bridgebio

hope through
rigorous science

R&D Day

October 12, 2021

Today's agenda

Introduction	**Grace Rauh** | V.P. Communications, BridgeBio Pharma
Genetic Basis of Disease	**Richard Scheller, Ph.D.** | Chairman of R&D, BridgeBio Pharma
BridgeBio's Endless Summer	**Neil Kumar, Ph.D.** | Founder and CEO, BridgeBio Pharma
Precision Cardiorenal Introduction	**Cameron Turtle, D. Phil.** | Chief Strategy Officer, BridgeBio Pharma
Acoramidis: TTR Stabilizer for ATTR	**Jonathan Fox, M.D., Ph.D.** | Chief Medical Officer, BridgeBio Cardiorenal
Encaleret: CaSR Inhibitor for ADH1	**Mary Scott Roberts, M.D.** | Sr. Director, Clinical Development, BridgeBio Cardiorenal
Gene Therapy Platform	**Eric David, M.D., J.D.** | CEO, BridgeBio Gene Therapy
Mendelian Programs: PH1, LGMD2i, RDEB	**Uma Sinha, Ph.D.** | Chief Scientific Officer, BridgeBio Pharma
Precision Oncology Programs: KRAS, SHP2	**Eli Wallace, Ph.D.** | Chief Scientific Officer, BridgeBio Oncology
BridgeBioX	**Charles Homcy, M.D.** | Chairman of Pharmaceuticals, BridgeBio Pharma
Conclusion	**Neil Kumar, Ph.D.** | Founder and CEO, BridgeBio Pharma
Q&A	

TTR = Transthyretin amyloidosis, ADH1 = Autosomal Dominant Hypocalcemia Type 1, PH1 = Primary Hyperoxaluria Type 1, LGMD2i = Limb-Girdle Muscular Dystrophy Type 2i, RDEB = recessive dystrophic epidermolysis bullosa

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Statements in this Presentation that are not statements of historical fact are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements include, without limitation, statements regarding BridgeBio Pharma, Inc.'s (the "Company's") research and clinical development plans, expected manufacturing capabilities, commercialization and general strategy, regulatory matters, market size and opportunity, future financial position, future revenue, projected costs, prospects, plans, objectives of management, and the Company's ability to complete certain milestones. 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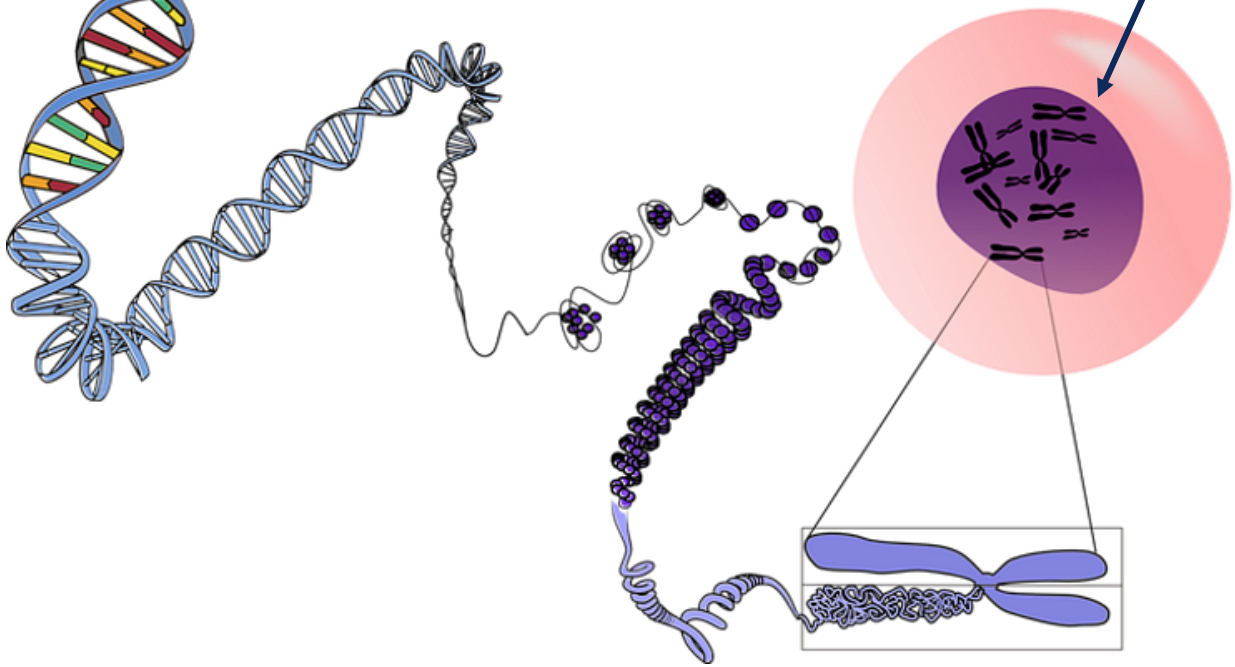
Genetic basis of disease

Richard Scheller, Ph.D.

Chairman of R&D

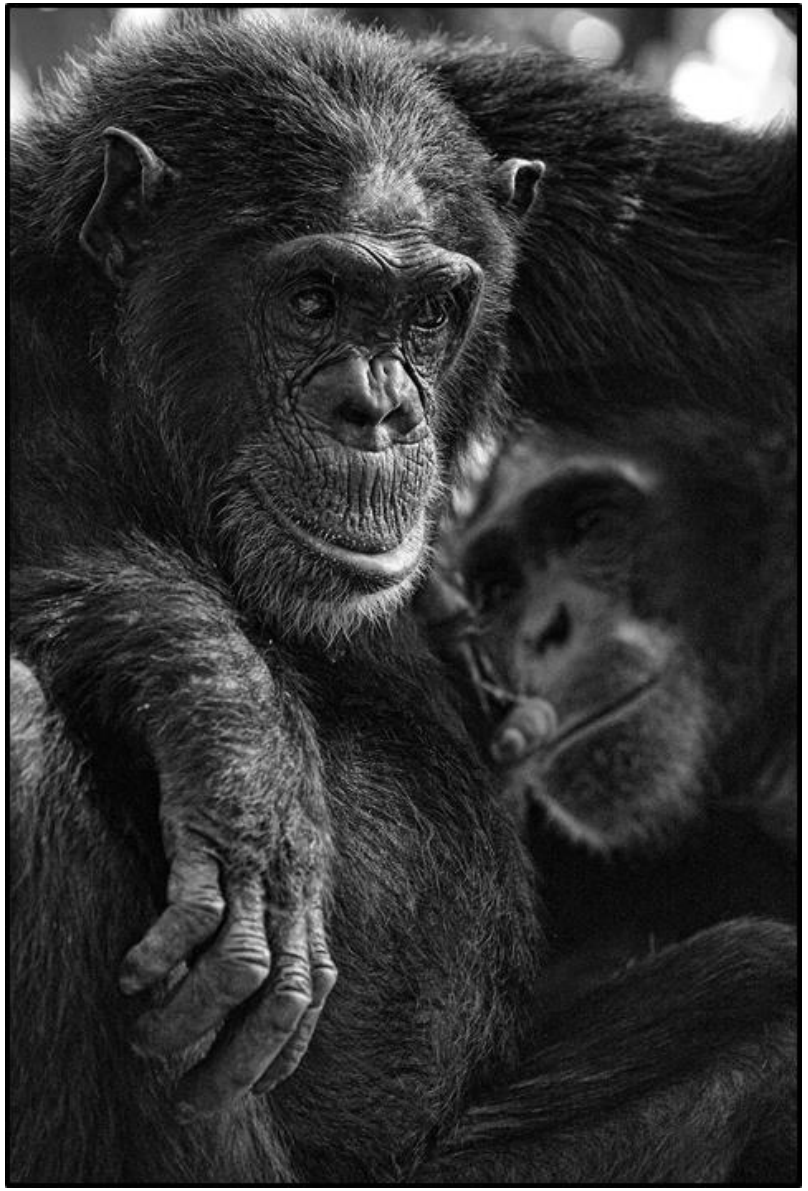
DNA structure

3.4 billion base pairs

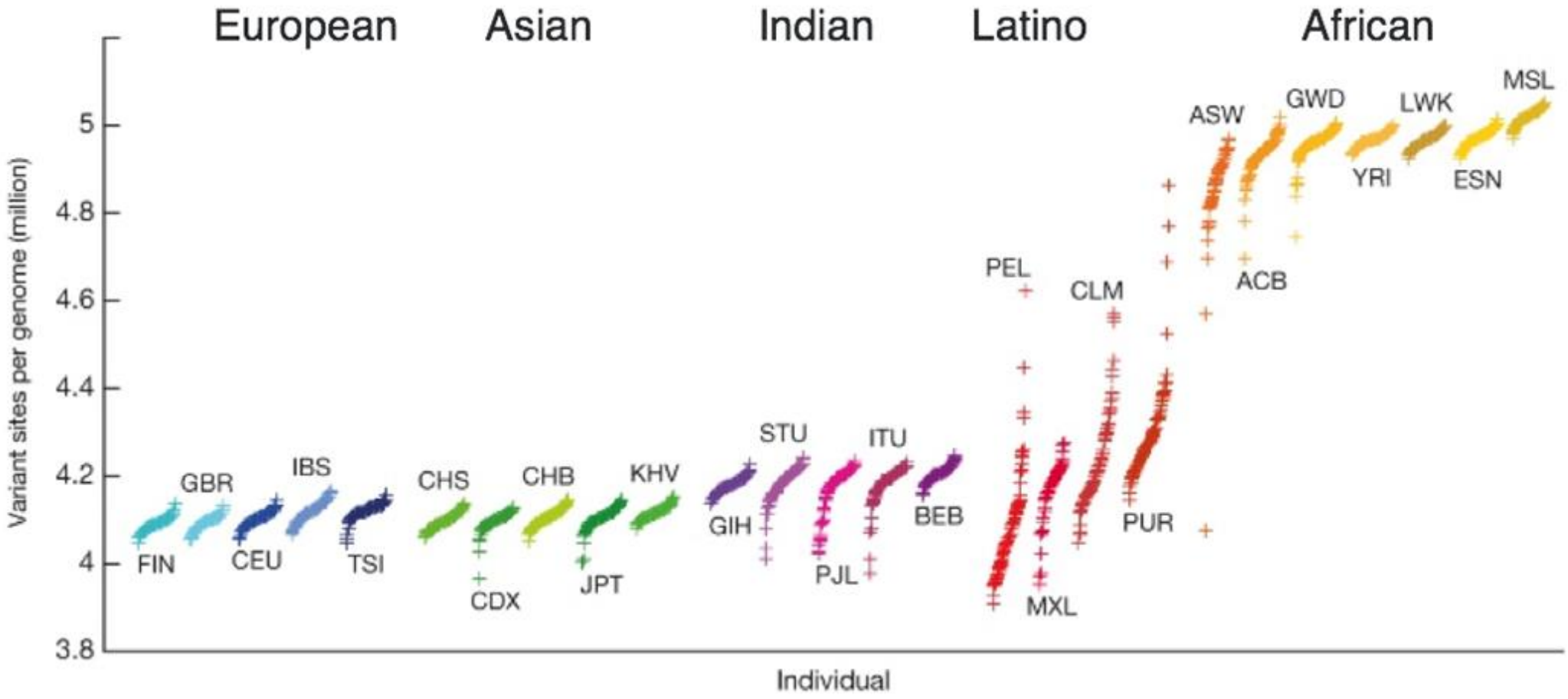


23 chromosomes

The human genome differs from our closest animal relatives by approximately 50M changes



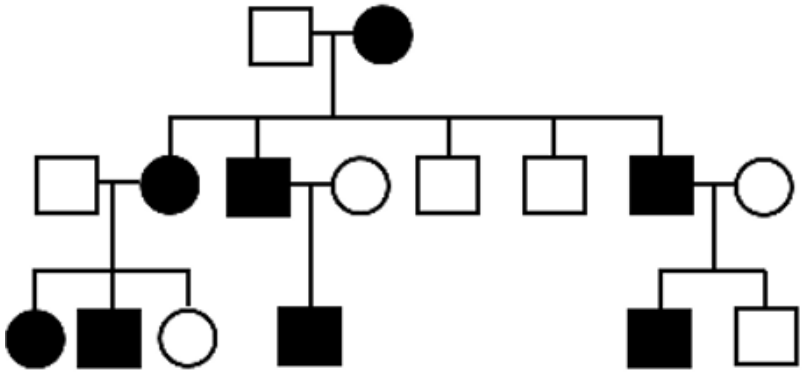
We differ from each other by 4-5 million variants - African genomes are the most diverse



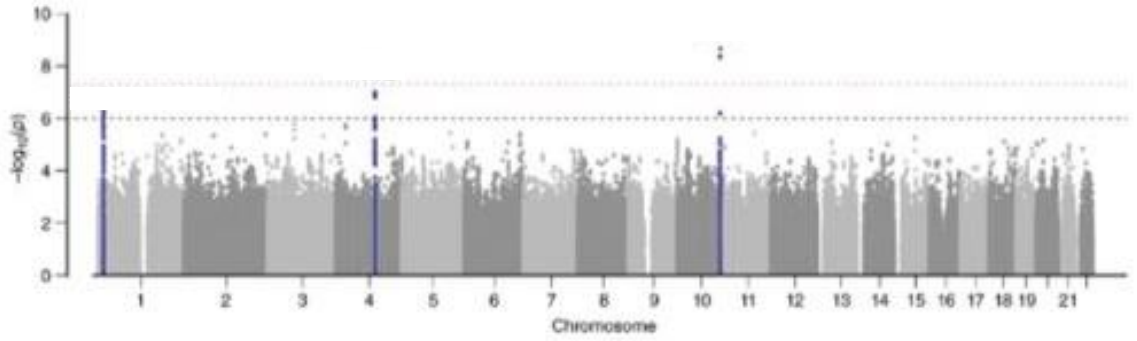
Source: A. Auton et al. Nature 526, 68-74 (2015) doi: 10. 1038/nature15393

Investing in computational genetics and academic partnerships for:

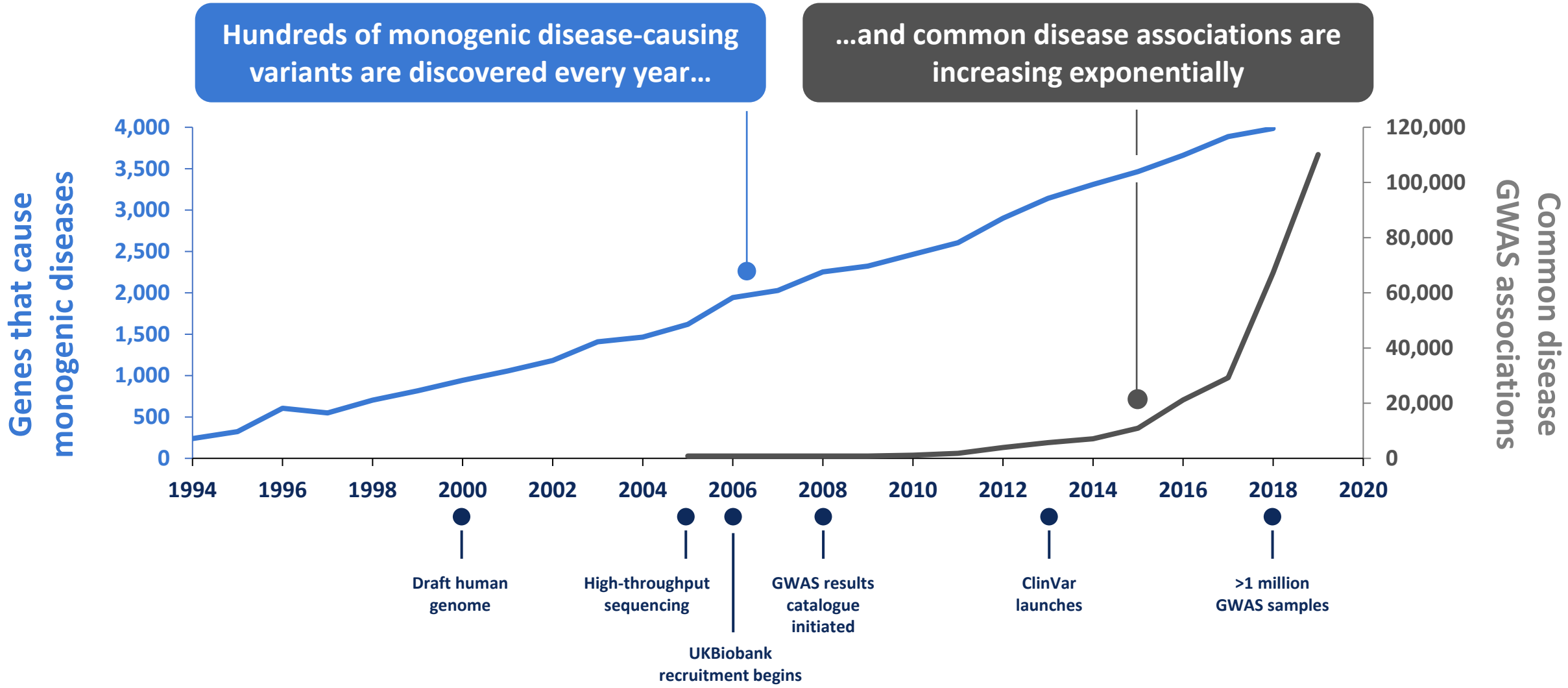
Monogenic target identification & validation



Indication expansion into common diseases

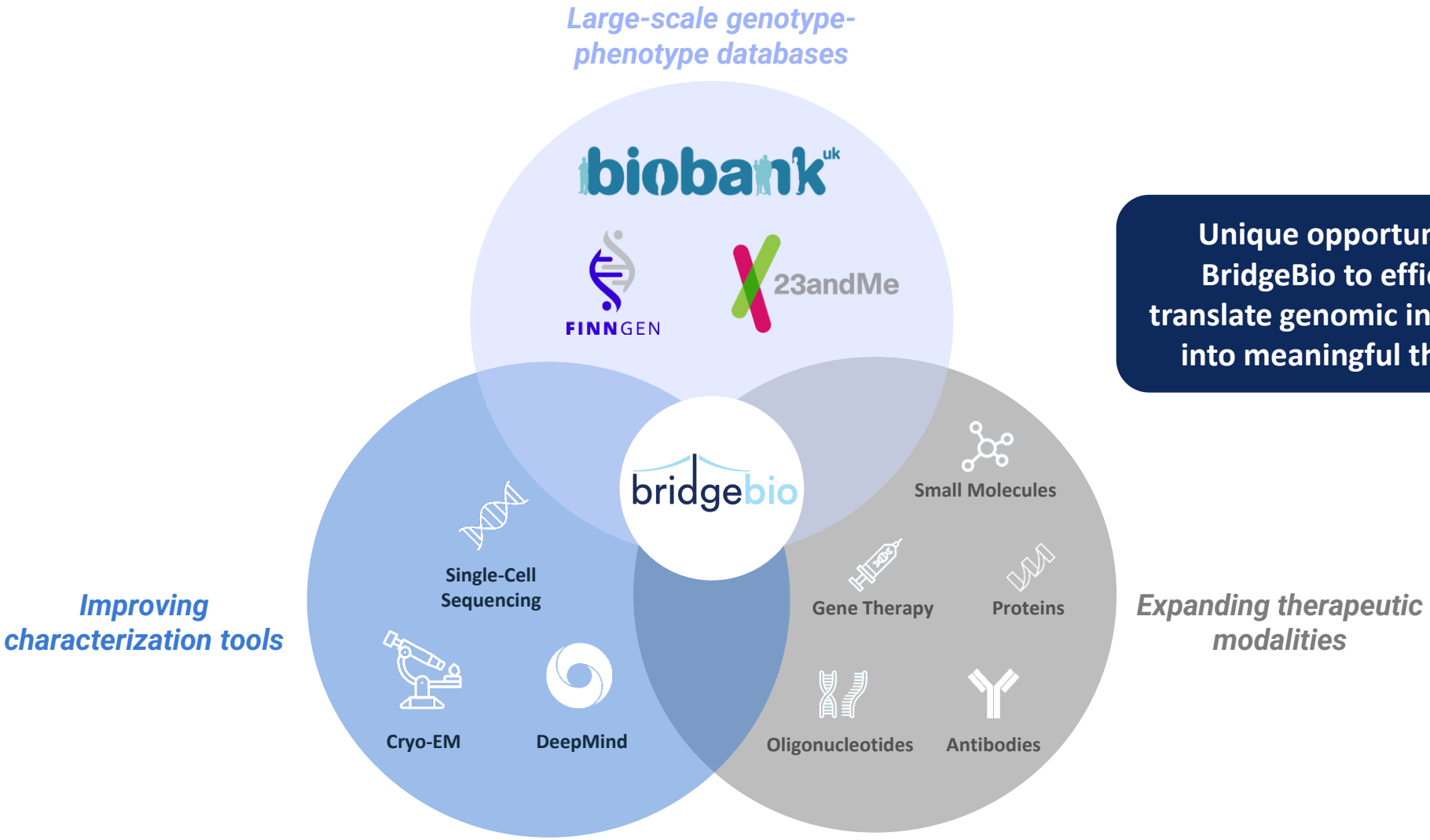


Single gene variants can cause or contribute to disease



Source: Claussnitzer et al., Nature 2020

Convergence of genetic innovation driving drug development



Unique opportunity for BridgeBio to efficiently translate genomic information into meaningful therapies

BridgeBio's endless summer

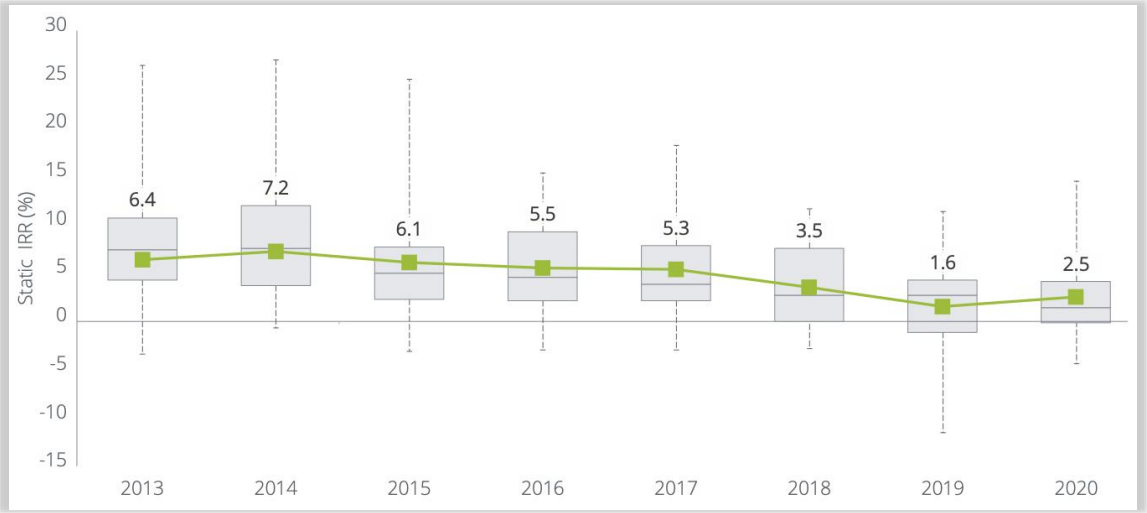
Neil Kumar, Ph.D.

Founder and CEO

Currently, few examples of sustainable innovation engines for genetic medicines

Big pharma R&D destroys value in aggregate

Big pharma R&D IRR



- R&D IRR is less than cost of capital for big pharma

Biotech companies have expectations that can't be met

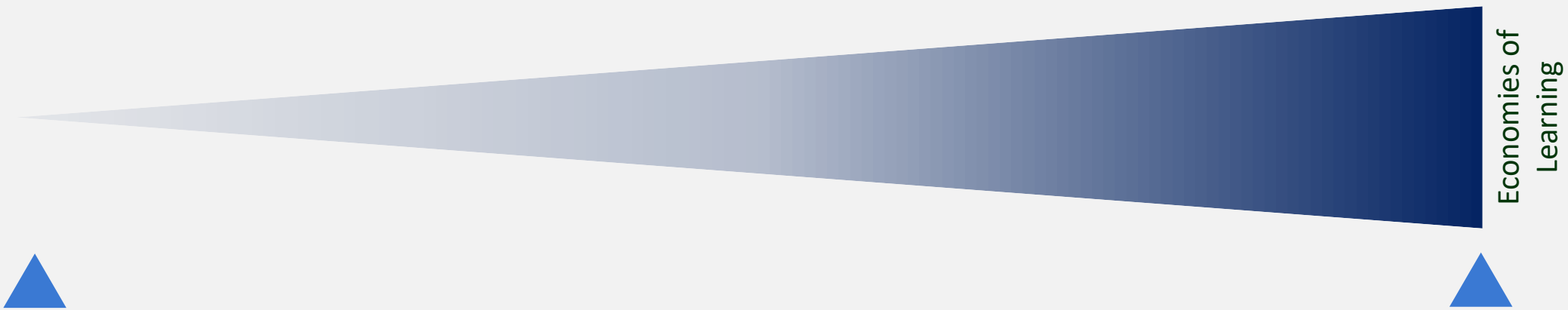
The biotech market requires constant and significant innovation to create long term stable ROIC

- Currently, biotech EV is ~$1.4 trillion
  - Assume – One wants to grow market cap by 12% YoY
  - Roughly, capital leaving the system by dividends + M&A = capital raised by IPOs + follow-ons
- If 70% of the value comes from new drugs, biotech would need to generate drugs worth ~$2 trillion over the next 10 years, or approvals with aggregate **~$40 billion peak year sales every year**

Source: Deloitte, FactSet, Internal BridgeBio analysis

What does a sustainable genetic medicine innovation ecosystem look like? Criteria #1

Criteria #1: Need to solve for diseconomies of scale early, and economies of scale late

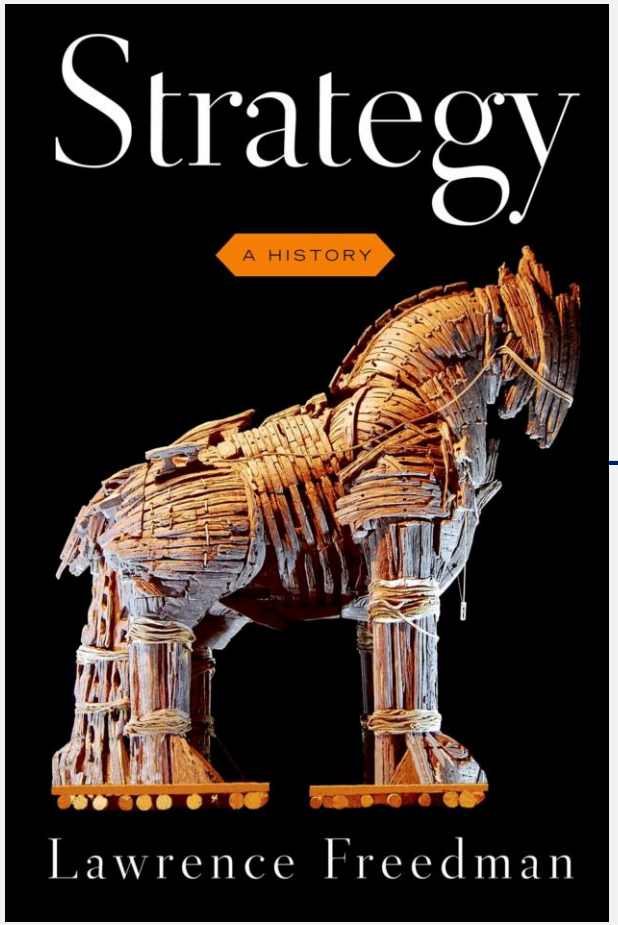


Decentralized R&D enables focus at the level of each asset driving value (Biotech)

Scale and economies of learning drive value in a commercial organization (consolidation)

What does a sustainable genetic medicine innovation ecosystem look like? Criteria #2

Criteria #2: Each program needs to be NPV positive and supported by beautiful science



- Each program is NPV positive
  - **Realistic market size estimates**
    Only 2.3% of brands today >$2 Bn
  - **Capital efficient**
    IND cost < $15 Mn for small molecule
- Beautiful science
  - **High POTS programs**
    More like engineering, less biology
  - **Product market fit**
    Therapies which match patient need

Source: Evaluate Pharma

BridgeBio satisfies the criteria of a sustainable genetic medicine innovation engine

Key criteria of a sustainable genetic medicine innovation engine	Key attributes of BridgeBio
Criteria #1	▪ **The willingness and scale to fail** and to re-allocate capital, within a decentralized company model
	▪ **Focus at the level of individual diseases and assets.** Drug R&D is a game of details
Criteria #2	▪ **Distinctive early-stage asset selection,** based on a deep understanding of clinical unmet need, genetics, and underlying molecular pathophysiology
	▪ **Efficient corporate structure** that cuts no corners on science and medicine, but limits G&A, infrastructure and needless management
People	▪ **Experienced, product-focused R&D leadership** that can define go / no-go's, required product attributes, and can drive programs through the clinic efficiently

Putting it all together: The opportunity to build the next great genetic medicine company

Traditional genetic medicines players fall into 1 of 2 archetypes

1

Blockbuster product, limited pipeline

ALEXION®

VERTEX®

bridgebio

- Acoramidis for ATTR as a blockbuster market opportunity
- Large pipeline, high probability of success
- Fully integrated rare disease commercial org

2

Smaller products, large pipeline

BIOMARIN®

sobi rare strength

ultragenyx pharmaceutical

Fingerprints of hope – #1 BridgeBio's distinctive productivity

In less than 6 years since inception, BridgeBio has delivered…

2 APPROVED PRODUCTS

Nulibry (fosdenopterin) for injection

TRUSELTIQ (infigratinib) capsules

30+ ACTIVE R&D PROGRAMS ACROSS 4 MODALITIES

20 ONGOING CLINICAL TRIALS ACROSS >450 SITES

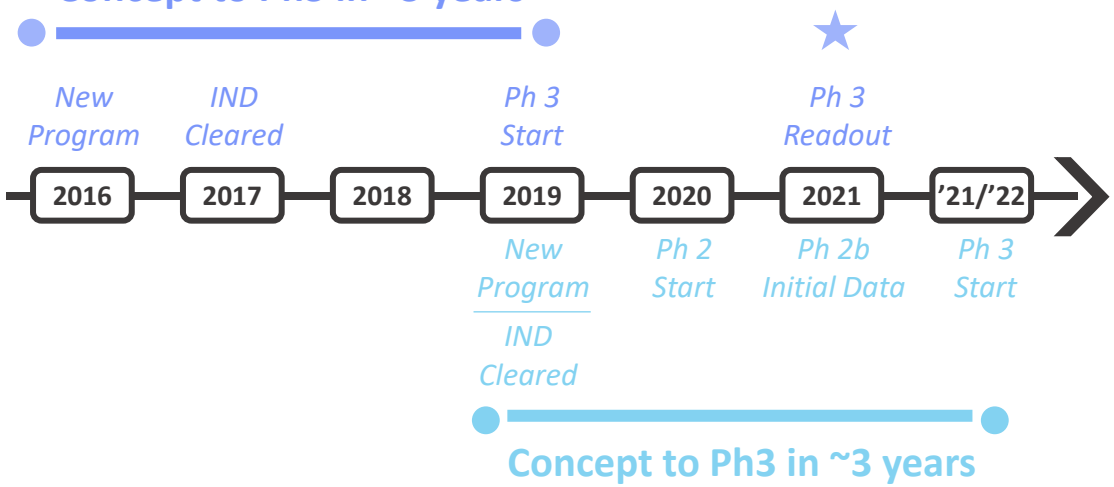
460 FULL-TIME EMPLOYEES

15 INDs (AVERAGE ~3 PER YEAR)

Select Programs:

ATTR

Concept to Ph3 in ~3 years



ADH1

…building the framework for efficient, repeatable results

Fingerprints of hope – #2 BridgeBio's unique product platform

Recent Additions

- 4 new databases
- Bayesian methods for precise disease prevalence estimates
- 14 new university partnerships
- >5,000 new rare variants, >100 new causal genes discovered

- NMR spectroscopy for new drug targets
- AI for deciphering new protein structures
- Phenotypic screening for largest genetic diseases
- ASO screens for haploinsufficiency diseases

- 4 new clinical trials
- Activated 62 new sites in 11 countries
- Telperian partnership for ML empowered precision analytics
- Science 37 partnership for agile, decentralized clinical trials

- Two commercial launches (MoCD Type A, 2L CCA)
- 95% of lives covered in 6mths of NULIBRY launch
- Established a PAP to provide qualified patient's free access
- European office open, LATAM office upcoming

DISCOVER

Computational genomics, systemic disease mapping, broad network of academic partnerships

CREATE

Molecular dynamics assisted chemistry, gene therapy, therapeutic proteins, antisense oligos

TEST

20 ongoing trials across >450 sites and 26 countries, central operations toolkit and analytics

DELIVER

Global infrastructure, diagnostics, patient support, disease state awareness

Fingerprints of hope – #3 BridgeBio's great drug developers

Scientific insight and judgment from industry leaders with a proven track record

Charles Homcy, MD
Founder and Chairman of Pharmaceuticals
MyoKardia GBT

Frank McCormick, PhD
Founder and Chairman of Oncology
ONYX PHARMACEUTICALS UCSF

Richard Scheller, PhD
Chairman of R&D
Genentech 23andMe

Len Post, PhD
Advisor
BIOMARIN LEAD THERAPEUTICS

Phil Reilly, MD, JD
Advisor
THIRD ROCK VENTURES bluebirdbio

Experienced team of R&D operators responsible for 100+ INDs and 20+ approved products

Mendelian / Cardiorenal

Uma Sinha, PhD
Chief Scientific Officer
GBT PORTOLA PHARMACEUTICALS

Robert Zamboni, PhD
Chemistry
MERCK FROSST

Jonathan Fox, MD, PhD
Chief Medical Officer, Cardiorenal
MyoKardia AstraZeneca

Oncology

Eli Wallace, PhD
Chief Scientific Officer, Oncology
Peloton Therapeutics ARRAY BIOPHARMA

Pedro Beltran, PhD
SVP, Oncology
AMGEN UNITY BIOTECHNOLOGY

Fingerprints of hope – #4 BridgeBio's pipeline, including potential best-in-class candidates

	Indication	Drug Mechanism	Pt. pop. (US+EU)	Discovery	Pre-IND	Phase 1	Phase 2	Phase 3	Approved	Partner
Mendelian	MoCD type A	NULIBRY™ (Synthetic cPMP, fosdenopterin)	100						Nulibry	MEDISON
	Achondroplasia	Low-dose FGFRi (infigratinib)	55k							
	LGMD2i	Glycosylation substrate (ribitol)	7k							
	RDEB	Recombinant COL7 (BBP-589)	2k							
	PKAN / organic acidemia	Pank activator (BBP-671)	7k							
	VM / LM	Topical PI3K inhibitor (BBP-681)	117k							
	Netherton	Topical KLK inhibitor (BBP-561)	11k							
	PTEN autism	PI3Kb inhibitor (BBP-472)	120k							
	4 undisclosed small molecule programs		>500k							
	4 undisclosed antisense oligonucleotide programs		>300k							
Precision Cardiorenal	ATTR amyloidosis	TTR stabilizer (acoramidis)	>400k							AstraZeneca
	ADH1	CaSR antagonist (encaleret)	12k[1]							
	PH1 / frequent stone formers	GO1 inhibitor (BBP-711)	5k / 1.5m							
	Undisclosed DCM small molecule program		>250k							
	Undisclosed DCM AAV gene therapy program									
Precision Oncology	FGFR2+ cholangiocarcinoma (2L)	TRUSELTIQ™ (FGFRi, infigratinib)	4k						TRUSELTIQ	
	FGFR2+ cholangiocarcinoma (1L)	FGFRi (infigratinib)								HELSINN
	FGFR3+ adjuvant urothelial	FGFRi (infigratinib)	21k							
	FGFR1-3+ tumor agnostic	FGFRi (infigratinib)	24k							
	FGFR1-3+ gastric cancer	FGFRi (infigratinib)	41k[2]							
	MAPK / RAS-driven cancer	SHP2i monotherapy (BBP-398)	>500k							
		SHP2i combo therapy (BBP-398)								Bristol Myers Squibb
	KRAS-driven cancer	KRAS G12C dual inhibitor	>500k							
		PI3Kα:RAS Breaker								
		KRAS G12Di								
	Solid tumors	GPX4i	>500k							
Gene Therapy	CAH	AAV5 gene therapy (BBP-631)	>75k							
	Canavan	AAV9 gene therapy (BBP-812)	1k							
	TMC1 hearing loss	AAV gene therapy (BBP-815)	2k							
	Galactosemia	AAV gene therapy (BBP-818)	>7k							
	TSC1/2	AAV gene therapy	>100k							
	Cystinuria	AAV gene therapy	20k							
	3 capsid discovery collaborations									

[1]US carriers
[2]China + Japan patient population

BridgeBio's endless summer

MoCD Type A
2L CCA

ATTR-CM/PN
ADH1
Achon
CAH

PKAN/OA
PH1/FSF, VM
SHP2, UC, RDEB
LGMD2i, Canavan

KRAS
ALS, Autism
CF, A1AT, GALT
TMC1, TSC1/2

Presentations to come

- Precision Cardiorenal:
  - Introduction – Cameron Turtle
  - Acoramidis, a TTR stabilizer, for ATTR – Jonathan Fox
  - Encaleret, a CaSRi, for ADH1 – Mary Scott Roberts
- Gene therapy platform – Eric David
- Wave 3 Mendelian programs – Uma Sinha
- Precision Oncology – Eli Wallace
- BridgeBioX – Charles Homcy

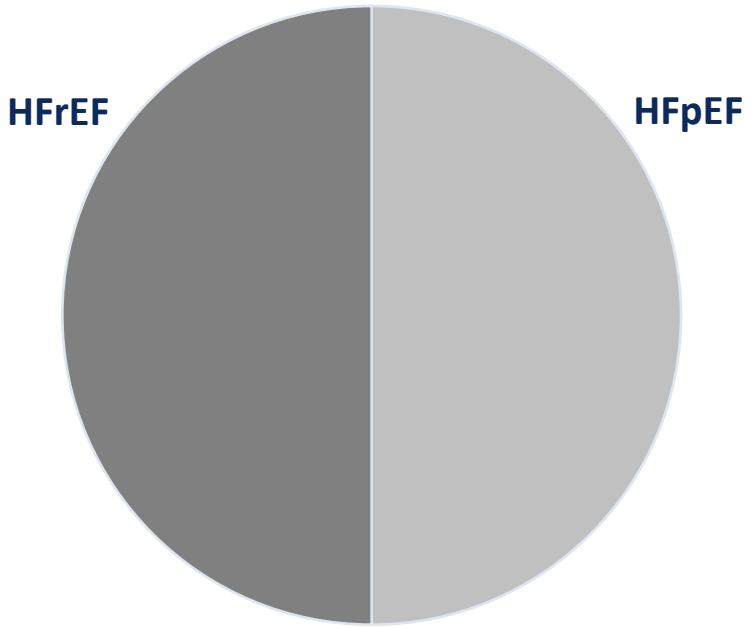
Precision cardiorenal

Cameron Turtle, D. Phil.

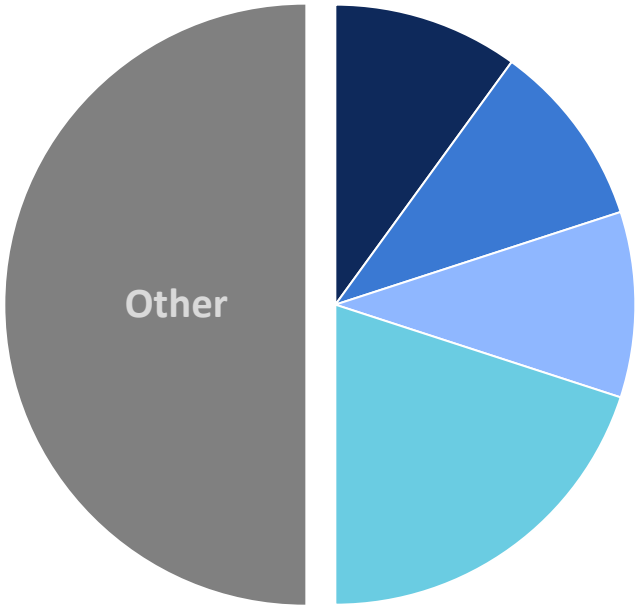
Chief Strategy Officer

Genetic drivers of cardiac disease are unlocking precision medicine targets

Diagnosis by phenotype



Diagnosis by mechanism – *genetic associations*



Amyloid – *TTR*

Contractile – *MYH7*, *MYBPC3*, *TNNT2*

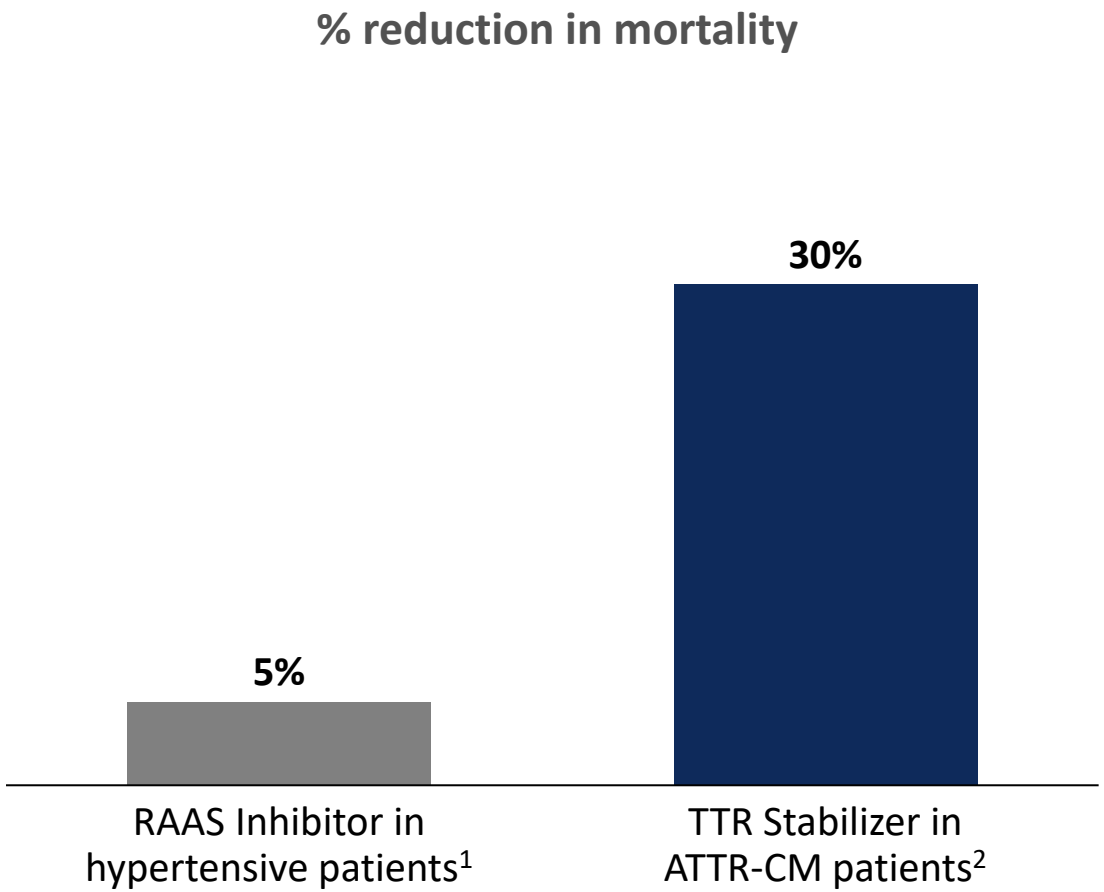
Structural/signaling – *TTN*, *LAMP2*, *BAG3*

Hyperlipidemia – *PCSK9, LDLR*

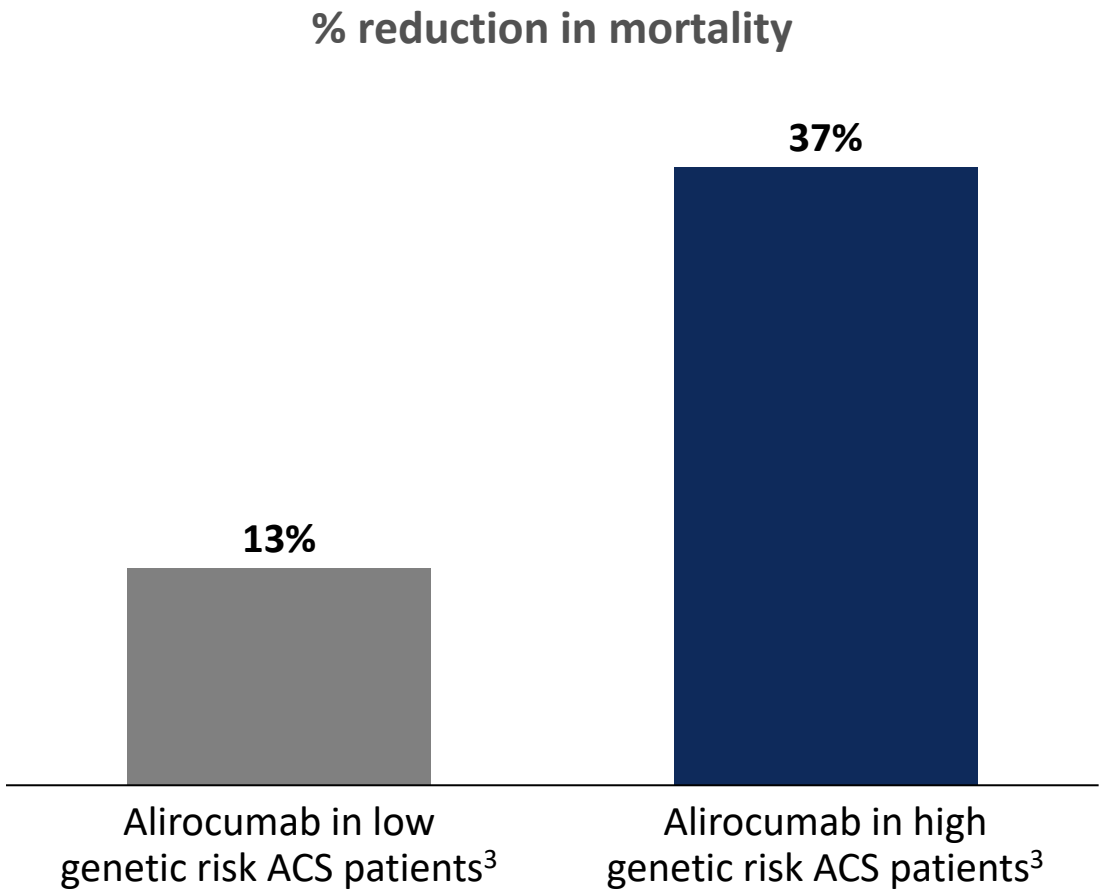
HFrEF = heart failure reduced ejection failure; HFpEF = heart failure preserved ejection failure
Note: Proportions not to scale, genetic associations not exhaustive

Precision medicines have delivered increased treatment effect sizes

Mendelian disease



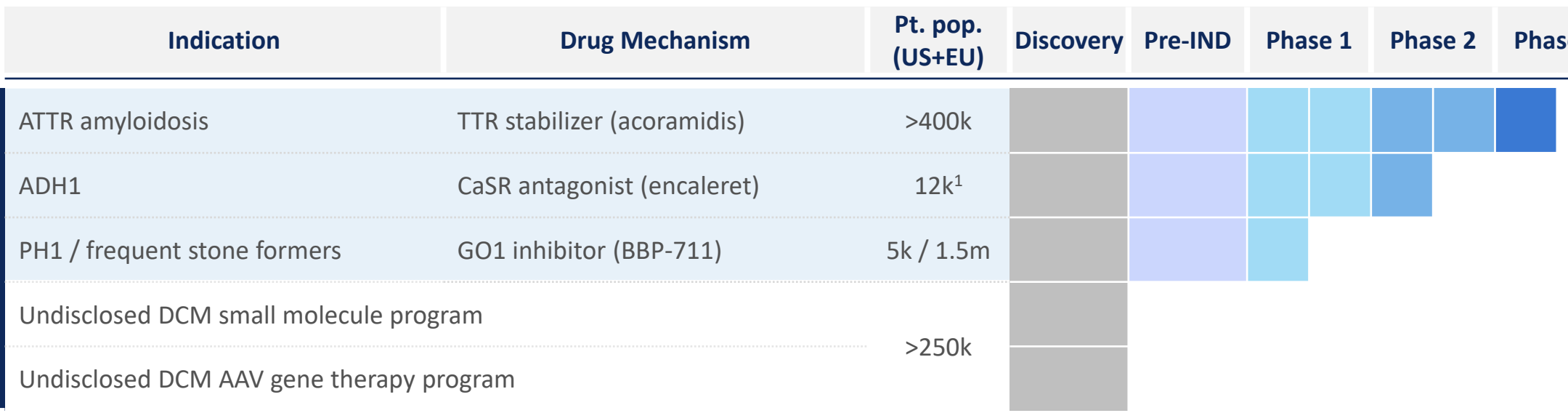
High genetic risk in broader diseases



[1]van Vark et al., EHJ 2012. [2]Maurer et al., NEJM 2018. [3]Damask et al., Circ 2020

Cardiorenal pipeline overview

	Indication	Drug Mechanism	Pt. pop. (US+EU)
Precision Cardiorenal	ATTR amyloidosis	TTR stabilizer (acoramidis)	>400k
	ADH1	CaSR antagonist (encaleret)	12k[1]
	PH1 / frequent stone formers	GO1 inhibitor (BBP-711)	5k / 1.5m
	Undisclosed DCM small molecule program		>250k
	Undisclosed DCM AAV gene therapy program		



Featured Programs

[1]US carriers

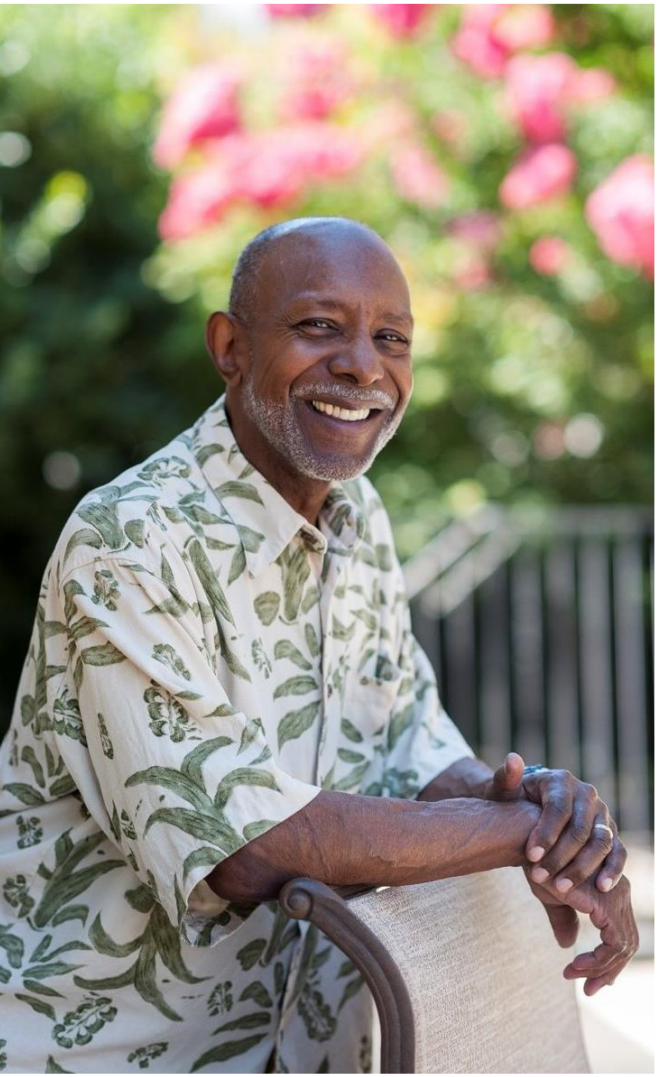
Acoramidis: TTR stabilizer for ATTR

Jonathan Fox, M.D., Ph.D.

Chief Medical Officer, Cardiorenal

Acoramidis is an investigational drug. Its safety and efficacy have not been full evaluated by any regulatory authority.

Acoramidis for transthyretin (TTR) amyloidosis (ATTR)



Len
Living with ATTR-CM

Prevalence

400k+

Worldwide

Pathophysiology

Systemic disease most commonly presenting as cardiomyopathy or peripheral neuropathy

Genetic Driver

Destabilized TTR leading to amyloid accumulation

Therapeutic Hypothesis

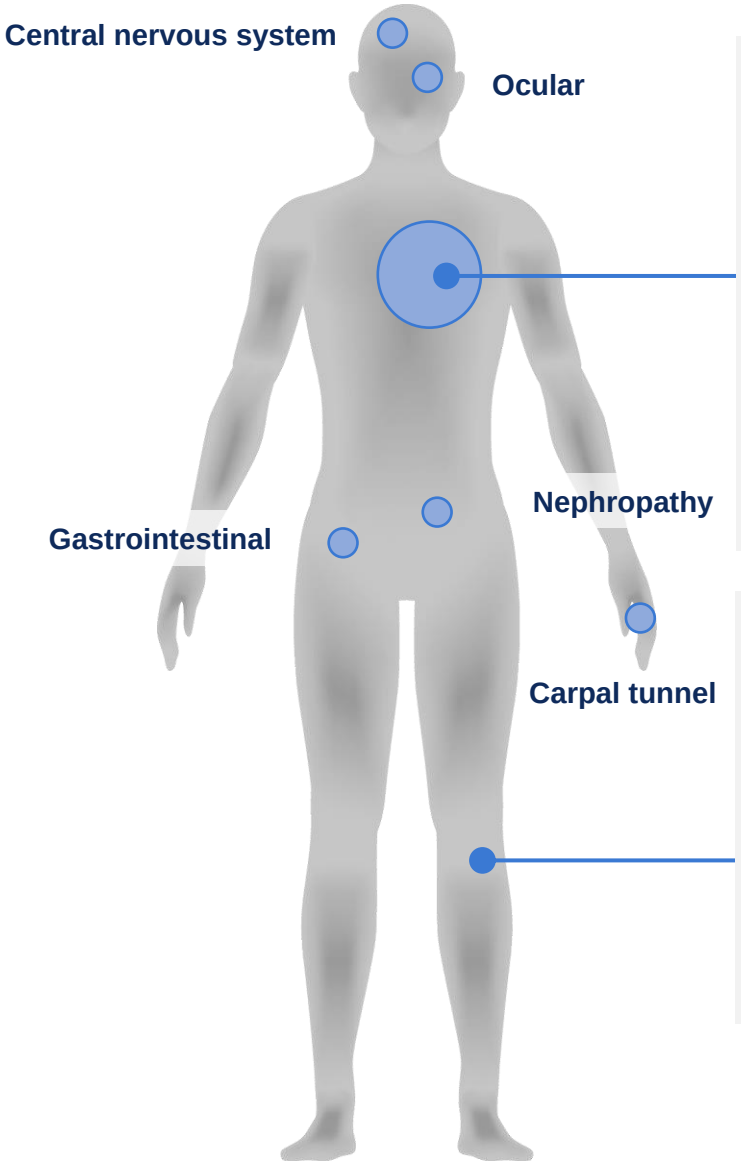
TTR stabilizer designed to mimic protective T119M mutation

Design Criteria for Optimal Therapy

- Near-complete stabilization of TTR
- Preservation of TTR tetramer
- Oral Dosing

ATTR is a systemic disease with multiple manifestations

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones



Cardiomyopathy (ATTRwt-CM or ATTRv-CM)

- Deposition of wild-type or variant (e.g., V122I) TTR amyloid in the heart, leading to predominantly diastolic heart failure
- Likely affects 400K+ worldwide, majority undiagnosed
- Late onset (age 50+), progressive and fatal with median survival of 3-5 years from diagnosis

Polyneuropathy (ATTR-PN)

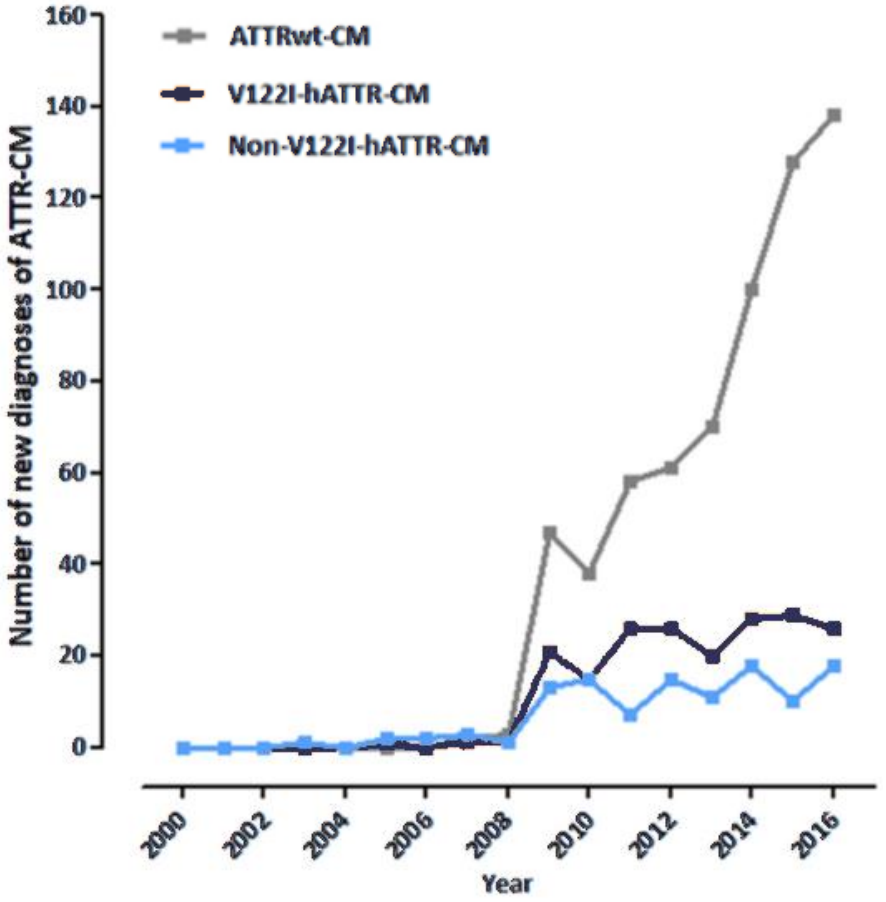
- Affects ~10K worldwide, primarily in EU and Japan
- Exclusively caused by variant TTR (e.g., V30M)
- Onset between ages of 30 and 50, progressive and fatal with median survival of 5-10 years from diagnosis

Source: Grogan, M et al. JACC 2016, 68:1014-20; Planté-Bordeneuve, V. and Said, G. Lancet Neurol 2011, 10:1086-97

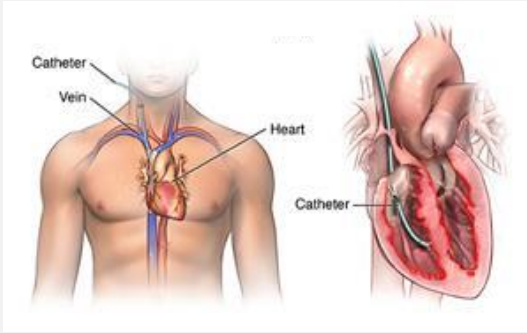
Rapid increase in patient finding driven by non-invasive diagnosis techniques

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

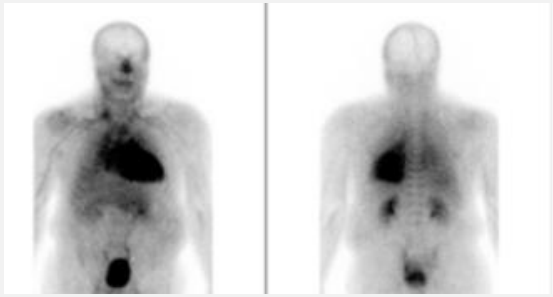
New ATTR-CM diagnoses per year at single site



Invasive heart biopsies



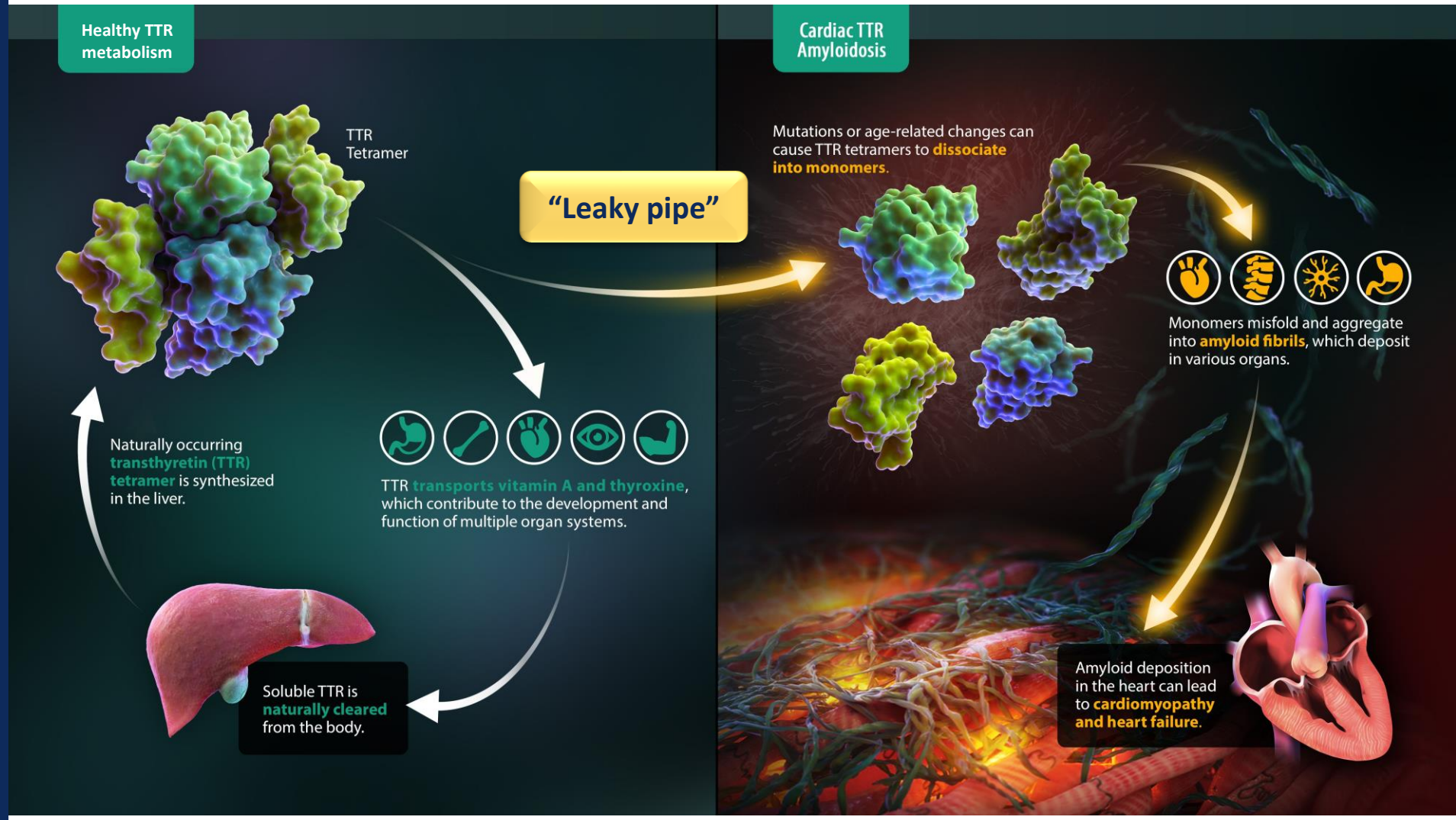
Non-invasive technetium scans



Source: Lane et al., 2019; Johns Hopkins Medicine; American College of Cardiology

TTR plays a physiological role in the body

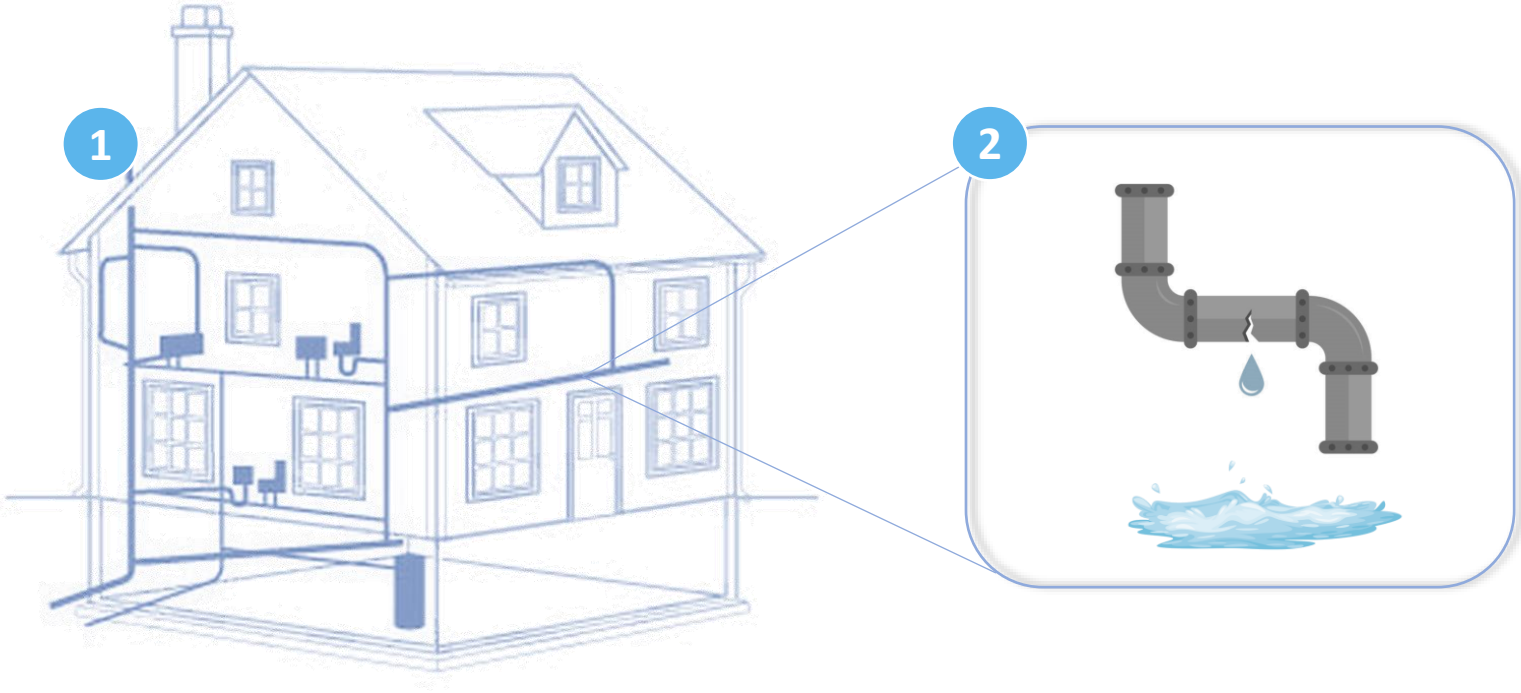
- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones



Targeting diseases at their source optimizes safety and efficacy

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

Two ways to stop a leaky pipe



Shut down the entire water line
(Target upstream)

Fix the leak
(Target the source)

Acoramidis was designed to treat ATTR at its source

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

Disease mechanism

Native TTR circulates in blood as a tetramer

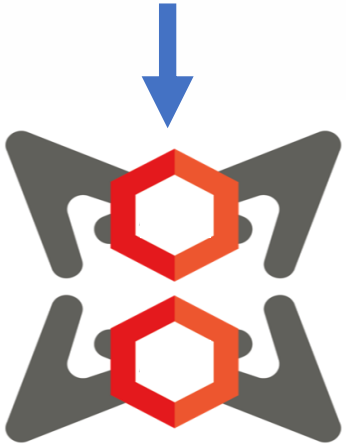
~130 known destabilizing variants

Protective T119M variant

Dissociation into monomers initiates pathogenesis

Monomers aggregate, causing disease

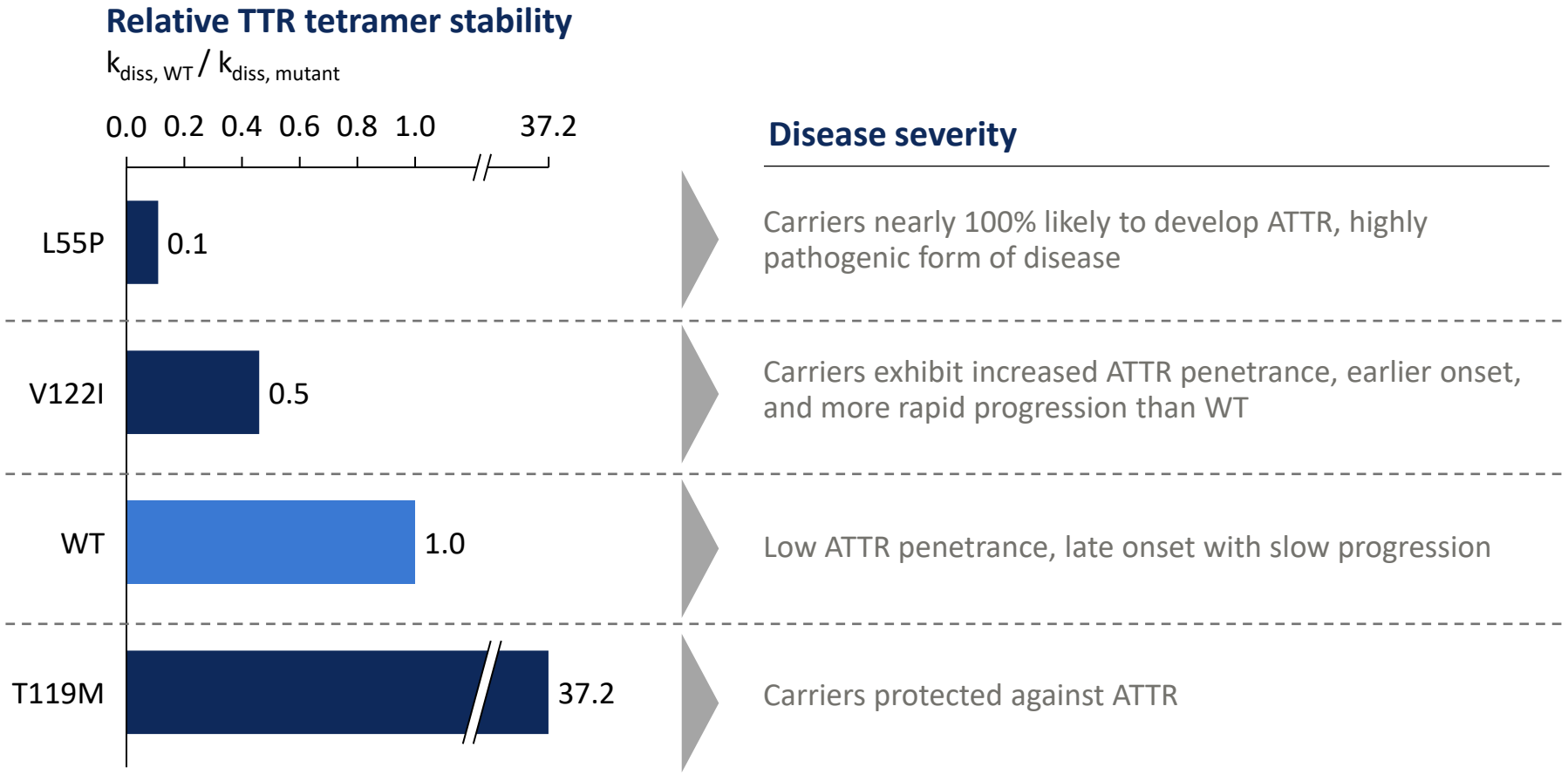
Therapeutic hypothesis



Acoramidis was designed to mimic protective T119M variant by stabilizing TTR tetramers to slow or halt disease progression

Human genetics suggest TTR instability is associated with disease severity

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones



- **Greater TTR destabilization correlates with earlier disease onset, increased disease severity**
- **ATTR-protective mutations stabilize TTR tetramer, preventing dissociation**

k_{diss} = dissociation constant
Source: Hammarstrom, P. et al. PNAS 2002, 99:16427-16432

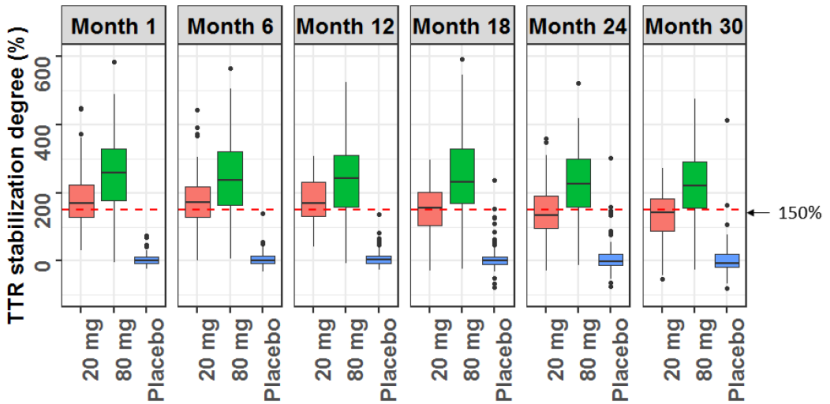
Higher dose of tafamidis increased stabilization and improved clinical benefit

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

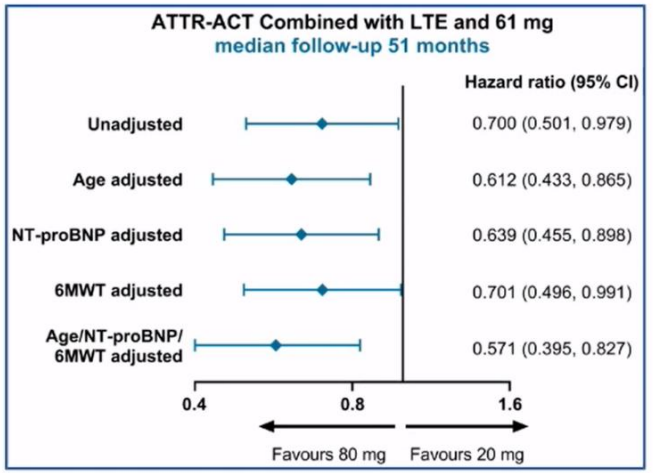
Phase 3 ATTR-ACT study tested two doses of tafamidis (20 mg & 80 mg) vs. placebo

- Participants receiving 80 mg of tafamidis (vs. 20 mg) exhibited greater TTR stabilization[1]
- Benefit of tafamidis 80 mg vs. 20 mg was evident on all-cause mortality in analysis of ATTR-ACT combined with long-term extension (LTE)[2]

TTR stabilization[1]



All-cause mortality[2]



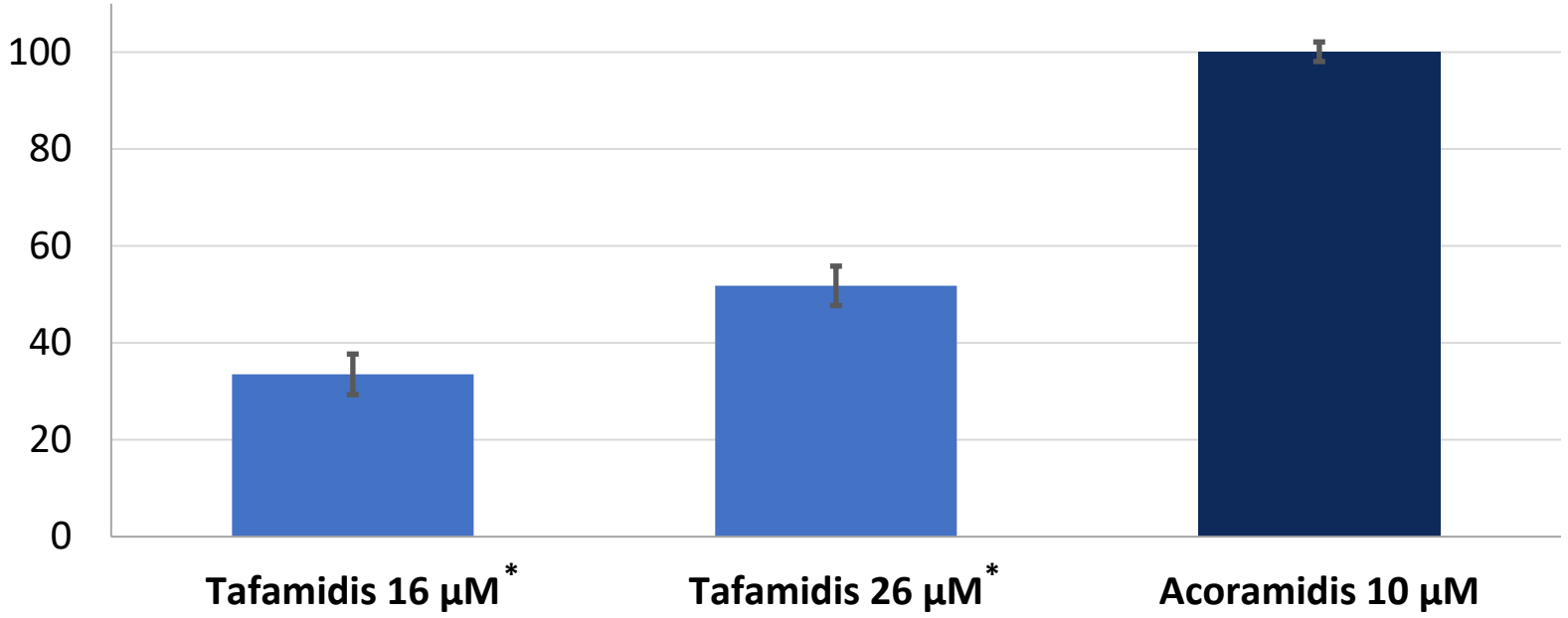
[1]FDA CDER Clinical Pharmacology and Biopharmaceutics, Clinical Review (Vyndaqel/Vyndamax), 2019
[2]Damy T, et al. Eur J Heart Fail. 2020. "Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study"

Acoramidis demonstrates near-complete stabilization of TTR

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

TTR target site occupancy by FPE assay[1]

%, mean +/- SD



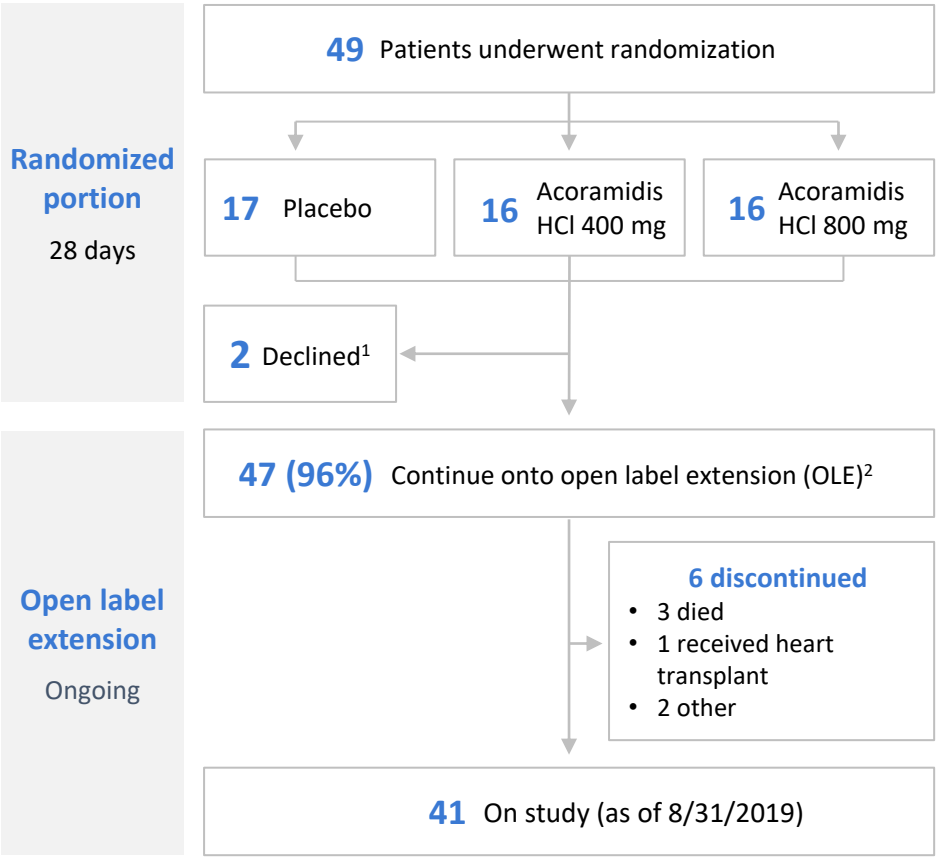
Acoramidis demonstrated near-complete TTR stabilization in vitro at clinical concentrations

Source: Ji, A.X., et al. Differential Transthyretin Binding, Kinetic Stability and Additive Ex Vivo Stabilization by AG10 Compared to Tafamidis. American Heart Association Scientific Sessions 2019
[1]FPE characterization of TTR binding site occupancy in serum incubated with stabilizer, n = 12
*Tafamidis 80 mg mean C_{min} and C_{max} per FDA review of tafamidis meglumine ATTR-CM NDA

Phase 2 ATTR-CM trial provided randomized 28-day and 15-month OLE data

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- **Published Data**
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

Schematic of acoramidis Phase 2 studies[4]



Outcomes

Primary

Safety and tolerability

- Adverse events
- Clinical events and vital signs
- Clinical laboratory parameters

Secondary and Exploratory

- Pharmacokinetics
- Pharmacodynamics
- Echocardiographic parameters

Publications to date:

- **Randomized 28-day study[3]**
- **Open label extension analysis as of 8/31/2019, median 65 weeks from acoramidis 201 initiation (randomized), median 53 weeks on acoramidis[4]**

[1]Both declined participation due to geographical constraints regarding study visits
[2]Median rollover period of 72 days (range 41-152 days)
[3]Judge, D.P. et al. JACC Vol. 74, No. 3, 2019:285 – 95
[4]Judge, D.P. et al. American Heart Association 2019

Acoramidis has been well-tolerated and demonstrated near-complete TTR stabilization in preclinical, Ph 1, and Ph 2 studies

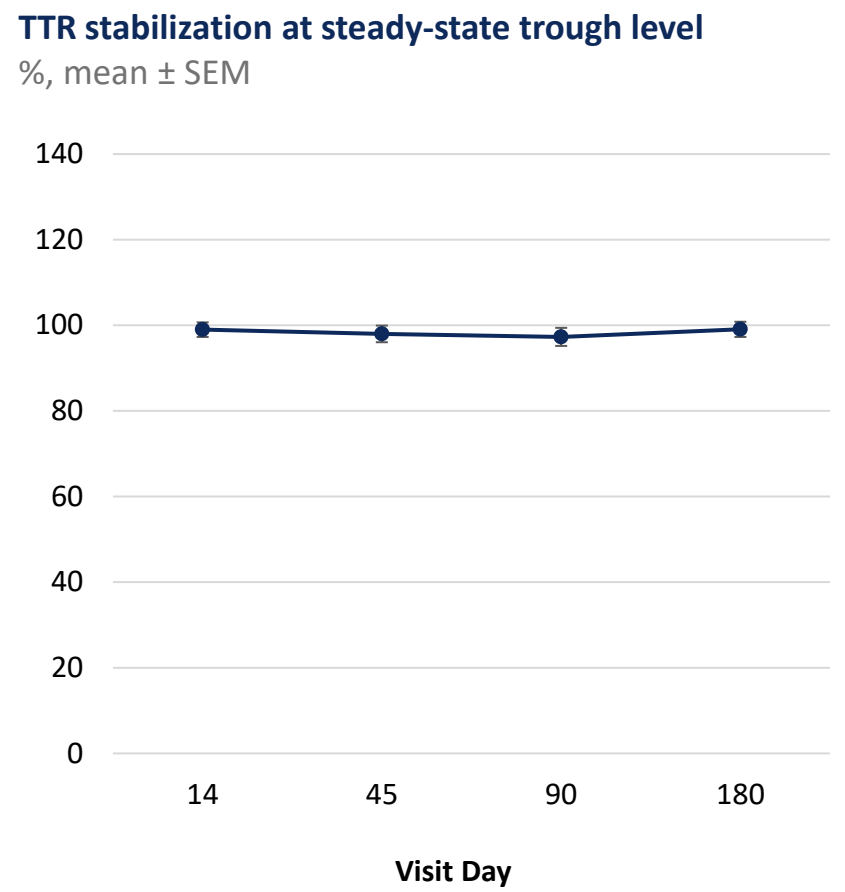
- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

Phase 2 safety summary[1]

Randomized portion	Placebo N = 17	Acoramidis (pooled doses) N = 32
Any Adverse Event	**15 (88%)**	**21 (66%)**
Mild	6 (35%)	11 (34%)
Moderate	8 (47%)	9 (28%)
Severe	1 (6%)	1 (3%)
Any SAE	**2 (12%)**	**1 (3%)**
AF and CHF	1 (6%)[1]	0
Leg cellulitis	1 (6%)	0
Dyspnea	0	1 (3%)

In long-term OLE, acoramidis was generally well tolerated with a pattern of adverse events consistent with underlying disease severity, concurrent illnesses, and age of participants

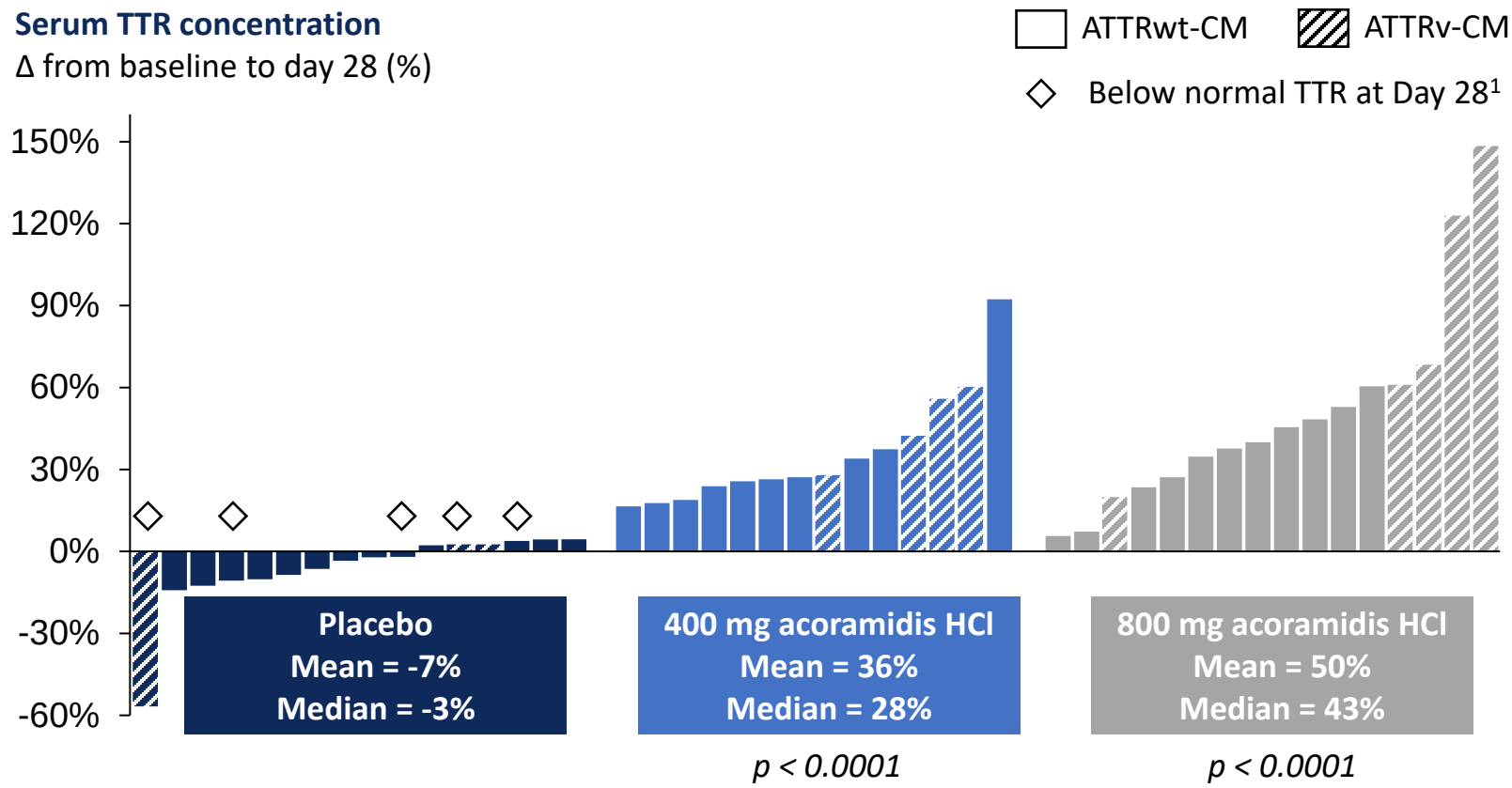
Phase 2 OLE TTR stabilization[2]



[1]Judge, D.P. et al. JACC Vol. 74, No. 3, 2019:285 – 95
[2]Judge, D.P. et al. American Heart Association 2019

Acoramidis increased serum TTR concentrations in a dose-dependent manner

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- **Published Data**
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones



- **Dose-dependent increase in serum TTR concentrations in acoramidis-treated subjects**
- **Greater effect observed in ATTRv subjects – final TTR concentrations normalized to comparable levels as in treated ATTRwt subjects**

Note: Serum TTR concentrations not available at baseline for one 400 mg subject and at Day 28 for one 400 mg and one placebo subject
Source: Judge, D.P. et al. J Am Coll Cardiol. 2019;74(3):285-295.
[1]Normal reference range for serum TTR 20-40 mg/dL (3.6-7.3 µM)

NT-proBNP and TnI remained stable in acoramidis-treated participants throughout OLE

Clinical Presentation

Diagnostic Approach

Therapeutic Approach

Published Data

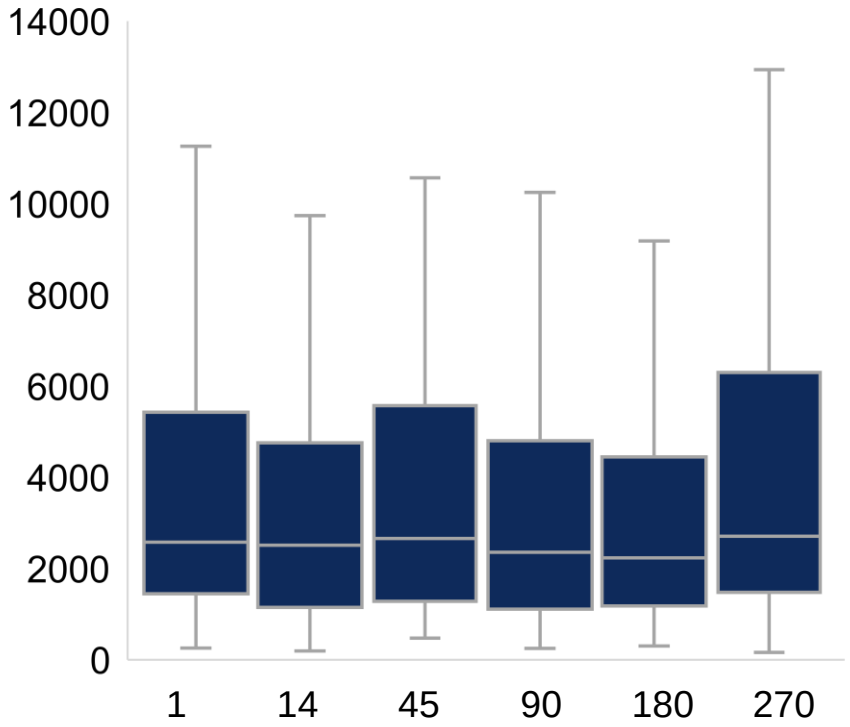
Pivotal Trial Design

6MWD Importance

Upcoming Milestones

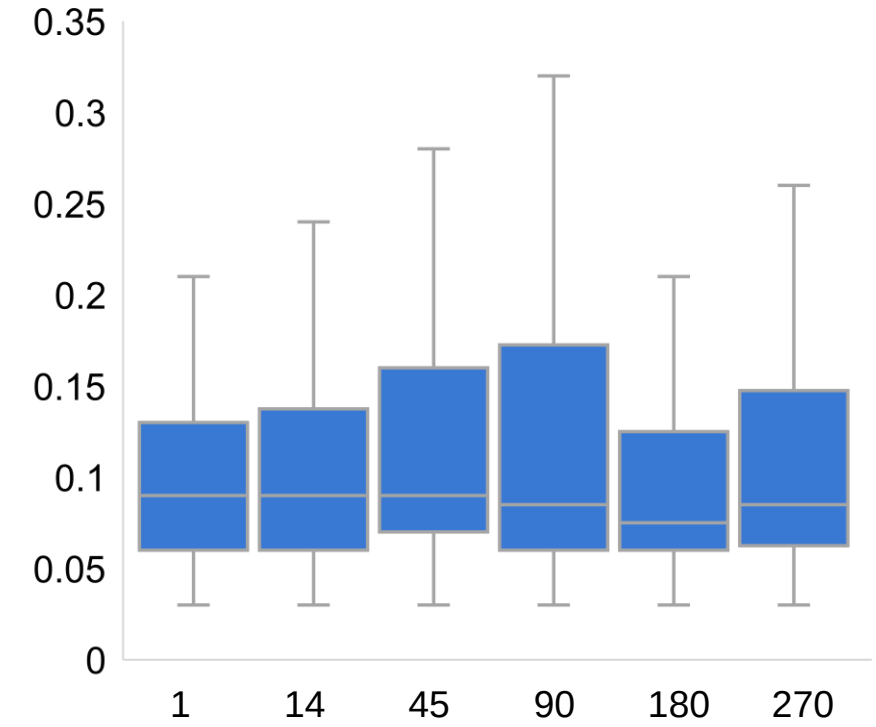
NT-proBNP[1]

pg/mL; 95% confidence interval, quartiles, median



TnI[1]

ng/mL; 95% confidence interval, quartiles, median



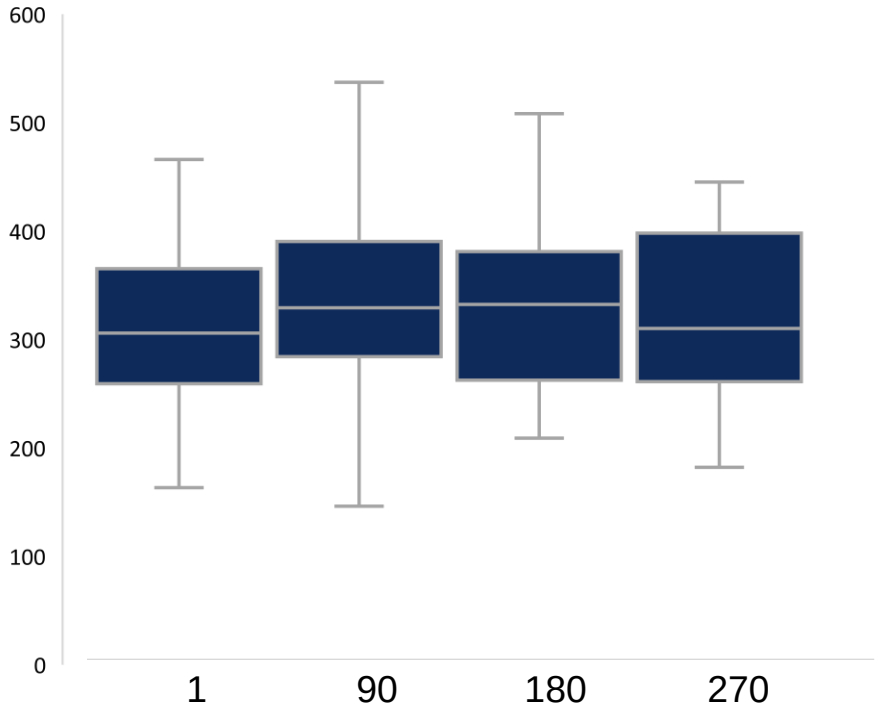
[1] Judge, D.P. et al. American Heart Association 2019. NT-proBNP = N-Terminal pro B-type Natriuretic Peptide. TnI = troponin I

Echocardiography parameters remained stable in acoramidis-treated participants throughout OLE

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

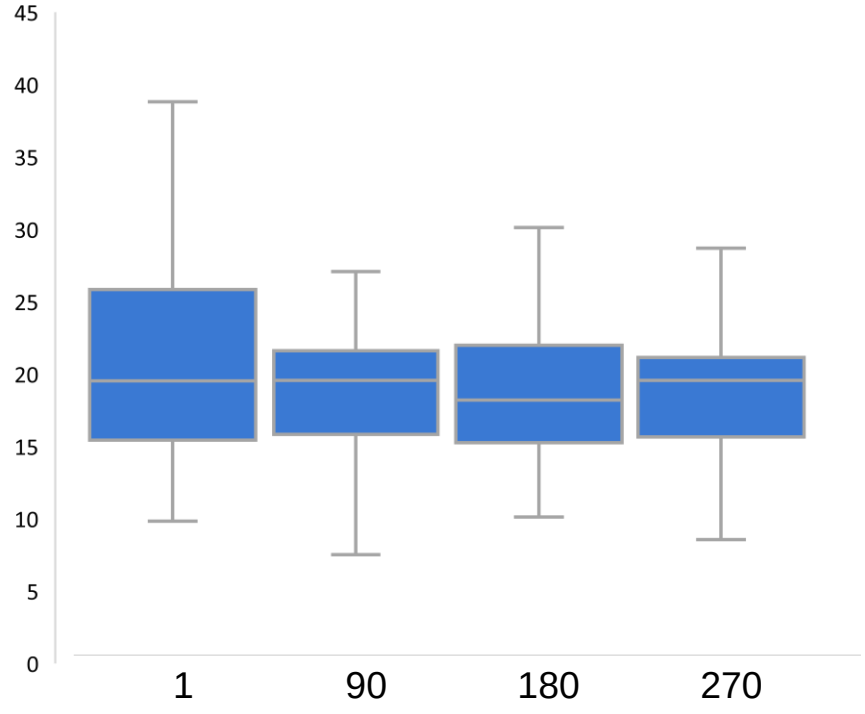
Left ventricular mass[1]

g; 95% confidence interval, quartiles, median



Left ventricular stroke volume index[1]

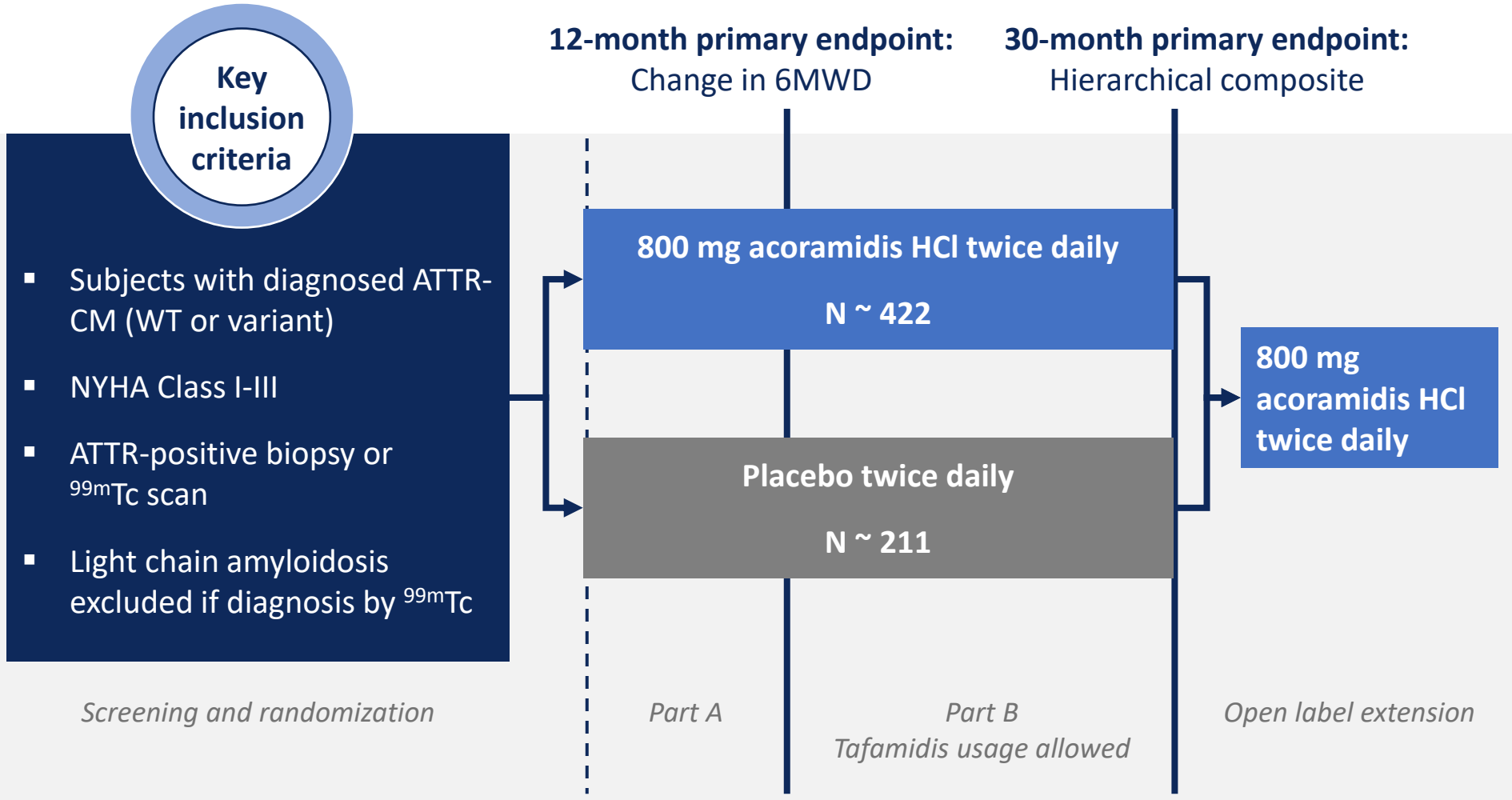
mL/m^2; 95% confidence interval, quartiles, median



[1] Judge, D.P. et al. American Heart Association 2019

Embedded Ph3 design includes 12-month and 30-month primary endpoints

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- **Pivotal Trial Design**
- 6MWD Importance
- Upcoming Milestones



Secondary endpoints include: Kansas City Cardiomyopathy Questionnaire, serum TTR, TTR stabilization
6MWD = Six minute walk distance; NYHA = New York Heart Association;
^{99m}Tc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); dx = diagnosis;
CV hosp = cardiovascular-related hospitalizations

6-Minute Walk Test is a clinically meaningful, treatment-responsive endpoint

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- **6MWD Importance**
- Upcoming Milestones

Simple, sub-maximal exercise test to assess aerobic capacity and endurance

Demonstrated to measure treatment benefit in heart failure, COPD, and pulmonary arterial hypertension

Higher rates of mortality observed with lower 6MWD in multiple cardiopulmonary diseases[1,2]

"The 6-minute walk test (6MWT), a measure of functional capacity, was identified as a **predictor of overall survival** in patients with ATTR-CM."

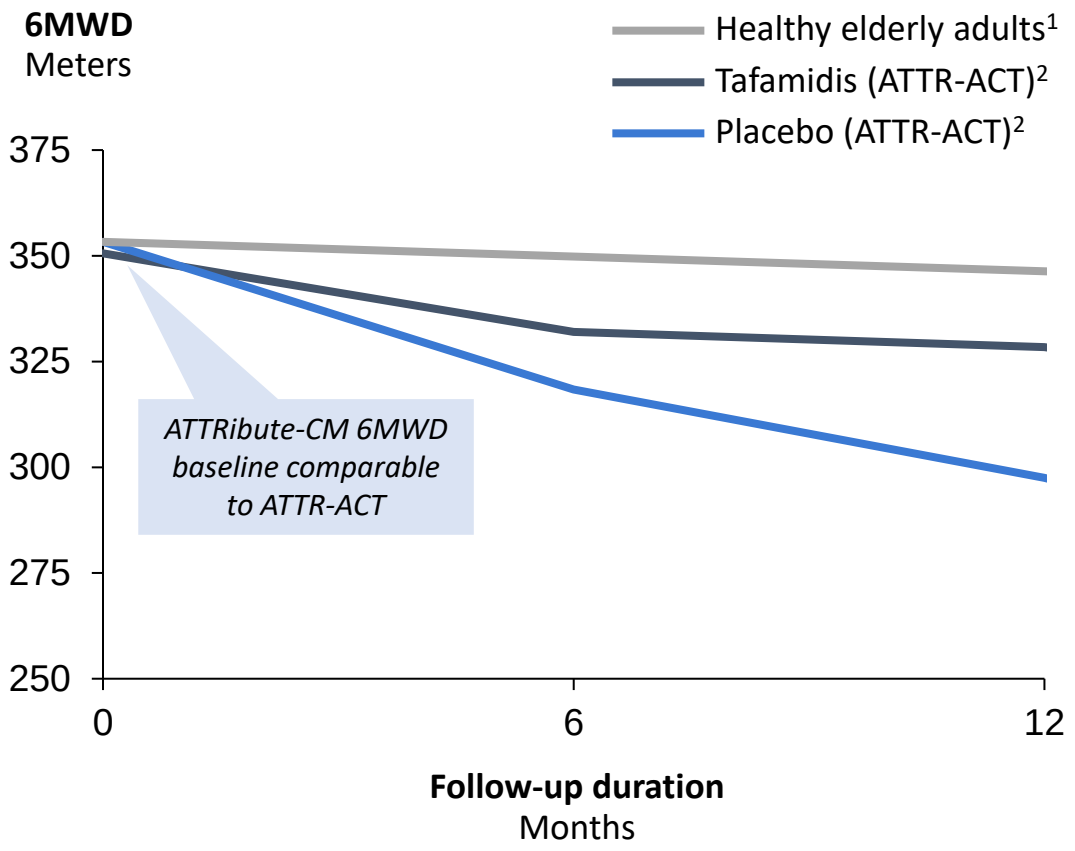
- Maurer et al., 2020

1 Ingle, L. et al., Biomed Res Int 2014
2 Lane, T. et al., Circulation 2019

Rapid functional decline in untreated ATTR-CM patients provides opportunity to demonstrate robust clinical benefit

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones

Summary of 6MWD data in ATTR and healthy cohorts



12-month decline:

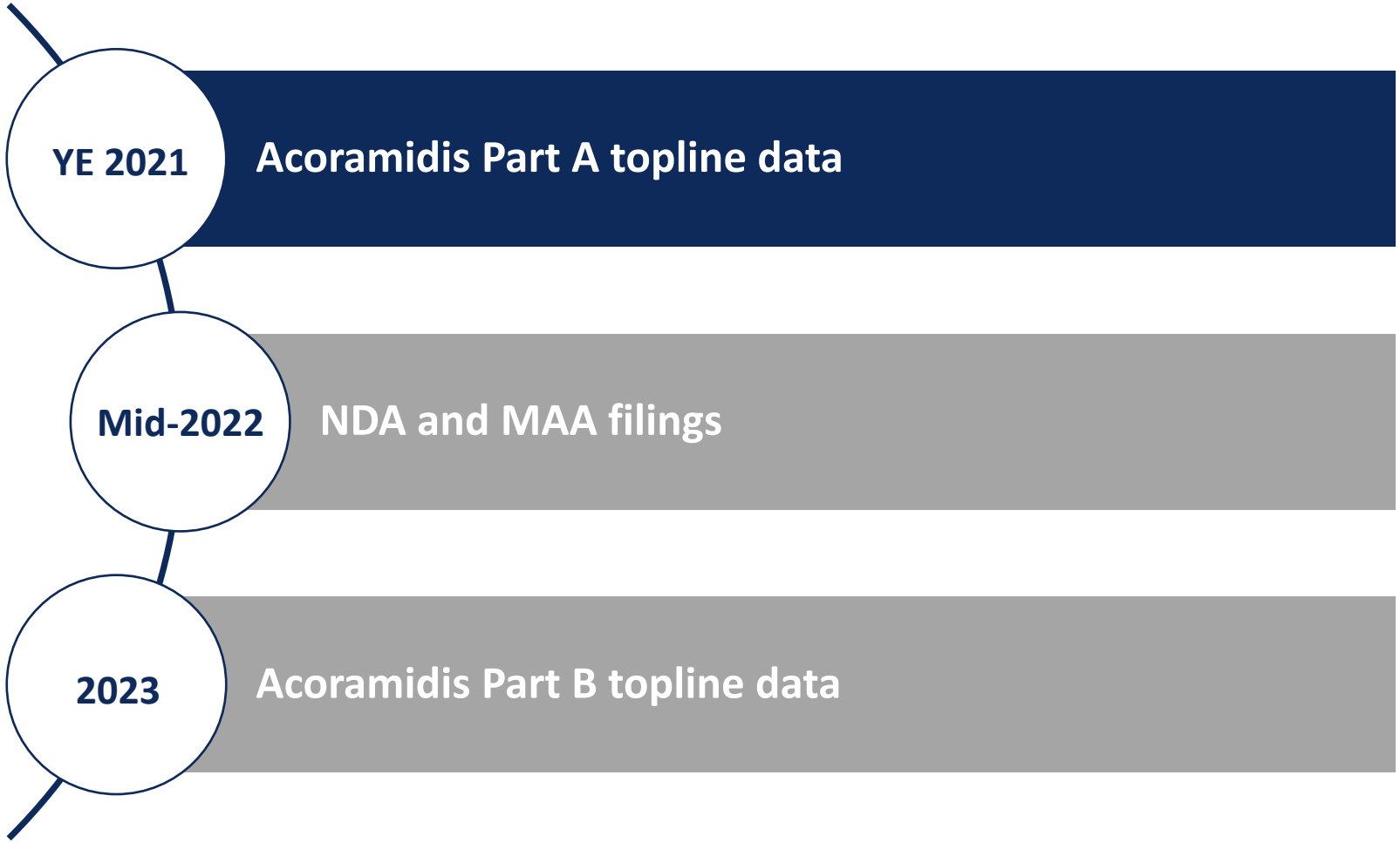
- Healthy elderly adult: -7m
- ATTR-ACT (tafamidis): -25m

Hypothesis: near-complete stabilization of TTR by acoramidis may slow or halt functional decline in 6MWD

[1]Enright, P.L. et al. Chest 2003. N = 3333 healthy elderly adults, baseline set to match ATTR-ACT placebo group
[2]Maurer, M.S. et al. NEJM 2018. N = 264 (tafamidis), N = 177 (placebo) ATTR-CM trial participants

Timeline of upcoming milestones

- Clinical Presentation
- Diagnostic Approach
- Therapeutic Approach
- Published Data
- Pivotal Trial Design
- 6MWD Importance
- Upcoming Milestones



Note: NDA/MAA filings to occur upon receipt of positive Part A

Encaleret: CaSR inhibitor for ADH1

Mary Scott Roberts, M.D.

Sr. Director, Clinical Development, Cardiorenal

Encaleret is an investigational drug. Its safety and efficacy have not been full evaluated by any regulatory authority.

Encaleret for autosomal dominant hypocalcemia type 1 (ADH1)

Alexis and Jackson
Living with ADH1

Prevalence

12k+

US

Pathophysiology

Decreased blood calcium, elevated urine calcium, and lower parathyroid hormone secretion

Genetic Driver

Hyperactivation of calcium-sensing receptor (CaSR)

Therapeutic Hypothesis

Selectively antagonize CaSR to normalize downstream effects

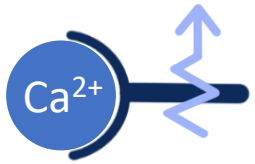
Design Criteria for Optimal Therapy

- Directly target CaSR to potentially resolve key symptoms
- Phase 2 data suggests potential to normalize blood Ca and urine Ca
- Oral Dosing

ADH1-causing variants hyperactivate the CaSR and disrupt calcium homeostasis leading to potentially life-threatening symptoms

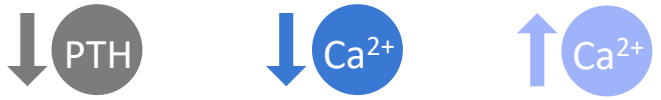
Disease Mechanism

Normal CaSR senses and regulates serum Ca levels to maintain calcium homeostasis



ADH1 CaSR is hyperactive

Hyperactive CaSR causes dysregulation of calcium homeostasis



Decreased *PTH secretion*

Decreased *serum calcium*

Increased *urine calcium*

Clinical Manifestation

Presenting symptoms

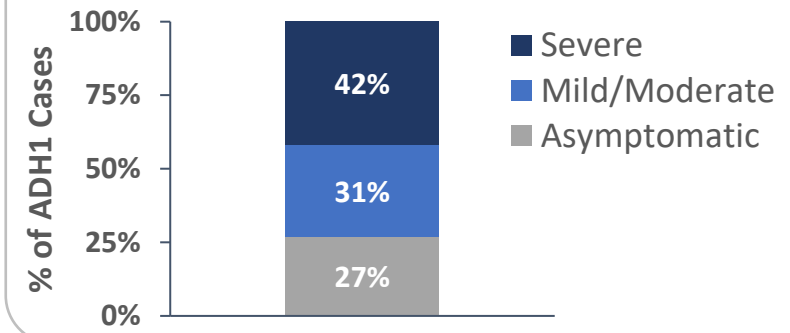
- Hypocalcemic seizures
- Tetany
- Paresthesia
- Muscle cramps

Long-term complications

- Nephrocalcinosis
- Chronic kidney disease
- Nephrolithiasis

Median age of ADH1 dx[1]: 25 (0-77) years

Symptom presentation[1]

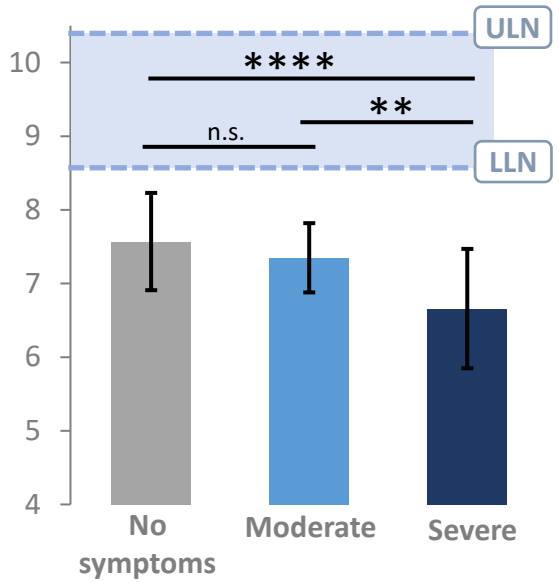


[1]Roszko, et al., ASBMR Annual Meeting, 2021. Abbreviations: dx = diagnosis. Age of dx presented as median (range)

ADH1 symptom severity is associated with blood calcium levels and current treatment inadequately addresses symptom burden

Blood calcium at clinical presentation

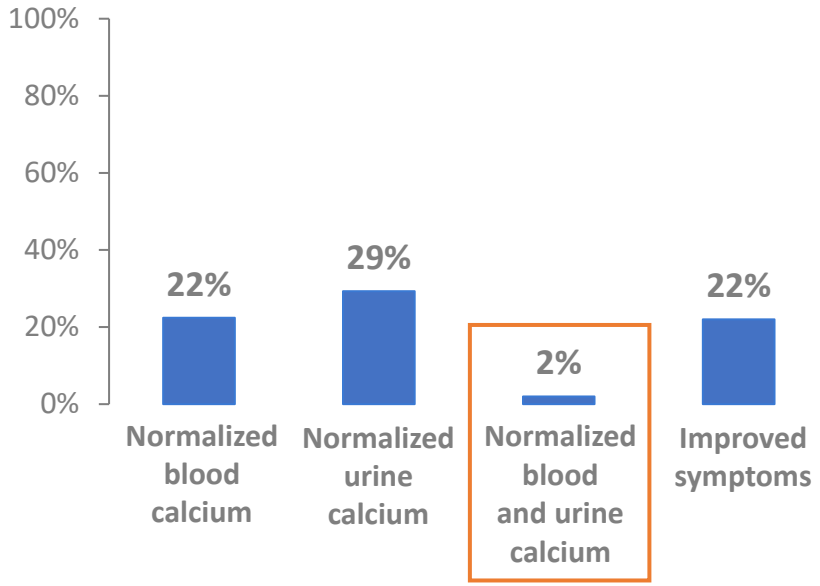
Blood corrected calcium
mg/dL, mean



Severely symptomatic individuals exhibited significantly lower blood calcium compared to asymptomatic and moderately symptomatic[1]

ADH1 medical intervention

Individuals on calcium and/or active vitamin D
%



Only 2% of individuals normalized both blood and urine calcium, and only 22% reported symptom improvement on-treatment[1]

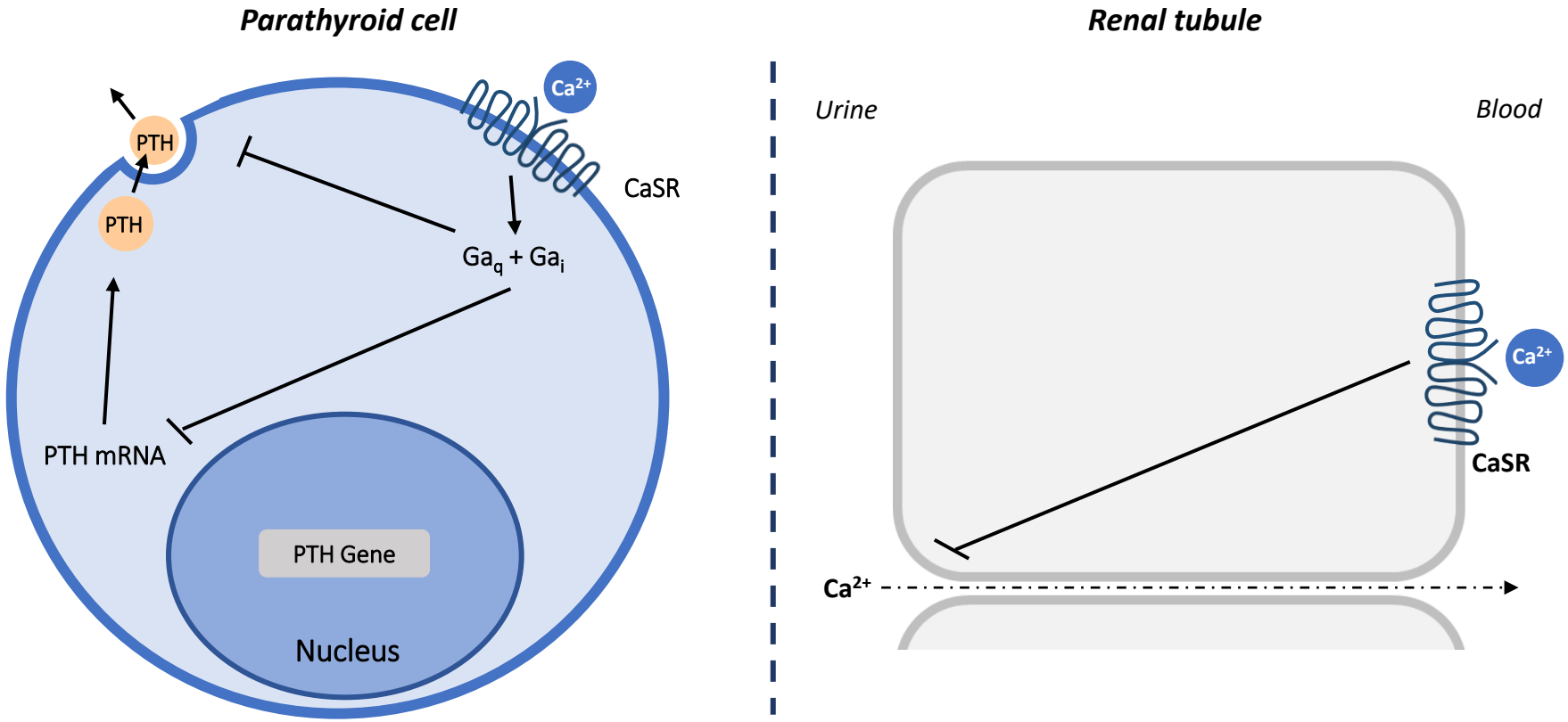
ULN = upper limit of normal, LLN = lower limit of normal. ** p-value <0.01. **** p-value < 0.0001. n.s. = not statistically significant

[1]Roszko, et al., ASBMR Annual Meeting, 2021

Successful CaSR antagonism would increase PTH secretion and renal calcium reabsorption

- Disease Overview
- Therapeutic Approach
- Phase 2 Design
- Phase 2 Clinical Data
- Summary & Next Steps

Parathyroid and renal CaSR antagonist action



Encaleret is designed to antagonize the CaSR to increase PTH release, increase blood calcium, and reduce urine calcium

Figures adapted from: [1]Berne and Levy Physiology, 6th ed. Chapter 39; [2]Toka, H.R., et al. Physiology. 2015

Encaleret is designed to address the underlying disease mechanism and simultaneously normalize blood calcium and urine calcium

Disease Overview

Therapeutic Approach

Phase 2 Design

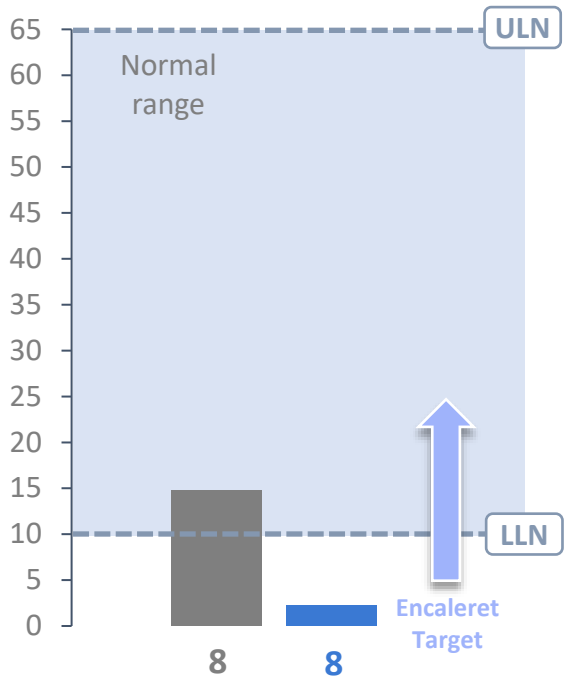
Phase 2 Clinical Data

Summary & Next Steps

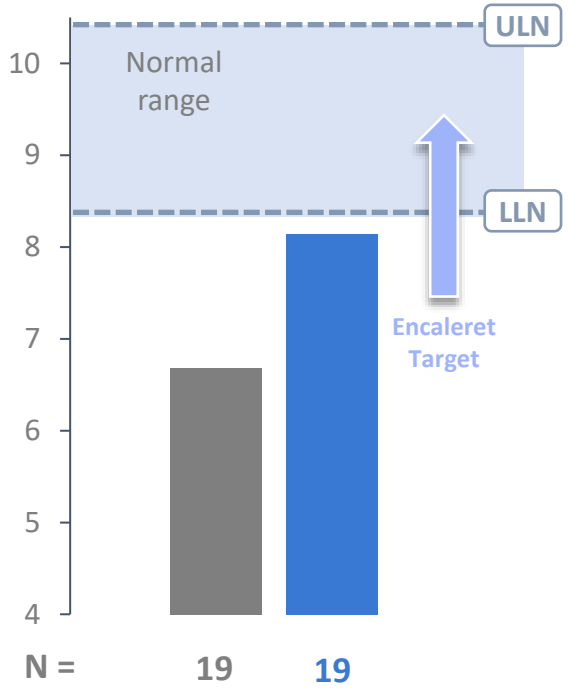
Summary of key disease measures in ADH1 patients with and without supplementation

Without supplementation With supplementation

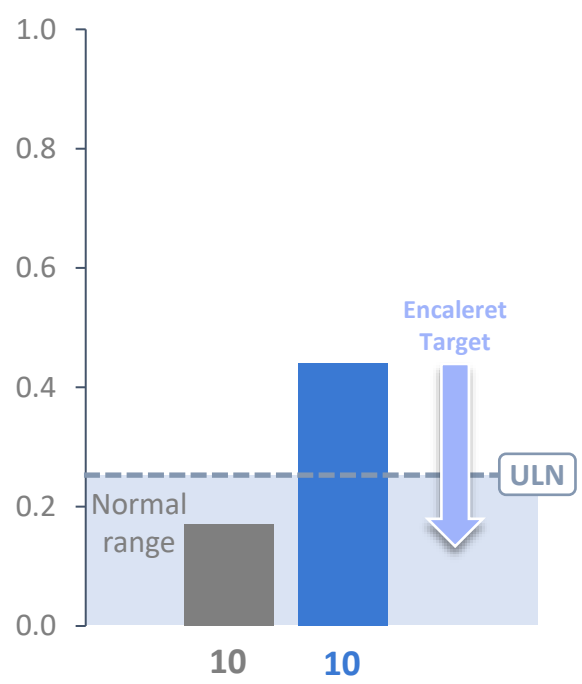
Blood parathyroid hormone
pg/mL, mean



Blood corrected calcium
mg/dL, mean



Urine calcium
Calcium: Creatinine ratio, mean



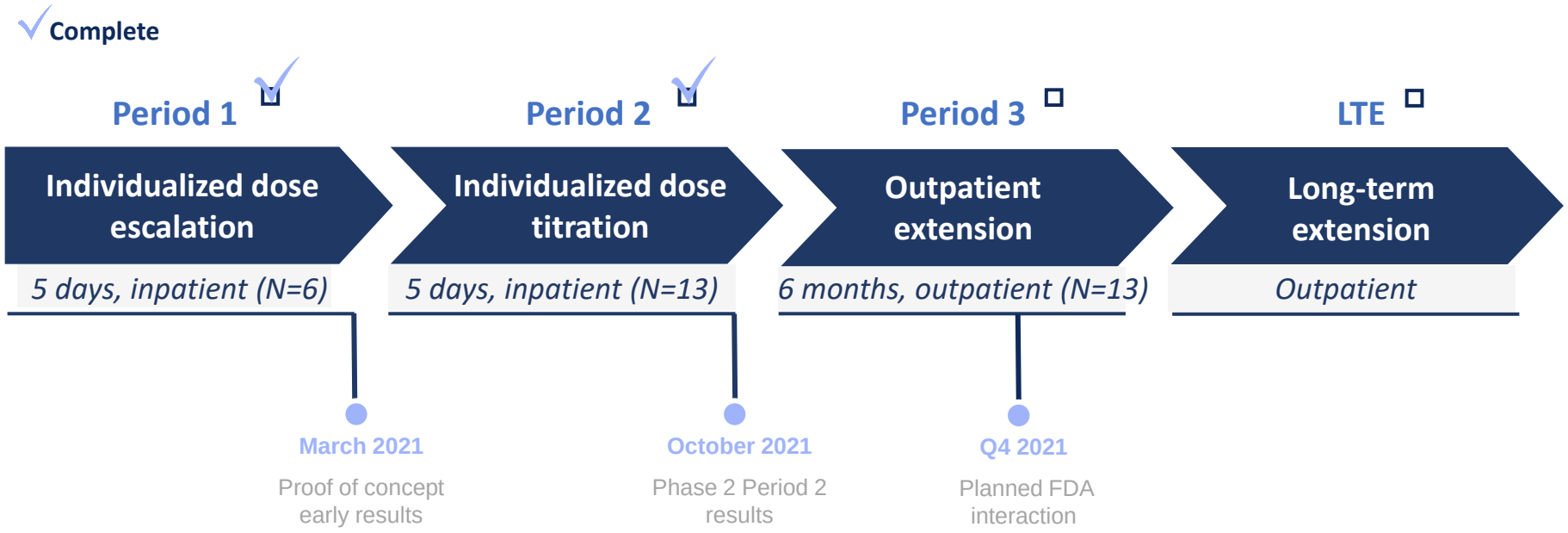
ULN = upper limit of normal, LLN = lower limit of normal

Source: Pearce et al., NEJM 1996. PTH values reported as below detection limit or undetectable were recorded as "0"

Encaleret Phase 2 study design

- Disease Overview
- Therapeutic Approach
- **Phase 2 Design**
- Phase 2 Clinical Data
- Summary & Next Steps

Program Overview



Key study objectives:

- Safety and tolerability
- Blood calcium concentration
- Urine calcium concentration
- Intact parathyroid hormone concentration

Additional measures:

- Blood 1,25-$(OH)_2$ Vitamin D, magnesium, and phosphate
- Urine creatinine, cAMP, citrate, phosphate, sodium, magnesium
- Bone turnover markers (serum collagen C-telopeptide, serum procollagen Type 1 N-propeptide)

Period 2 individualized dose titration phase resulted in a lower Day 5 mean encaleret dose as compared to Period 1

Disease Overview

Therapeutic Approach

Phase 2 Design

Phase 2 Clinical Data

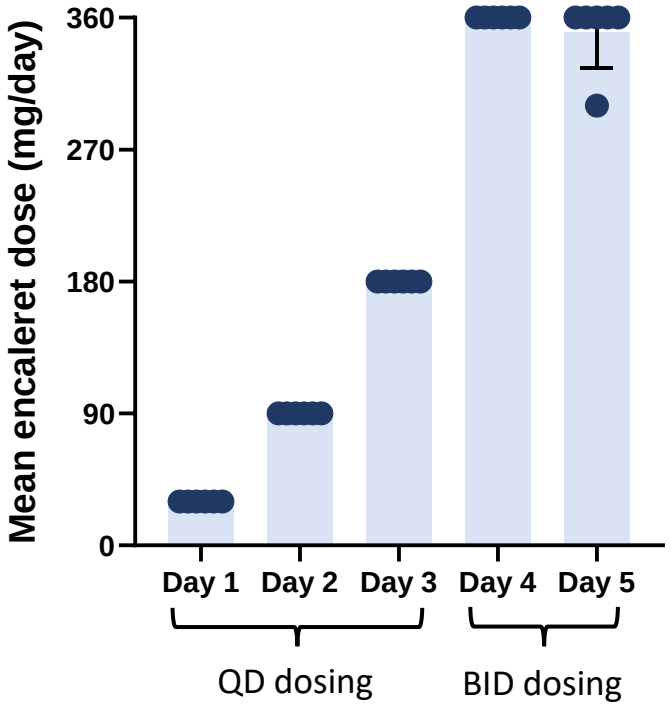
Summary & Next Steps

Period 1 and Period 2 encaleret dosing summary

Period 1 Dosing

Defined dose escalation

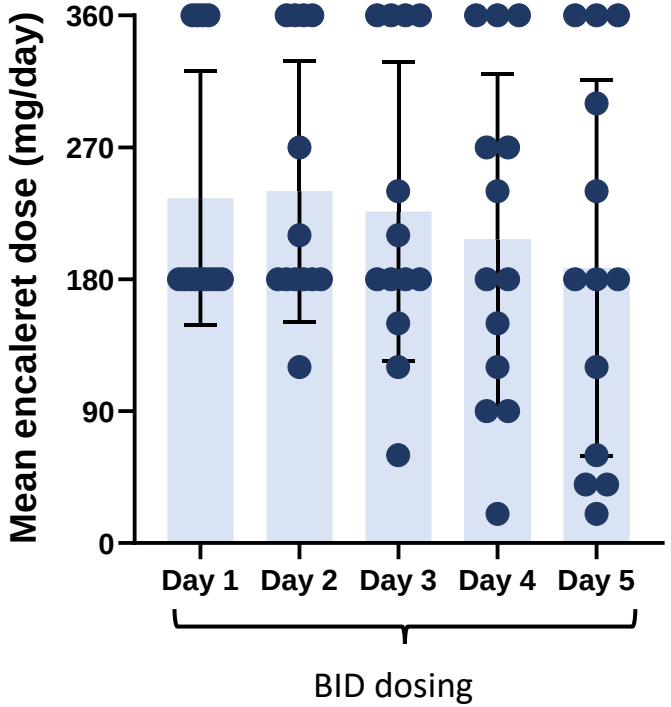
Day 5 Mean: 350.0±22.4 mg/day



Period 2 Dosing

Individualized dose titration

Day 5 Mean: 187.7±128.2 mg/day



Data reported as mean±SD.

Study participants exhibited hypocalcemia, elevated urine calcium, suppressed PTH, and elevated phosphate at baseline

Disease Overview

Therapeutic Approach

Phase 2 Design

Phase 2 Clinical Data

Summary & Next Steps

Baseline characteristics

Characteristic	Study Population N = 13	*Normal Range*
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Nephrocalcinosis, n (%)	10 (77%)	
ECG QT_cB (msec)	452 ± 16	*< 440*
Corrected Calcium (mg/dL)*	8.0 ± 0.7	*8.4 –10.2*
Intact PTH (pg/mL)*	2.8 ± 3.4	*15 – 65*
Phosphate (mg/dL)*	5.1 ± 1.1	*2.3 – 4.7*
Magnesium (mg/dL)*	1.8 ± 0.1	*1.6 – 2.6*
24h Urine Calcium (mg/24h)	441 ± 258	*< 250-300*
Supplements		
Elemental Calcium (mg/day) [mean (range)]	2628 (750-4800)	
Calcitriol (µg/day) [mean (range)]	0.8 (0.2-2.0)	
***CASR* Variants**	C131Y (2), P221L (2), E604K (1), A840V (3), F788C (1), T151M (1), Q245R (1), I692F (1), E228K (1)	

Data reported as mean±SD. ECG QTcB = electrocardiogram Bazett-corrected Q-T interval. *Measurements taken pre-dose Day 1 in Period 1 or Period 2

Encaleret continues to be generally well-tolerated with no serious adverse events reported[1]

Disease Overview

Therapeutic Approach

Phase 2 Design

Phase 2 Clinical Data

Summary & Next Steps

Summary of Period 1 and Period 2 safety measures

	Period 1 N = 6	Period 2 N=13
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**	**0 (0%)**
Number of subjects experiencing any Adverse Event	**6 (100%)**	**10 (77%)**
Mild	6 (100%)	10 (77%)
Moderate	1 (17%)	0 (0%)
Severe	0 (0%)	0 (0%)
Number of Adverse Events Reported	**19**	**12**
Mild	18 (95%)	12 (100%)
Moderate	1 (5%)	0 (0%)
Severe	0 (0%)	0 (0%)
Treatment-related Adverse Events[2]	**3 (16%)**	**8 (67%)**
Hypocalcemia	1 (33%)	0 (0%)
Hypophosphatemia	2 (67%)	7 (88%)
Hypercalcemia	0 (0%)	1 (12%)

[1]Data as of September 3, 2021. [2]Treatment-related adverse events were transient and resolved with dose-adjustment. Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs. The most common AEs (≥ 2 subjects) were hypophosphatemia, hypocalcemia, and headache

Encaleret treatment increased blood calcium and parathyroid hormone and decreased urine calcium in ADH1 participants during Period 1

Disease Overview

Therapeutic Approach

Phase 2 Design

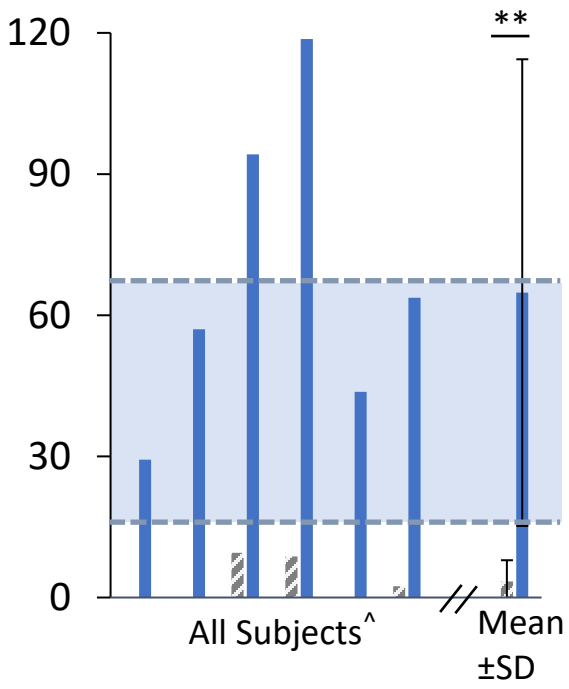
Phase 2 Clinical Data

Summary & Next Steps

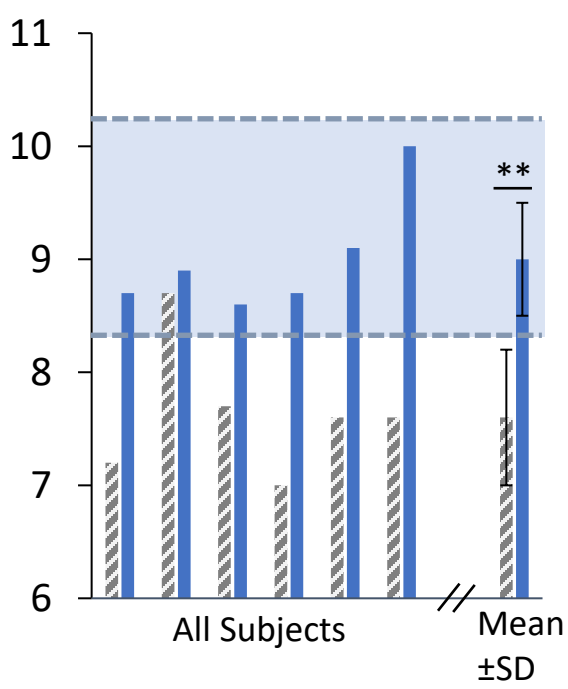
Individual and mean responses on Day 1 and 5 of Period 1 (N=6)

Baseline Value (Day 1) Mean Value (Day 5) on encaleret 180 mg BID§

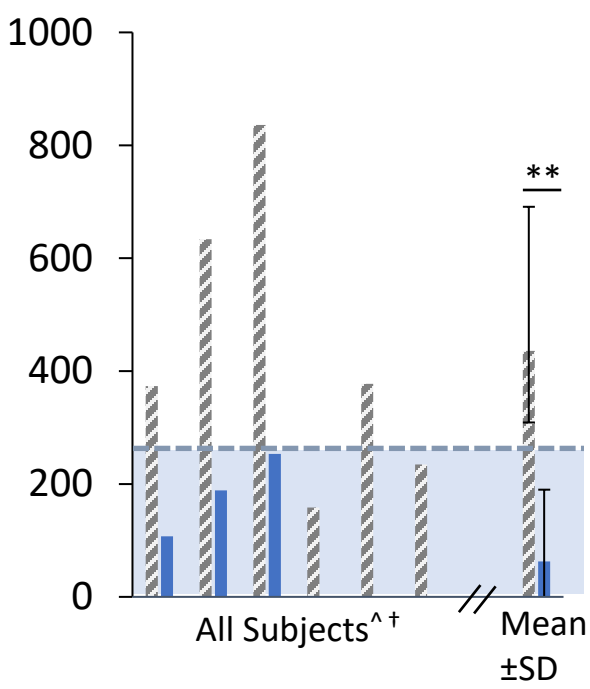
Blood parathyroid hormone
pg/mL



Blood corrected calcium
mg/dL



Urine calcium
mg/day



§ Encaleret dose adjusted to 180/120 in 1 subject on Day 5.^Values below limit of assay quantitation recorded as "0". † Day 4 values used in two subjects given Day 5 values unavailable. Gray shading reflects normal range. ** p-value < 0.01.

Blood phosphate and magnesium levels also normalized over 5-day dose escalation, on average. Data not plotted above.

Encaleret treatment normalized mean blood and urine calcium during Period 2

Disease Overview

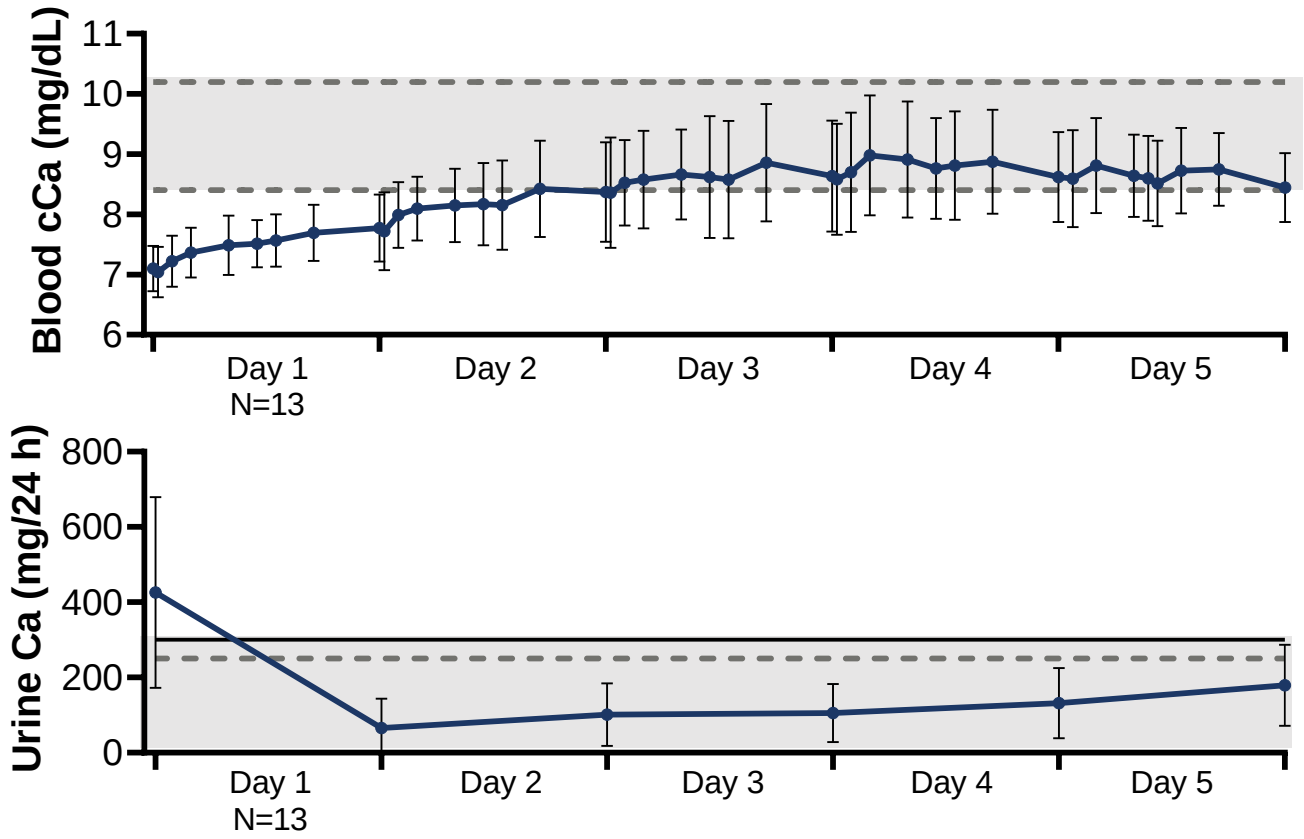
Therapeutic Approach

Phase 2 Design

Phase 2 Clinical Data

Summary & Next Steps

Mean responses on Day 1 through Day 5 in Period 2 (N=13)



Increasing urine calcium is likely due to both increasing corrected calcium and decreasing encaleret dose

Data reported as mean±SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women

Encaleret increased PTH and decreased mean blood phosphate during Period 2

Disease Overview

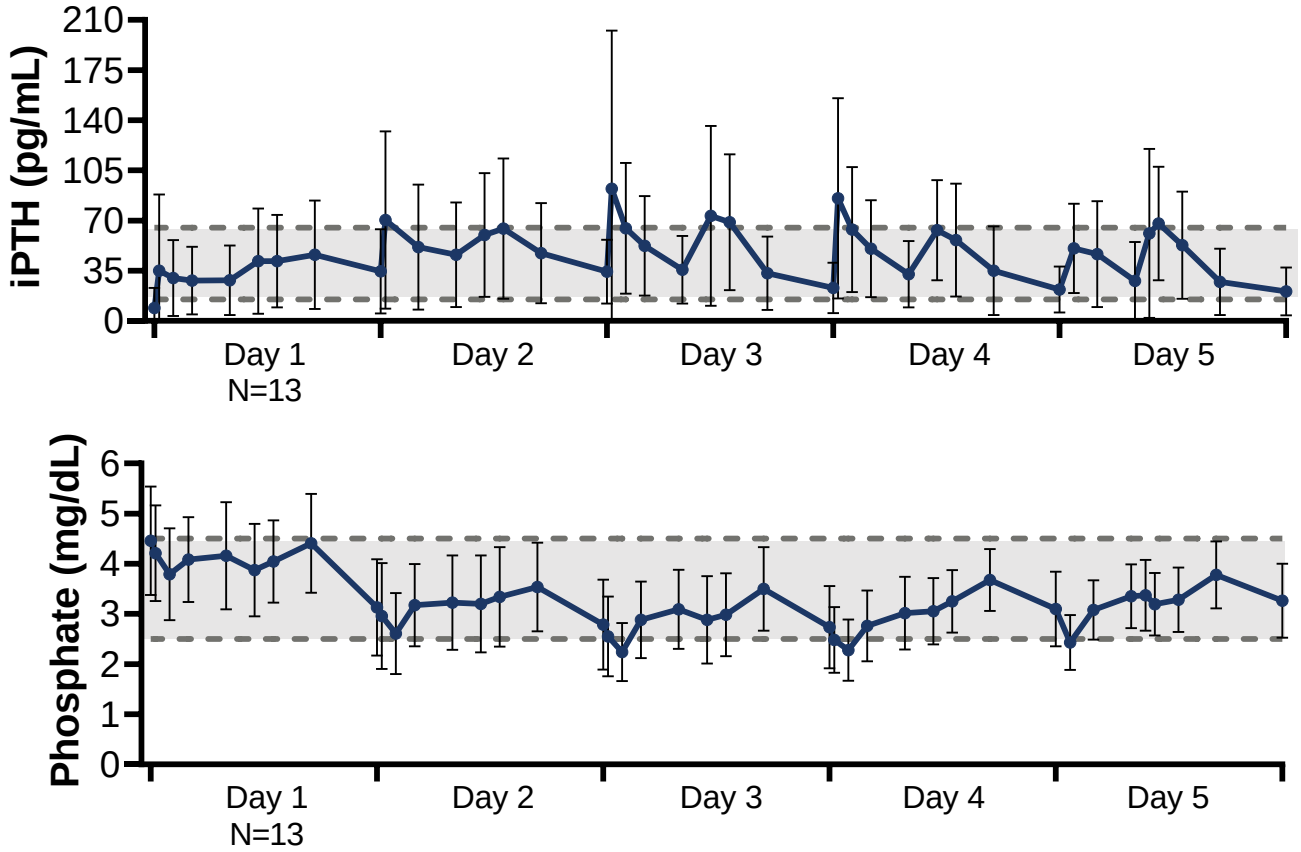
Therapeutic Approach

Phase 2 Design

Phase 2 Clinical Data

Summary & Next Steps

Mean responses on Day 1 through Day 5 in Period 2 (N=13)



Data reported as mean±SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range

Summary reported Phase 2 data and next steps

- Disease Overview
- Therapeutic Approach
- Phase 2 Design
- Phase 2 Clinical Data
- Summary & Next Steps

Summary of encaleret development program

- ☑ In 13 participants, encaleret normalized mean blood calcium and 24-hour urine calcium excretion, increased PTH, and decreased phosphate into the normal range during both Periods 1 and 2
- ☑ Individualized BID dosing in Period 2 resulted in a decrease in the mean Day 5 encaleret dose as compared to Period 1
- ☑ Encaleret was well-tolerated when administered once or twice daily over 5 days, with no serious adverse events reported
- ☑ Consistent improvements in mineral homeostasis suggest encaleret may become an effective treatment for ADH1
- ☑ Granted Fast Track Designation and Orphan Drug Designation by the FDA

Next 12 months

- ☐ Interact with FDA
- ☐ Present complete Phase 2 data
- ☐ Initiate Phase 3 registrational study

Planned activities

- Pediatric development program in ADH1
- Evaluation of encaleret in non-genetic hypoparathyroidism

BridgeBio Gene Therapy

Eric David, M.D., J.D.

CEO, BBGT

Gene therapy pipeline overview

	Indication	Drug Mechanism	Pt. pop. (US+EU)	Discovery	Pre-IND	Phase 1	Phase 2	Phase 3
Gene Therapy	CAH	AAV5 gene therapy (BBP-631)	>75k					
	Canavan	AAV9 gene therapy (BBP-812)	1k					
	TMC1 hearing loss	AAV gene therapy (BBP-815)	2k					
	Galactosemia	AAV gene therapy (BBP-818)	>7k					
	Tuberous sclerosis complex 1	AAV gene therapy	>100k					
	Tuberous sclerosis complex 2	AAV gene therapy						
	Cystinuria	AAV gene therapy	20k					
	Undisclosed DCM gene therapy program	AAV gene therapy						
	3 capsid discovery collaborations							

Featured Programs

Research and manufacturing capabilities

Facility | 20,000 sq ft lab space in Raleigh, NC

People | 60+ gene therapy employees (>50% in research or CMC)

Capabilities | Vector development, optimization, analytical development, and production (200L)

External Manufacturing | Dedicated GMP manufacturing suite at Catalent

BBGT program updates

Program	Status Update	Next Catalyst
Congenital Adrenal Hyperplasia (CAH)	Trial enrollment underway	Initial Phase 1/2 data
Canavan	Trial enrollment underway	Initial Phase 1 biomarker data
Transmembrane Channel Protein 1 (TMC1)	Proof-of-concept established in multiple disease models	IND enabling studies
NEW **Galactosemia**	Proof-of-concept established in disease model	IND enabling studies

BBP-631: AAV5 gene therapy for congenital adrenal hyperplasia (CAH)

Maddie
Living with CAH

Prevalence

>75k

US & EU

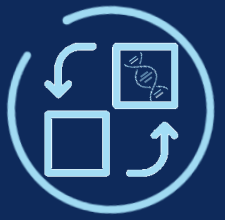
Pathophysiology

Inability to produce cortisol causes need for supraphysiologic doses of synthetic steroids, 3-4x increase in mortality risk, hirsutism, Cushingoid symptoms

Genetic Driver

Loss of function of 21-hydroxylase (21-OH)

Therapeutic Hypothesis



AAV5 gene therapy to provide 21-OH

Design Criteria for Optimal Therapy

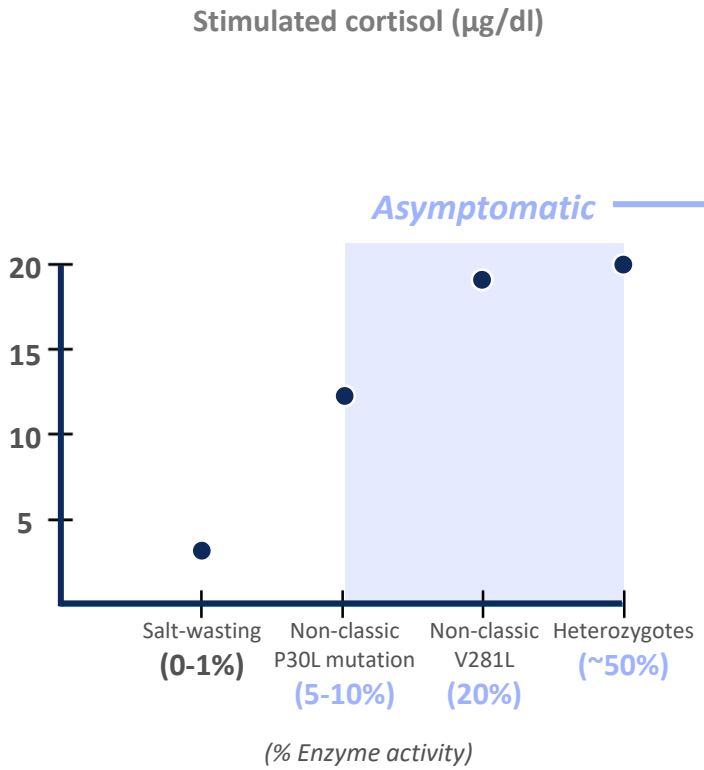
- Only approach designed to induce endogenous cortisol and mineralocorticoid production
- Durable transgene delivery to the adrenal gland of NHPs
- Low threshold to correct phenotype

5-10% of WT enzyme may be sufficient for clinical impact

Preclinical Data

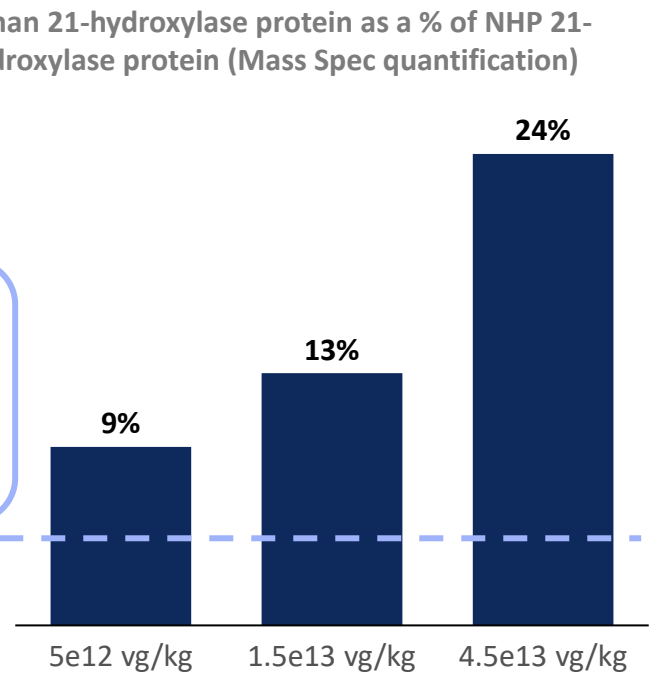
Phase 1/2 Design

Genotype-phenotype studies show that >5-10% of enzyme activity results in nonclassical CAH



As little as 5% of WT enzyme activity is associated with the mild/asymptomatic non-classic form of CAH

NHP protein data suggests potentially therapeutic levels of 21-hydroxylase enzyme



- Mass-spec methods to quantify protein expression by identifying differential peptides between human and NHP 21-OH
- Data suggest dose-dependent enzyme expression in the adrenal cortex from 9%-24% of WT levels

Source: Perdomini, Gene Therapy 2017; ESGCT 2019; data on file

Phase 1/2 first-in-human trial design

Preclinical Data

Phase 1/2 Design

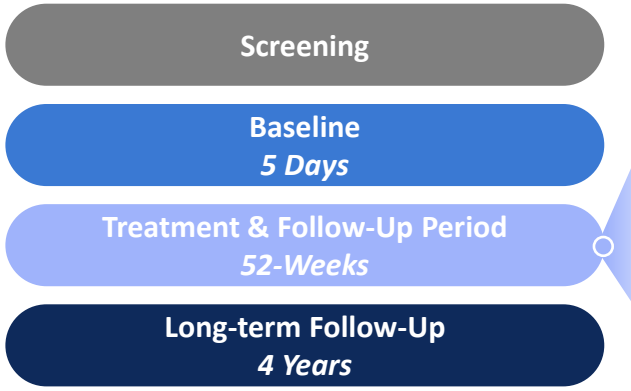
Status

- Trial enrollment underway

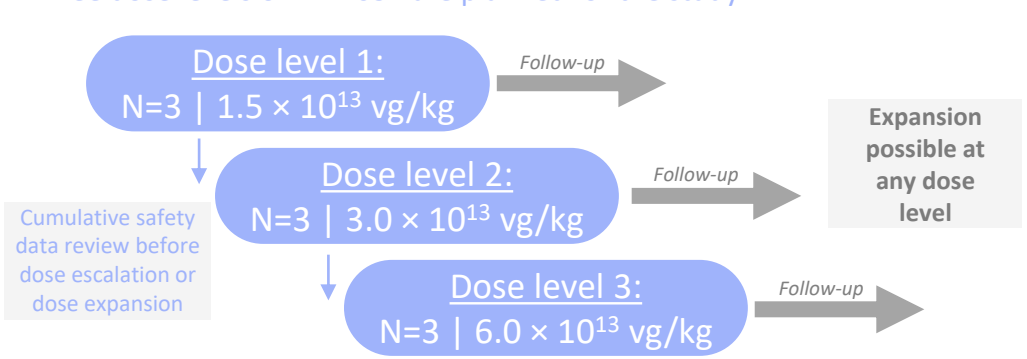
Eligibility

- Age >18 years with classic CAH (simple virilizing or salt-wasting) due to 21-Hydroxylase Deficiency (21-OHD)
- Screening/baseline 17-OHP levels > 5-10 × ULN

FIH Trial Design



Dose Escalation Design



Primary Objectives

- Evaluate safety
- Levels of endogenous cortisol (pre- and post-ACTH stimulation)
- Quality-of-life assessment

BBP-812: AAV9 gene therapy for Canavan disease

Tobin
Child with Canavan

Prevalence

~1k

US & EU

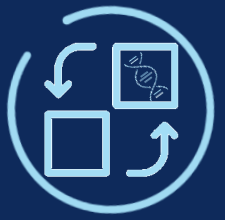
Pathophysiology

Dysregulated amino acid metabolism leads to neurodegeneration and loss of motor function. Most children do not live past age 10

Genetic Driver

Loss of function of aspartoacylase (ASPA)

Therapeutic Hypothesis



AAV9 gene therapy to provide ASPA

Design Criteria for Optimal Therapy

- Profound phenotypic rescue observed in mouse models by Dr. Guangping Gao
- IV delivery enables widespread delivery across CNS
- Clear PD biomarkers to measure effect of gene therapy (NAA)

CAN*Aspire*, our FIH trial for BBP-812, will assess two doses before expanding

Phase 1/2 Design

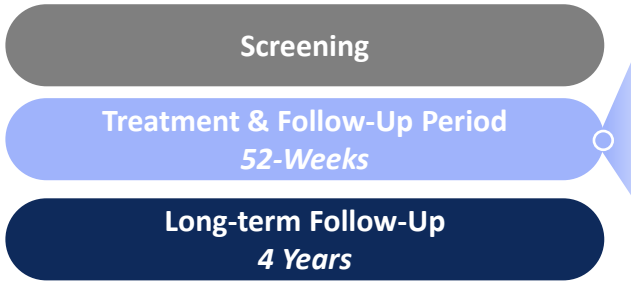
Status

- Trial enrollment underway

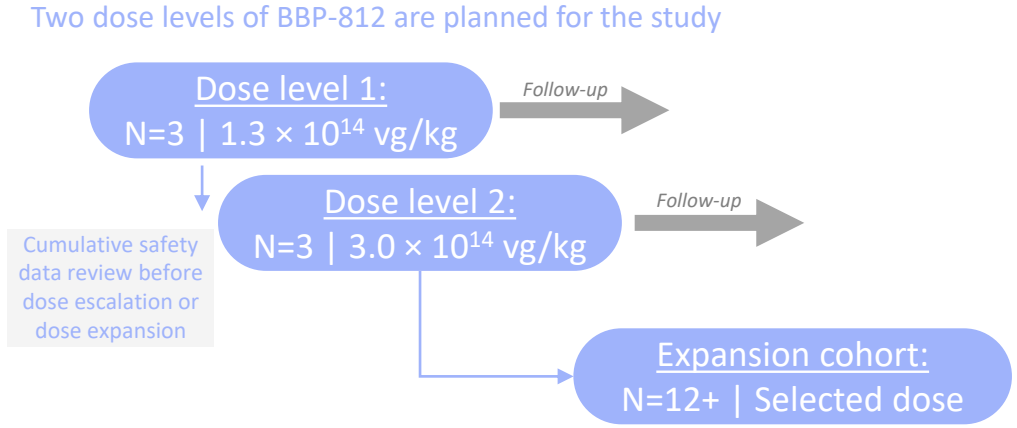
Eligibility

- Age ≤ 30 months with Canavan disease
- Stable health with no acute or chronic renal and liver disease
- Negative for AAV9 total antibodies

FIH Trial Design



Dose Escalation and Expansion Design



Primary Objectives

- Evaluate safety and tolerability
- Levels of NAA (CSF, urine)
- Developmental milestones (e.g., TIMPSI, GMFM-88, Canavan Disease Rating Scale)

BBP-815: AAV gene therapy for TMC1 genetic hearing loss

Addressable Prevalence

~2k

US & EU

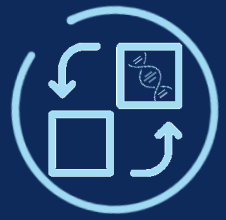
Pathophysiology

Lack of functional TMC1 protein in the inner and outer hair cells of the cochlea leads to severe-to-profound bilateral hearing loss

Genetic Driver

Loss of function of transmembrane channel protein 1 (TMC1)

Therapeutic Hypothesis



Intracochlear delivery of AAV gene therapy to provide TMC1 and enable natural hearing processes

Design Criteria for Optimal Intervention

- Only approach designed to enable natural hearing
- Dose-dependent, durable rescue of the hearing phenotype in profoundly deaf mice
- Near complete transduction of inner and outer hair cells in NHPs

Gene therapy is the only modality designed to address TMC1 hearing loss at its source and allow for endogenous production of the TMC1 protein

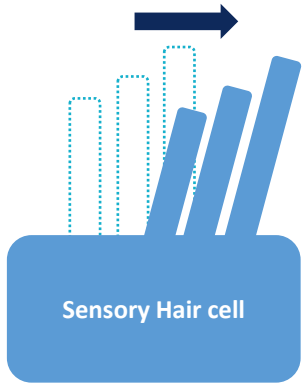
Therapeutic Approach

Preclinical Data

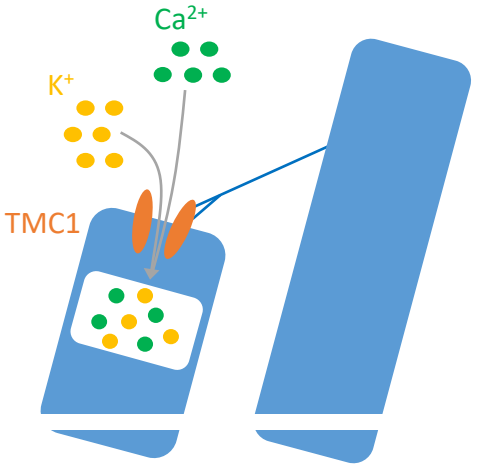
BBP-815 is the only intervention designed to enable natural hearing

TMC1 = transmembrane channel protein 1

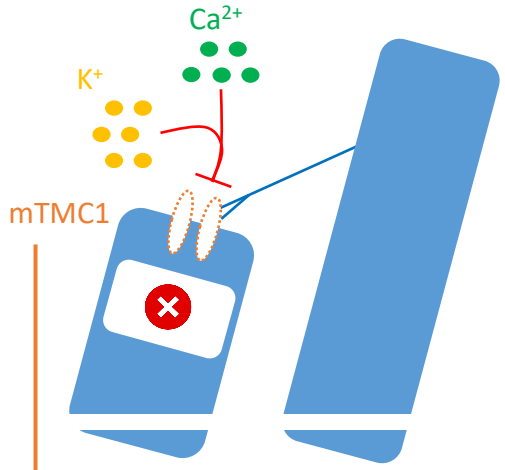
Sound-evoked displacement of hair cell stereocilia



Functional TMC1 enables hair cell depolarization



Mutated TMC1 disrupts electrical response to sound



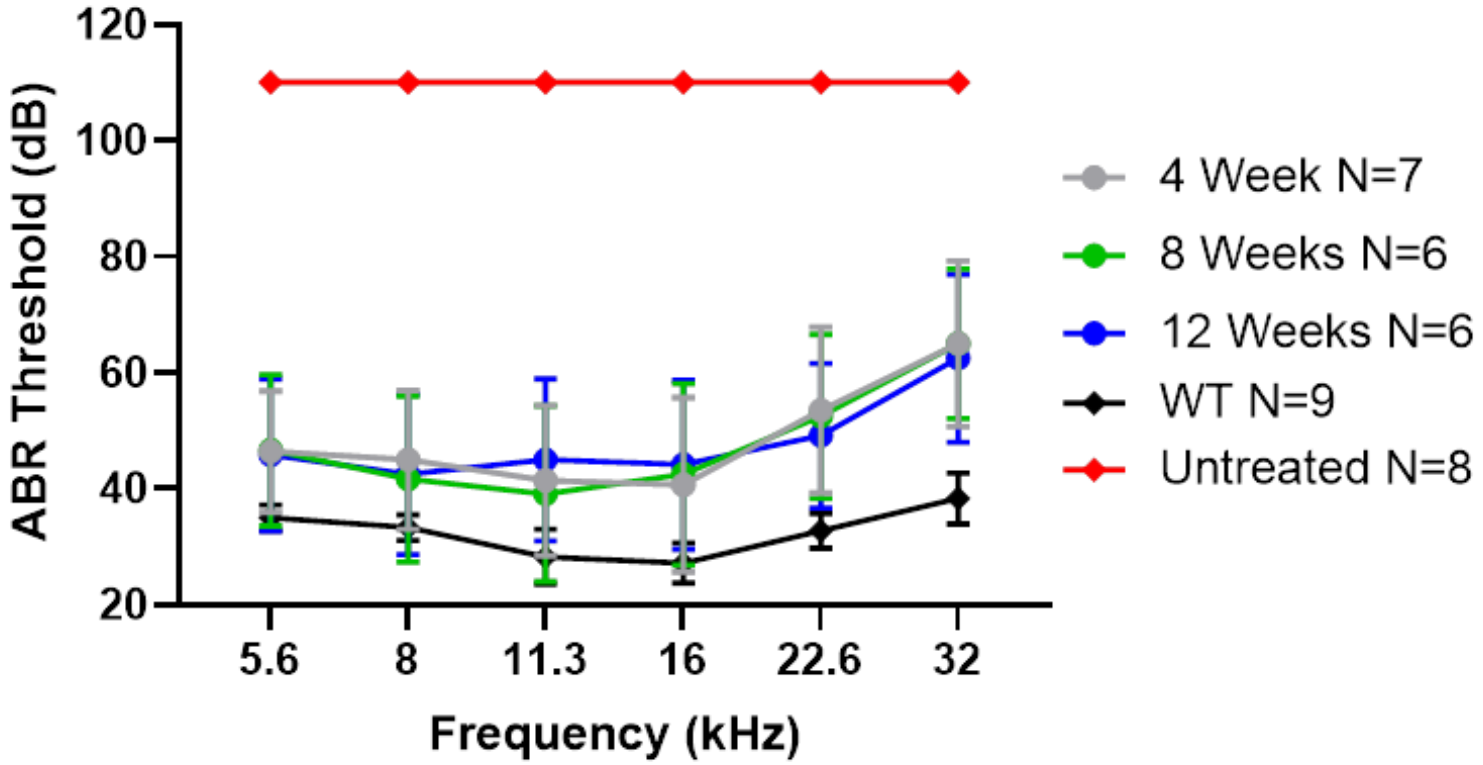
BBP-815 is designed to produce the TMC1 protein directly in hair cells of the cochlea and enable mechanotransduction of sound

BBP-815 durably rescues hearing in profoundly-deaf mice

Therapeutic Approach

Preclinical Data

Durability of Auditory Brainstem Response (ABR) in TMC1-N193I mice dosed with BBP-815



Source: BridgeBio Gene Therapy data on file

BBP-818: AAV gene therapy for classic galactosemia type I

Prevalence

7k+

US & EU

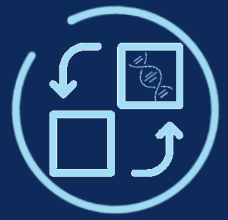
Pathophysiology

Inability to metabolize galactose leads to impaired speech, developmental delays, impaired motor function, primary ovarian insufficiency, and osteopenia

Genetic Driver

Loss of function of galactose-1-phosphate uridylyltransferase (GALT)

Therapeutic Hypothesis



AAV gene therapy to provide GALT enzyme and enable galactose metabolism

Design Criteria for Optimal Therapy

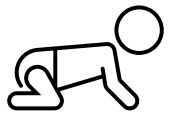
- Only approach designed to enable galactose metabolism, reduce gal-1p, and restore galactosylation of lipids and proteins
- Dose-dependent, durable restoration of the GALT enzyme in liver and CNS
- Low threshold to correct phenotype

Classic galactosemia is a slowly progressive disease that impacts development of the CNS, ovaries, and bone despite strict dietary restrictions

Unmet Need

Therapeutic Approach

Preclinical Data

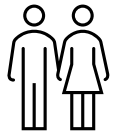


Toddlers/Children

- Speech/ language disorders
- Developmental delays
- Impaired growth
- Cataracts
- Learning delays
- Neurological Impairments, including gait, balance, fine motor tremors
- Behavioral and emotional issues
- Tremor

Teens

- Puberty and fertility problems (females)
- Primary ovarian insufficiency (POI)
- Anxiety
- Growth delays
- Social challenges
- Learning difficulties
- Tremor



Adults

- Tremor
- Seizures
- Anxiety
- Depression
- ADHD
- Cataracts
- Early-onset dementia

Top 3 Lifelong Complications (despite dietary restriction):

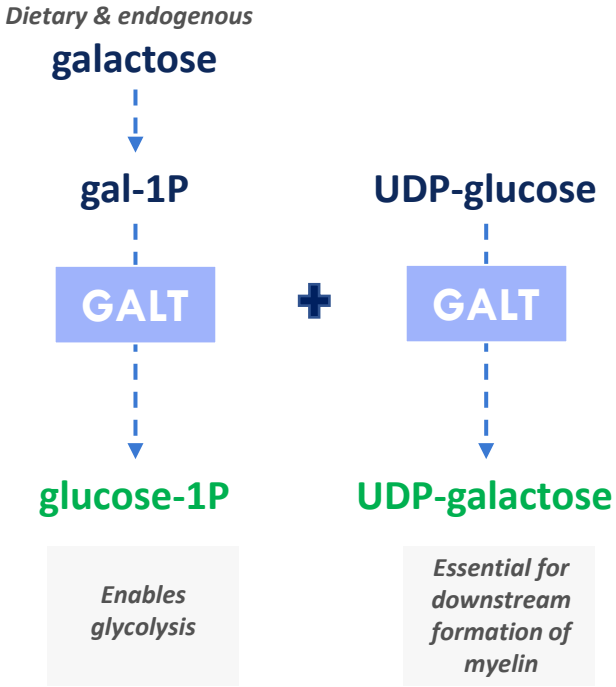
- **85% had impaired CNS development**
- 80% had impaired ovarian development
- 26.5% had impaired bone development

Source: Berry. Classic Galactosemia and Clinical Variant Galactosemia. 2021

Gene therapy is the only therapy designed to treat galactosemia at its source and allow for endogenous production of the GALT enzyme

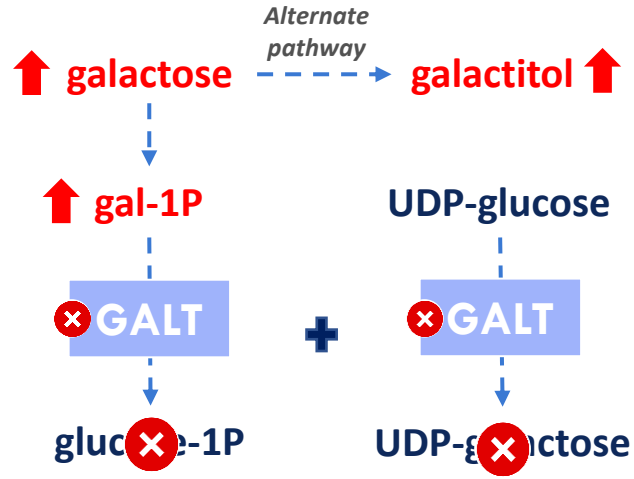
- Unmet Need
- **Therapeutic Approach**
- Preclinical Data

Functional galactose metabolism (Leloir Pathway)



- In typical galactose metabolism, galactose from both diet and endogenous production is processed by the GALT enzyme into downstream glucose-1P and UDP-galactose

Dysregulation of galactose metabolism in type I galactosemia



- In type I galactosemia, gal-1P is unable to be processed, leading to buildup of gal-1P, galactose, and galactitol, all of which are toxic.
- UDP-glucose is unable to be converted into UDP-galactose, which is essential for myelination
- Key symptoms include speech impairment, ataxia, significant developmental delays, primary ovarian insufficiency and osteopenia

GALT = Galactose-1-phosphate-uridylyltransferase; gal-1P = galactose-1-phosphate
Source: Berry. Classic Galactosemia and Clinical Variant Galactosemia. 2021

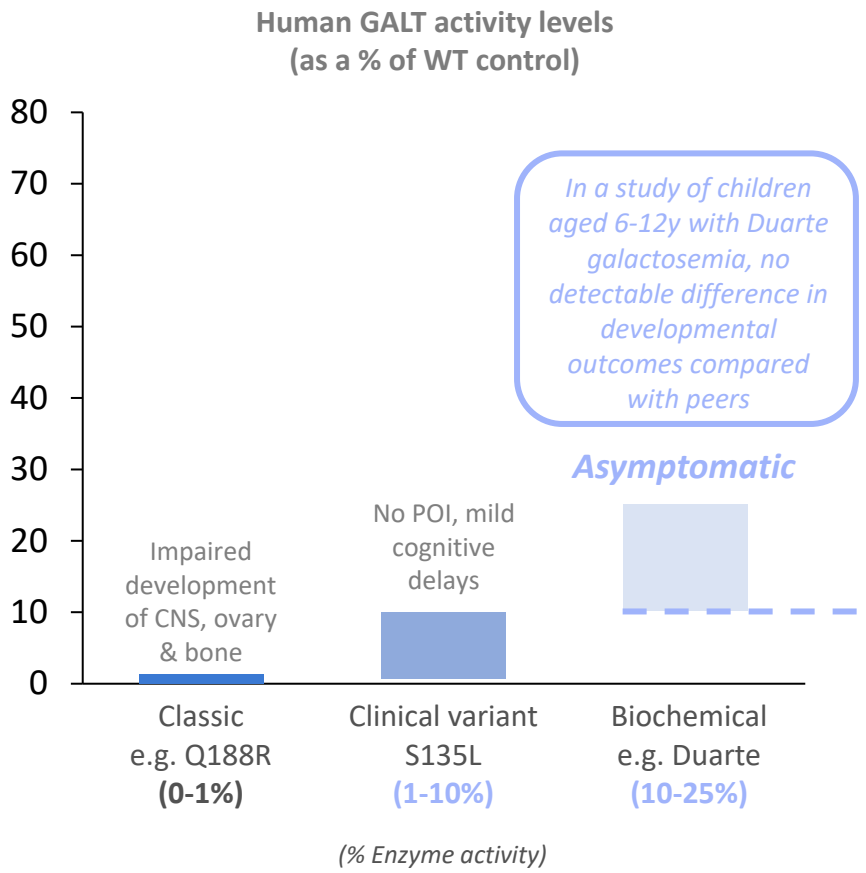
BBP-818 achieves significant, dose-dependent production of the GALT enzyme in GALT-KO mouse brain; these levels may be sufficient for clinical impact

Unmet Need

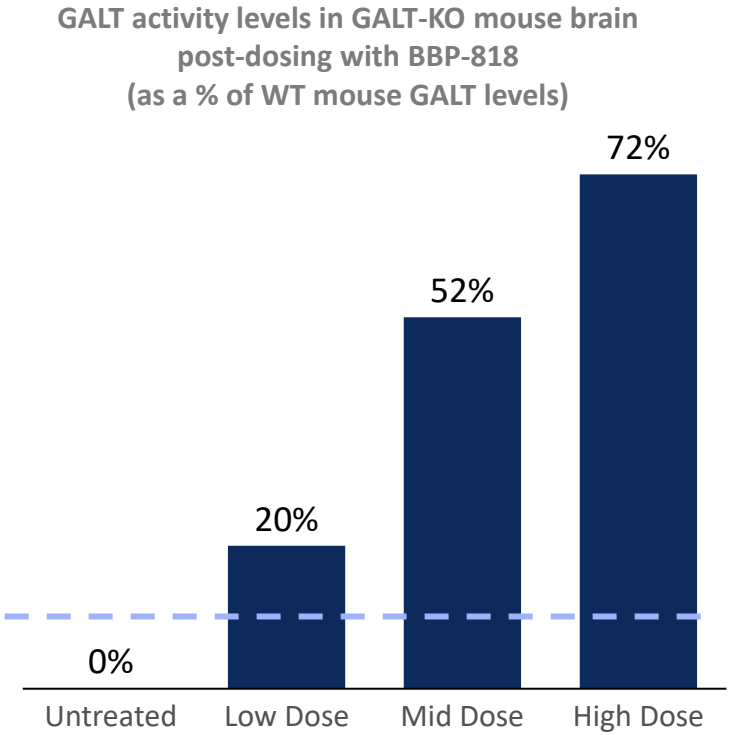
Therapeutic Approach

Preclinical Data

Genotype-phenotype studies show patients with >10% of GALT activity tend to be asymptomatic, and those with >1% tend to have much milder phenotype



GALT-KO mouse data suggests potentially therapeutic levels of GALT enzyme production



- Data suggest dose-dependent enzyme expression in the brain from 20%-72% of WT levels

Source: BridgeBio Gene Therapy data on file, Berry 2021, Fridovich-Keil 2014

BridgeBio Gene Therapy

EXPERIENCED GENE THERAPY TEAM

Senior leadership team of industry veterans

BIOMARIN
NOVARTIS
PRECISION BIOSCIENCES
gsk
Abeona THERAPEUTICS
FDA

FLEXIBLE MANUFACTURING MODEL

In-house capabilities & flexible facility build-out

20,000 sq ft lab space in Raleigh, NC

GROWING PIPELINE

Robust pipeline with clinical readouts in 2022

- 2 clinical programs
- 2 pre-IND programs
- 4 discovery programs
- 3 capsid discovery collaborations

Mendelian Wave 3 Programs

Uma Sinha, Ph.D.

Chief Scientific Officer

Mendelian pipeline overview

	Indication	Drug Mechanism	Pt. pop. (US+EU)	Discovery	Pre-IND	Phase 1	Phase 2	Phase 3	Approved
Mendelian	MoCD type A	NULIBRY™ (synthetic cPMP, fosdenopterin)	100						Nulibry (fosdenopterin) for injection
	Achondroplasia	Low-dose FGFRi (infigratinib)	55k						
	LGMD2i	Glycosylation substrate (ribitol)	7k						
	RDEB	Recombinant COL7 (BBP-589)	2k						
	PKAN / organic acidemia	Pank activator (BBP-671)	7k						
	VM / LM	Topical PI3Ki (BBP-681)	117k						
	Netherton	Topical KLKi (BBP-561)	11k						
	PTEN autism	PI3Kb inhibitor (BBP-472)	120k						
	4 undisclosed small molecule programs		>500k						
	4 undisclosed antisense oligonucleotide programs		>300k						
Precision Cardiorenal	ATTR amyloidosis	TTR stabilizer (acoramidis)	>400k						
	ADH1	CaSR antagonist (encaleret)	12k[1]						
	PH1 / frequent stone formers	GO1 inhibitor (BBP-711)	5k / 1.5m						
	2 undisclosed DCM programs		>250k						

Featured Programs

[1]US carriers

Primary Hyperoxaluria Type 1 (PH1)

Violet
Living with PH1

Prevalence

5k

US & EU

Pathophysiology

Excess oxalate result in the buildup of oxalate stones in the kidneys, urinary tract, and other vital organ

Genetic Driver

Loss of function of AGXT gene causing excess oxalate

Therapeutic Hypothesis

GO1 inhibitor to reduce oxalate production

Design Criteria for Optimal Therapy

- Highest pharmacodynamic response (max inhibition of GO)
- Oral dosing

GO = glycolate oxidase

GO1 inhibitor (BBP-711) is designed to treat PH1 at its genetic source

PH1 Program Overview

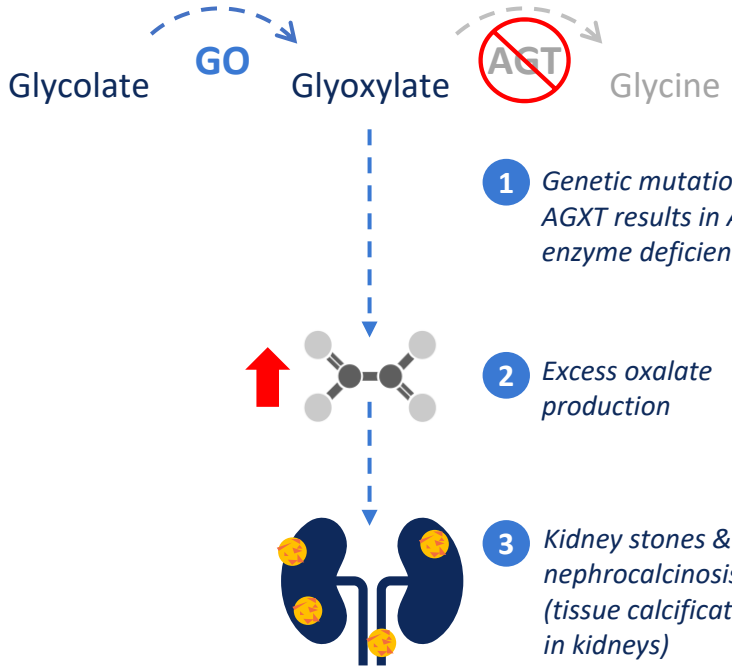
Phase 1 Clinical Data

Expansion opportunity

Disease Mechanism

Functional AGXT metabolizes glyoxylate into glycine resulting in normal oxalate production

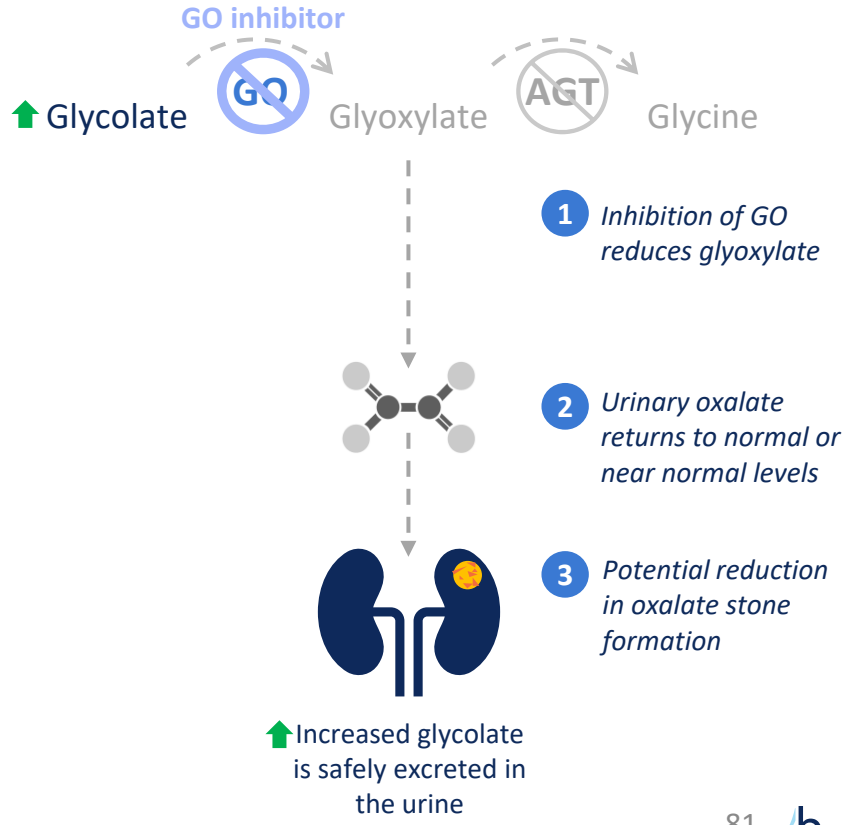
Loss of function mutation in AGXT results in excess oxalate production, causing oxalate stone formation



Hyper - oxal - uria = Excess - oxalate - in the urine

Therapeutic Approach

Inhibition of GO reduces the precursor substrate (glyoxylate) for oxalate production



Well tolerated in Phase 1 with dose-dependent increases in plasma glycolate

PH1 Program Overview

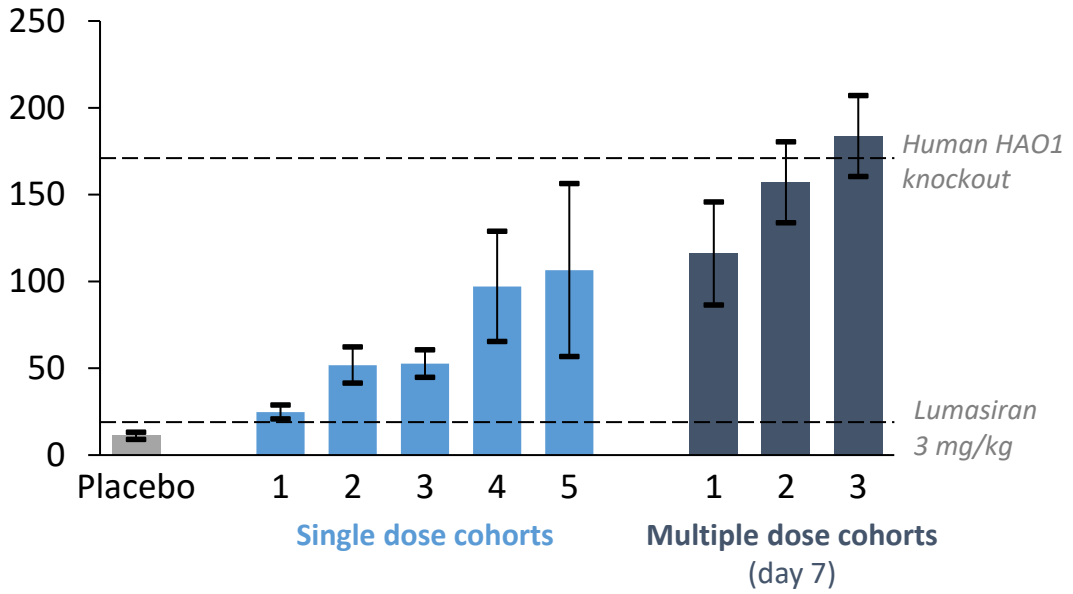
Phase 1 Clinical Data

Expansion opportunity

Oral doses in healthy adult volunteers

Mean maximal plasma glycolate concentration
Mean ± SD (µM)

Preliminary and interim data



Well tolerated

- No safety signals of clinical concern
- All AEs were mild or moderate

Favorable PK/PD profile

- Potential to maximally inhibit GO with once-daily dosing
- Largest glycolate response observed to date by targeting GO

Timeline

2022

Phase 1 data
& Phase 2/3 start

Key Endpoints

- Increase in plasma glycolate
- Safety and tolerability
- Pharmacokinetic profile

Source: Frishberg, Yaacov, et al. *CJASN* (2021); McGregor, Tracy et al. *eLife* (2020)

Expansion opportunity in recurrent stone formers with hyperoxaluria

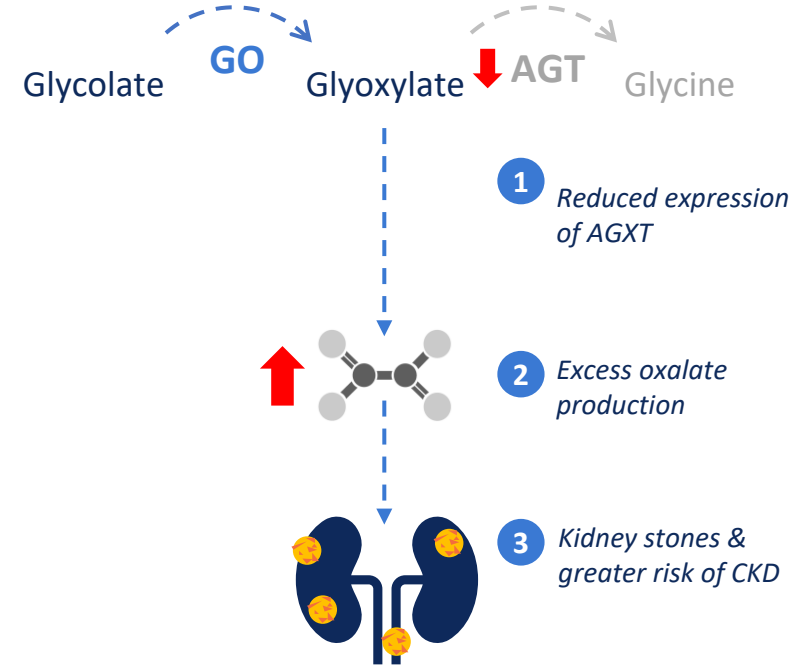
PH1 Program Overview

Phase 1 Clinical Data

Expansion opportunity

Disease Mechanism

Epigenomic changes in AGXT results in excess oxalate production, causing oxalate stone formation



Prevalence

~1.5M

US & EU

Epigenomic Driver

Hypermethylation and downregulation of AGXT causing excess oxalate

Gianmoena, Kathrin, et al. "Epigenomic and transcriptional profiling identifies impaired glyoxylate detoxification in NAFLD as a risk factor for hyperoxaluria." *Cell Reports* 36.8 (2021): 109526.

Limb-Girdle Muscular Dystrophy Type 2i (LGMD2i)

Seamus
Living with LGMD2i

Prevalence[1]

7k

US & EU

Pathophysiology

Progressive muscle weakness resulting in the loss of ability to perform routine daily functions

Genetic Driver

Loss of function of FKRP gene

Therapeutic Hypothesis

Add glycosylation substrate to drive residual enzyme activity

Design Criteria for Optimal Therapy

- Naturally occurring compound with strong safety profile
- First potential disease targeting therapy
- Oral dosing

[1]Includes all patients with potentially treatable mutations

Ribitol (BBP-418) is being investigated as an upstream substrate to drive residual activity of the mutant FKRP enzyme

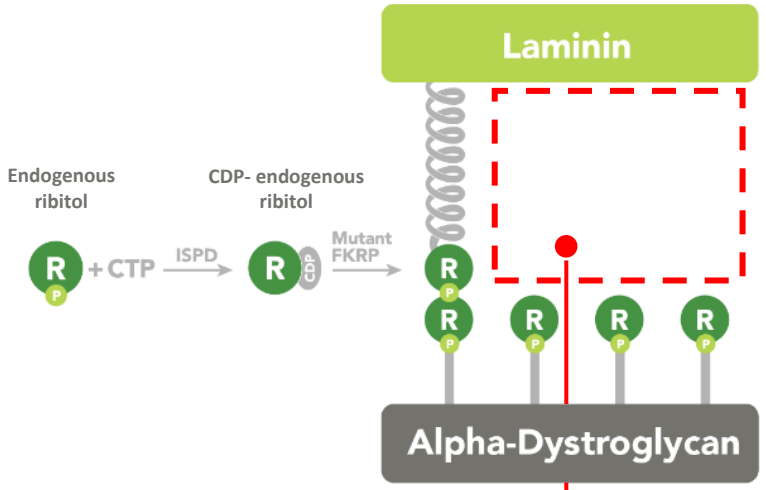
LGMD2i Program Overview

Update / Next Steps

Disease Mechanism

Functional FKRP fully glycosylates alpha-dystroglycan (α-DG) which stabilizes cells by binding extracellular ligands

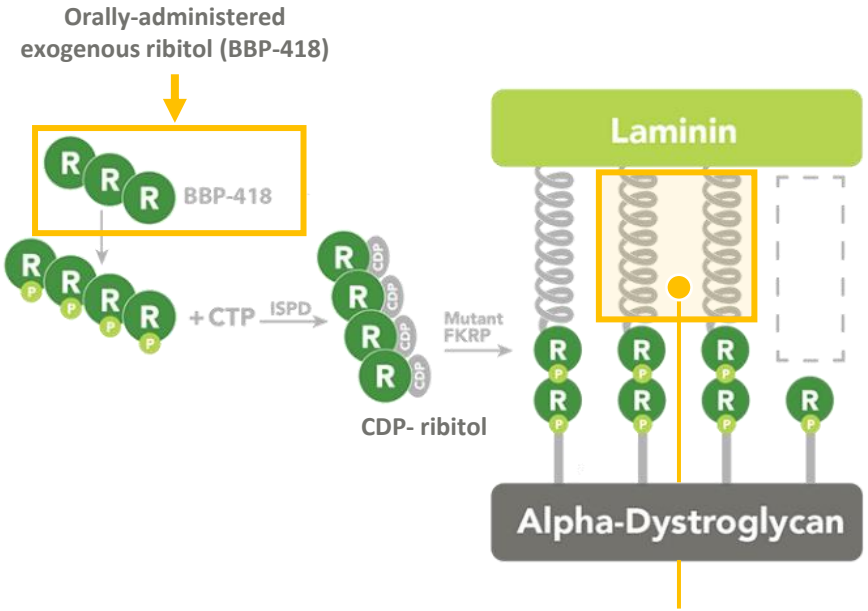
Partial loss of function mutation in FKRP result in dysfunctional, hypo-glycosylated α-DG in muscle cells which increases cell susceptibility to damage



Mutations in FKRP prevent addition of CDP-ribitol to alpha-dystroglycan (hypo-glycosylated α-DG) limiting α-DG's ability to function as a "shock absorber" for muscle fibers

Therapeutic Approach

Supply supraphysiological levels of ribitol upstream to drive residual activity of mutant FKRP enzyme and increase α-DG glycosylation levels



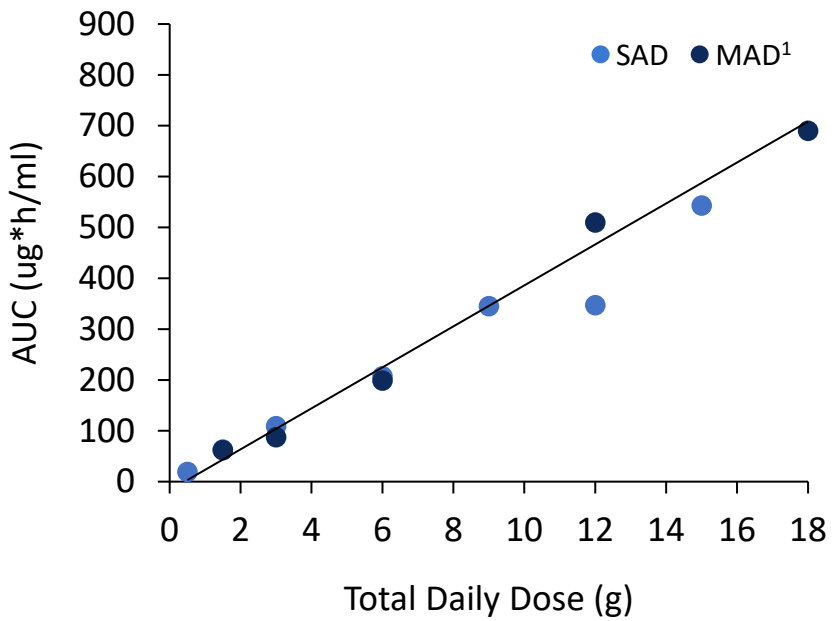
Potential partial restoration of α-DG glycosylation

Strong safety profile in Phase 1 with first LGMD2i patient dosed in 1Q21

LGMD2i Program Overview

Update / Next Steps

Phase 1 findings: Exposure by total daily dose for healthy volunteers



- ***Strong safety profile*** *with all doses well-tolerated*
- ***Dose-proportional exposures*** *up to the highest dose tested*
- ***Informed Phase 2*** *dosing selection*
- ***Phase 2*** *ongoing*

[1]MAD cohorts include 1.5g QD, 3g QD, 3g BID, 6g BID, 9g BID

Timeline

2022

Phase 2 Data

Key Endpoints

- **Safety and tolerability**
- **Functional clinical assessments**
- **Glycosylated α-DG**
- **Creatine Kinase (marker of muscle breakdown)**

Recessive Dystrophic Epidermolysis Bullosa (RDEB)

Child Living with RDEB

Prevalence

2k

US & EU

Pathophysiology

Loss of structural adhesion causes debilitating blistering, tearing and scarring of the skin and impacts oral and GI

Genetic Driver

Loss of function of collagen type VII protein (C7)

Therapeutic Hypothesis

Systemic treatment by providing C7 replacement therapy through IV infusion

Design Criteria for Optimal Therapy

- Only systemic treatment targeting RDEB
- Potential to provide GI & oral benefits while also proactively improving the quality of wounds
- Convenient dosing schedule for patient and families

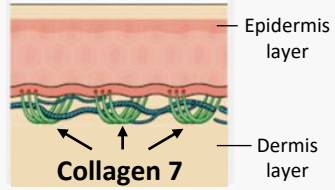
PTR-01 is currently the only systemic treatment targeting RDEB at its source

RDEB Program Overview

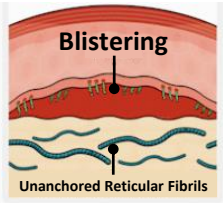
Update / Next Steps

Disease Mechanism

Functional C7 forms anchoring fibrils (AFs) to secure the epidermis to the dermis in healthy skin



Mutated C7 causes severe blistering due to loss of structural adhesion



Symptoms

Localized skin

- Severe blistering
- Wounding
- Extensive scarring

Universal skin

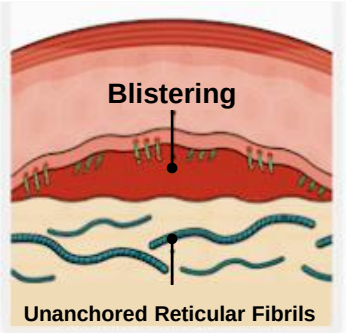
- Dystrophy and loss of nails
- Mitten deformity of hand and feet
- Higher risk for aggressive squamous-cell carcinoma

Systemic tissues

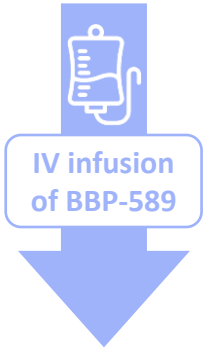
- Joint contractures
- Oral and dental malformations
- Severe impact to upper GI track
- Nutritional deficits and anemia

Therapeutic Approach

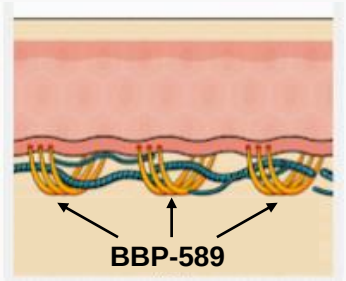
RDEB Patient



BBP-589 deposits in the skin, assembles into functional AFs, and reconstitutes DEJ adhesion in patients with RDEB



Treated Patient



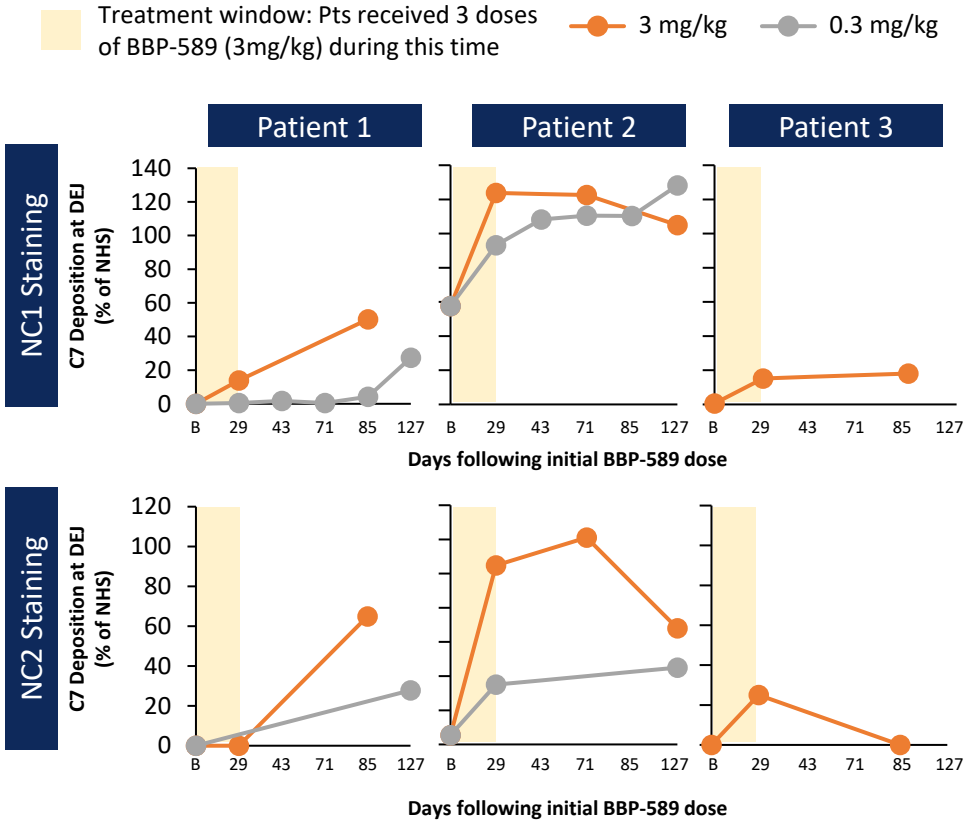
DEJ: dermal-epidermal junction

Well tolerated in Phase 1 with dose-dependent increase in C7 skin deposition

RDEB Program Overview

Update / Next Steps

Phase 1: Immunofluorescence C7 Deposition



All 3 patients receiving 3mg/kg dose exhibited increased C7 deposition at the DEJ

Timeline

1H22

Phase 2 data

Key Endpoints

- Wound improvement
- Deposition of C7 in skin biopsy
- Safety and tolerability

Patients 1 and 2 participated in the 3mg/kg and 0.3mg/kg cohorts. DEJ: dermal-epidermal junction

Mendelian program summary

15+ Mendelian Disease Programs	
1 FDA approval	MoCD Type A Nulibry (fosdenopterin) for injection
5 mid/late-stage programs	ATTR, Achondroplasia, ADH1, RDEB, LGMD2i
3 early clinical programs	PH1, PKAN, VM/LM
10+ preclinical programs	
Catalysts (YE21 / 2022)	
Acoramidis – Part A readout	4Q 2021
Achondroplasia, RDEB, LGMD2i, PH1	2022

Precision Oncology: Program Updates

Eli Wallace, Ph.D.

Chief Scientific Officer, Oncology

Precision oncology pipeline overview

	Indication	Drug Mechanism	Pt. pop. (US+EU)	Discovery	Pre-IND	Phase 1	Phase 2	Phase 3	Approved
Precision Oncology	FGFR2+ cholangiocarcinoma (2L)	TRUSELTIQ™ (FGFRi, infigratinib)	4k						
	FGFR2+ cholangiocarcinoma (1L)	FGFRi (infigratinib)							
	FGFR3+ adjuvant urothelial	FGFRi (infigratinib)	21k						
	FGFR1-3+ tumor agnostic	FGFRi (infigratinib)	24k						
	FGFR1-3+ gastric cancer	FGFRi (infigratinib)	41k[1]						
	MAPK / RAS-driven cancer	SHP2i monotherapy (BBP-398)	>500k						
		SHP2i combo therapy (BBP-398)							
	KRAS-driven cancer	KRAS G12C dual inhibitor	>500k						
		PI3Kα:RAS Breaker							
		KRAS G12Di							
	Solid tumors	GPX4i	>500k						

TRUSELTIQ™ (infigratinib) capsules

Featured Programs

[1]China + Japan patient population

KRAS mutant-driven cancers

Basia

Living with pancreatic cancer (>90% KRAS-driven)

Prevalence

>500k

US & EU

Pathophysiology

RAS is the most frequently mutated oncogene, leading to abnormal cell proliferation and survival

Program Highlights

G12C dual inhibitor

MOA: first to directly bind and inhibit both GTP (active) and GDP (inactive) states of $KRAS^{G12C}$

PI3Kα:RAS Breaker

MOA: first to block RAS-driven PI3Kα activation with the potential to avoid adverse effects on glucose metabolism

G12D inhibitor

MOA: directly bind and inhibit $KRAS^{G12D}$ - the single most prevalent KRAS mutant

MOA = mechanism of action

Partnerships afford us exceptional collaborators and resources

Research Capabilities

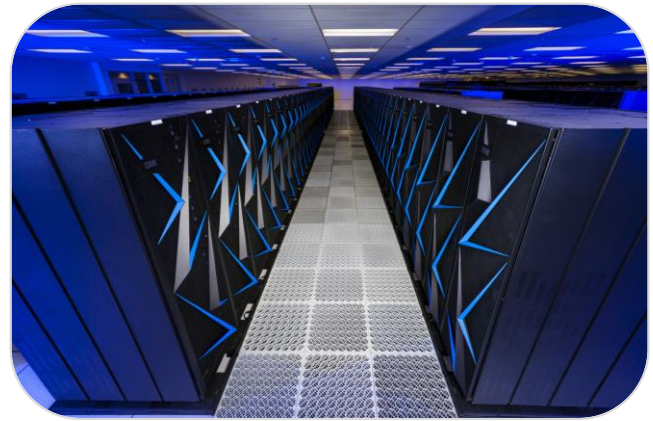
G12C Dual Inhibitor

PI3Kα:RAS Breaker

NIH NATIONAL CANCER INSTITUTE

- Partnership with the National RAS Initiative, including **60 of the world's foremost academic RAS researchers**
- Cutting edge RAS **structural biology expertise**
- Utilization of **cutting-edge instrumentation and techniques**, as well as the **expertise** to lead experiments

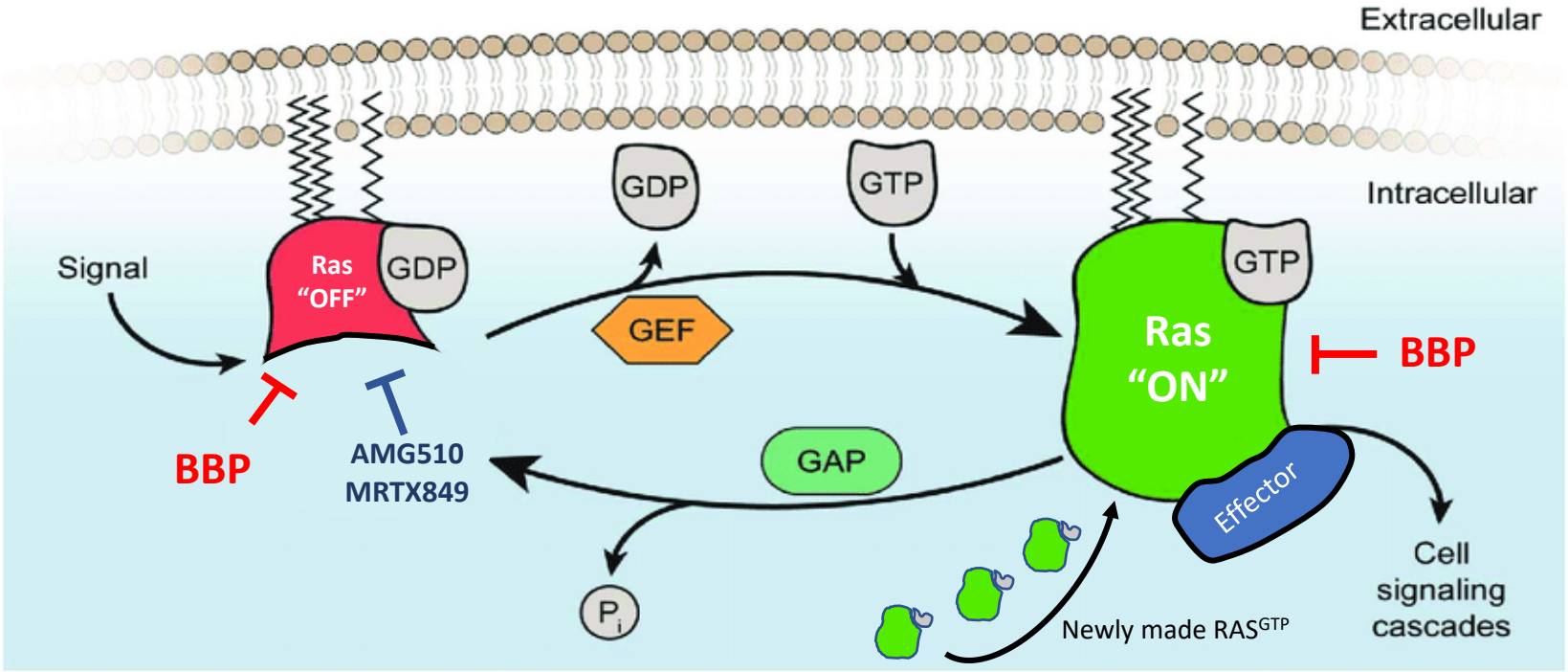
Lawrence Livermore National Laboratory



- Home to Sierra: the **world's 3rd fastest computing system**
- Enables **multi-microsecond molecular dynamics simulations** of protein complexes, and highly efficient in silico docking simulations
- This computing power, combined with RAS structural biology expertise at the NCI, delivers **unique insights that fuel our drug design**

We hypothesize that a compound that inhibits both GTP (active) and GDP (inactive) forms of KRAS^{G12C} will be superior to one that only inhibits the latter

- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker



		GTP (active) / GDP (inactive) dual inhibitor e.g. BBP compounds	GDP (inactive) inhibitors e.g. AMG510, MRTX849
1	Blocks oncogenic signaling from KRAS^{G12C} GTP (active)	✓	
2	Prevents KRAS^{G12C} GDP (inactive) from cycling to KRAS^{G12C} GTP (active)	✓	✓
3	Prevents resistance from residual KRAS^{G12C} GTP (active) signaling	✓	

Source: Adapted from Schoneborn & Heumann, IJMS, 2018. Note: Conclusions based on preclinical models

BridgeBio G12C inhibitors modify both GTP (active) and GDP (inactive) forms of $KRAS^{G12C}$

- Research Capabilities
- **G12C Dual Inhibitor**
- PI3Kα:RAS Breaker

			BBP	AMG510	MRTX849
% modified	$KRAS^{G12C}$ GTP (active)	15’	100	0	0
		120’	100	0	0
	$KRAS^{G12C}$ GDP (inactive)	15’	100	80	73
		120’	100	83	80
$KRAS^{G12C}$: RAF1 Effector Binding IC_{50} (nM)			35	>100,000	20,000
H358 pERK IC_{50} @ 30’ (nM)			8	50	310

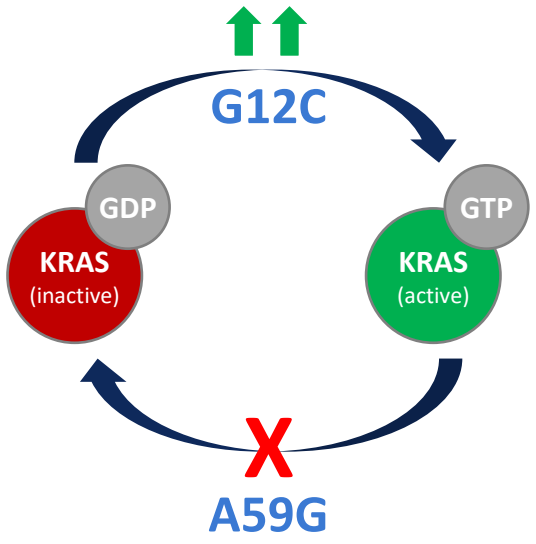
Multiple series of dual inhibitors progressing to identify development candidate

Note: Conclusions based on preclinical models

RAS-GTP “locked” mutant A59G, provides strong evidence for cellular GTP-state inhibitor activity

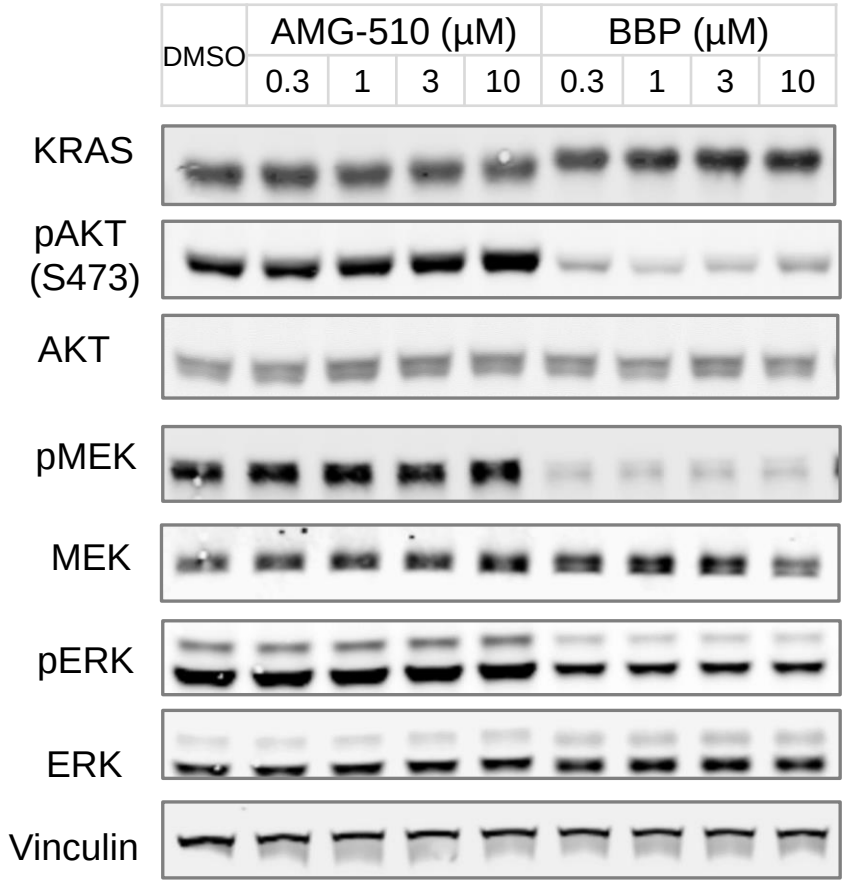
- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker

Impact of KRAS Mutations on Nucleotide Turnover



A59G is a 'transition state' mutant that abrogates GTPase activity and locks KRAS in GTP-state

$KRAS^{G12C/A59G}$



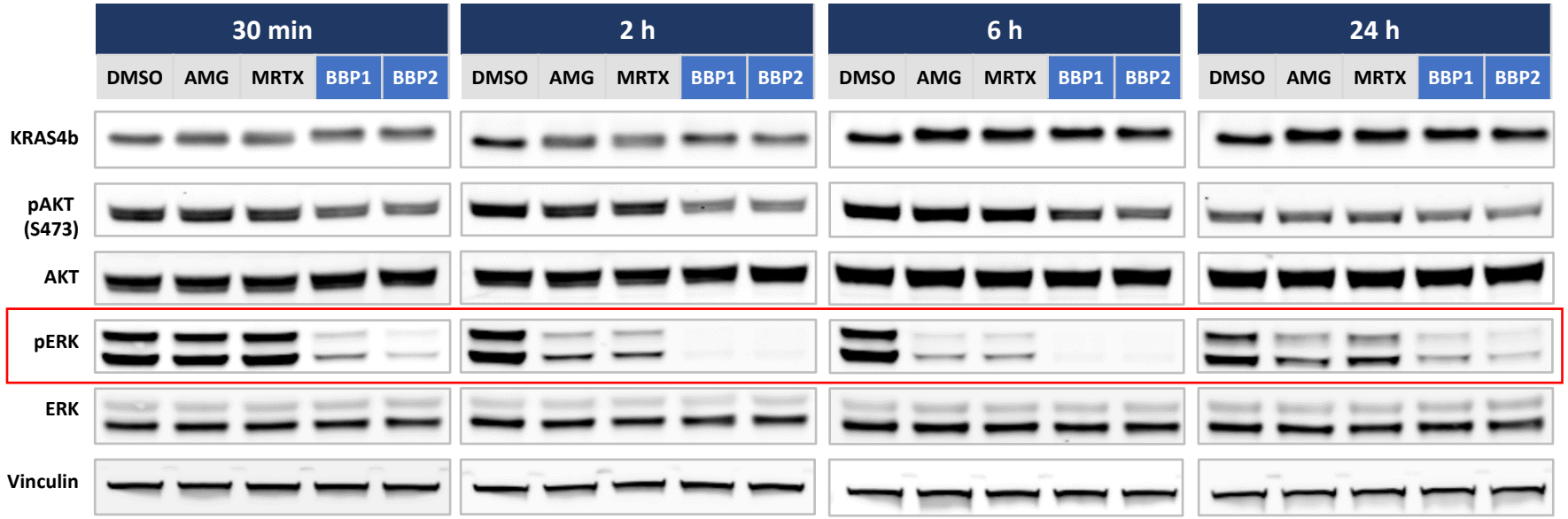
Strong pAKT, pMek and pERK inhibition observed with BBP KRAS-GTP/GDP dual inhibitor

Note: Conclusions based on preclinical models

BridgeBio G12C dual inhibitors engage KRAS^{G12C} more quickly and potently than inhibitors that only target the GDP (inactive) form

- Research Capabilities
- **G12C Dual Inhibitor**
- PI3Kα:RAS Breaker

KRAS^{G12C} homozygous, p53 mutant CRC



GTP/GDP dual inhibitors:

- ✓ Quickly engage the target because they do not depend on nucleotide cycling to reveal the substrate
- ✓ Show faster and greater inhibition of pERK and pAKT than GDP (inactive) inhibitors

Note: Conclusions based on preclinical models

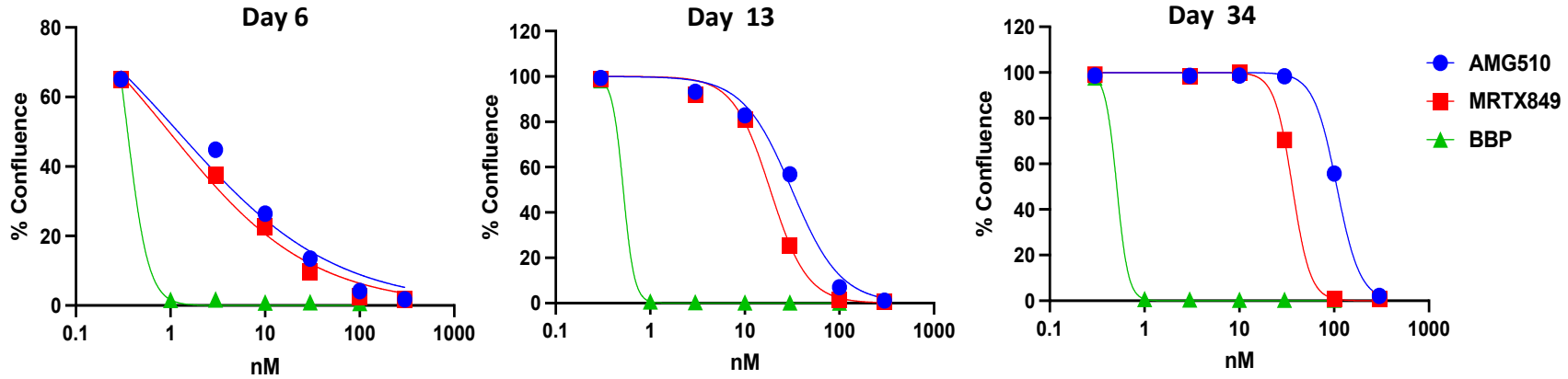
BridgeBio G12C dual inhibitors are more potent and retain activity compared to inhibitors that only target the GDP (inactive) form

Research Capabilities

G12C Dual Inhibitor

PI3Kα:RAS Breaker

Clonogenic Assay



	% Confluence (IC_{50}, nM)		
	BBP	AMG510	MRTX849
Day 6	< 1	7	5
Day 13	< 1	32	19
Day 34	< 1	107	36

GTP/GDP dual inhibitors:

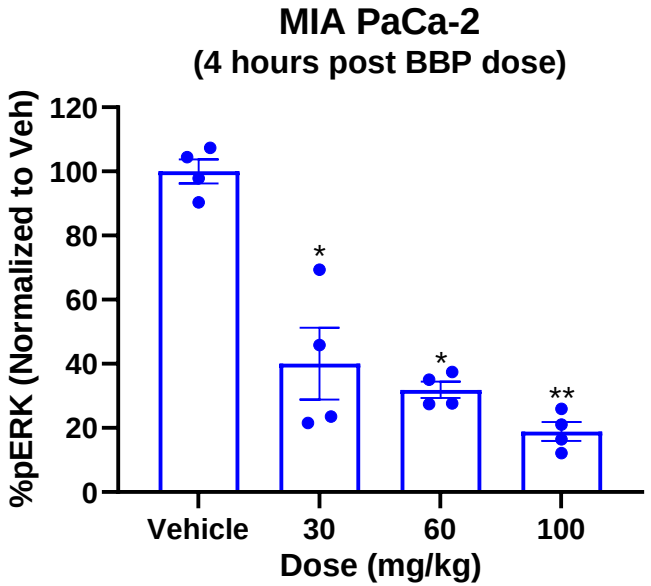
- ✓ Potently inhibit colony formation
- ✓ Retain potent activity suggesting that inhibiting both states of mutant KRAS reduces or delays development of resistance

Note: Conclusions based on preclinical models

BridgeBio dual GTP/GDP inhibitors show potent and sustained inhibition of pERK in vivo

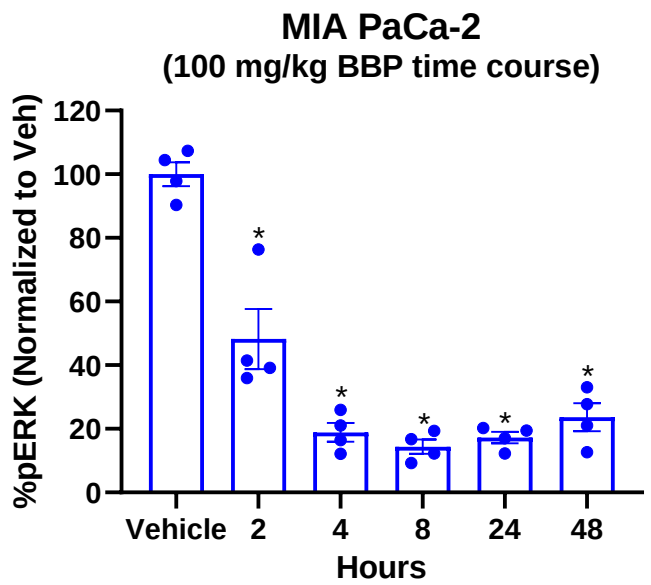
- Research Capabilities
- **G12C Dual Inhibitor**
- PI3Kα:RAS Breaker

Dose Response



One-way ANOVA with Tukey's test vs vehicle *p<0.001, **p<0.0001

Time Response



One-way ANOVA with Tukey's test vs vehicle *p<0.0001

GTP/GDP dual inhibitors:

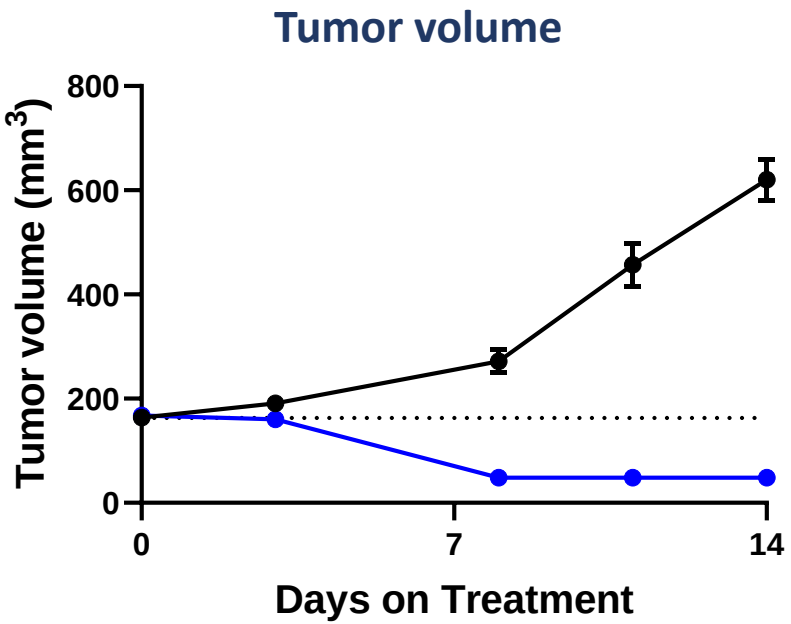
- ✓ Dose dependently inhibit pERK
- ✓ Provide sustained pERK inhibition over 48 hours after a single dose

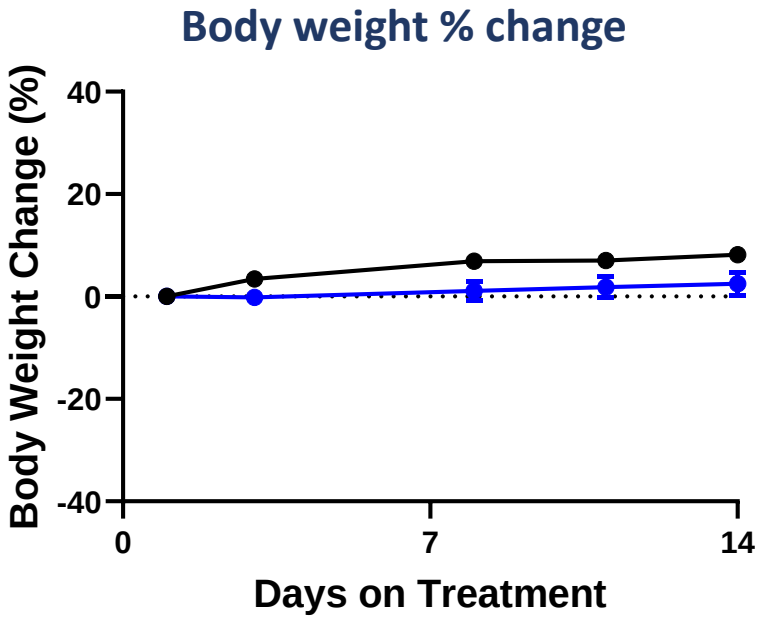
Note: Conclusions based on preclinical models

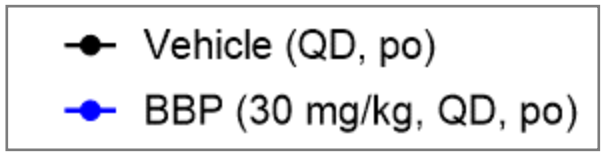
BBP induces tumor regressions and is well tolerated in the MIA PaCa-2 CDX model

- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker

MIA PaCa-2 pancreatic CDX ($KRAS^{G12C}$)







Note: Conclusions based on preclinical models

Novel approach to target PI3Kα is tumor cell specific and differentiates from kinase inhibitors

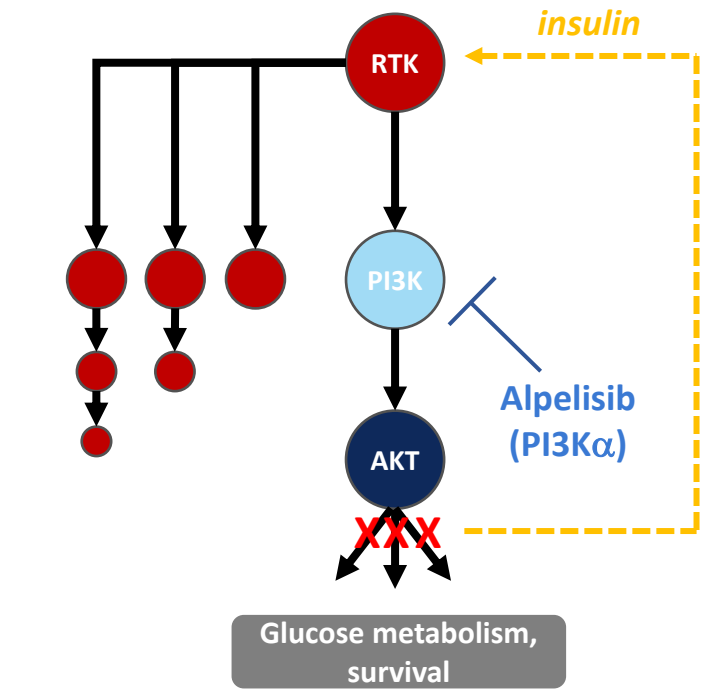
Research Capabilities

G12C Dual Inhibitor

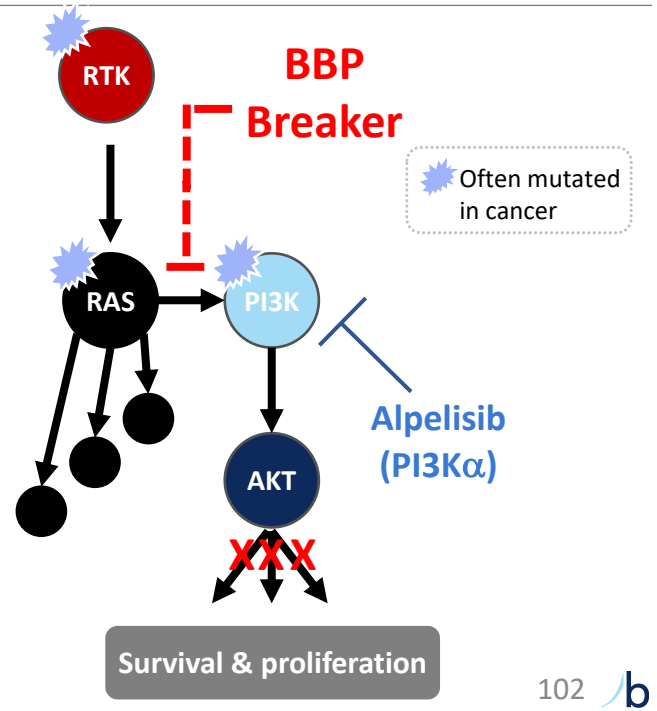
PI3Kα:RAS Breaker

- PI3Kα kinase inhibitors ***block normal cell signaling*** as well as RAS-driven PI3Kα pathway activation in tumor cells, resulting in ***dose-limiting hyperglycemia and insulin-driven resistance***
- Our novel approach of inhibiting PI3Kα:RAS PPI with a ***"PI3Kα Breaker"*** should avoid hyperglycemia and insulin-driven resistance by specifically targeting tumor cells and may provide multiple therapeutic opportunities:
  - ***Tumors with RAS or PI3Kα helical mutations and RTK mutant/amplified drivers***
  - ***Potential combination with ERK pathway inhibition (BRAFi, MEKi, ERKi, KRAS^{G12C}i)***

Normal Cells



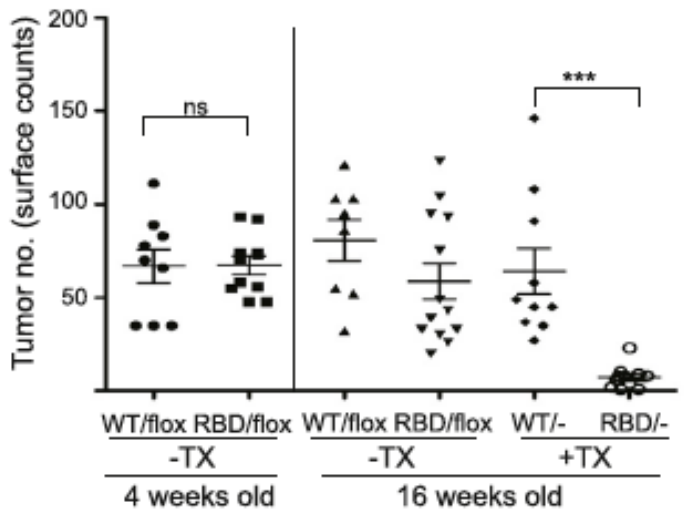
Tumor Cells



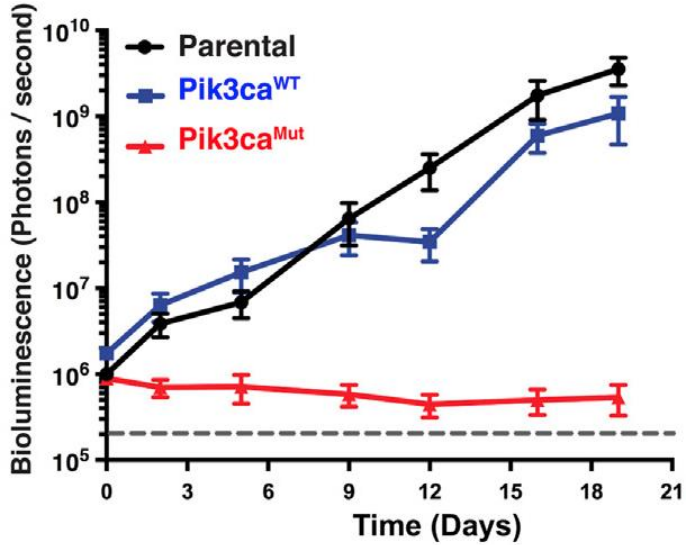
Impairing the PI3Kα:RAS interaction blocks oncogene-driven NSCLC tumor growth in vivo

- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker

$KRAS^{G12D}$-driven tumor growth is inhibited in mice with T208D and K227A mutations in the RAS-Binding Domain (RBD) of PIK3CA



Mutating the RBD of PIK3CA in the $EGFR^{T790M/L858R}$ mutant NSCLC model H1975 abrogates xenograft tumor growth

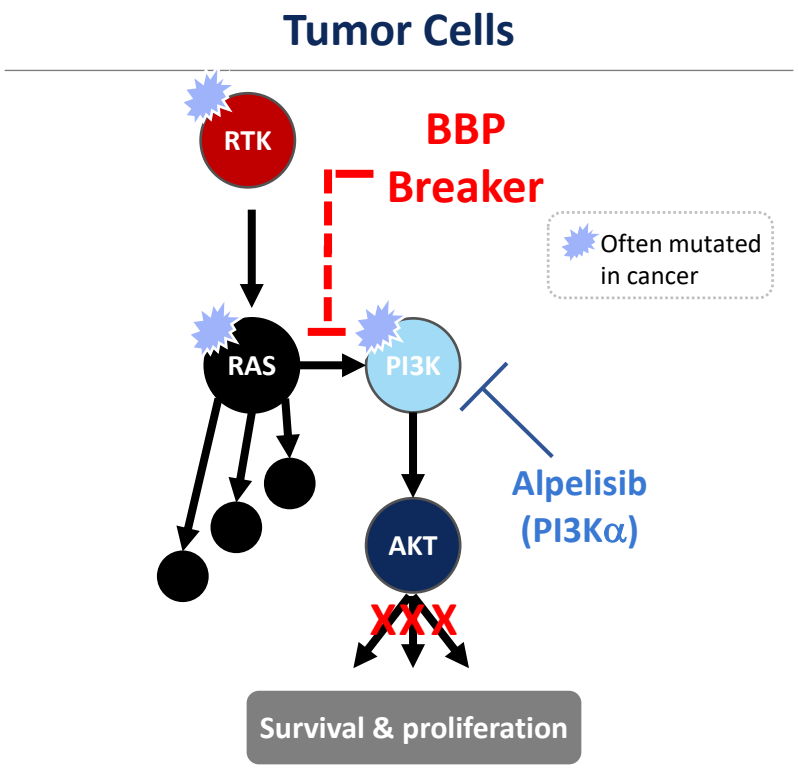


- Mutating the RBD of PIK3CA in NSCLC models has profound effects on EGFR- and $KRAS^{G12D}$-driven tumorigenesis
- RBD mutant mice have normal glucose metabolism

Sources: Gupta et al Cell 2007; Castellano et al Cancer Cell 2013; Murillo et al., Cell Reports 2018

BridgeBio has discovered potent and selective PI3Kα:RAS breakers

- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker



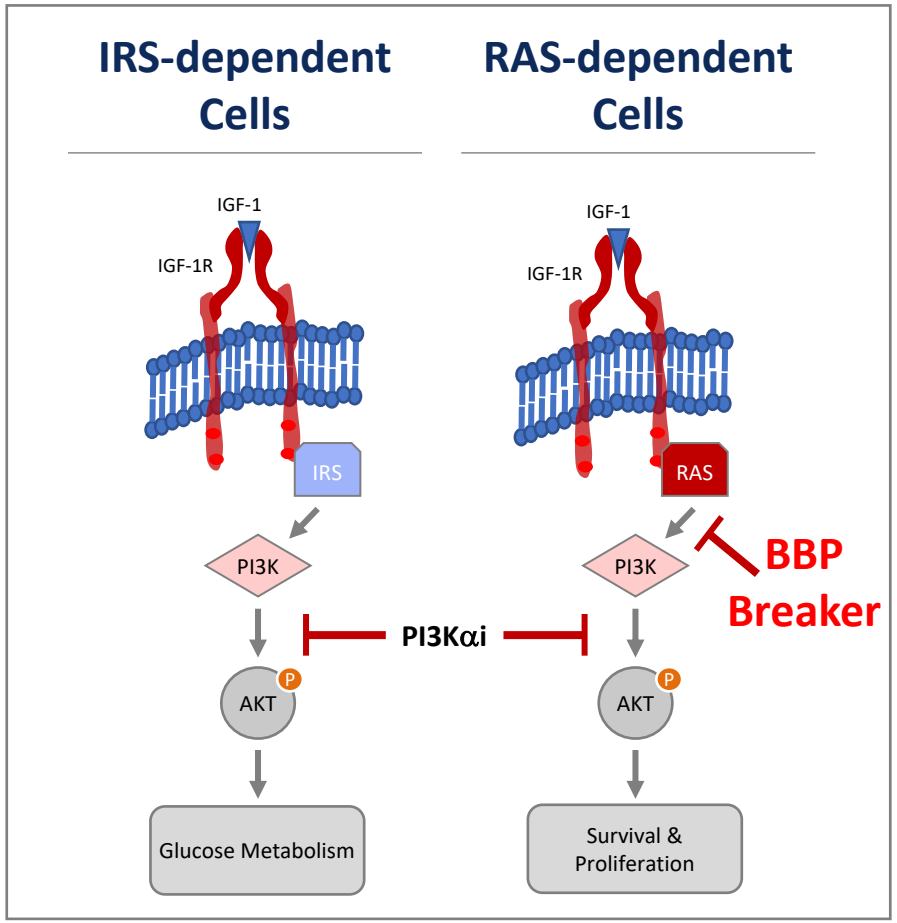
- Structural insights provide a novel approach to develop PI3Kα:RAS breakers
- PI3Kα:RAS breakers selectively bind to PI3Kα
  - PI3Kα amino acid sequence in the region of the binding pocket is unique amongst all the isoforms
  - No binding affinity to KRAS
- PI3Kα:RAS breakers do not affect kinase activity of PI3Kα

	BBP	Alpelisib
PI3Kα Binding (IC_{50}, nM)	177	N/A
pAKT (IC_{50}, nM)	21	169
Cell Viability	134	744

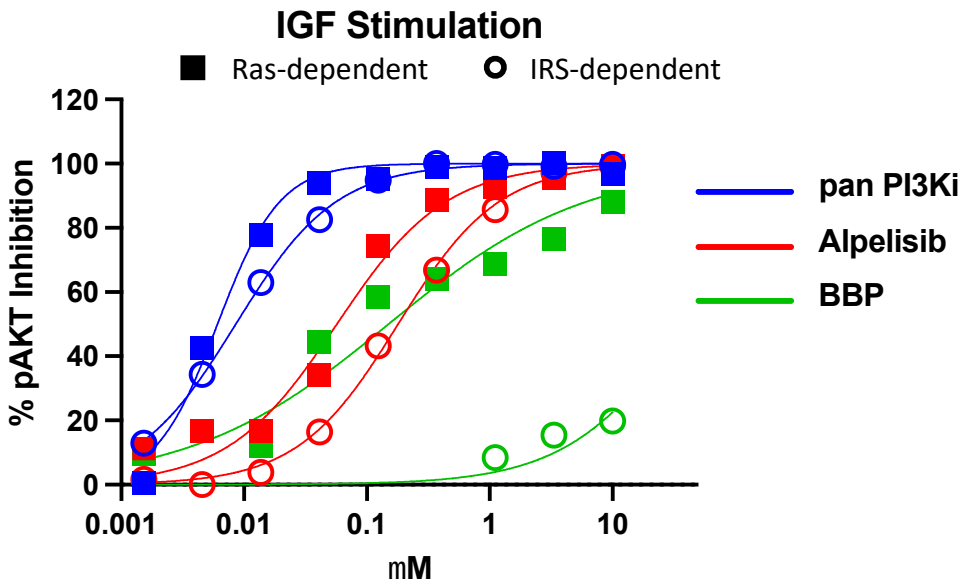
Multiple series of compounds have been identified as potent PI3Kα:RAS PPI inhibitors

Cellular experiments show that only PI3Kα breaker differentiates between RAS and IRS-driven pAKT activation

- Research Capabilities
- G12C Dual Inhibitor
- PI3Kα:RAS Breaker



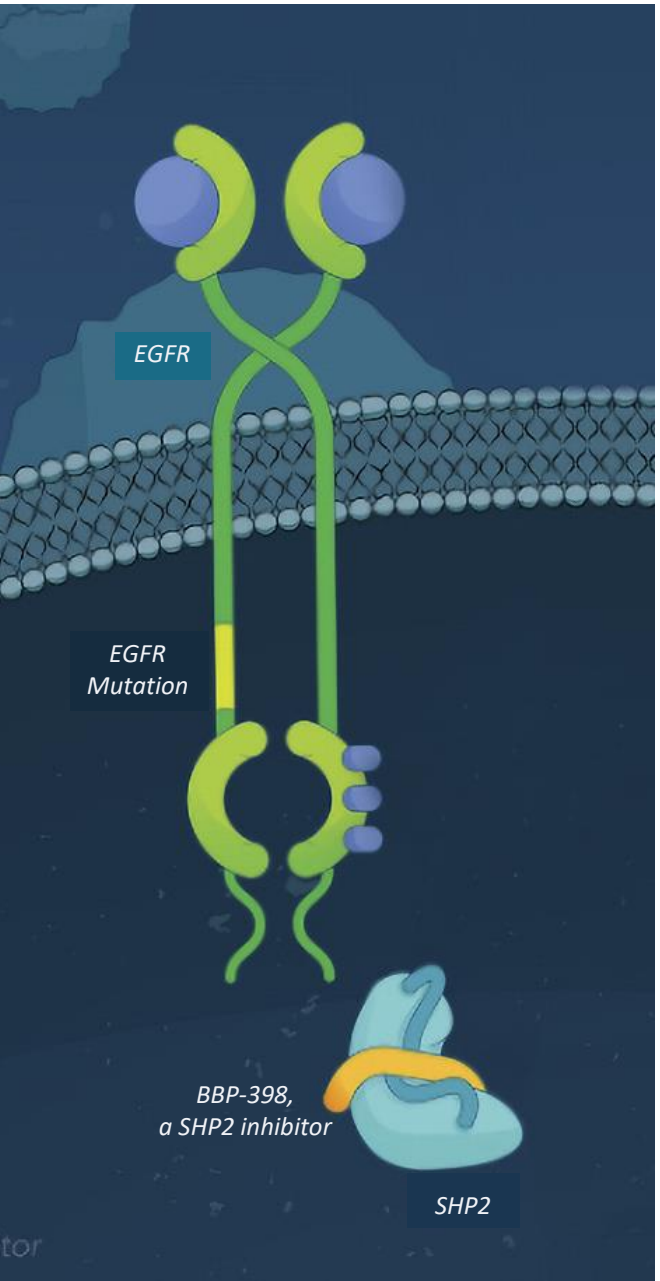
% AKT inhibition in cells treated with IGF



These data suggest that PI3Kα breakers may avoid the on-target hyperglycemia associated with PI3Kα kinase inhibitors

IRS – insulin receptor substrate; IGF-1 – insulin-like growth factor-1

BBP-398: SHP2 inhibitor for treatment resistant cancer



Prevalence

>500k

US & EU

Pathophysiology

SHP2 acts upstream of RAS/ERK in RTK and cytokine signaling to regulate cell proliferation, survival, adhesion, and migration

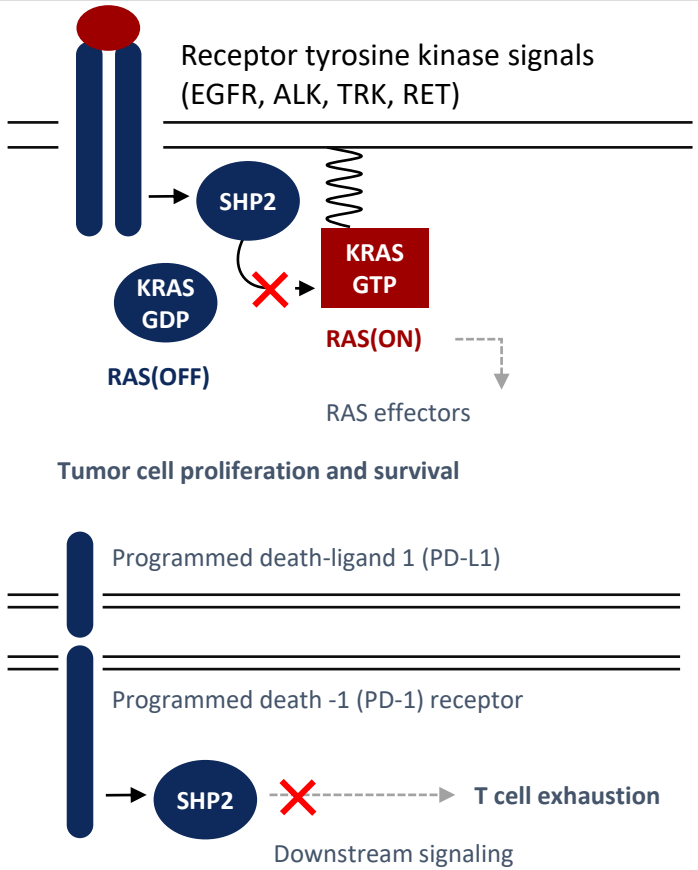
Program Highlights

- BBP-398 is a selective, orally bioavailable, allosteric SHP2 inhibitor
- Potential to be best-in-class based on optimal PK profile that may enable tolerable once-daily dosing
- Monotherapy dose escalation is ongoing with plans to initiate combination studies next year

BBP-398 shows best-in-class potential in a large cancer market

- Overview
- Preclinical Data
- Phase 1 Dose Escalation

Our SHP2i blocks downstream MAPK signaling and abrogates T cell exhaustion



We believe BBP-398 has the ideal properties for combination with a multitude of other therapeutic classes

- ✓ Human half life: ~10-15 hours
- ✓ Optimal PK profile which may enable better tolerability in combination

Initial clinical combinations of focus based on SHP2i preclinical data

Combination Agent	Patient Population[1]
KRAS G12Ci	70,000
EGFRi (LianBio)	150,000
PD-1 Bristol Myers Squibb™	700,000

[1]US incidence estimated from SEER, TCGA; all scaled for WW incidence

Predicted BBP-398 pharmacokinetics support once daily oral administration to achieve target coverage

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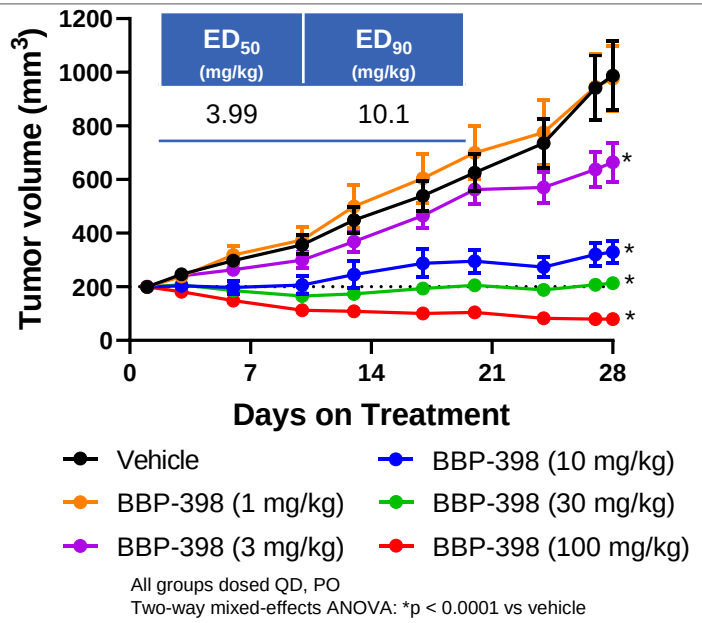
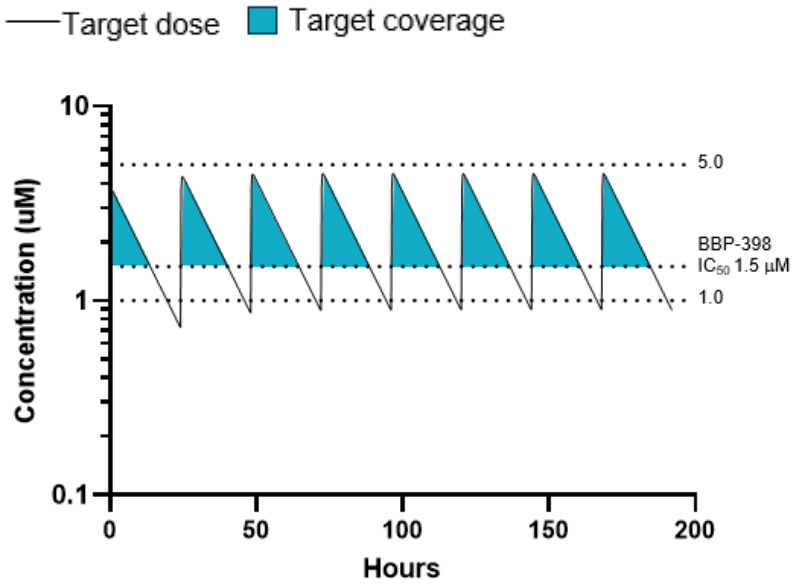
HCC827 ($EGFR^{ex19del}$ & $EGFR^{amp}$) - NSCLC CDX



All groups dosed QD, PO
Two-way mixed-effects ANOVA: *p < 0.0001 vs vehicle

BBP-398 steady-state PK simulation for optimal efficacy



Predicted clinical exposure supports coverage of efficacy target in patients may be achieved with continuous once daily dosing

Phase 1 dose escalation with BBP-398 is ongoing: Observed PK/PD is in-line with preclinical predictions

Overview

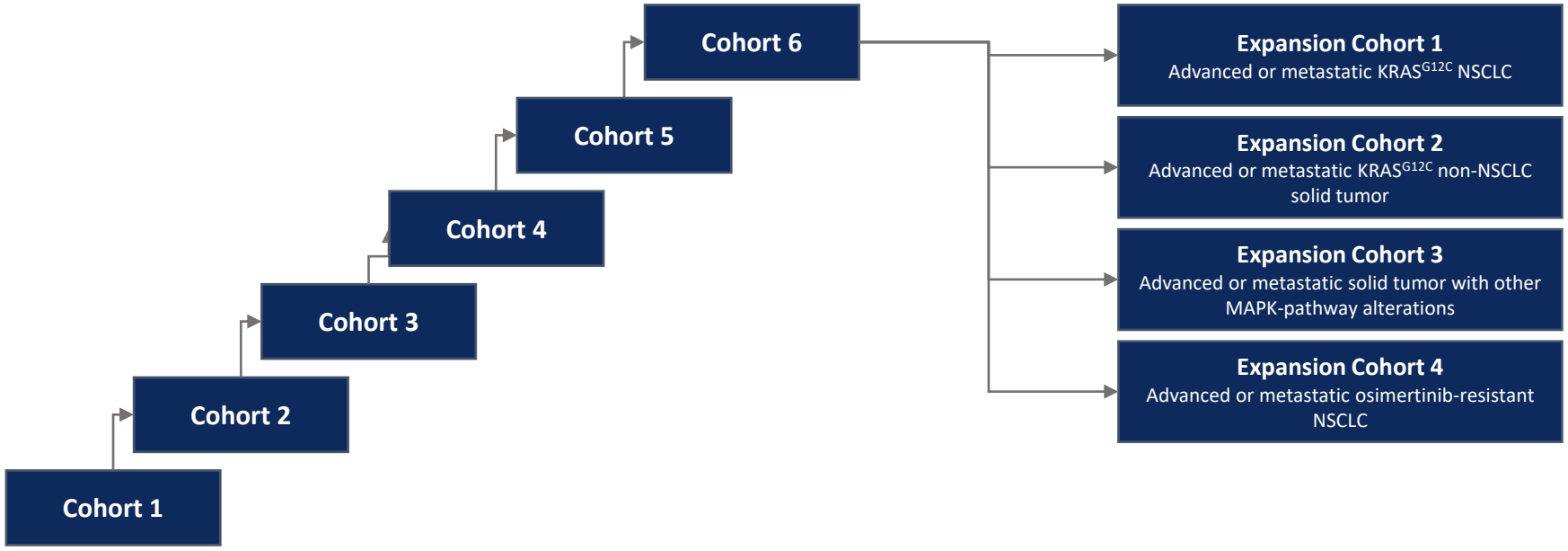
Preclinical Data

Phase 1 Dose Escalation

Dose escalation cohorts

Dose expansion (at RP2D)

Key enrollment criteria: Patients with MAPK-pathway alterations (e.g., $KRAS^{G12C}$, EGFR-mutant, but excluding $BRAF^{V600X}$ mutations).



BBP-398 dose escalation ongoing
Dose expansion at RP2D and combinations with Nivolumab and G12Ci planned for 2022

Precision oncology summary

BridgeBio Oncology

- ☑ Infigratinib approved for 2nd line FGFR2 fusion cholangiocarcinoma with multiple late-stage studies ongoing
- ☑ Identified multiple series of differentiated novel $KRAS^{G12C}$ GTP/GDP inhibitors
- ☑ Identified multiple series of differentiated novel PI3Kα:RAS Breakers
- ☑ Progressing potentially best-in-class SHP2 inhibitor BBP-398 with differentiated pharmacokinetic profile that may enable once-daily dosing in combination studies

2022 Targets

- ☐ RAS development candidate
- ☐ Present BBP-398 Phase 1 monotherapy data
- ☐ Initiate BBP-398 combination studies (KRAS G12Ci, IO, EGFRi)

BridgeBioX

Charles Homcy, M.D.

Chairman of Pharmaceuticals

bridgebio lab at Stanford

Our discovery lab is located in the Stanford Life Sciences District – we aim to create an academic/industry hybrid environment, and foster a culture driven by **intellectual curiosity** and a dedication to **patient impact**