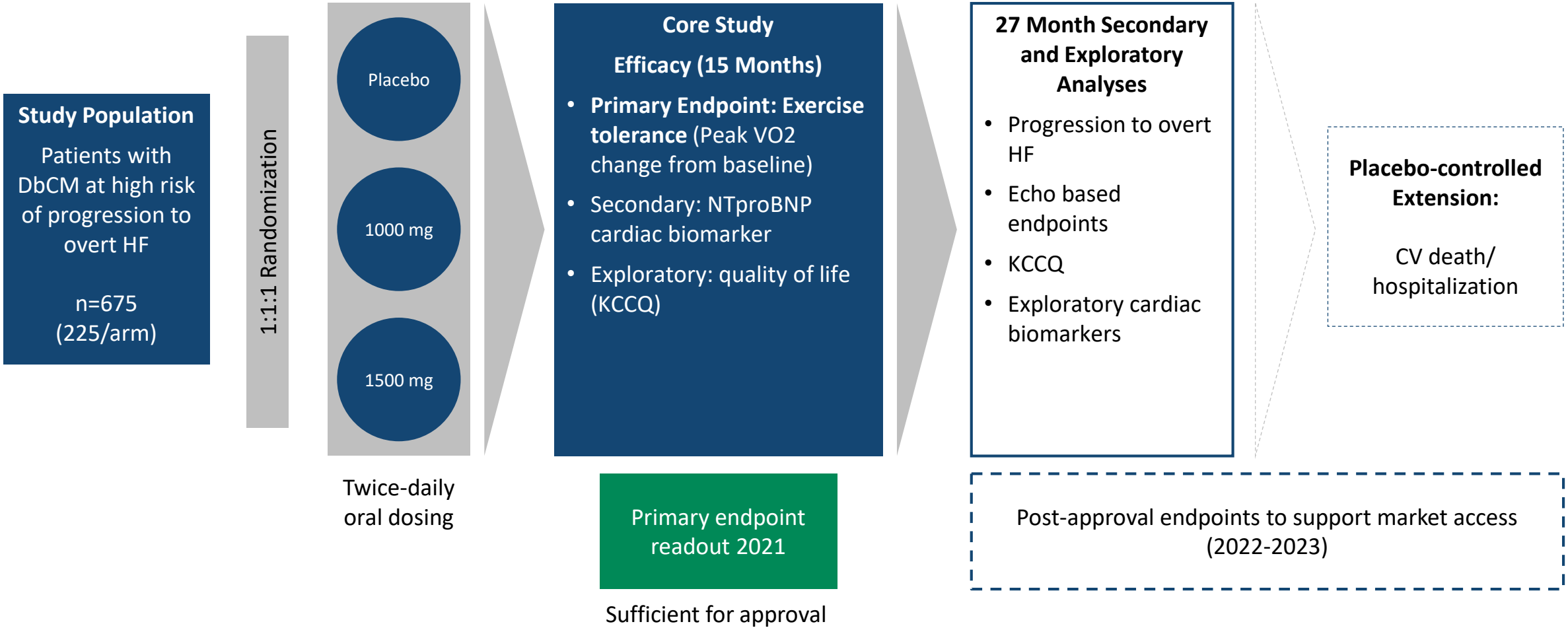
DbCM Phase 3 Registrational Study (ARISE-HF)

Randomized, Placebo-Controlled Study in DbCM Patients at High Risk of Progression



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Appendix / Backup Slides

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Addressing Large Indications in Areas of High Unmet Medical Need – Opportunities for Abbreviated Clinical Development

Indication	Prevalence	Market	Unmet Need	Development Strategy
Diabetic Cardiomyopathy	17-24% Diabetics	~77M patients worldwide	• No therapies approved • No known drugs in development • Entresto approved in stage 4 disease	Independent; Abbreviated Development
Retinopathy	35% Diabetics	~158M patients worldwide	• 2 therapies approved (intravitrial injection) • Anti-VEGFs only for late stage disease	Independent; Abbreviated Development
Diabetic Peripheral Neuropathy	50% Diabetics	~226M patients worldwide	• No disease-modifying therapies approved • Only symptomatic treatments available (Lyrica) • Epalrestat, an off-patent ARI, approved in Japan, China, India	Strategic Partner; Standard Development
Galactosemia	1/50k to 1/90k	~2,800 patients in the US	• No therapies approved; lactose dietary restriction not sufficient • No known drugs in development	Independent; Abbreviated Development (includes PRV)

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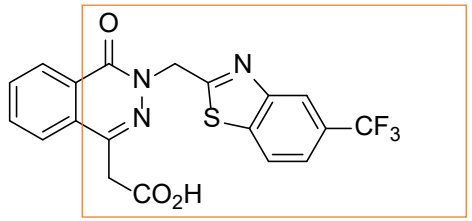
Novel Chemistry For Better Drugs

Backbone



zopolrestat

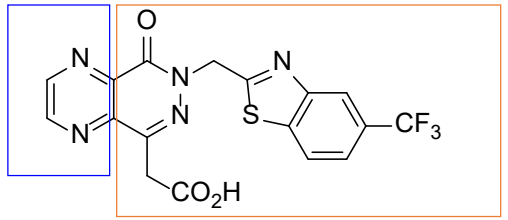
Similar backbone to zopolrestat (prior best in class efficacy, but liver tox issues)

Technological Advancements

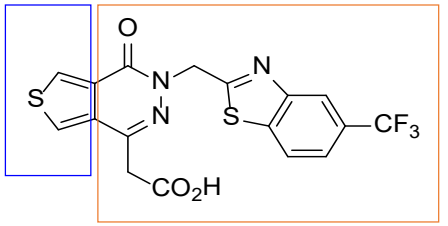
- Advanced crystallography provided novel understanding of structural changes within AR active site
- Many prior ARIs were unable to inhibit redox-activated AR

Impact of Modified Structure

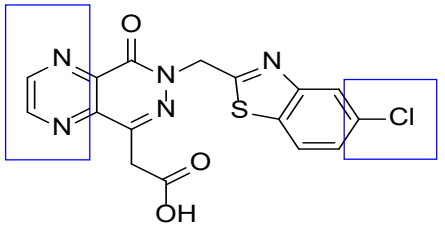
- Functional modifications improve compound's binding affinity and specificity
- Novel dimeric binding within the catalytic core
- Higher enzymatic inhibitory activity
- Increased selectivity leads to less off-target activity and potentially better safety



AT-001



AT-007



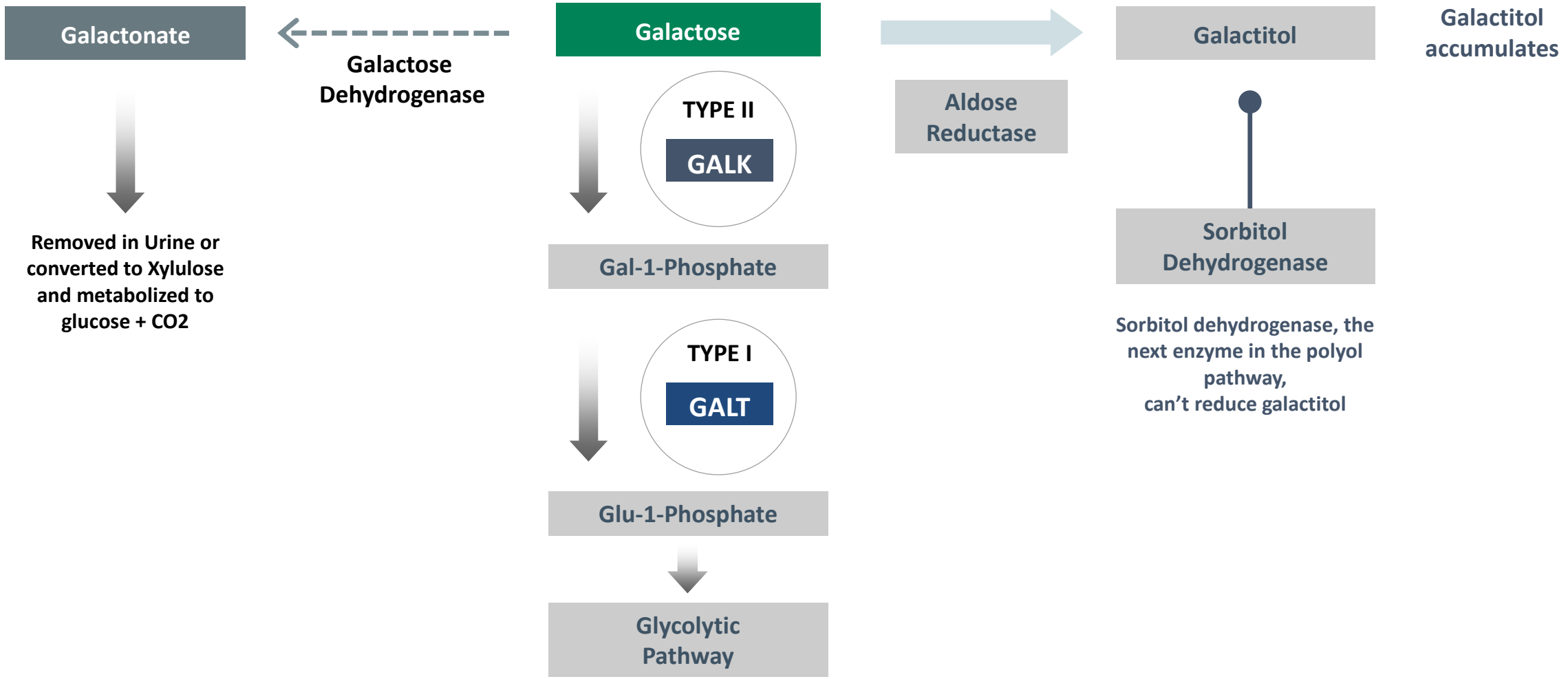
AT-003

APPLIED THERAPEUTICS

Intellectual Property Summary

- Dominant IP and Freedom to Operate on all compounds & all target indications
- Expected IP runway of at least 10 years post-launch in key indications
- Composition of matter patents that cover AT-001 and related compounds obtained US, EP, JP, CA and AU
  - Patent protection through 2031, regulatory extension of term possible
  - Method claims obtained or currently being pursued
- Composition of matter patent that covers AT-007 and related compounds obtained in US
  - Pending on fast track in Europe, pending in other countries
- Company-owned international applications (PCT) cover methods for treating Galactosemia and additional compound derivatives

If Blocking AR Doesn't Increase Galactose or Gal-1P…..
Where Does the Extra Substrate Go?



APPLIED THERAPEUTICS

Diabetic Peripheral Neuropathy

Burden of Disease

- Aldose Reductase activity in neurons causes osmotic dysregulation and cell death/neuronal dysfunction
- Tingling/burning/stinging sensation and loss of feeling in peripheral tissues
- Significant impact on quality of life and pharmacoeconomic metrics (ability to work)

Standard of Care

- No disease modifying therapies approved
- Epalrestat (ARI) approved for 20+ years in Japan: dosed 3-5x/day; numerous side effects
- Standard of care outside of Japan/China is analgesic (pain) management, primarily Lyrica

Building on Prior Body of Evidence

- Epalrestat is understood to be safe and moderately effective, but unfavorable PK profile (5X daily dosing)
- Never approved in US/EU; now generic in Japan/China
- Phase 4 trials in Japan demonstrated statistical effects on MNCV and symptomatic pain (Hotta et al)

Current Phase 1 SAD/MAD Trial

- Current AT-001 Phase 1 results show favorable PK vs. Epalrestat
- DPN metrics (MNCV) will be captured in Phase 2/3 pivotal Diabetic Cardiomyopathy trial
- Demonstrate POC for AT-001 in DPN and inform on dose selection for registrational DPN trials

Future Path to Registration

- Will require “typical” path to registration
  - 2 large Phase 3 trials
- Design will follow Epalrestat Phase 4 trials– careful selection of patient population and performance of endpoint testing
- Likely to pursue strategic partnership with large pharmaceutical company

APPLIED THERAPEUTICS

AT-003 for Diabetic Retinopathy

Burden of Disease

- One of the major causes of blindness worldwide
- Current therapies (anti-VEGFs) are high cost biologics that require intravitreal administration by an ophthalmologist
- Limited access for patients and high economic burden
- AR is an upstream target vs. VEGF – opportunity to blunt damage to the eye at the earliest stages

Standard of Care

- Current treatments (anti-VEGF therapies) target downstream consequences of diabetic complications in the eye
- Lucentis & Eylea are leading approved therapies for DME; limited to treating later stage / more severe stages of disease

Building on Prior Body of Evidence

- Clear proof of mechanism: AR activation / increased sorbitol as the initial pathogenesis of retinopathy is well supported
- Sorbitol build up in the lens causes osmotic dysregulation
- AR knock-out mice do not develop diabetic retinopathy; AR over-expressing mice develop retinopathy earlier than WT
- 2 prior ARIs met endpoints in Phase 2 trials, but were toxic

AT-003 in Preclinical Development

- Proof-of-concept in animal models of retinopathy
- AT-003 displays a similar PK to AT-001, but has greater retinal penetrance
- IND-enabling studies and manufacturing scale up are under way

APPLIED THERAPEUTICS

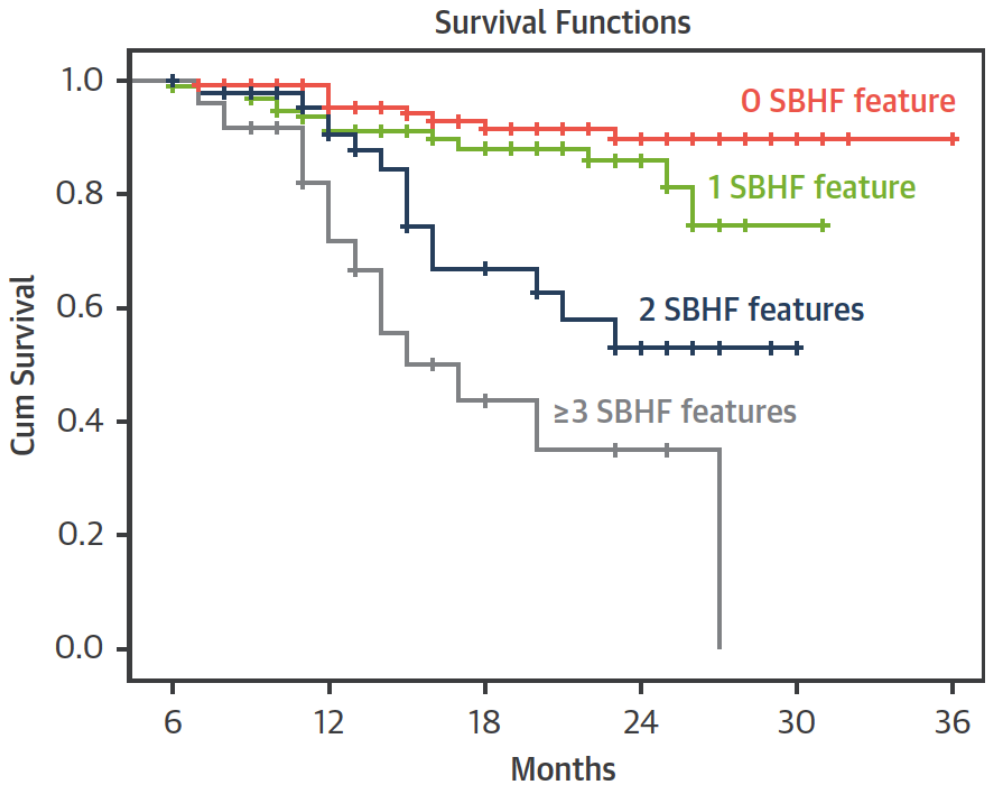
Anticipated Changes in Functional Capacity and Progression to Overt Heart Failure in Study Population

Anticipated mean baseline peak VO2<6 METS (21ml/kg/min) represents a steep slope of decline and strong relationship between changes exercise capacity and ability to perform everyday tasks

	Peak VO2	Metabolic 'Cost' of Activity
Light and moderate intensity	3.5	Rest
	7.0-10.5	Walking 2mph, eating, dressing
	14.0-17.5	Walking 4mph, household tasks
	21.0-24.5	Walking up stairs, Stage 2 Bruce: 2.5mph, 12%
Vigorous intensity	28.0-31.5	Swimming, tennis
	35.0-38.5	Jogging 10 min/miles, Stage 3 Bruce: 3.4mph, 14%
	42.0-49.0	Intense aerobic sports, squash Stage 4 Bruce: 4.2mph, 16%
	>70.0	Professional athletes/Olympians

AMA Guides to the Evaluation of Permanent Impairment, Sixth Edition. Author: Robert D. Rondinelli, MD, PhD

Progression to Overt Heart Failure



Wang Y, Marwick TH. JACC: CV Imaging 2018

APPLIED THERAPEUTICS