



CORPORATE OVERVIEW MAY 2020

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Investment Highlights



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

- Positive Ph2 (pivotal) Galactosemia data announced April 2020; NDA expected ~YE 2020
- Diabetic Cardiomyopathy pivotal data expected 2021



Distinct late-stage commercial opportunities

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



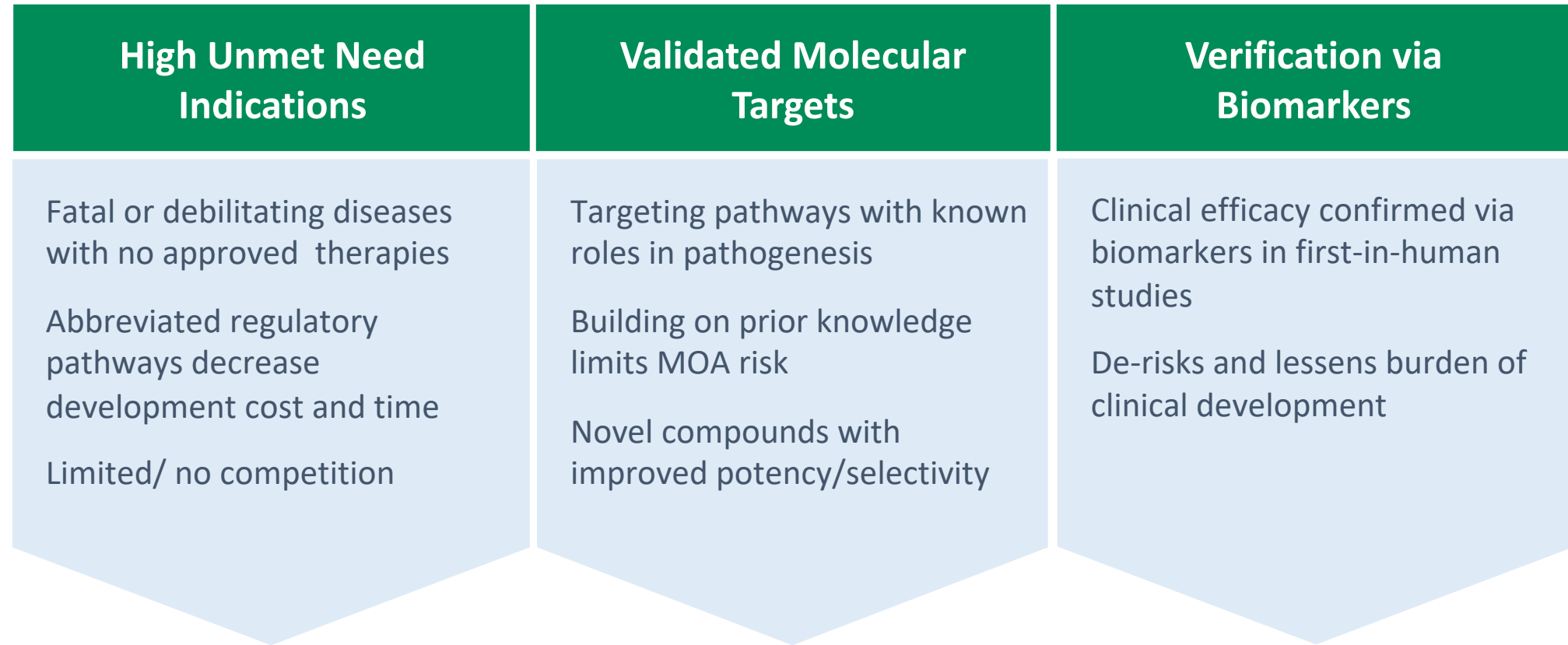
Reproducible discovery and development strategy

- Additional rare metabolic diseases targeting aldose reductase (SORD Deficiency, PMM2-CDG)
- Early stage pipeline in orphan oncology indications targeting PI3k

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



Applying Science to Transform Lives



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

Pipeline

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing Route	Target Tissue	Milestones
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Aldose Reductase Franchise

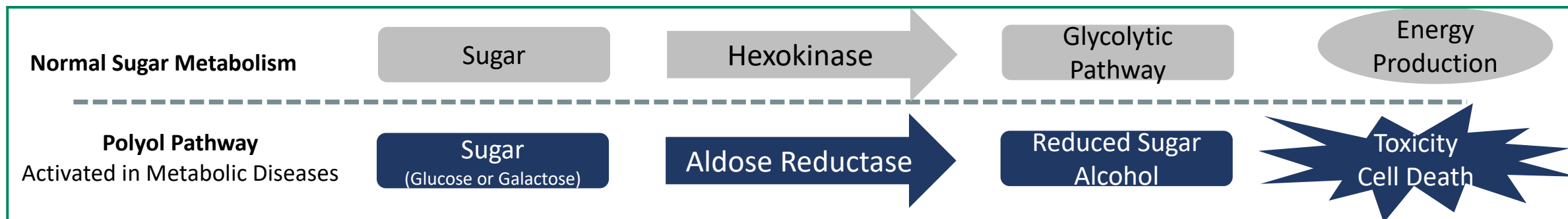
AT-007	Galactosemia – Pivotal Ph 2 Study				Oral	CNS	Full results of pivotal Ph 2 adult ACTION-Galactosemia released; pediatric study June 2020
AT-007	SORD Deficiency				Oral	CNS	Phase 2 ready; clinical study start 2021
AT-007	PMM2-CDG				Oral	CNS	Phase 2 ready
AT-001	Diabetic Cardiomyopathy – Pivotal Ph 3 Study				Oral	Systemic	Ph 3 trial initiated in Q3 2019; data in 2021
AT-001	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial
AT-003	Diabetic Retinopathy				Oral	Retina	Preclinical data 2019; Initiate Ph 1 2021

PI3 Kinase Franchise

AT-104	PTCL, CTCL, TALL*				SC / Oral	Selective δ/γ inhibitor	Initiate Ph 1 2021
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* Peripheral T-cell lymphoma, cutaneous T-cell lymphoma and T-cell acute lymphoblastic leukemia

Unlocking the Potential of Aldose Reductase Inhibition Across Multiple Metabolic Diseases



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

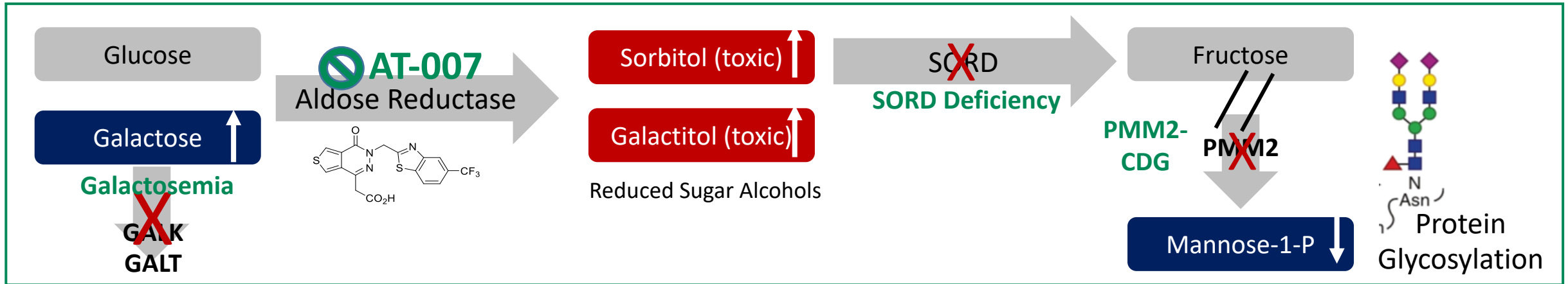
R&D and Regulatory Opportunities

- 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

AT-007 for CNS Rare Metabolic Diseases

AT-007 for CNS Rare Metabolic Diseases

Galactosemia, SORD Deficiency, PMM2-CDG



Galactosemia

(pivotal study complete)

- GALT/ GALK deficiency (enzymes required for galactose metabolism)
- Results in galactitol formation (aberrant metabolite of galactose)
- Galactitol toxicity results in CNS complications (cognitive, motor, seizures, tremor) & cataracts
- ~2,900 patients in US (~7,000 worldwide)

SORD Deficiency

(biomarker Ph 2 pivotal study 2021)

- Deficiency in Sorbitol Dehydrogenase (SORD)¹
- High sorbitol levels (>1,000X)
- Sorbitol toxicity results in severe peripheral neuropathy and motor neuron disease
- 3,500-5,000 patients in US (~10,000 worldwide)

PMM2-CDG

(Ph 2 ready)

- Decreased PMM2 enzyme activity (catalytic site or dimerization mutations)^{2,3}
- Decreased protein glycosylation results in systemic and CNS complications; severe disease
- Polyol pathway (AR) feeds into glycosylation pathway
- ~1,000 patients worldwide

Galactosemia

Pathogenesis of Disease

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

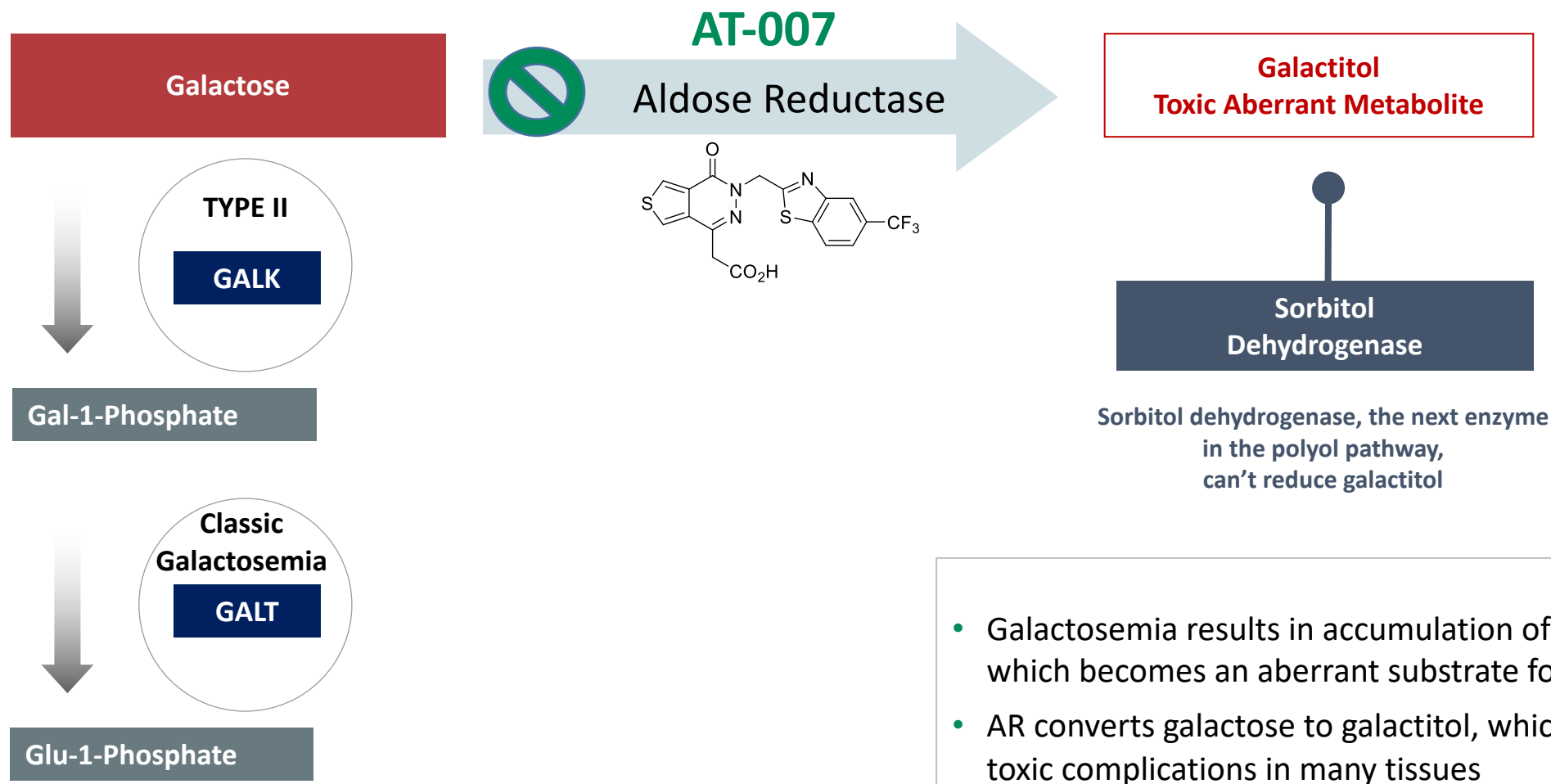
Standard of Care

- 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; comparatively low commercial investment required**
 - >90% patients seen by ~20 specialists worldwide
 - High prescriber awareness of Applied clinical development program

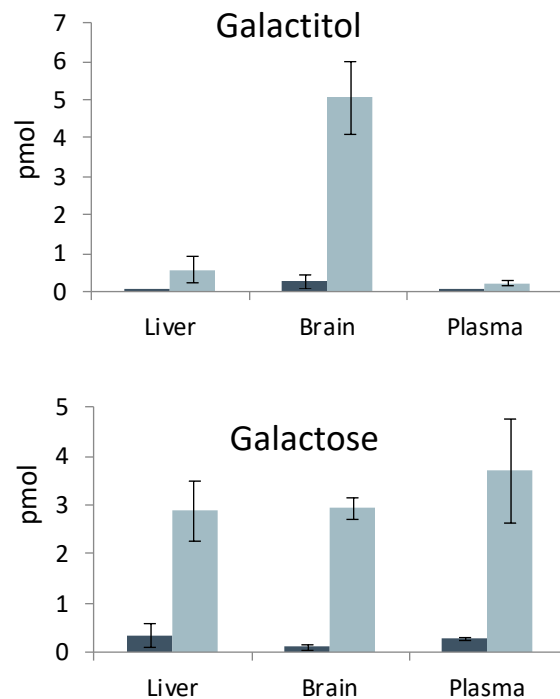
AT-007, a CNS-Penetrant Novel Aldose Reductase Inhibitor, Prevents Galactitol Formation and Accumulation



GALT Deficient Rat Model Closely Mirrors Human Disease

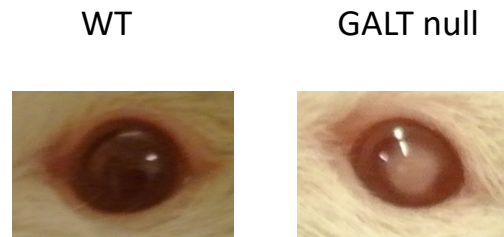
Biochemical Effects

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



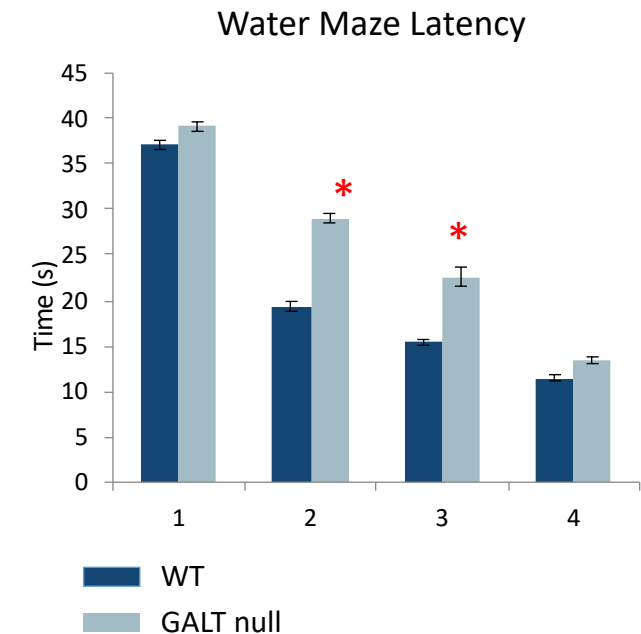
Tissue Deposition of Galactitol

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



CNS Outcomes

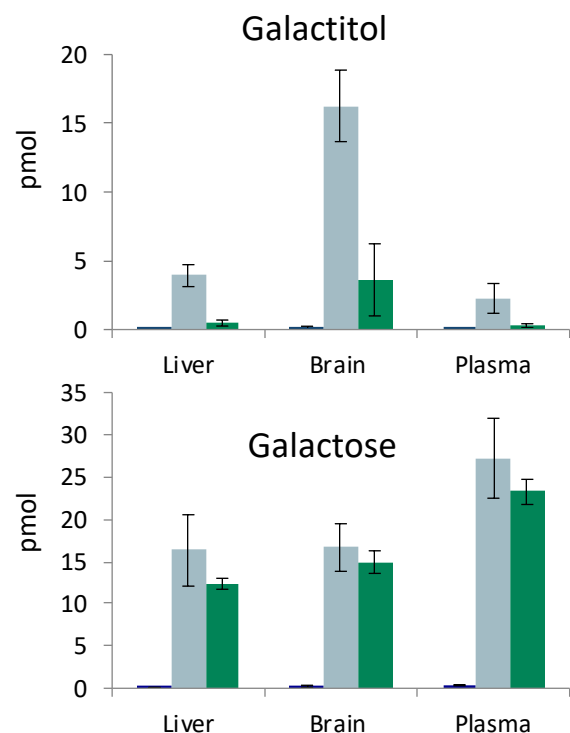
GALT null rats display deficiencies in learning, cognition, and motor skills as measured by rotarod and water maze



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

Biochemical Effects

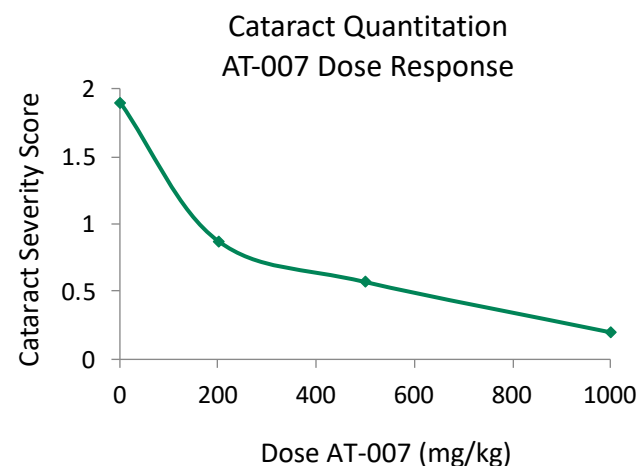
AT-007 treatment significantly reduced galactitol levels in all tissues without increasing galactose or Gal1p



■ Wild Type ■ GALT null placebo ■ GALT null AT-007

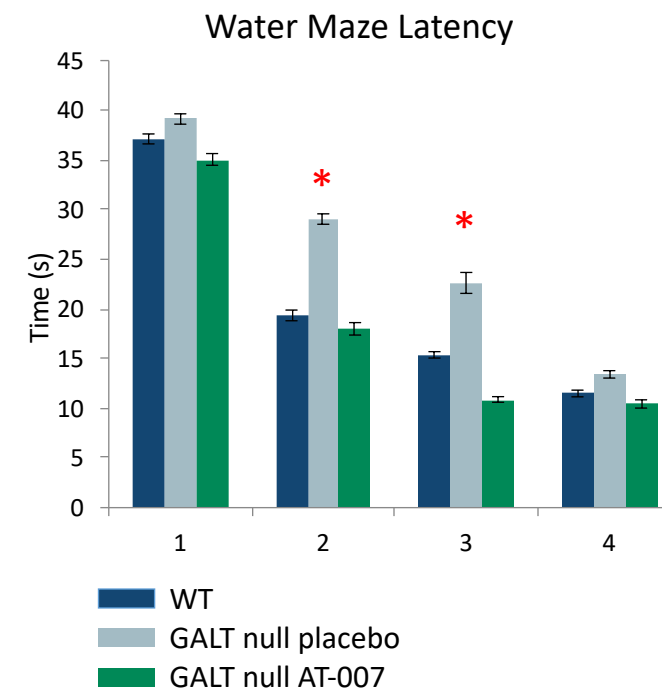
Tissue Deposition of Galactitol

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



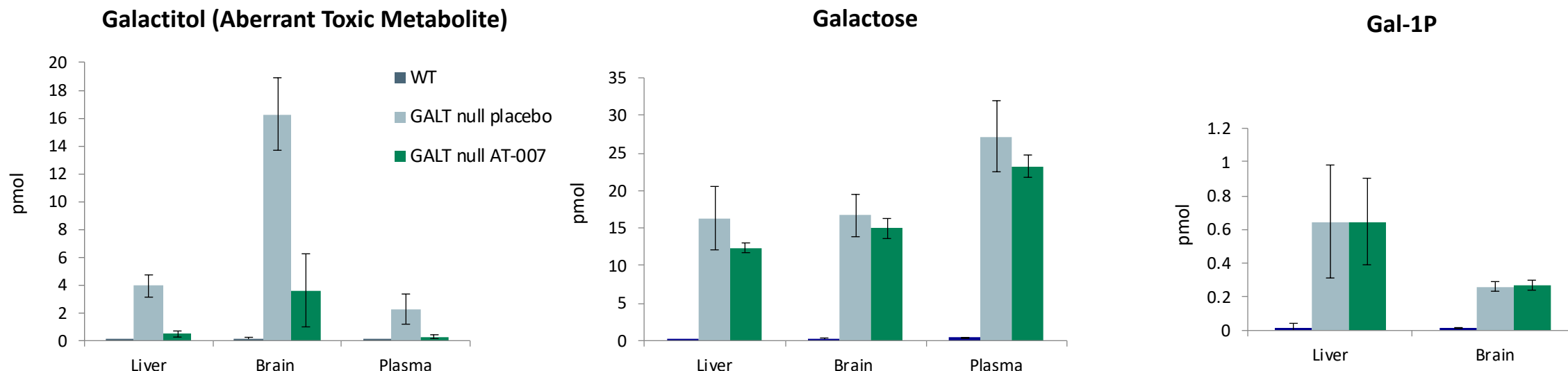
CNS Outcomes

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

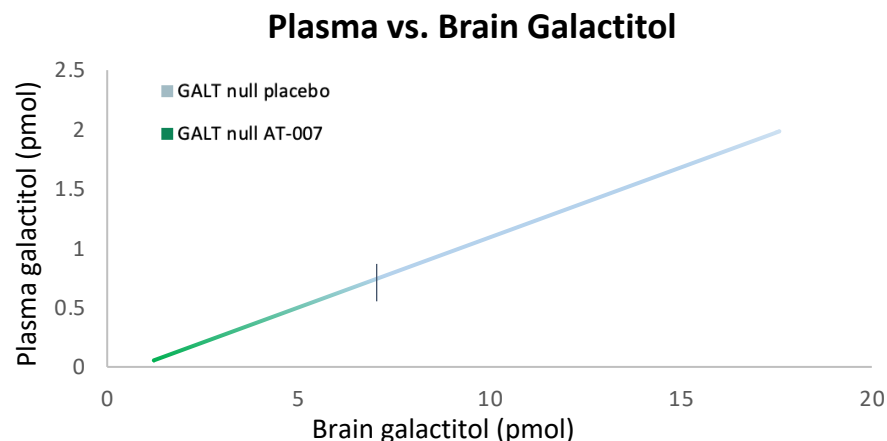


* Statistically significant vs. WT & AT-007 treated

A Closer Look: AT-007 Significantly Reduces Galactitol Levels in all Target Tissues Without Increasing Galactose or Gal-1P



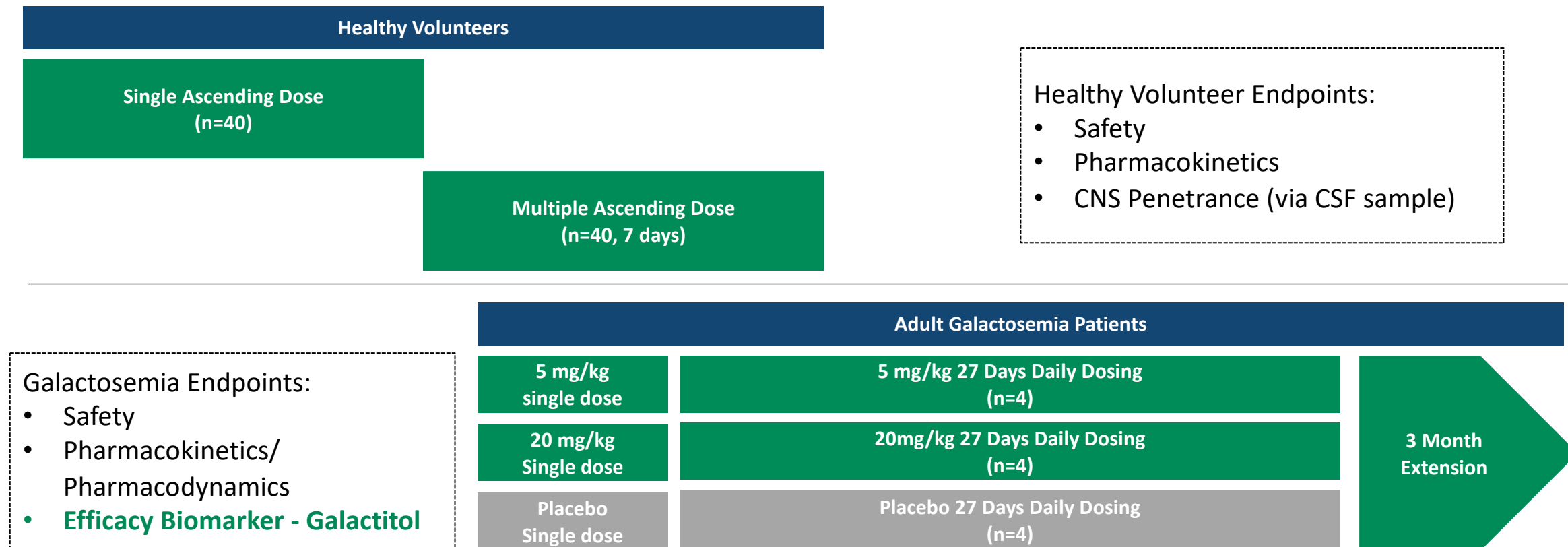
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- AT-007 treatment from neonatal Day 1 to Day 10 significantly reduced galactitol in liver, brain and plasma
- AT-007 treatment did not increase galactose or Gal-1P levels; similar results seen at Day 22 and age 5 months
- Levels of galactitol in plasma and brain correlated in individual animals; reduction in galactitol induced by AT-007 treatment correlated in plasma and brain

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

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



Based on initial topline data from Jan 2020, the study was expanded to include a 40mg/kg dose in healthy volunteers and then Galactosemia patients

Safety and PK Summary in Galactosemia Patients

Pharmacokinetics

- PK supports once-daily dosing
- Linear increase in AT-007 dose-dependent plasma concentration
- Similar exposure levels in Galactosemia patients and healthy volunteers

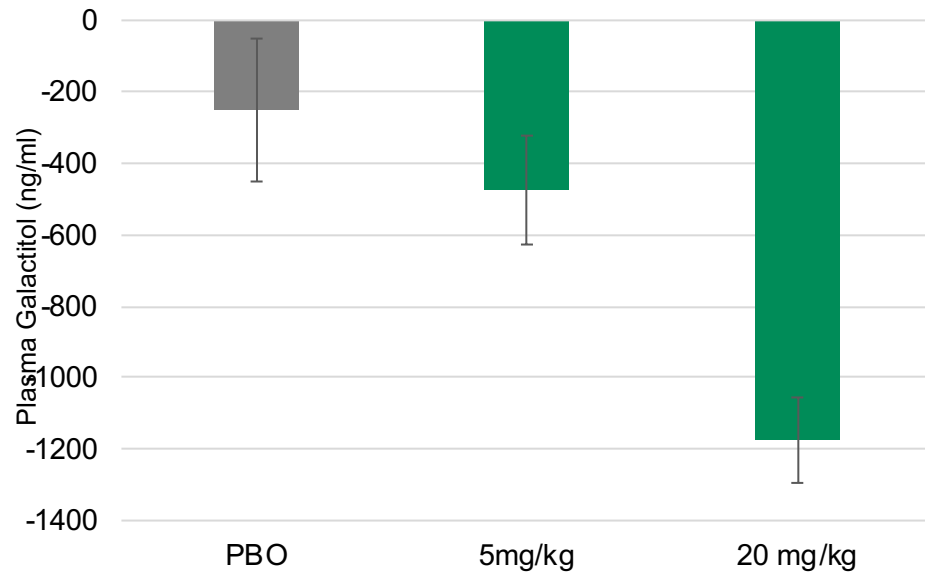
Safety

- AT-007 was safe and well-tolerated
- No treatment-related discontinuations
- No treatment-related Adverse Events
- No treatment-related lab abnormalities

AT-007 Significantly Decreased Galactitol Levels in All Treated Patients

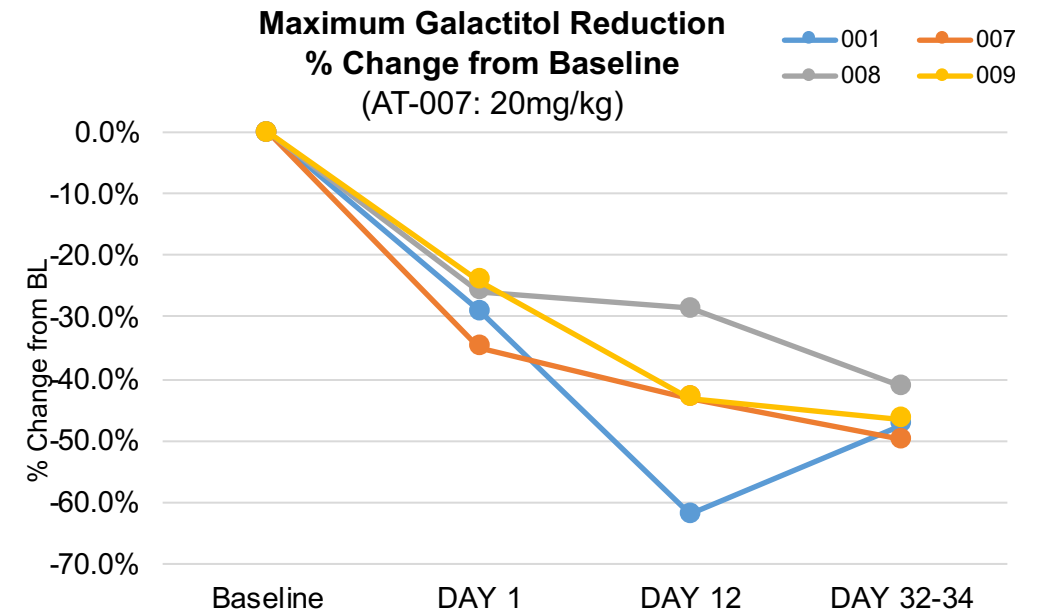
Decrease was Dose-Dependent, Rapid and Sustained

Maximum Galactitol Reduction (by Cohort)



P<0.01 for 20mg/kg vs. placebo

Individual Reduction in Galactitol at 20mg/kg ~50%



Further Characterization of AT-007

ACTION-Galactosemia

Long-term safety in adult Galactosemia patients

Initiate pediatric study in Q2 2020

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 2 adult Galactosemia patient study
- 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)
- Initiate pediatric study in Q2 2020
- Ongoing 90-day long-term safety extension of ACTION-Galactosemia in adult Galactosemia patients

Sorbitol Dehydrogenase (SORD) Deficiency

Burden of Disease

- Progressive hereditary neuropathy
- Pediatric-to-adolescent onset of disease
- Manifestations include difficulty walking, lower limb atrophy, and distal muscle weakness predominantly in lower limbs and frequently upper limbs
- Often diagnosed symptomatically as a subtype of CMT2

Standard of Care

- No approved therapies

Building on Prior Body of Evidence

- Patients with SORD have very high levels of sorbitol in their cells and tissues as a result of the enzyme deficiency, which results in tissue toxicities such as neuropathy
- Recent research in drosophila and cell models demonstrates that treatment with an ARI that blocks sorbitol production may provide benefit in this disease

Development

- Preclinical studies initiated
- Leverage prior Phase 1 development work in healthy volunteers – Phase 2 ready asset
- Plan to initiate SORD deficiency clinical study in 2021; potential for biomarker-based pivotal study (reduction in sorbitol)

Phosphomannomutase 2 deficiency (PMM2-CDG)

Burden of Disease

- Most common congenital disorder of glycosylation
- Classical presentation includes cognitive deficiencies, developmental delay, severe encephalopathy with axial hypotonia, psychomotor retardation, and cerebellar hypoplasia
- Many patients present with abnormal fat distribution and cardiomyopathy in infancy and childhood
- High infant mortality rate in the first few years of life

Building on Prior Body of Evidence

- PMM2-CDG patients have high levels of Sorbitol in blood and urine, presumably because PMM2 deficiency deranges the homeostatic feedback mechanisms involved in the polyol pathway
- Epalrestat (old ARI) shown to be potent activator of enzyme activity in PMM2-CDG patient fibroblasts
 - Data suggest Aldose Reductase inhibition act post-translationally to increase PMM2 enzyme activity

Standard of Care

- No approved therapies

AT-007 in Preclinical Development

- Initial data in fibroblast cell lines derived from PMM2-CDG patients; AT-007 increases phosphomannomutase 2 activity
- Potential to pursue clinical development in 2021

AT-001 for Diabetic Cardiomyopathy

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

DbCM Commercial Opportunity: Blockbuster Potential with Limited Capital Requirement

Regulatory	Commercial Market	Point of Care
<ul style="list-style-type: none">• Clear path to registration based on functional capacity endpoint (exercise tolerance)• Single Phase 3 trial required	<ul style="list-style-type: none">• 10M patients in the US; 77M worldwide• Sufficiently narrow heart failure population - can be targeted with limited commercial investment• High disease awareness	<ul style="list-style-type: none">• 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

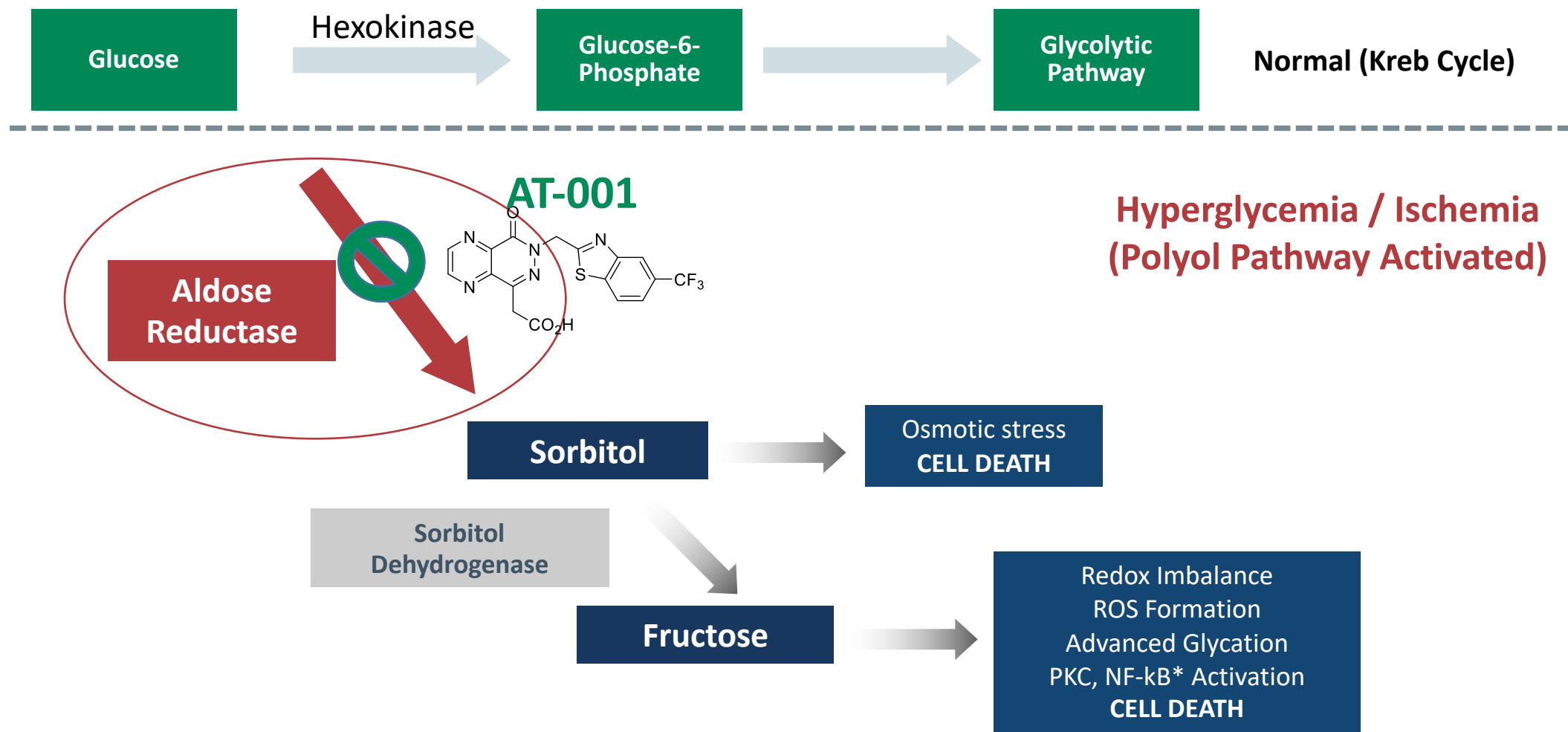
AT-001's Robust Pre-Clinical Profile

- 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)

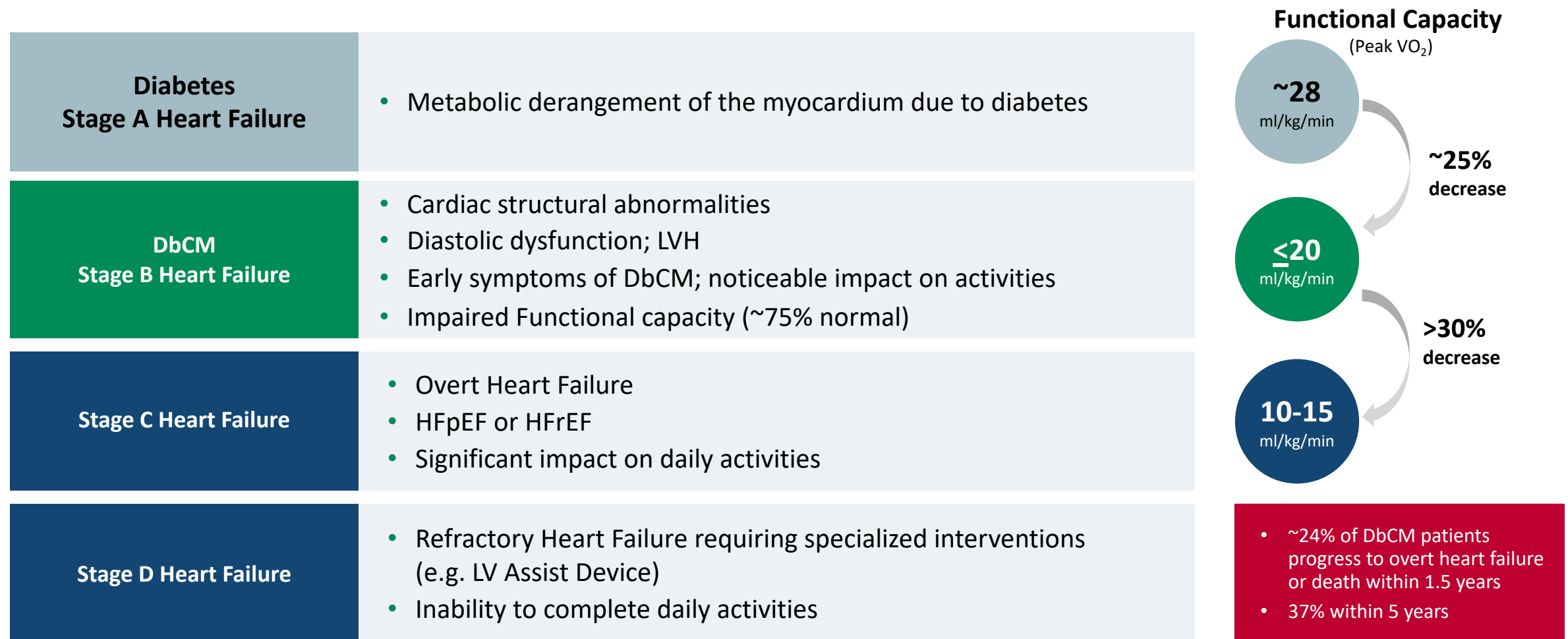
- Clinical proof-of-concept via sorbitol biomarker observed in T2D patients
- No drug related AEs observed at any dose; well tolerated
- Heart inflammatory biomarkers in 28 day arm in DbCM patients informed dose selection for pivotal study

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

Understanding Diabetic Cardiomyopathy as a Form of Heart Failure



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

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

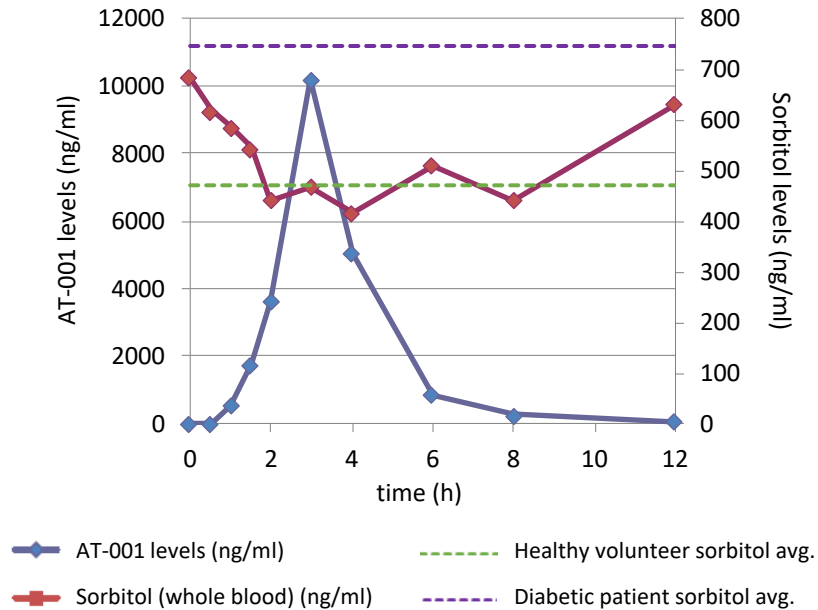
- 30 DbCM patients
- 10 patients per cohort (8 drug treated, 2 placebo)
 - Placebo
 - 1,500mg BID
 - 1,000mg TID

Results

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

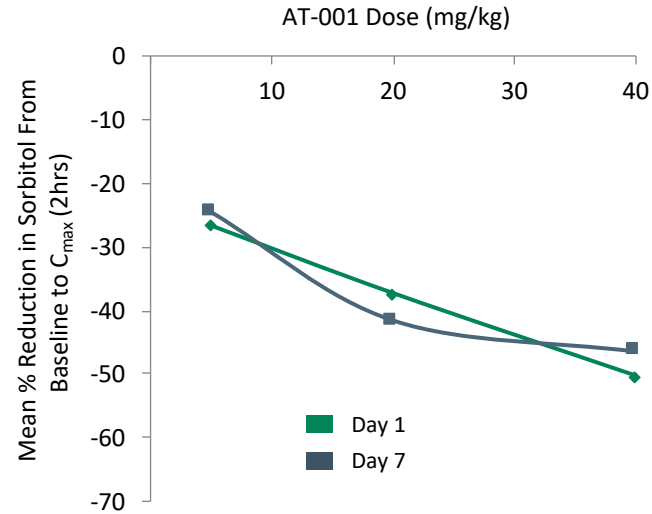
AT-001 Normalizes Sorbitol, a Biomarker of AR Activity, in Diabetic Patients

Proof of Biological Activity



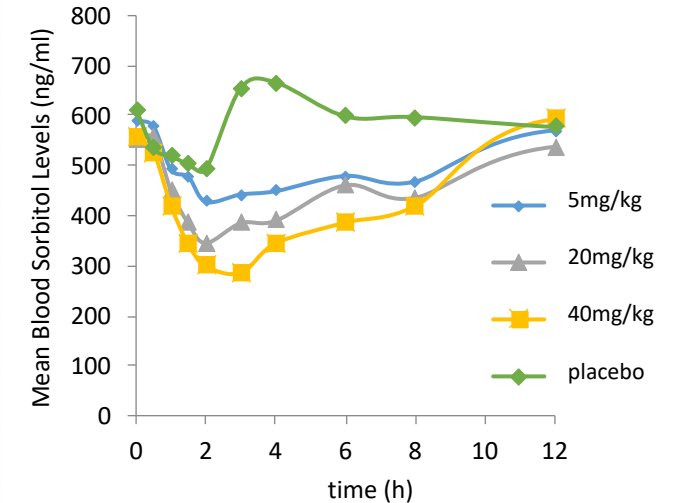
- Drug treatment with AT-001 normalized sorbitol in diabetics to healthy volunteer levels

Sorbitol Reduction by Dose



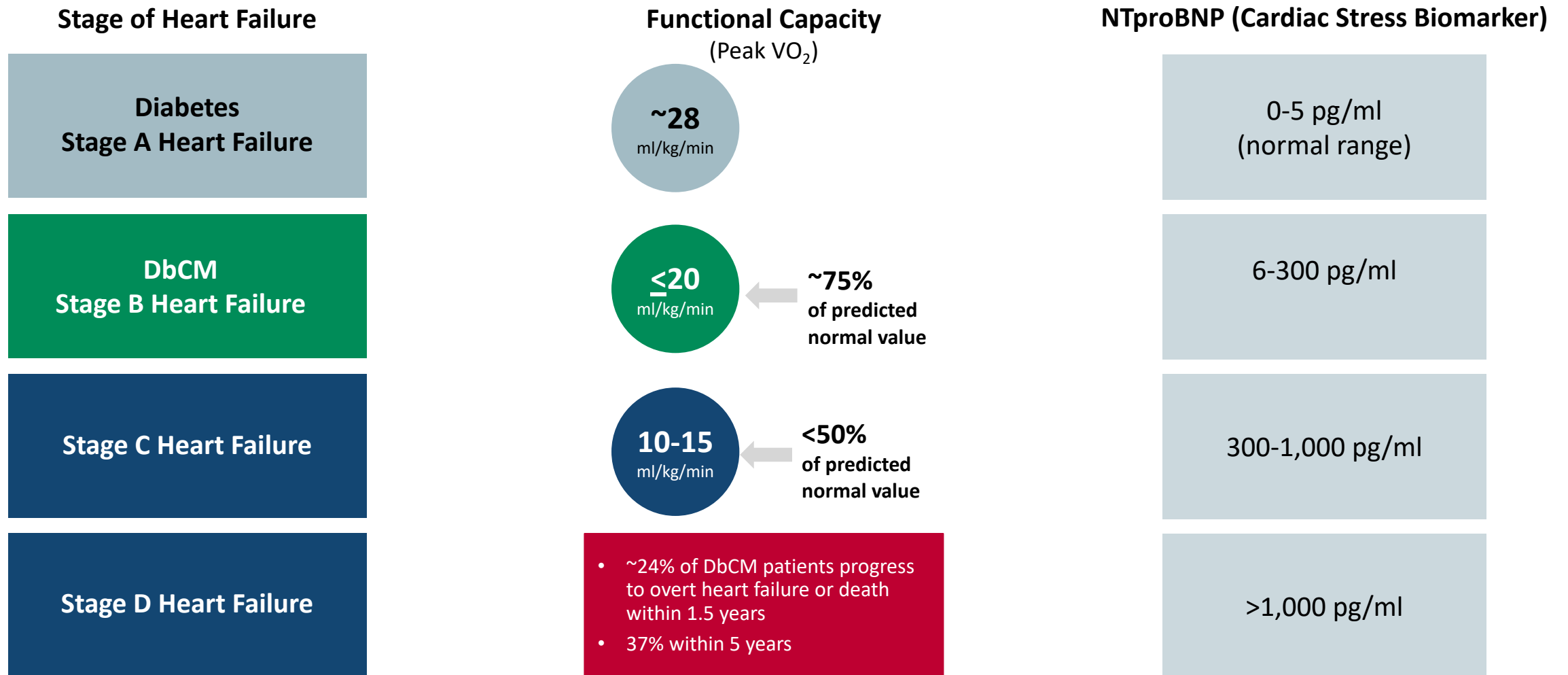
- Mean reduction in sorbitol at Day 1 and Day 7: Results are persistent over 1 week of treatment
- At 40mg/kg patients were normalized to healthy volunteer sorbitol levels, demonstrating complete AR inhibition

Sorbitol Normalization Over Time



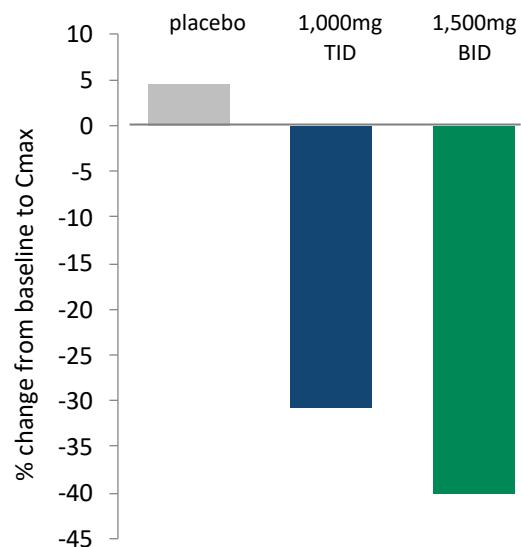
- Rapid release capsule provides sorbitol normalization effects (PD biomarker) through 10-12hrs post-dose at >10mg/kg
- Includes protection from food-related sorbitol spikes during times of post-prandial hyperglycemia

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



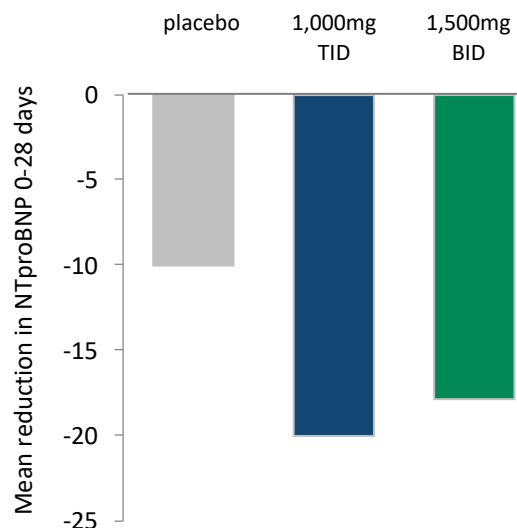
AT-001 Reduced Levels of NTproBNP Cardiac Stress Biomarker Over 28 Days of Treatment

Sorbitol Normalization



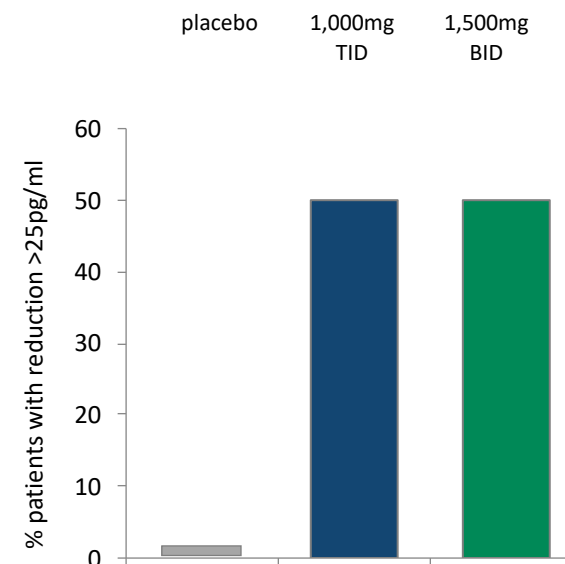
- Significant sorbitol reduction achieved by both 1,000mg TID and 1,500mg BID AT-001
- Higher C_{max} achieved with BID slightly beneficial – normalizes sorbitol to healthy volunteer levels

Mean Reduction in NTproBNP



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

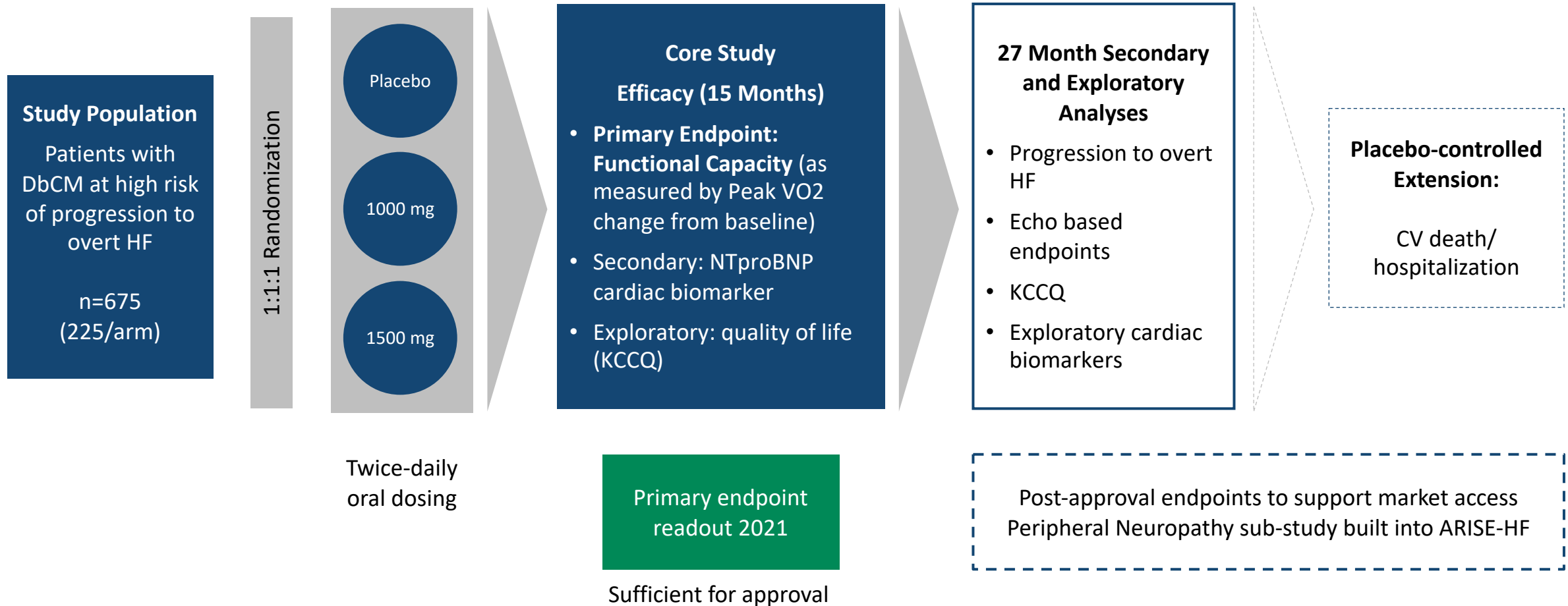
Clinical Responder Analysis



- ~50% AT-001 treated patients demonstrated a clinically meaningful reduction in NTproBNP over 28 days
 - >25pg/ml reduction from baseline

DbCM Phase 3 Registrational Study (ARISE-HF)

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



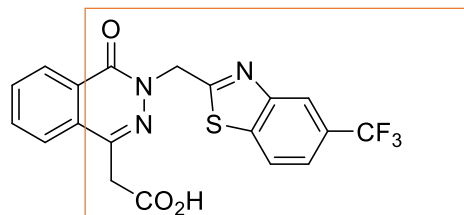
Appendix / Backup Slides

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	<ul style="list-style-type: none"> No therapies approved No known drugs in development Entresto approved in stage 4 disease 	Abbreviated Development
Retinopathy	35% Diabetics	~158M patients worldwide	<ul style="list-style-type: none"> 2 therapies approved (intravitreal injection) Anti-VEGFs only for late stage disease 	Abbreviated Development
Diabetic Peripheral Neuropathy	50% Diabetics	~226M patients worldwide	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> No therapies approved; lactose dietary restriction not sufficient No known drugs in development 	Abbreviated Development (includes PRV)
SORD Deficiency	>1/100k	~3,300 patients in the US	<ul style="list-style-type: none"> No therapies approved No known drugs in development 	Abbreviated Development (eligible for PRV)
PMM2-CDG	<1/1M	~1,000 patients worldwide	<ul style="list-style-type: none"> No therapies approved No known drugs in development 	Abbreviated Development (eligible for PRV)

Novel Chemistry For Better Drugs

Backbone



zopolrestat

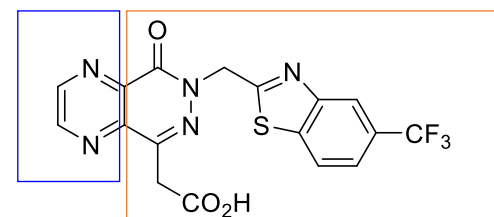
Similar backbone to zopolrestat (prior best in class efficacy, but liver tox issues)

Technological Advancements

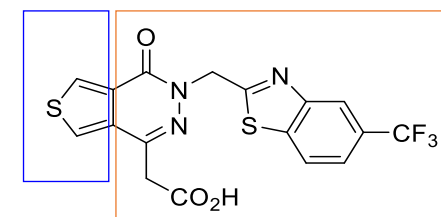
- Advanced crystallography provided novel understanding of structural changes within AR active site
- Many prior ARIs were unable to inhibit redox-activated AR

Impact of Modified Structure

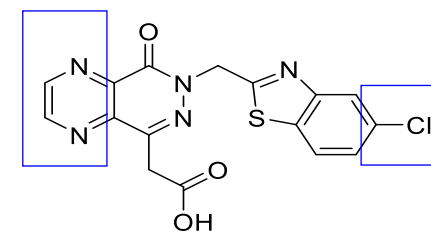
- Functional modifications improve compound's binding affinity and specificity
- Novel dimeric binding within the catalytic core
- Higher enzymatic inhibitory activity
- Increased selectivity leads to less off-target activity and potentially better safety



AT-001



AT-007

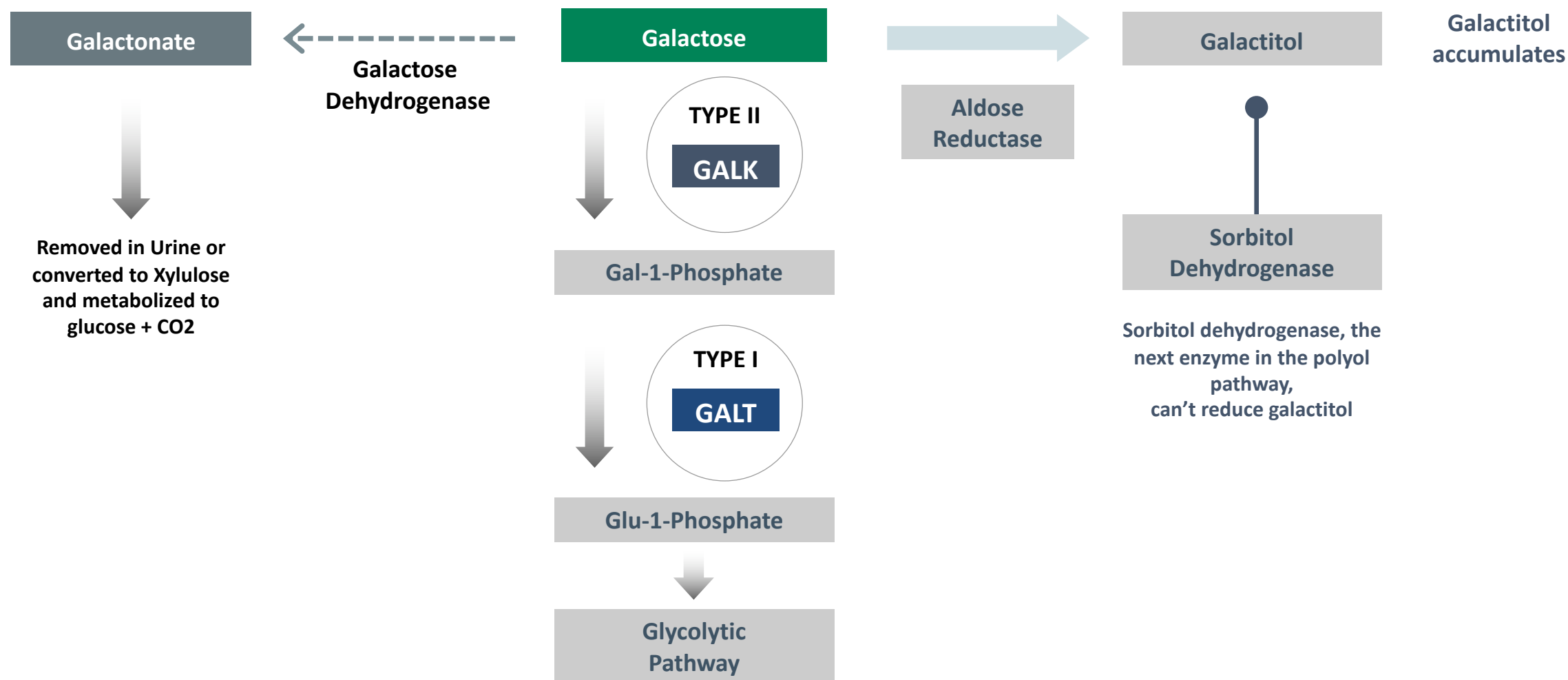


AT-003

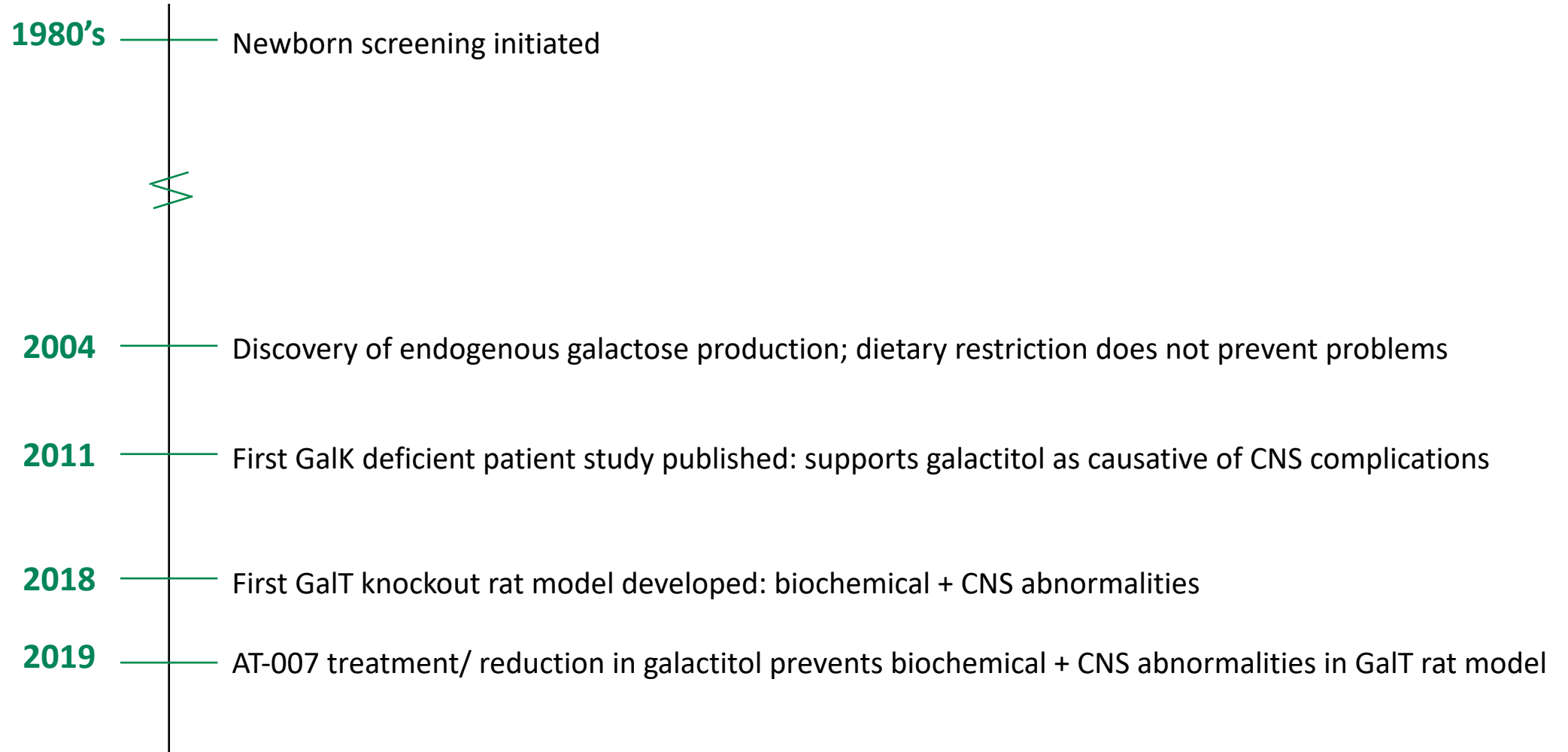
Intellectual Property Summary

- 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 obtained in the US that cover AT-007 and related compounds
 - Patent protection through 2037, regulatory extension of term possible
 - European patent application has been allowed (patent has not yet issued); patent applications are pending in other countries
- 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
- 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?



Galactosemia History Timeline



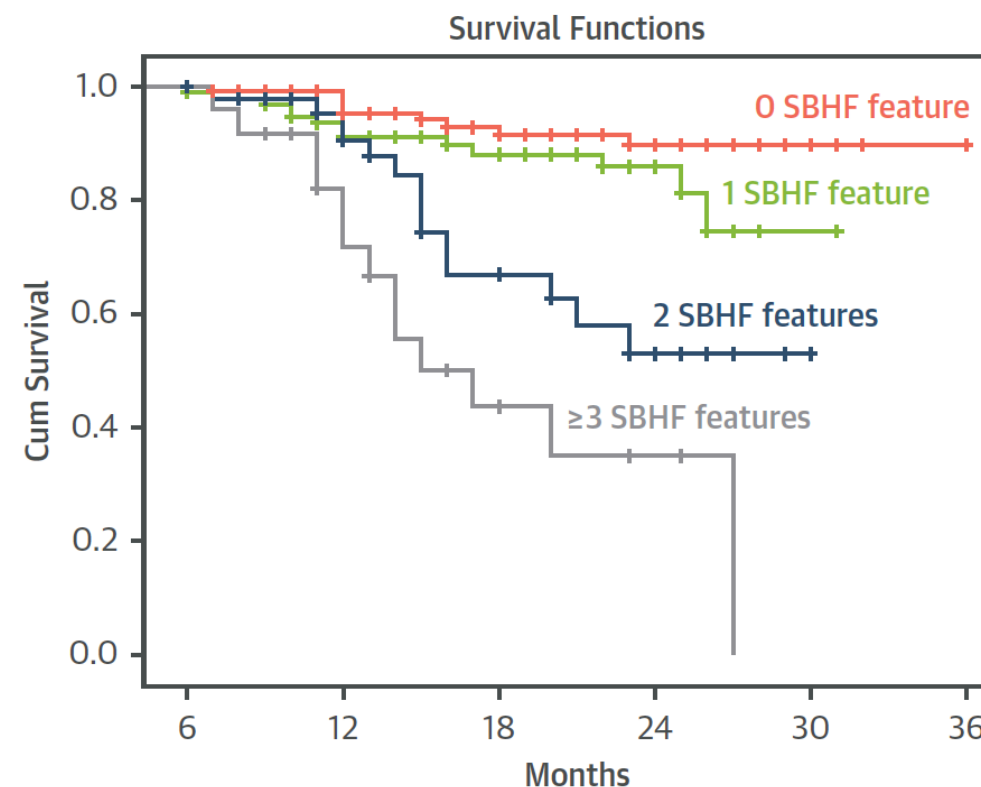
Anticipated Changes in Functional Capacity and Progression to Overt Heart Failure in Study Population

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

	Peak VO ₂	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