bridgebio

hope through
rigorous science

Corporate presentation

May 2022

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BridgeBio Pharma: Hope through rigorous science

Our mission: To **discover**, **create**, **test** and **deliver** transformative medicines to treat patients who suffer from genetic diseases and cancers with clear genetic drivers

BridgeBio today – what is in focus

	Description	Program(s)	Potential future analogs
1	Potential best-in-class drug in a multi-billion-dollar market	Acoramidis for ATTR-CM (Ph3)	VERTEX, Alnylam
2	Multiple potential first- or best-in-class compounds in large genetic disease markets	Encaleret for ADH1 (Ph2) Low-dose infigratinib for achondroplasia (Ph2) Ribitol for LGMD2i (Ph2) AAV5 gene therapy for CAH (Ph2) Multiple additional discovery programs in high unmet need diseases	BIOMARIN, ultragenyx, ascendis pharma
3	Potential best-in-class precision oncology portfolio	SHP2i for SHP2-driven cancer (Ph1) KRAS portfolio including next-gen G12Ci and novel RAS/PI3K breaker MOA for KRAS-driven cancer (both in late lead opt)	REVOLUTION MEDICINES, RELAY THERAPEUTICS, ERASCA

We have sufficient cash to deliver against our portfolio in focus

- Cash balance[1] of $633mn as of 1Q22 expected to provide runway into 2024
- Capital access: Expect to monetize priority review voucher[2] and have ability to draw additional capital under senior secured facility if necessary
- Net cash use in 2022 driven primarily by investment in 5 mid-to-late-stage clinical programs (acoramidis for ATTR-CM, encaleret for ADH1, low-dose infigratinib for achondroplasia, ribitol for LGMD2i, and AAV5 gene therapy for CAH)
- In parallel, we are making focused investments in discovery research including our RAS portfolio and BridgeBioX innovation engine, all targeting large markets, but requiring small investment today
- Anticipate a QoQ decline in operating expenses from 2Q22 onward as a result of restructuring initiatives which began in January 2022

[1] Cash, cash equivalents, and marketable securities as of March 31, 2022. [2] David Ridley. Priority review voucher value. Duke Fuqua School of Business.

2022 has been a year of focused execution

- Delivered positive Ph2 proof of concept data from our LGMD2i asset at MDA (March)
- Announced positive long-term data from our acoramidis Ph2 study in ATTR cardiomyopathy at ACC (March)
- Put the company in place to announce two additional POC readouts by the end of summer (ADH1, achondroplasia)
- Took measures to focus the portfolio including two BD transactions:
  - Announced updated collaboration giving Helsinn the exclusive license to develop and commercialize TRUSELTIQ worldwide[1] in oncology indications[2]
  - Completed NULIBRY asset purchase agreement with Sentynl therapeutics
  - Together these transactions are expected to result in $100mn+ in opex savings in 2022-2023 while allowing BridgeBio to retain upside in the form of milestones and royalties
- Continued focus on partnering, necessary program prioritization and headcount reductions

[1] Excludes mainland China, Hong Kong and Macau
[2] BridgeBio retains all rights to develop, manufacture, and commercialize infigratinib in skeletal dysplasia, including achondroplasia.

We believe BridgeBio is poised to deliver on multiple catalysts over the near term with existing cash on hand

		2022	2023
Phase 3	Acoramidis		★ Topline Ph3 30-month mortality data (mid-23)
Phase 3	ADH1	★ Ph2 6-month POC data (1H22 @ ENDO)	Topline Ph3 data (2023) ★
Proof of Concept	LGMD2i	✓ Proof-of-concept (1Q22 @ MDA) ★ Additional Ph2 data (2H22)	
Proof of Concept	Achon / Hypochon	★ Ph2 data update (Mid-22)	
Proof of Concept	CAH	★ Initial data from Ph1/2 study (2H22)	
Dis-covery	KRAS Franchise	★ Clinical candidate selection (2H22)	

BridgeBio pipeline

	Indication	Drug Mechanism	Pt. pop. (US+EU)	Discovery	Pre-IND	Phase 1	Phase 2	Phase 3	Approved	Partner
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							
Mendelian	**Achondroplasia**	Low-dose FGFRi (infigratinib)	55k							
	LGMD2i	Glycosylation substrate (ribitol)	7k							
	PKAN / organic acidemia	Pank activator (BBP-671)	7k							
Precision Oncology	**MAPK / RAS-driven cancer**	SHP2i monotherapy (BBP-398)	>500k							Bristol Myers Squibb, AMGEN
		SHP2i combo therapy (BBP-398)								
	KRAS-driven cancer	KRAS G12C dual inhibitor	>500k							
		PI3Kα:RAS Breaker								
Gene Therapy	**CAH**	AAV5 gene therapy (BBP-631)	>75k							
	Canavan	AAV9 gene therapy (BBP-812)	1k							
	TSC1/2	AAV gene therapy	100k							
	Cystinuria	AAV gene therapy	30k							
Disc-overy	bridgebio	5+ undisclosed programs in large genetic disease markets								

[1]US carriers

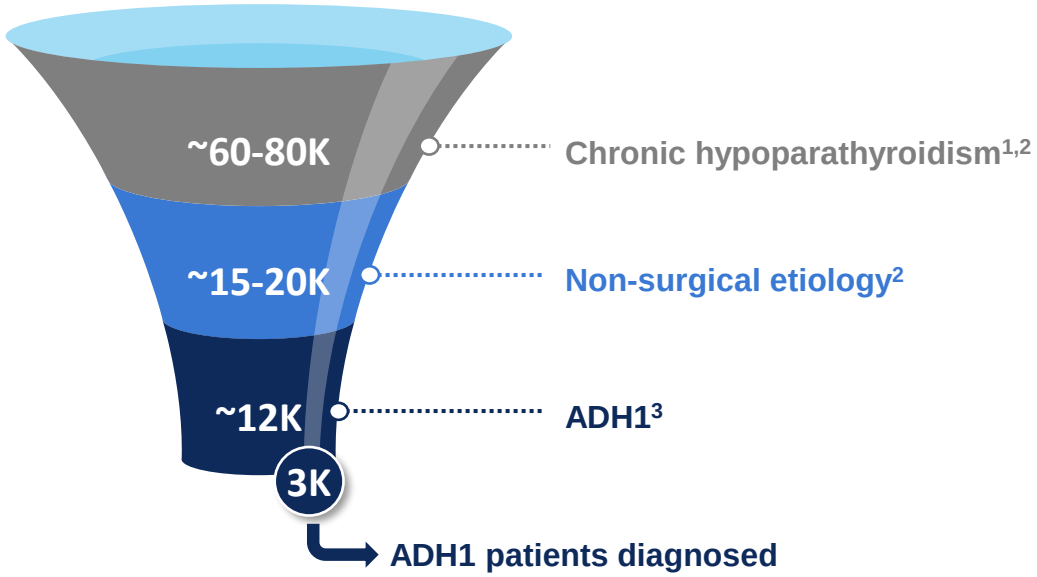
Encaleret for autosomal dominant hypocalcemia type 1 (ADH1)

- Prevalence (US): **12K**
- Stage: **Phase 2**
- Next Catalyst: **Phase 2 Period 3 data 1H 2022 (ENDO)**

Alexis and Jackson
Living with ADH1

ADH1 is a serious condition for which treatable patient numbers may grow meaningfully as diagnosis rates increase

12k genetic carriers, largely underdiagnosed with ~3K ADH1 patients diagnosed in US



- High unmet need for early diagnosis as ADH1 patients are largely hidden in hypoparathyroidism diagnosis
- Current standard of care does not adequately address disease mechanism and is primarily palliative

Analogous ADH1 market includes XLH

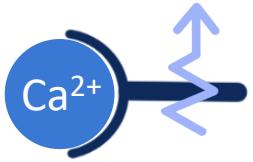
	XLH	ADH1
Prevalence (US)	12K[4]	12K
Disease burden	Hypophosphatemia	Acute hypocalcemia risk, long-term hypercalciuria risk
Standard of care	Vitamin D, daily phosphate	Vitamin D, daily calcium
Registrational endpoint	Serum phosphate	Blood and urine calcium
Projected peak year sales	>$2bn[5]	~$700m[6]

ATTR-PN = transthyretin amyloid polyneuropathy; XLX = x-linked hypophosphatemia. [1]Powers, et al. J Bone Miner Res. 2013. [2]Mannstadt, et al. Nat Rev Dis Primers. 2017. [3]Dershem, et al. Amer Jour of Hum Genetics 2020. [4]Ultragenyx public materials. [5]Evaluate. [6]BridgeBio Sell-side consensus.

ADH1 is a genetic cause of hypoparathyroidism resulting from gain-of-function variants in the CaSR which disrupt calcium homeostasis

Disease Mechanism

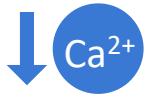
Normal CaSR senses and regulates serum Ca levels to maintain calcium homeostasis



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

Paresthesia

Tetany

Muscle cramps

Long-term complications

Nephrocalcinosis

Nephrolithiasis

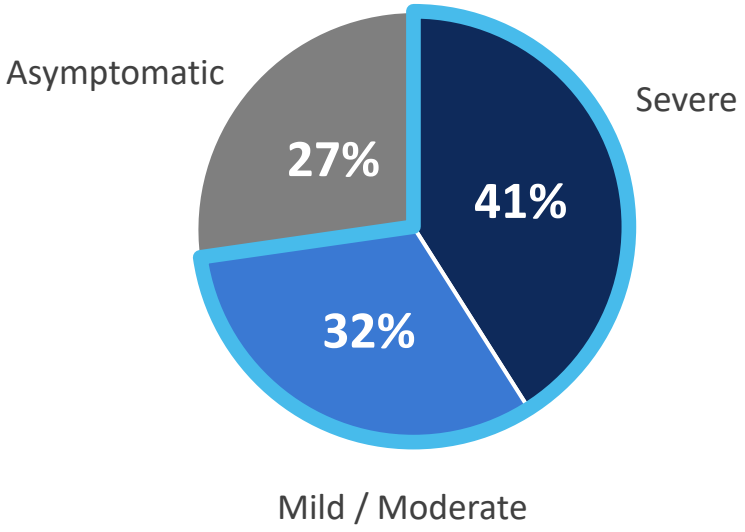
Chronic kidney disease

ADH1 unmet need is large with significant disease burden and no interventions specifically approved

>70% of patients experience moderate to severe symptoms

ADH1 cases

%

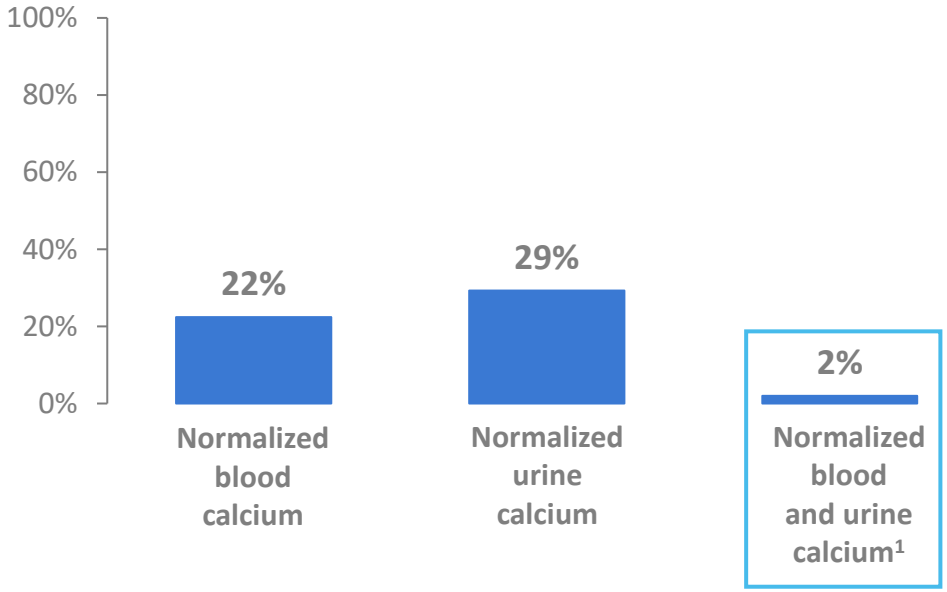


Median age of diagnosis[1]: 25 years
Range: 0 – 77 years

Current treatments inadequately address symptom burden

Individuals on calcium and/or active vitamin D

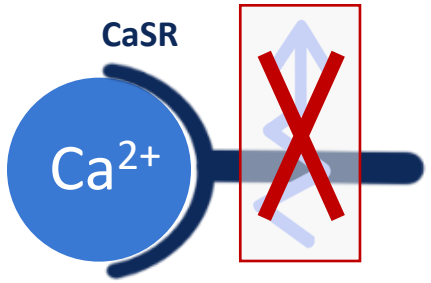
%



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

Encaleret directly targets CaSR to potentially resolve key symptoms

Molecule overview



- Encaleret is an oral CaSR inhibitor designed to normalize PTH, serum Ca and urine Ca levels, potentially resolving key symptoms of disease
- Encaleret was well-tolerated in prior osteoporosis development program (evaluated in >1,200 participants)

IP & partnership overview

- Issued and filed patents expected to provide market protection to 2041
  - Key patent covering formulation and methods published in 2022
- Orphan drug designation (ODD) provides 7 years of regulatory exclusivity in the US and 10 years in EU
- Encaleret selected as optimal CaSR antagonist for use in ADH1 and licensed in 2018
  - Low financial burden with <$2m owed in development milestone payments and low single digit revenue royalties

Complete Phase 2 data expected 1H 2022 with plans to initiate Phase 3 registrational study in 2022

Period 1 ✓	Period 2 ✓	Period 3 ☐	LTE
Individualized dose escalation	**Individualized dose titration**	**Outpatient extension**	**Long-term extension**
5 days, inpatient (N=6)	*5 days, inpatient (N=13)*	*6 months, outpatient (N=13)*	*Outpatient*
Results / next steps			
March 2021: Proof of concept early results	**October 2021:** Updated results of individualized dosing from Period 2	**Q1 2022:** FDA interaction **1H 2022:** Present Period 3 results	

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)

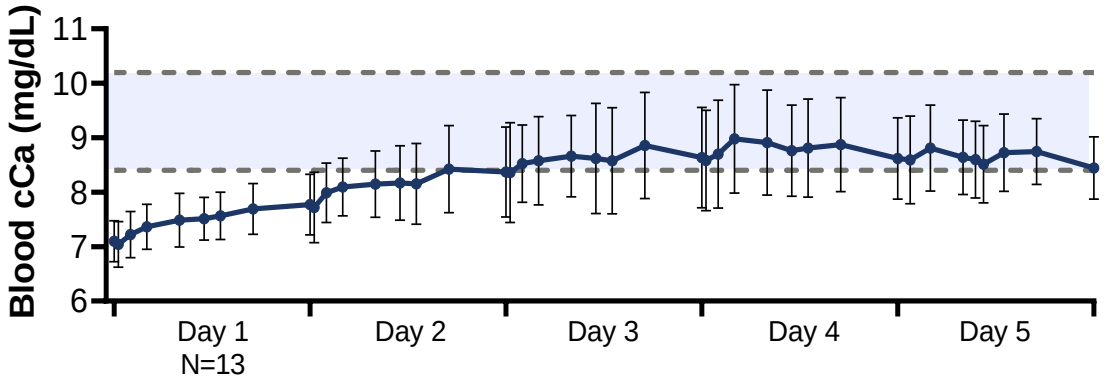
BridgeBio has generated compelling Phase 2 data to date

Phase 2 data suggests potential to normalize blood Ca and urine Ca

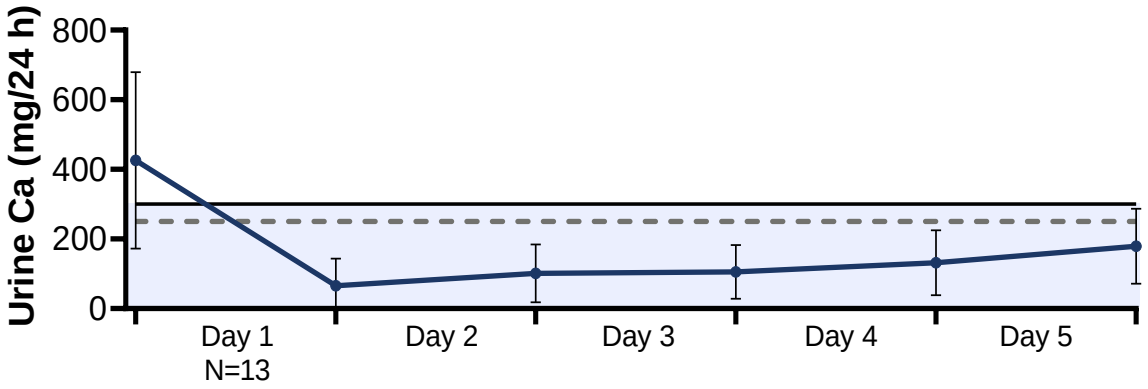
Mean responses on Day 1 through Day 5 in Period 2 (N=13)

Normal Range

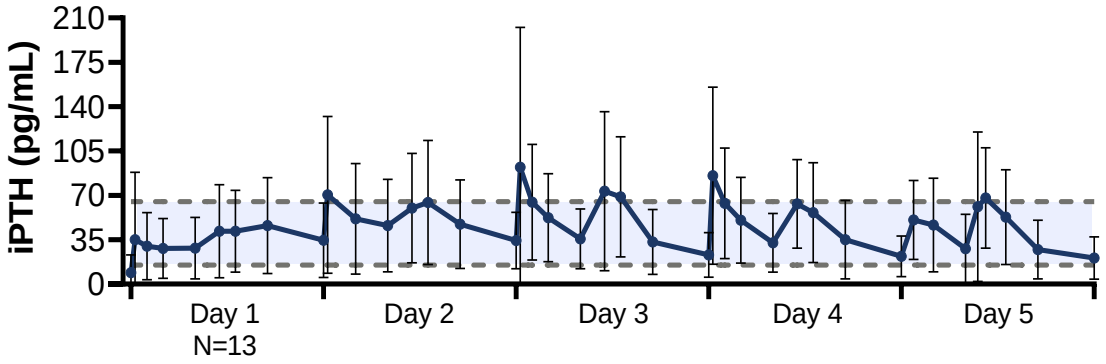
Blood Calcium



Urine Calcium



PTH



- Encaleret was generally 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

Encaleret has advanced in ADH1 from IND to Phase 3 in 3 years

Summary of encaleret development program

- ✓ Reported PoC concept Phase 2 data in 2021
- ✓ Consistent improvements in mineral homeostasis suggest encaleret may become an effective treatment for ADH1
- ✓ Granted Fast Track Designation (FTD) by FDA and Orphan Drug Designation (ODD) by the FDA and EMA[1]
- ✓ Additional follow-on IP filed to contemplate encaleret use in ADH1

Next steps

- ☐ **1H 2022**: Present 6-month Phase 2 data
- ☐ **1H 2022**: Announce registrational study design
- ☐ **2022**: Initiate Phase 3 registrational study
- ☐ **2023**: Announce top line Phase 3 data

2019
- IND opened

2020
- Phase 2 initiated
- US ODD granted

2021
- PoC data reported
- FTD granted
- EU ODD granted

2022
- Interact with regulatory authorities
- Initiate Phase 3
- Publish follow-on formulation and methods IP[2]

2023+
- Report Phase 3 data
- Evaluate encaleret in pediatric ADH1

[1] Orphan designation includes 7 years of market exclusivity in the US and 10 years in EU. [2]Anticipate term of follow-on IP to extend into 2041.

Low-dose FGFR inhibitor (infigratinib) for achondroplasia and hypochondroplasia

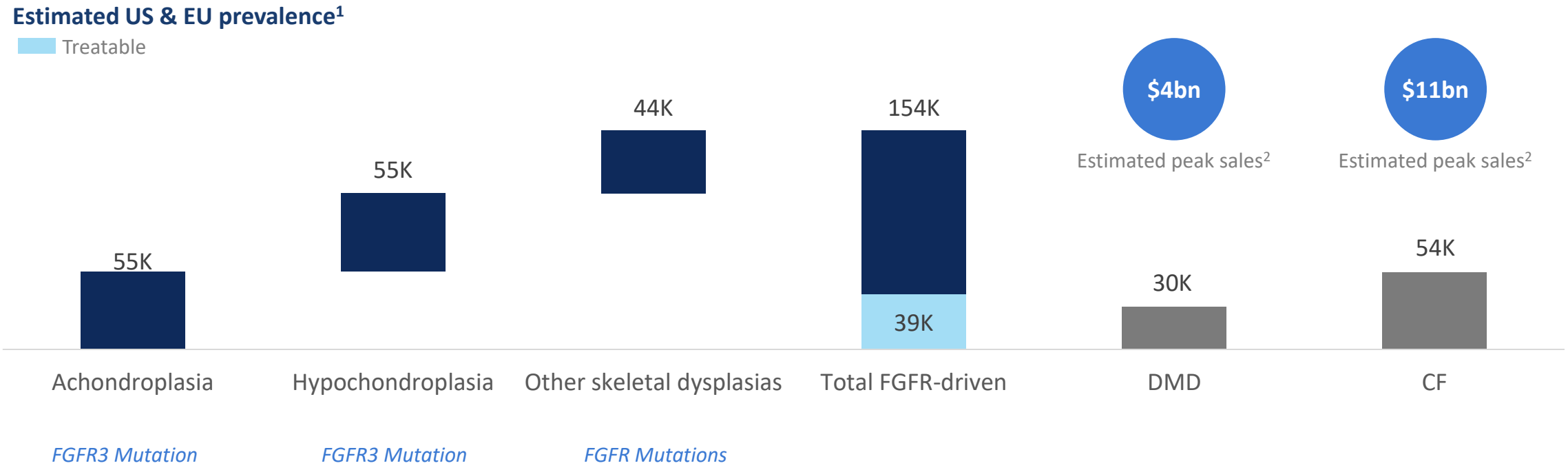
- Prevalence (US & EU): **55K**[1]
- Stage: **Phase 2**
- Next Catalyst: **Phase 2 data update Mid-2022**

Miguel
Living with achondroplasia

[1]55k prevalence in achondroplasia; 55k prevalence in hypochondroplasia

Achondroplasia and related FGFR-driven skeletal dysplasias are one of the largest genetic disease marketplaces

Achondroplasia is only half the story: expansion into hypochondroplasia and other dysplasias could result in a total treatable population on par with other large genetic medicine franchises



Source: [1]CDC estimates, Crisafulli, S., Sultana, J., Fontana, A. et al. Orphanet J Rare Dis. 2020, Farrell 2008 J Cystic Fibrosis. [2]Evaluate. DMD = duchenne muscular dystrophy. CF = cystic fibrosis

Achondroplasia is the most common form of hereditary short stature & can have serious comorbidities

55,000 people in the US and EU with achondroplasia, including up to 13,000 children and adolescents with open growth plates

80% of cases are from *de novo* mutations, children born to parents of typical stature

Achondroplasia is associated with multiple comorbidities

- **Disproportionate short stature** (height of ~4 ft), at times leading to functional impairment
- **Narrowed foramen magnum**, which can result in the need for urgent surgical intervention
- **Spinal stenosis** and compression, kyphosis, and back pain
- Obstructive **sleep apnea**
- Recurrent childhood **infections**, especially in the ears
- **Obesity**

Diagnosis rates for FGFR dysplasias are high, with most children diagnosed in infancy

Source: Ornitz DM et al. Developmental Dynamic 2017; Richette Joint Bone Spine 2007; Unger Curr Osteoporos Rep 2017, Hoover-Fong Am J Gen Med 2017

Against this large unmet need, BBIO is developing a potentially best-in-class – and the only oral – compound

bridgebio Infigratinib	BIOMARIN Vosoritide	ascendis pharma TransCon CNP	Pfizer Recifercept
FGFR 1-3 inhibitor	CNP analog	CNP analog	Soluble FGFR3 (“Ligand trap”)
Daily oral	Daily subQ	Weekly subQ	1-3x per week subQ
Mid-2022 Phase 2 data update	2021 Approved	4Q 2022 Phase 2 topline	2023 Expected primary completion

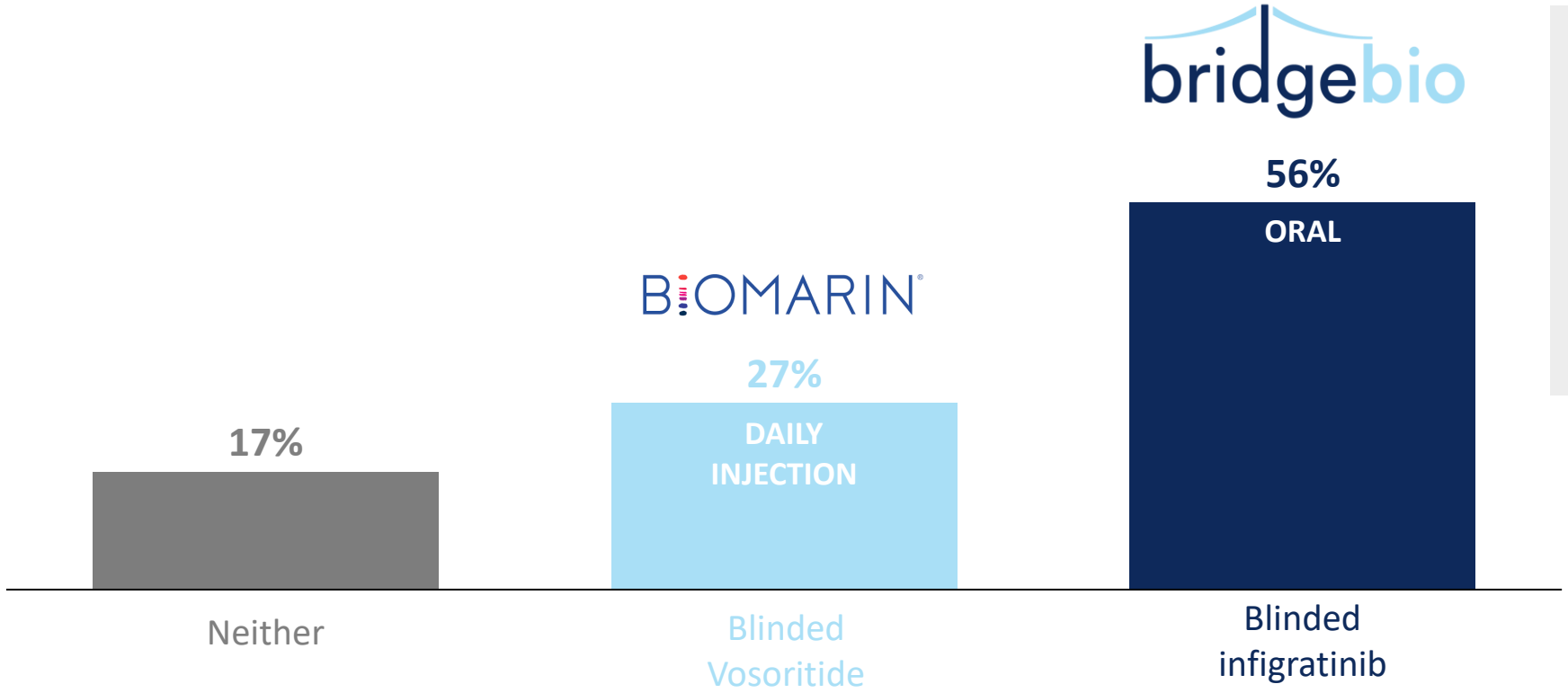
Source: Company websites, press releases, investor presentations, clinicaltrials.gov; BioMarin

Potential to capture majority market share

Oral route of administration commands majority share with physicians even if there were no efficacy or launch time advantage

HCP Survey: Vosoritide vs. low-dose infigratinib showing equivalent efficacy

% of children with achondroplasia who would receive each product[1]

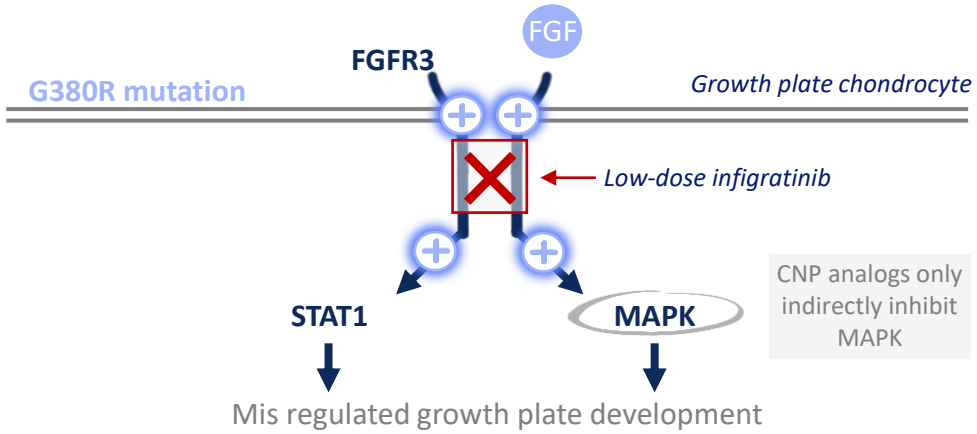


Clear share preference for an **oral solution** for achondroplasia vs. daily injection for children

Source: US market research testing blinded product profiles for vosoritide and infigratinib among HCPs who treat children with achondroplasia; responses weighted by specialty (31 endos, 23 geneticists).
1 Question text: Imagine that Product A [blinded vosoritide] has been on the market for some time and Product B [blinded infigratinib with equivalent efficacy] has just now been approved. Consider the children you manage with ACH not already receiving therapeutic treatment: what percentage of these children would receive each product?

Low-dose infigratinib directly inhibits the causal gain-of-function mutation in FGFR3, potentially reversing all key drivers of symptoms

Molecule overview



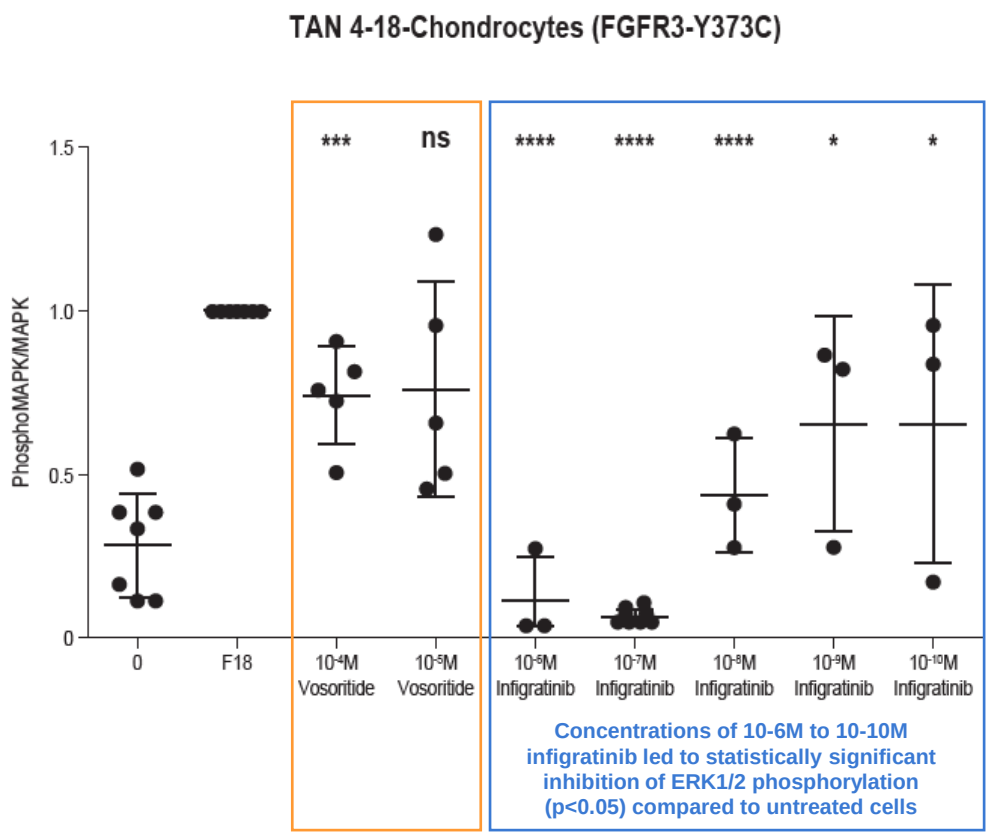
- Only oral direct inhibitor designed to treat achondroplasia at its source by normalizing both the STAT1 and MAPK pathways
- Well tolerated in prior oncology development program (evaluated in >700 participants)
- Kid friendly formulation

IP & partnership overview

- Portfolio of issued and filed patents expected to provide market protection to 2041
- Orphan drug designation (ODD) provides 7 years of market exclusivity in the US and 10 years in EU with potential pediatric extension
- Partnered with Novartis in 2018
  - Low milestone burden with tiered royalty payments starting in low teens

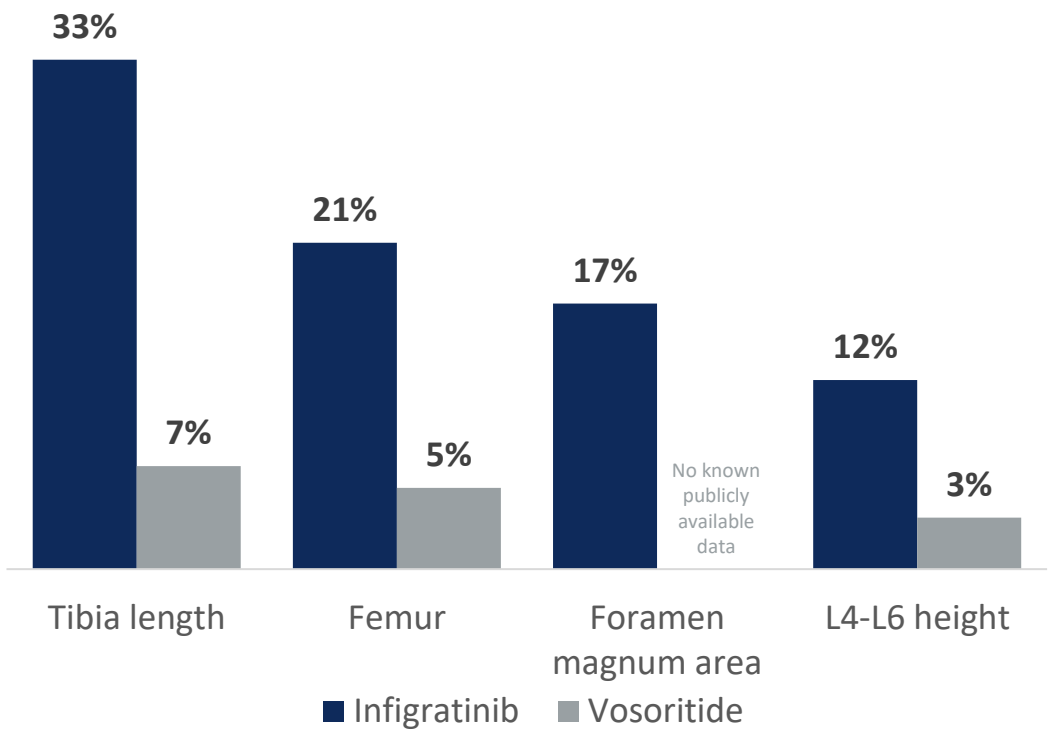
Potential best in-class preclinical profile in validated ACH mouse model

Infigratinib pERK data vs. vosoritide



Preclinically, infigratinib has shown remarkable efficacy in bone length and a foramen magnum effect

Percent increase compared to non-treated mouse



Source: Komla-Ebri et al., J Clin Inv 2016, Lorget et al., Am J Hum Genet 2012, Garcia et al., Science Trans Med 2013, Breinholt ENDO 2017
Note: subcutaneous doses, percent increase compared to vehicle treated FGFR3$^{Y367C/+}$, FGFR3$^{ACH/+}$ mouse as noted in "Mouse model" columns

The PROPEL clinical program is enrolling with data expected in Mid-2022

Observational run-in → **Ph2 Dose-finding (n=40)** → **Long-term extension (n=~20)**

Key inclusion criteria

- Children 2.5 – 10 years old
- Clinical and molecular ACH diagnosis

Children are followed for a minimum of 6 months to establish baseline annualized growth velocity (AGV)

0.128 mg/kg n=10

0.064 mg/kg n=10

0.032 mg/kg n=10

0.016 mg/kg n=10

Select dose → **12 months at recommended dose** long-term extension

Potential to enroll 20 additional subjects at selected dose

Primary objectives

- Collect baseline annualized growth velocity (AGV)

- Identify safe therapeutic dose for expansion / pivotal study
- Safety and tolerability
- Change from baseline in AGV

- Long-term safety and efficacy

Next Steps

Phase 2 data update

Mid-2022

Following POC, Phase 3 trial start

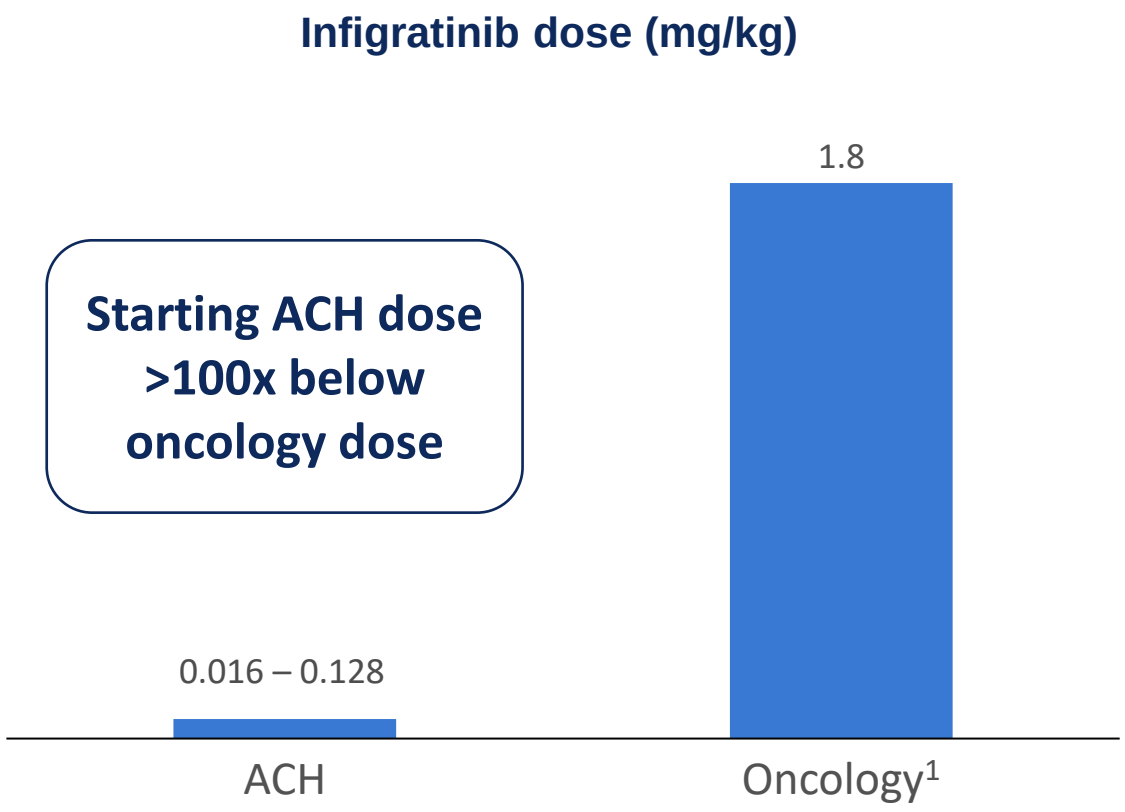
2023

Future indications

- Infigratinib has potential applications beyond Achondroplasia
- Exploring additional FGFR-driven skeletal dysplasias including hypochondroplasia
- Pre-clinical data in hypochondroplasia expected in June 2022 (ENDO)

Low dose infigratinib in achondroplasia is well-tolerated and does not result in meaningful changes in phosphate

Achondroplasia dose much lower than in oncology where hyperphos has been observed



All four cohorts of our Phase 2 dose escalation have been fully enrolled with positive safety data to date

Cohort	Dose (mg/kg)	Enrolled	Safety cleared by Data Review Committee
1	0.016	8 children	✓
2	0.032	13 children	✓
3	0.064	12 children	✓
4	0.128	12 children	N/A

Source: Demuynck B et al. ENDO 2020, Data on file. [1]Approximate based on 70kg adult

Multiple near-term inflection points following proof-of-concept in 2022

Low-dose infigratinib program highlights

- ✓ Infigratinib is the only asset in the clinic that directly targets the underlying cause of achondroplasia, FGFR3 overactivity
- ✓ Potential best in-class preclinical profile in validated achondroplasia mouse model
- ✓ Well understood safety profile from prior oncology program
- ✓ Oral route of administration highly favored by HCPs

Next steps

Achondroplasia	☐ Mid 2022: Phase 2 data update ☐ 2023: Phase 2 dose expansion data ☐ 2023: Initiate Phase 3 registrational study
Hypochondroplasia	☐ 2022: Present preclinical data
Additional FGFR-driven skeletal dysplasias	☐ 2023: Present preclinical data

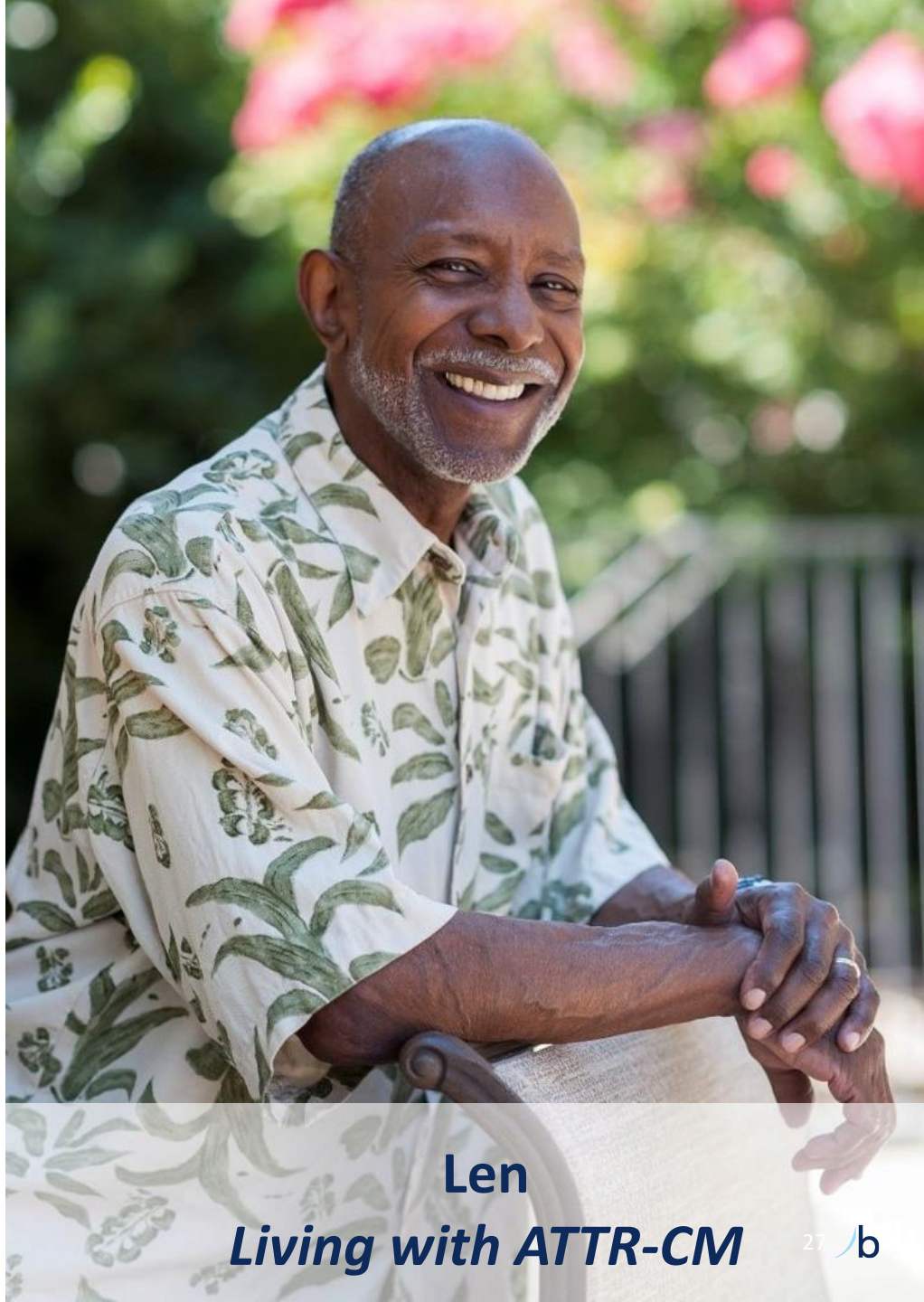
2020
- IND Opened
- Phase 2 initiated

2022
- Report Phase 2 data update

2023+
- Initiate Phase 3
- Infigratinib indication expansion

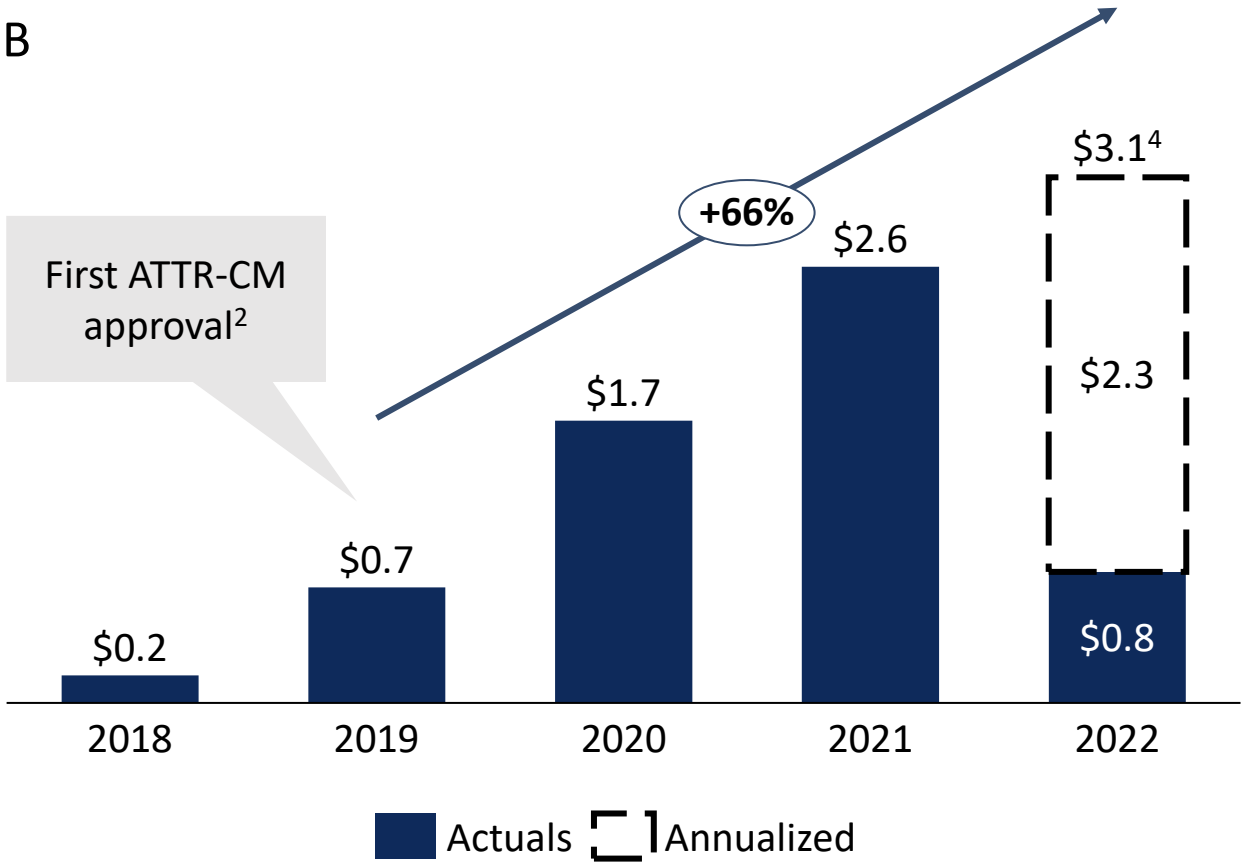
Acoramidis for transthyretin (TTR) amyloidosis (ATTR)

- Prevalence (WW): **400K**
- Stage: **Phase 3**
- Next Catalyst: **Phase 3 30-month all-cause mortality & CV hospitalization data Mid-2023**



ATTR market is annualizing at >$3 billion as of 1Q22

Global annual ATTR market sales[1]



Significant ATTR market growth driven by:

- Increasing diagnosis in established geographies *(>30K ATTR-CM US patients currently diagnosed vs. <5k before first approval[3])*
- Launch and patient finding in new geographies

[1]ATTR market includes all approved drugs for ATTR-PN and ATTR-CM: Vyndaqel/Vyndamax (Pfizer), Onpattro (Alnylam), Tegsedi (Ionis)
[2]First ATTR-CM sales occurred in Q2 2019
[3]Pfizer press release and transcript
[4]Assumes linear annualization of sales through Q2 – Q4 2022

Acoramidis was designed to treat ATTR at its source

Disease mechanism

Native TTR circulates in blood as a tetramer

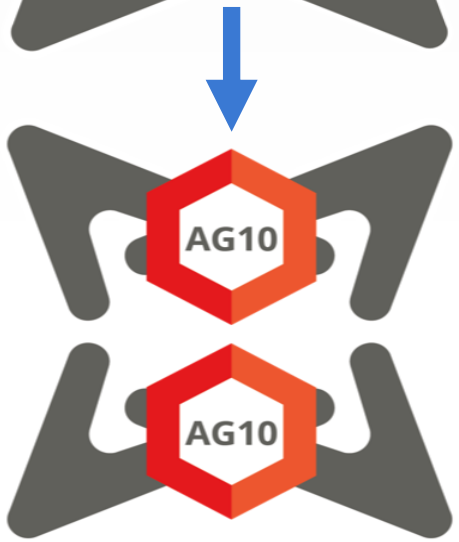
~130 known destabilizing mutations

Protective T119M mutation

Dissociation into monomers initiates pathogenesis

Monomers aggregate, causing disease

Therapeutic hypothesis



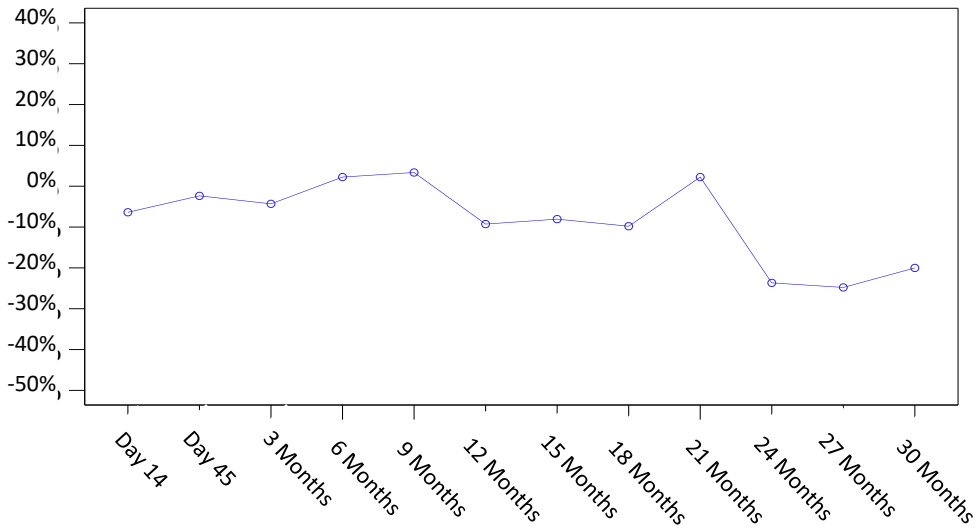
Acoramidis was designed to mimic protective T119M mutation by stabilizing TTR tetramers to slow or halt disease progression

Updated Phase 2 OLE results presented at ACC 2022

Based on data available through August 31st 2021[1], acoramidis demonstrated:

- ✓ Median decline in NT-proBNP
- ✓ Near-complete TTR stabilization
- ✓ Sustainably increased serum TTR concentration
- ✓ No safety signals of clinical concern

Median percent change from baseline in NT-proBNP[2]



N[3]	47	45	46	43	40	38	33	24	11	23	17	22

- **At Month 30, median change from baseline was -437 pg/mL [-950, 316]**
- **At Month 30, 15/22 (68%) participants had NT-proBNP levels below their baseline[2]**

Source: BridgeBio press release published 4/3/2022
1Median 38 months from initial Phase 2 randomization. Median 35 months on open-label acoramidis
2NT-proBNP was a reported laboratory parameter, not a pre-specified safety endpoint. Baseline defined as the date of the first dose of acoramidis.
3Represents all evaluable data from participants who continued in the study

ATTRibute-CM set to provide 30-month mortality and CV hospitalization data despite its 12-month 6MWD primary endpoint miss

12-month endpoints:
Primary: Change in 6MWD
Key secondary: Change in KCCQ

30-month endpoints:
Primary: Hierarchical composite[1]
Key secondary: Change in 6MWD, KCCQ

Key eligibility criteria

- Subjects with diagnosed ATTR-CM (WT or mutant)
- NYHA Class I-III
- ATTR-positive biopsy or ^{99m}Tc scan
- Light chain amyloidosis excluded if diagnosis by ^{99m}Tc

800 mg acoramidis twice daily
N ~ 421

Placebo twice daily
N ~ 211

800 mg acoramidis twice daily

Screening and randomization

Part A

Part B
Tafamidis usage allowed

Open-label extension

6MWD = Six-minute walk distance KCCQ = Kansas City Cardiomyopathy Questionnaire NYHA = New York Heart Association
^{99m}Tc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD) CV = cardiovascular-related
[1]Primary analysis will use the Finkelstein-Schoenfeld method

We remain confident in our acoramidis Phase 3 Month 30 primary endpoint including all-cause mortality and CV hospitalization

Month 12 | acoramidis vs. placebo

NT-proBNP Cardiac biomarker associated with survival	**>20%*** Relative decrease
Serum TTR Measure of TTR stabilization	**>35%*** Relative increase
KCCQ Quality-of-Life Measurement	**+3pt *** Relative increase

* Statistically significant improvements vs. placebo

Month 30 | What gives us confidence

- Acoramidis was **generally well-tolerated** and demonstrated **potent, sustained TTR stabilization**
- Acoramidis **significantly improved quality-of-life** and **survival-associated biomarkers** vs. placebo
- **Blinded all-cause mortality events** in ongoing study are consistent with our expectations and **support planned analysis at Month 30**

Summary of 12-month 6MWD results

Based on data available at Month 12, acoramidis demonstrated relative to placebo:

? No improvement in functional status as measured by 6MWD

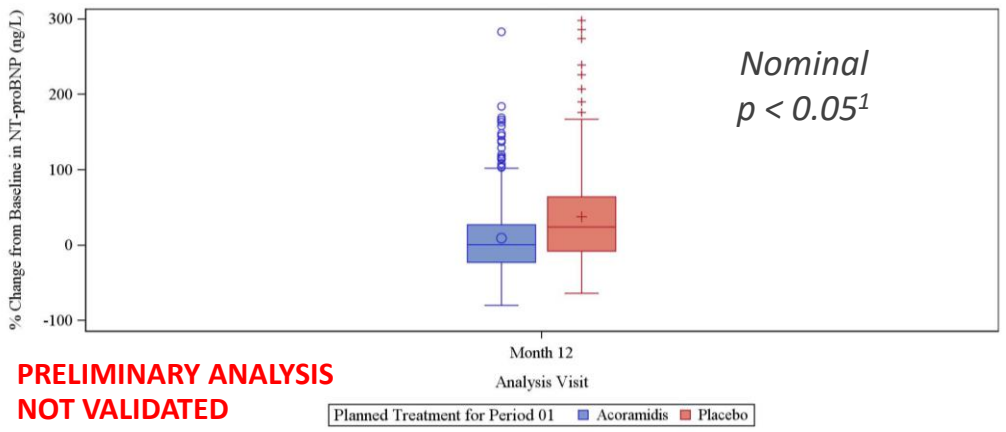
✓ Positive improvement in KCCQ-OS

✓ Positive reduction in NT-proBNP

✓ Positive improvement in serum TTR

✓ No safety signals of clinical concern identified and lower reported rates of SAEs and AEs leading to death

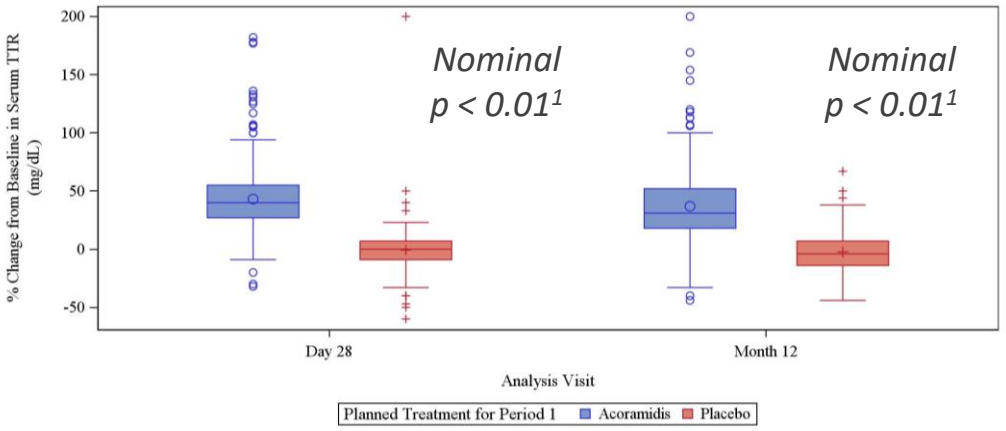
Percent change from baseline in NT-proBNP at Month 12[2]



PRELIMINARY ANALYSIS
NOT VALIDATED

Note: to facilitate a focused review of the vast majority of the data, outliers greater than 300% change from baseline are not included in this plot.

Percent change from baseline in serum TTR by treatment and visit[2]



Note: to facilitate a focused review of the vast majority of the data, outliers greater than 200% change from baseline are not included in this plot.

[1]Inference analysis (p-value) based on absolute change from baseline between groups
[2] Modified intent-to-treat (mITT) population defined as all randomized subjects who have received at least one dose of IMP and have at least one post baseline efficacy evaluation. mITT population pre-specified to exclude subjects with baseline eGFR < 30 mL/min/1.73 m^2

ATTRibute-CM baseline characteristics

Baseline trait	ATTRibute-CM (mITT)[1]	ATTR-ACT[2]
Age		
Mean	77.0	74.3
Median	78.0	74.6
NYHA Class		
Class I	11.2%	8.4%
Class II	72.7%	59.6%
Class III	16.1%	32.0%
6MWT (m)		
Mean	360	352
NT-proBNP (ng/L)		
Median	2778	3062
KCCQ-OS		
Mean	71.4	66.7[3]
Serum TTR (mg/dL)		
Mean	23.2	21.5[4]
Genetic TTR status		
Variant	9.7%	24.0%
Wildtype	90.3%	76.0%
Geography		
US	19.3%	63.3%
Ex-US	80.7%	36.7%

[1]BridgeBio, data on file. [2]Maurer MS, et al. N Engl J Med. 2018;379(11):1007-16. [3]Tafamidis CDER NDA filing. [4]Approximated from Hanna M, et al. HSFA 2019.

Ribitol for Limb-Girdle Muscular Dystrophy Type 2i (LGMD2i)

- Prevalence (US & EU): **7K**[1]
- Stage: **Phase 2**
- Next Catalyst: **Additional Ph2 data 2H 2022**

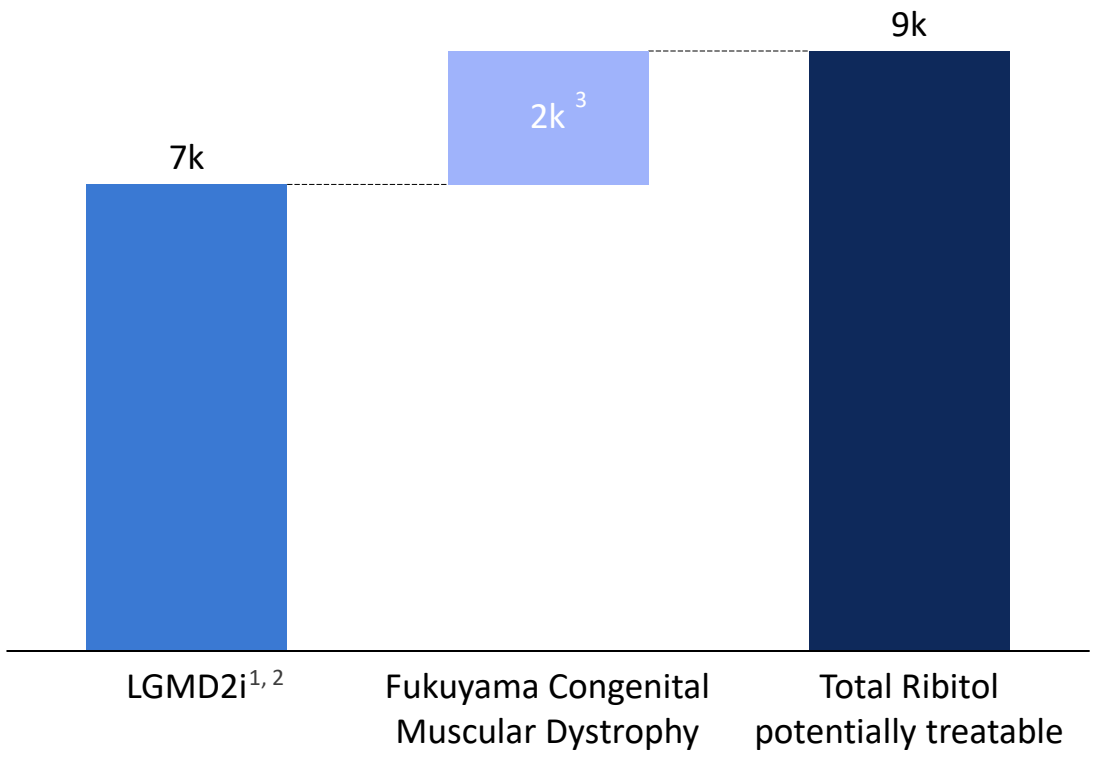
Seamus
Living with LGMD2i

[1]Includes potential treatable mutations

LGMD2i is one of the most common forms of LGMD

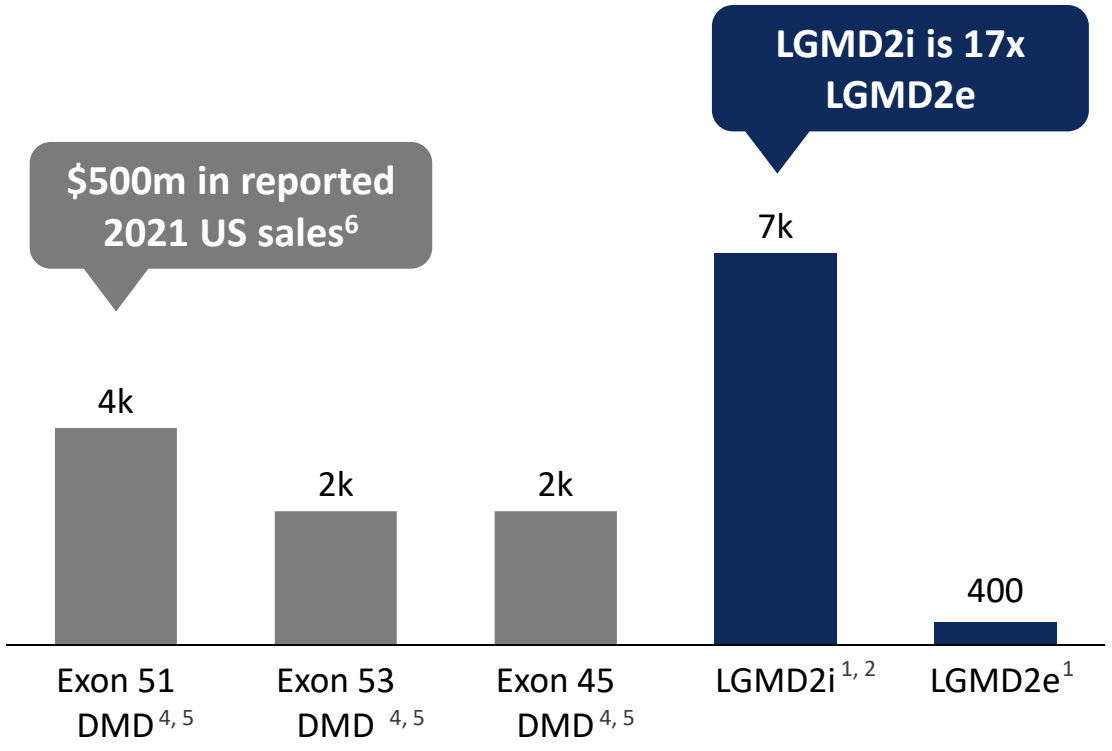
9k treatable patient population

Estimated US & EU prevalence



Prevalence benchmarks

Estimated US & EU prevalence



Source: [1]Liu, et al. Genetics in Medicine. 2019. [2]Includes all patients with potentially treatable mutations in LGMD2M and LGMD2U in US and EU. [3]Japan only. [4]Crisafulli, S., Sultana, J., Fontana, A. et al. Orphanet J Rare Dis. 2020. [5]Fletcher, S., et. al. The American Society of Gene & Cell Therapy. 2010. [6]Bloomberg.

Disease severity includes loss of ambulation, respiratory decline, and cardiac dysfunction

L276I is the most common mutation causing LGMD2i

Birth	Early Childhood	Late Childhood	Adolescence to Adulthood
• Asymptomatic	• **Age of symptom onset 5 ± 1 years old** • Lower limb & proximal weakness • +/-calf hypertrophy, muscle pain, hyper-CKemia	• Lower limb & proximal weakness • +/-calf hypertrophy, muscle pain, hyper-CKemia	**Loss of ambulation:** most by age 20 **Respiratory decline**: Invasive assistance required by 5% by age 30 **Cardiac dysfunction**: 25% by age 30

- No approved disease modifying agents for LGMD2i
- Current standard of care is aimed at symptom management and includes physical therapy, steroids and pain management
- Standard of care does not prevent continuous progressive decline in LGMD2i patients

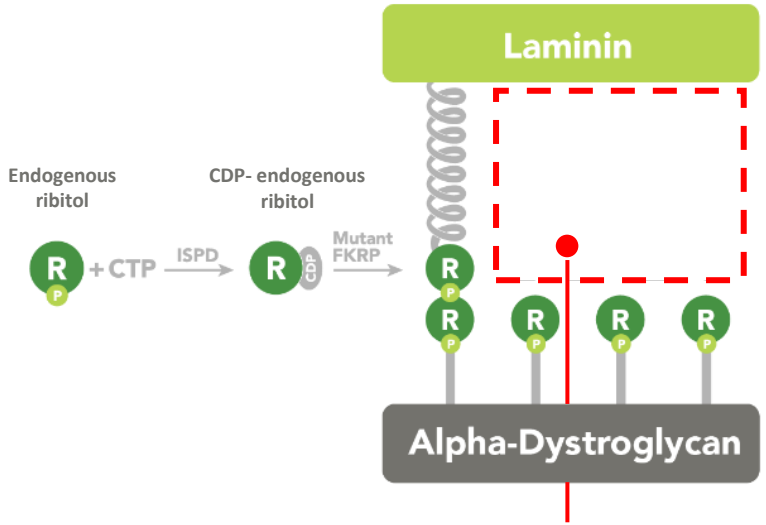
Note: Clinical manifestations illustrated are of a heterozygote patient
Source: Sveen et al, Annals of Neurology, 2006; Richard et al, Neuromuscular Disorders, 2016; Gedlinske et al, Neurology, 2020.

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

Disease Mechanism

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

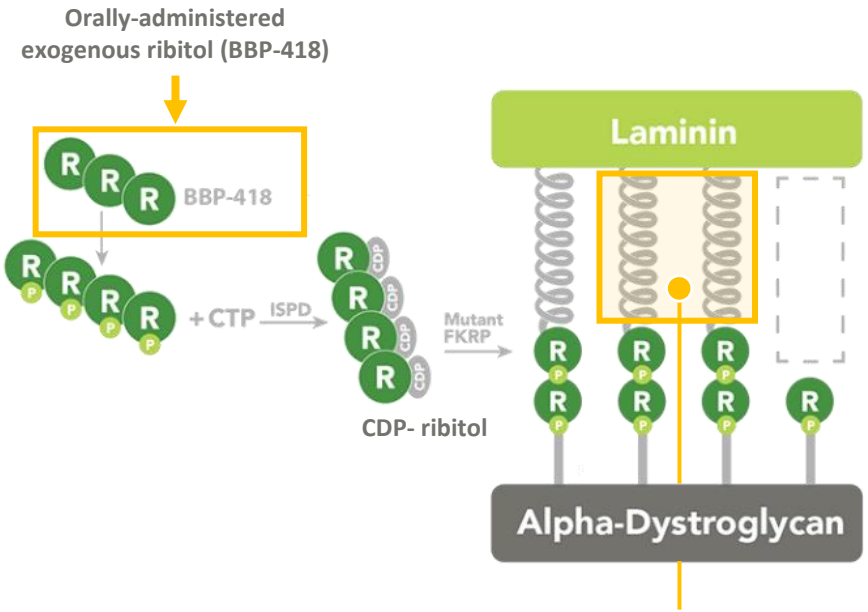
Partial loss of function mutation in FKRP result in dysfunctional, hypo-glycosylated α-DG in muscle cells which increases cell susceptibility to damage



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

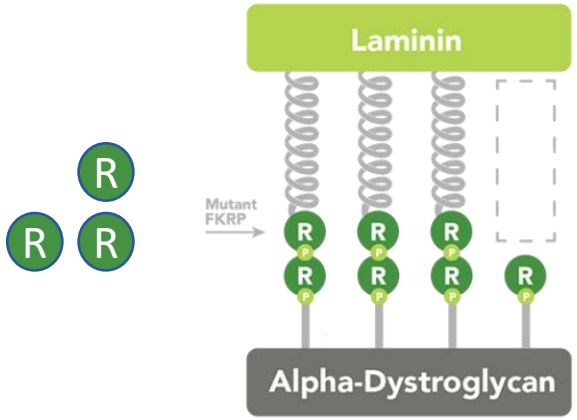
Supply supraphysiological levels of ribitol upstream to drive residual activity of mutant FKRP enzyme and increase α-DG glycosylation levels



Potential partial restoration of α-DG glycosylation

Ribitol is the only oral therapy in the clinic designed to provide disease modifying effects to LGMD2i

Molecule overview



- Only oral therapy designed to potentially increase FKRP enzymatic activity leading to increases in glycosylated α-DG
- Safe and well-tolerated from Ph1 studies

IP & molecule history overview

- Portfolio of issued and filed patents expected to provide market protection to 2040+
- Orphan drug designation (ODD) provides 7 years of market exclusivity in the US and 10 years in EU
- Exclusive license from Atrium Health in 2019

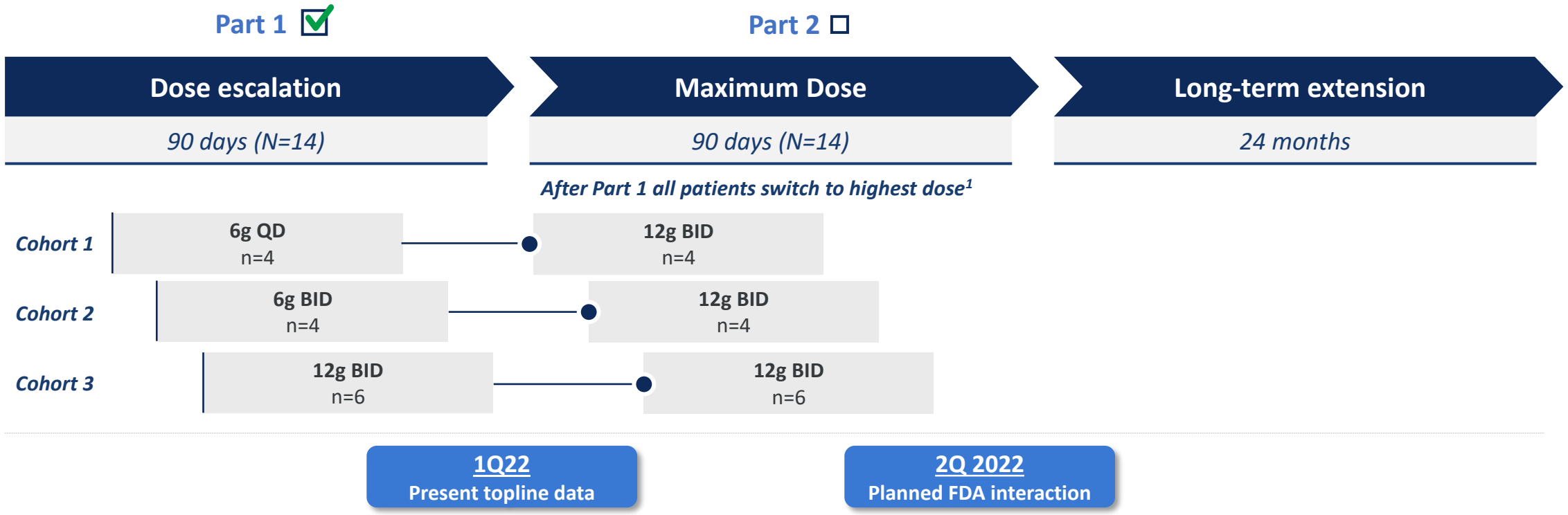
Limited competition with two gene therapy agents nearing the clinic 1H22

bridgebio BBP-418	AskBio MAKING HISTORY	GENETHON CURE THROUGH INNOVATION
Small molecule	AAV gene therapy	AAV gene therapy
Oral therapy	Gene therapy	Gene therapy
1Q 2022 Phase 2 POC	1H 2022 Planned Ph 1/2 start	1H 2022 Planned Ph 1/2 start

- BBP-418 is the only oral therapy currently in the clinic with ability to adjust dose / re-dose
- BBP-418 maintains various advantages over gene therapy, including tolerability profile, durability, and cost
  - FKRP is a challenging gene therapy target given status as a loss of function mutation with residual enzymatic activity
  - Early pre-clinical gene therapy data showed dose dependent worsening of disease[1]
- Future potential combination approach for ribitol and gene therapy given different mechanisms of action

Source: [1]Gicquel et al, Human Molecular Genetics, 2017.

Full part 1 and partial part 2 data from Phase 2 is available



Key study objectives:

- Safety and tolerability
- Dose selection for Phase 3
- Key biomarker parameters

Key endpoints:

- Creatine Kinase
- Ratio of glycosylated α-DG to total α-DG
- NSAD
- PUL2.0
- 10MWT
- FVC

Note: Doses were adjusted for weight using the following schema: 0-50 kg 6g BID, >50-70kg 9g BID, >70kg 12g BID. [1]Cohort 3 continues same dose. 10MWT = 10-meter walk test; NSAD = North star assessment for dysferlinopathy; FVC = Forced vital capacity; PUL = Performance of upper limb

BridgeBio has generated compelling Phase 2 data to date

BBP-418 (Ribitol) increased glycosylated alpha-dystroglycan, decreased creatine kinase and increased velocity in 10MWT at 90 days

	Ratio of Glycosylated αDG / total αDG	Creatine Kinase (CK)	10 Meter Walk Test (10MWT)
Normal Range	1.0	32 - 267 IU/L	No change
LGMD2i Natural History	0.6[1]	1000 - 5000 IU/L	0.12 m/sec annual decline
Expected threshold to address phenotype[3, 4]	10% increase from baseline	50% decrease from baseline	Slowing of decline vs. natural history
BBP-418 Phase 2 result	43% increase from baseline	70% decrease from baseline	0.08 m/sec increase from baseline 0.14 m/sec increase from natural history

[1]Data on file. [2]Sveen et al, Annals of Neurology, 2006. [3]Cataldi, et al, 2018, Nature Comms. [4]KOL interviews, 2021. Note: Heterozygote average ratio of glycosylated aDG / total aDG

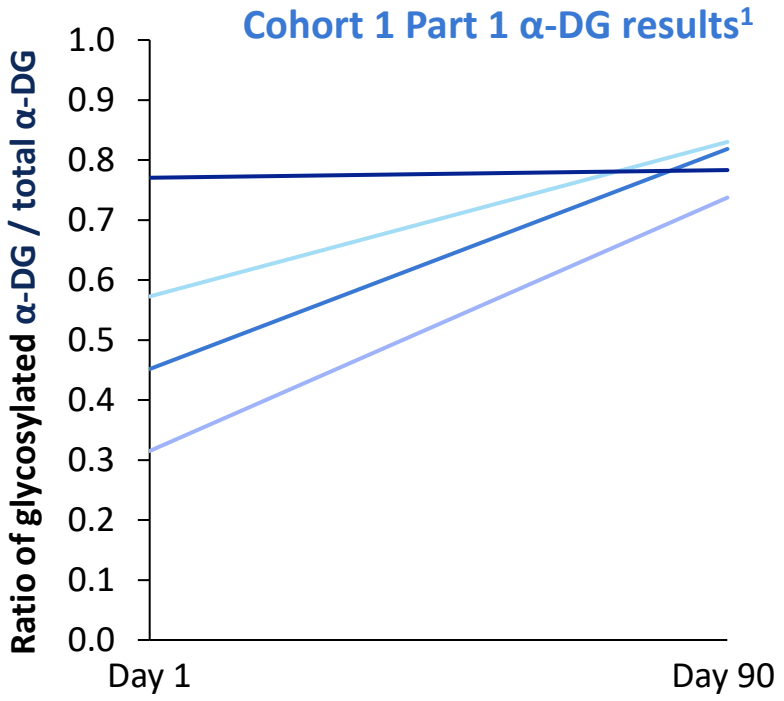
BBP-418 (Ribitol) has been well-tolerated to date with only minor GI related adverse events observed in Phase 2

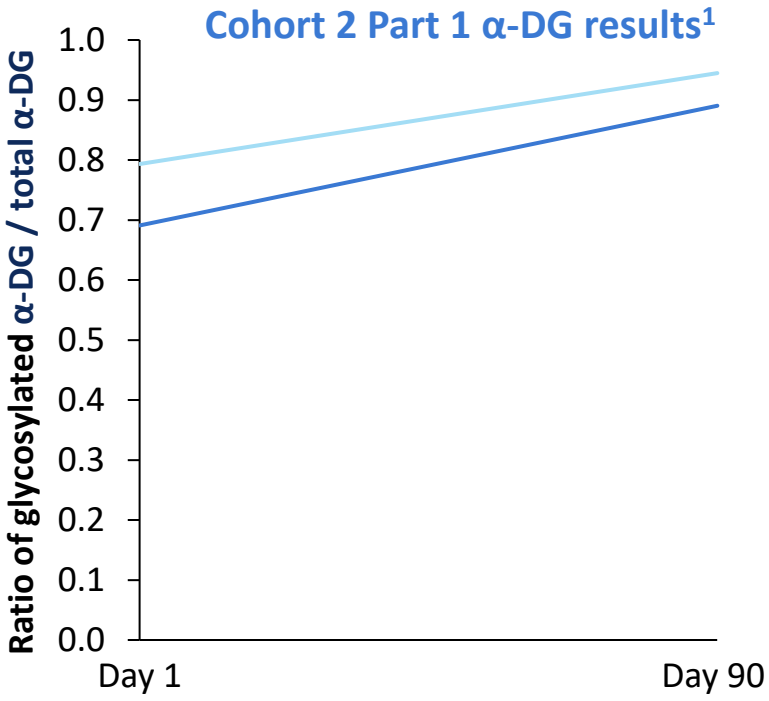
- 58 adverse events were recorded with 8 possibly or probably related to treatment
- 1 SAE recorded unrelated to the treatment

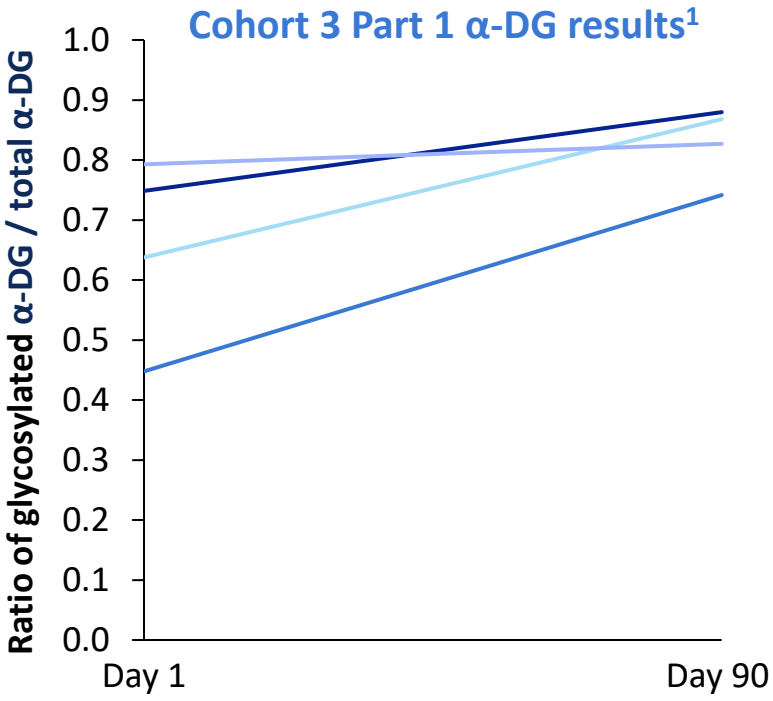
TEAE	Number of incidents	Severity
Diarrhea	4	75% Grade 1
Nausea	2	100% Grade 1
Dyspepsia	1	100% Grade 1
Stomachache	1	100% Grade 2
Overall	8	75% Grade 1

Phase 2 safety data aligns with both preclinical and Phase 1 data supporting strong safety and tolerability

Average increase of 43% in glycosylated α-DG / total α-DG was measured across cohorts at 90 days



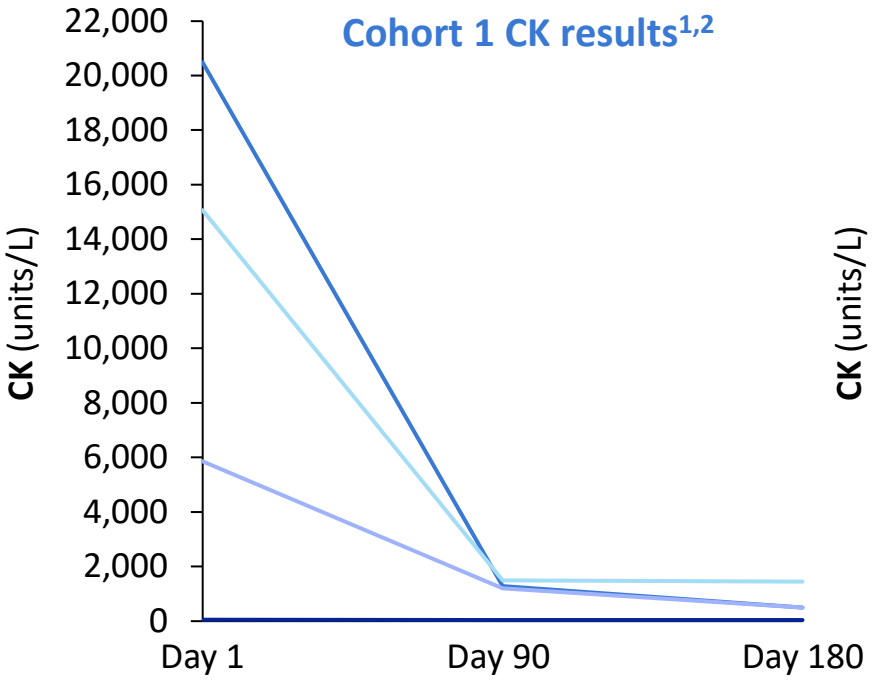


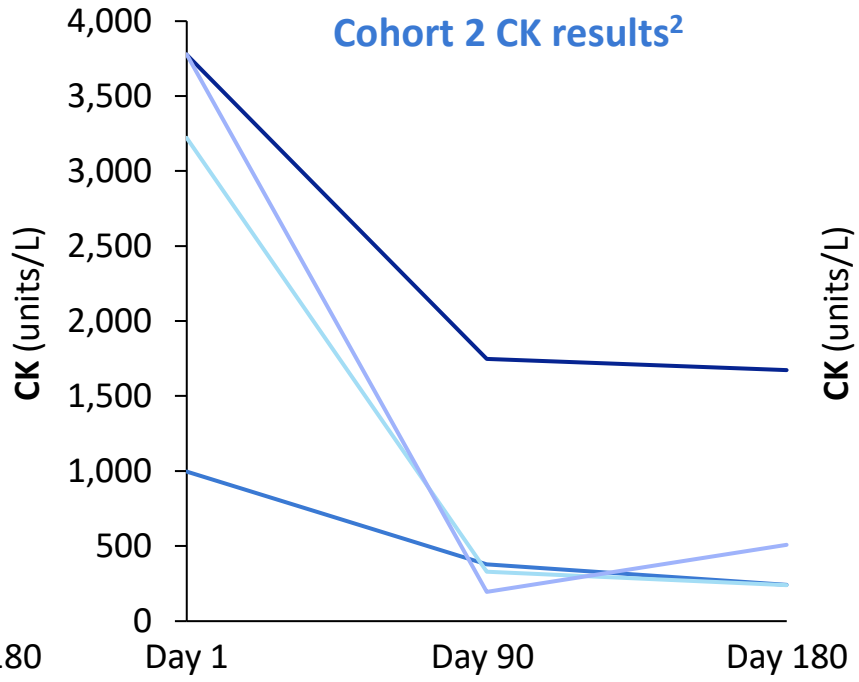


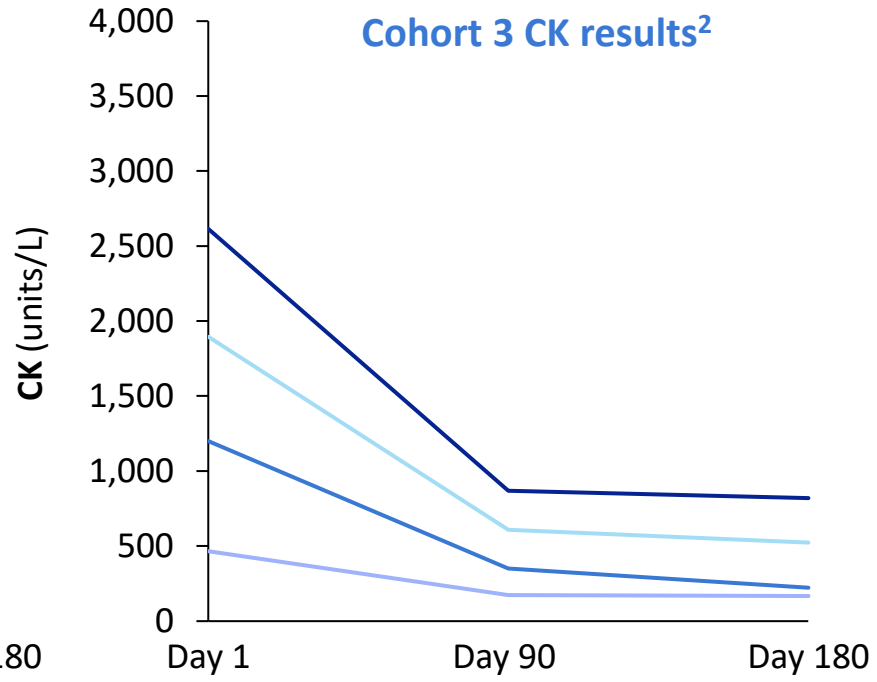
Cohort	# pt	Baseline αDG ratio	Absolute change αDG ratio at day 90 (%)
1 (6g QD)	n=4	0.53	+0.28 (65%)
2 (6g BID)	n=2[2]	0.74	+0.18 (24%)
3 (12g BID)	n=4	0.66	+0.17 (31%)
Total	**N=10**	**0.62**	**+0.21 (43%)**

[1]Ratios are normalized against healthy control samples; normalization technique under development and subject to change
[2]Values excluded where signal intensities were below reliable quantification threshold

All cohorts show significant declines in creatine kinase, 70% from baseline at day 90 and 77% at day 180







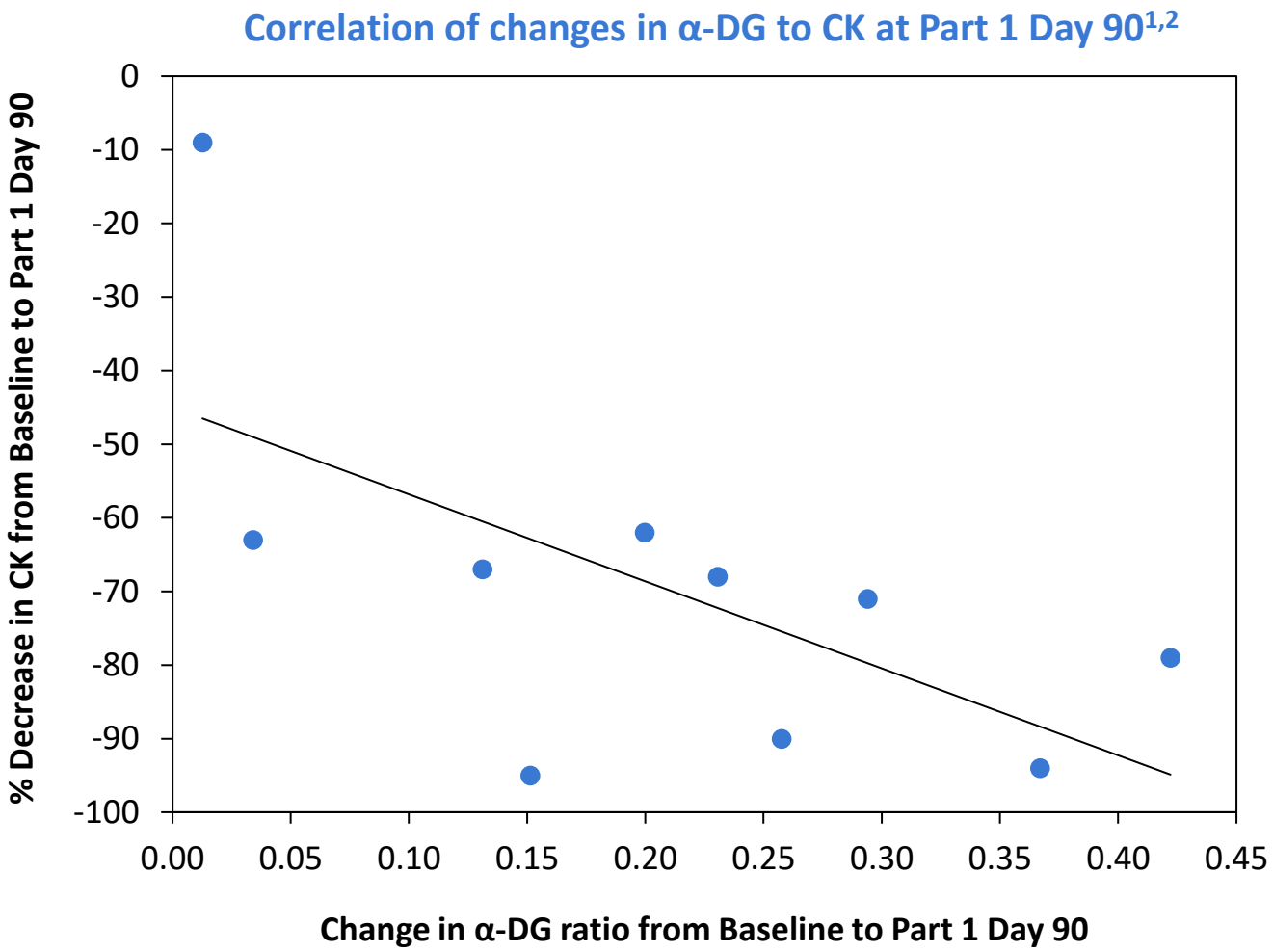
Cohort	# pts	Baseline CK Day 1	Average % change part 1 day 90	Average % change part 2 day 90
1 (6g QD)	N=4	10,364[1]	-68%	-77%
2 (6g BID)	N=4	2,943	-75%	-78%
3 (12g BID)	N=4	1,543	-67%	NA
Total	**N=12**	**4,950**	**70%**	**77%**

[1]Cohort 1 Day 1 CK draws taken after functional assessments; all other draws done prior to functional assessment. Comparing cohort 1 lead-in CK values to baseline Ph2 values suggests little impact of function assessments on CK

[2]Reference range for CK is 55-170 units/L for men and 30-135 units/L for women

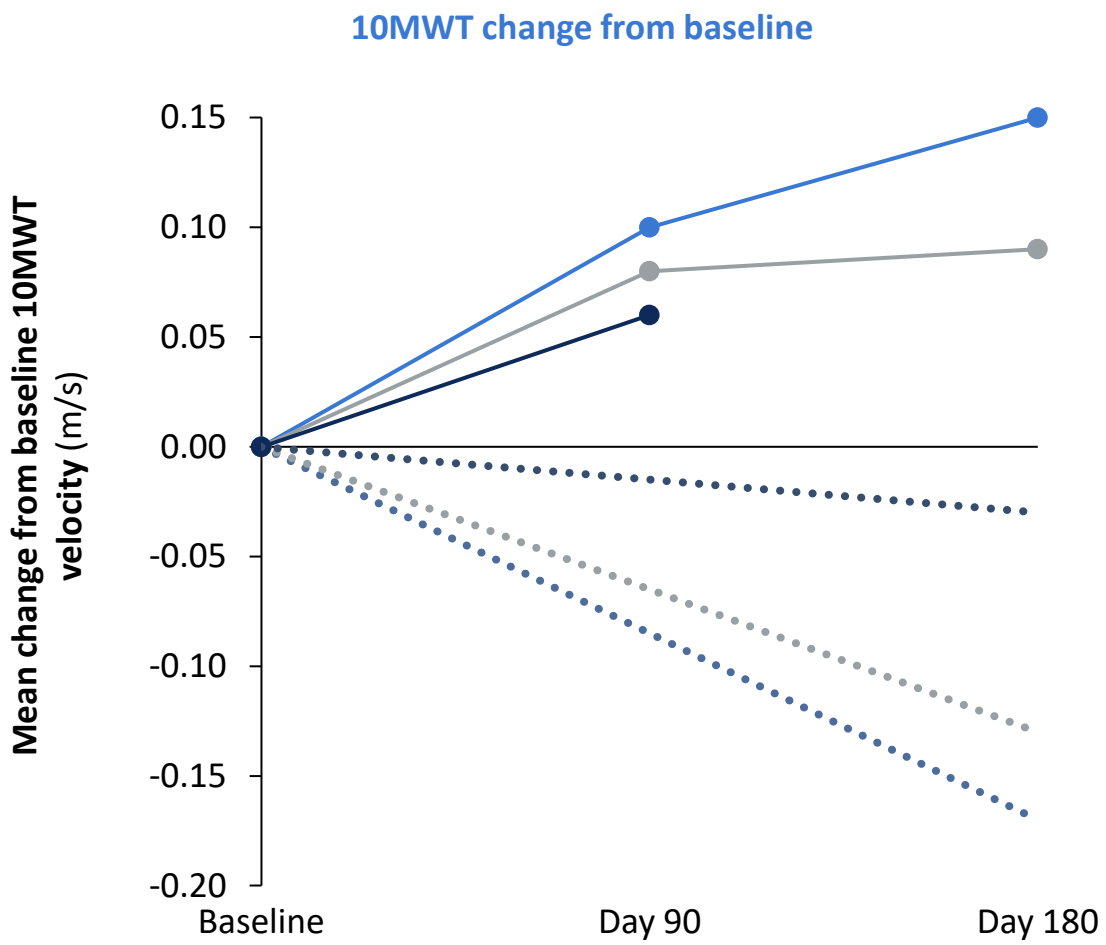
[3]CK change from baseline at part 1 day 90 is statistically significant with $P < 0.05$

Increases in α-DG glycosylation are correlated to decreases in CK observed over 90 days

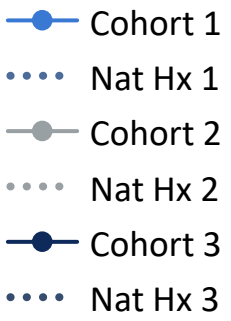


[1]Ratios are normalized against healthy control samples; normalization technique under development and subject to change
[2]Values excluded where signal intensities were below reliable quantification threshold

Increases were observed in the 10MWT in comparison to consistent declines noted in natural history



Natural history declines from baseline were measured from the MLB-01-001 Lead-in Natural history study for the same group of patients over six months and compared to velocities after 90 and 180 days of treatment



Cohort	# pts	Baseline	Part 1 Day 90	Part 2 Day 180
		Average 10MWT Velocity (m/sec) (Change from baseline)		
1 (6g QD)	N=3[1]	2.72	2.82 (+0.10)	2.87 (+0.15)
2 (6g BID)	N=4	1.48	1.56 (+0.08)	1.57 (+0.09)
3 (12g BID)	N=3[1]	1.06	1.12 (+0.06)	NA
Total	**N=10**	**1.72**	**1.80 (+0.08)**	**2.12 (+0.12)**

[1]Includes ambulatory patients only defined by the ability to complete the 10MWT ≤12 seconds

BBP-418 rapidly progressed from pre-IND to Phase 2 in less than 3 years

Summary of BBP-418 development program

- Presented Phase 2 part 1 and partial part 2 data demonstrating a 43% increase in ratio of glycosylated α-DG / total α-DG and 70% reduction in creatine kinase from baseline at day 90 and 77% reduction at day 180
- Improvements in functional benefit observed at 90 days and 180 days vs. natural history
- BBP-418 was well-tolerated across a wide range of dose levels with no observed treatment-related serious adverse events, dose limiting toxicities or discontinuations
- Portfolio of issued and filed patents expected to provide market protection to 2040+
- Granted Fast Track Designation (FTD) by FDA and Orphan Drug Designation (ODD)[1] by the FDA and EMA

Next 12 months

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

2019
- US ODD granted

2020
- IND cleared
- EU ODD granted

2021
- Phase 2 start
- FTD granted

2022
- Presented initial Phase 2 data
- Interact with regulatory authorities
- Present add'l Phase 2 data
- Initiate Phase 3

2023+
- Report Phase 3 data
- Evaluate BBP-418 in expansion indications

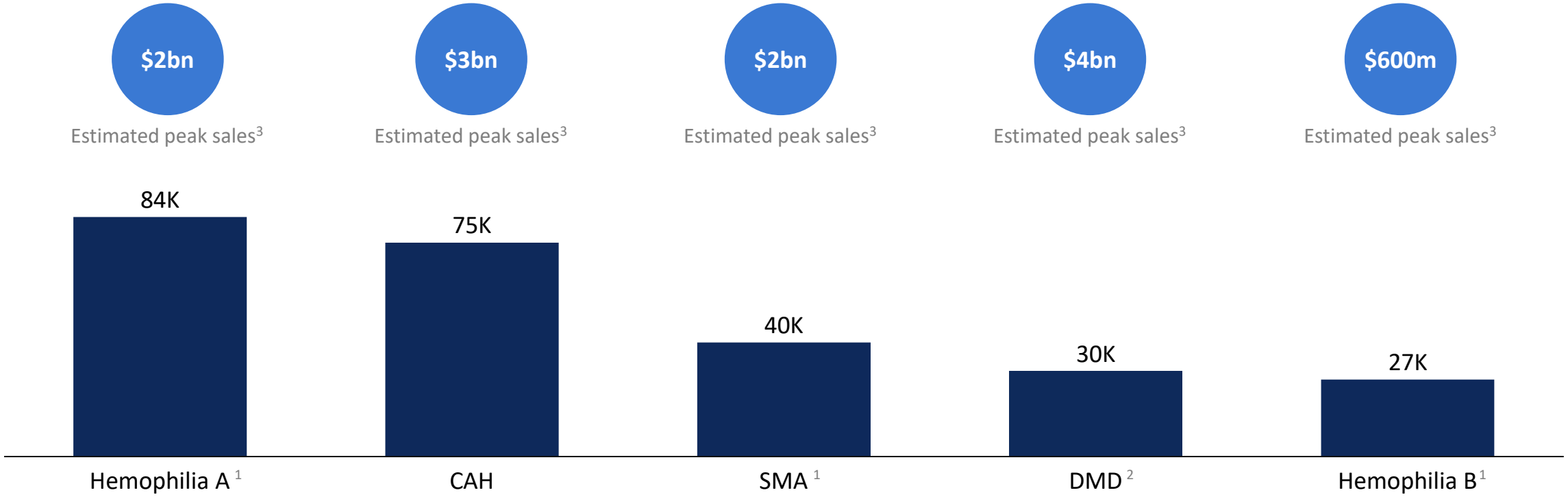
[1] Orphan designation includes 7 years of market exclusivity in the US and 10 years in EU.

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

- Prevalence (US & EU): **75K**
- Stage: **Phase 1 / 2**
- Next Catalyst: **Initial Phase 1 / 2 data 2H 2022**

CAH due to 21-Hydroxylase deficiency has one of the largest patient populations being treated by gene therapy

US & EU Prevalence



Source: [1]NORD, Cleveland clinic. [2]Crisafulli, S., Sultana, J., Fontana, A. et al. Orphanet J Rare Dis. 2020. [3]Evauate, FactSet and Bloomberg, CAH estimates from BBIO sell-side models. Note: Estimated gene therapy sales for Hemophilia A and B.

CAH is a chronic, potentially lethal disease with significant unmet need

75,000 people in the US and EU with CAH – high diagnosis rate due to newborn screening

90% of cases are from mutations in CYP21, which accounts for the 21-hydroxylase enzyme

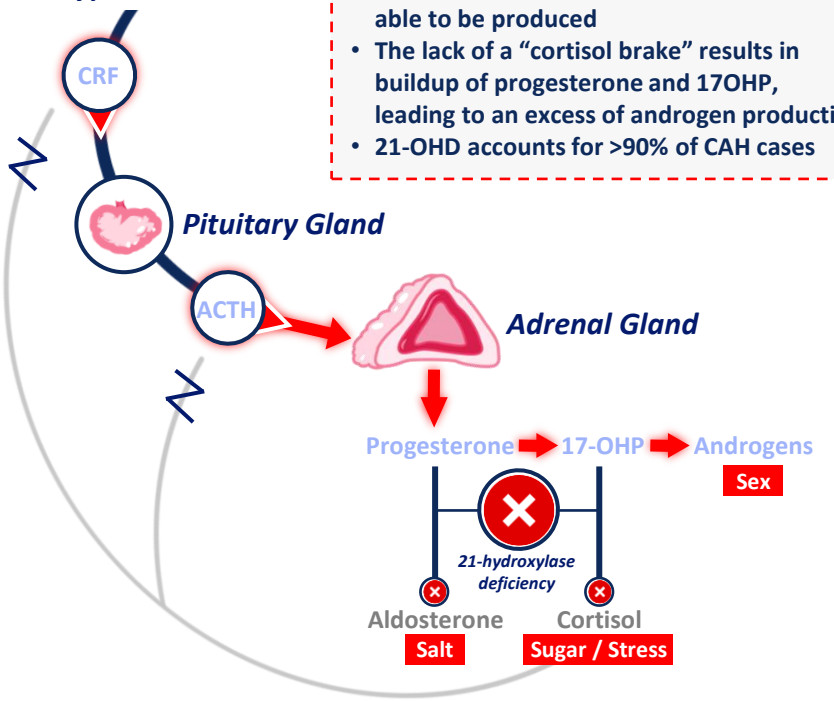
Natural history studies demonstrate heightened mortality, as well as significant morbidity

- **3-5x** higher risk of **all-cause mortality**
- **Poor hormonal control**
- **Chronic disease burden** associated with **glucocorticoid supplementation**
- **Reduced height** with mean adult height SD score of −1.0 ± 1.1
- **Infertility issues** with 44% of adult males have testicular adrenal rest tumors (TARTs)

Gene therapy is the only known modality designed to treat CAH at its source and allow for production of endogenous cortisol

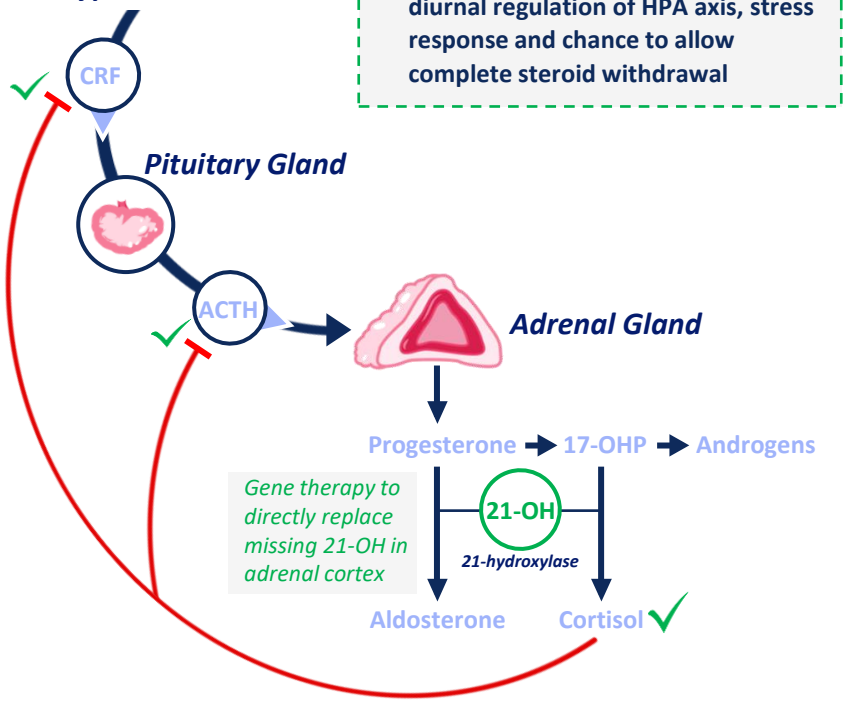
Hormonal dysregulation in HPA Axis due to 21-Hydroxylase Deficiency (21-OHD)

- In CAH, cortisol and aldosterone are not able to be produced
- The lack of a "cortisol brake" results in buildup of progesterone and 17OHP, leading to an excess of androgen production
- 21-OHD accounts for >90% of CAH cases



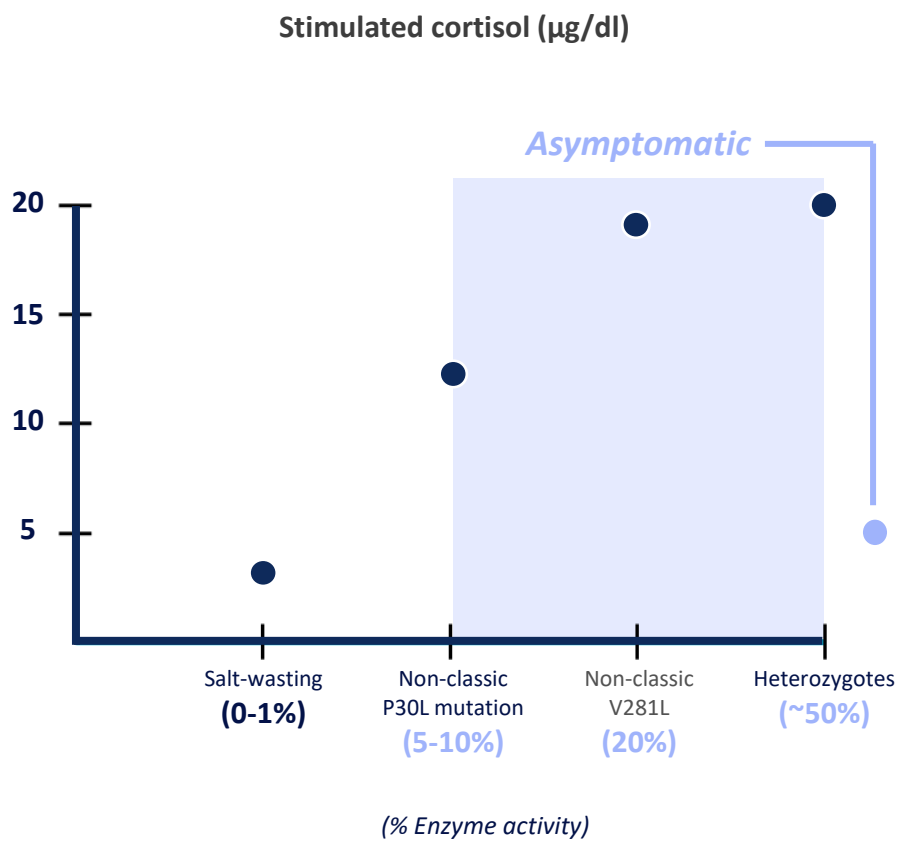
BBP-631 is designed to restore endogenous cortisol production

- BBP-631 has the potential to restore diurnal regulation of HPA axis, stress response and chance to allow complete steroid withdrawal



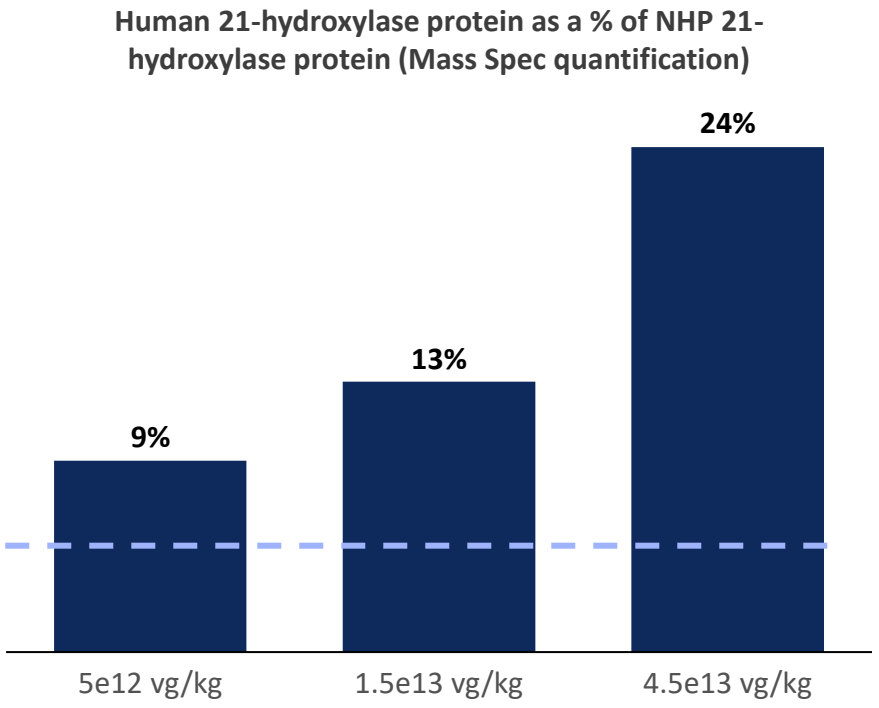
5 – 10% of WT enzyme may be sufficient for clinical impact

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

Clinicians are enthusiastic about the prospect of gene therapy in both pre- and post-pubescent patients with CAH

If BBP-631 were able to REDUCE reliance on exogenous glucocorticoid usage, physicians would offer BBP-631 to…

68% of post-pubescent CAH patients

64% of pre-pubescent and pubescent CAH patients

If BBP-631 were able to ELIMINATE reliance on exogenous glucocorticoid usage, physicians would offer BBP-631 to…

84% of post-pubescent CAH patients

90% of pre-pubescent and pubescent CAH patients

PRELIMINARY MARKET RESEARCH

Preliminary market research; Blinded physician interviews conducted November 2021; Physicians were shown illustrative target product profiles where treatment with BBP-631 either reduced or eliminated exogenous glucocorticoid use and were asked what percentage of their CAH patients across three age groups (pre-pubescent, pubescent, post-pubescent) they would consider recommending BBP-631 to.

Our Phase 1/2 first-in-human trial design is enrolling with data expected 2H 2022

Status: Dosed first patient 1Q22 | 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

Dose Escalation Design

Expansion possible at any dose level

Three dose levels of BBP-631 are planned for the study

Cumulative safety data review before dose escalation or dose expansion

Dose level 1: N=3 | 1.5×10^{13} vg/kg → *Follow-up*

Dose level 2: N=3 | 3.0×10^{13} vg/kg → *Follow-up*

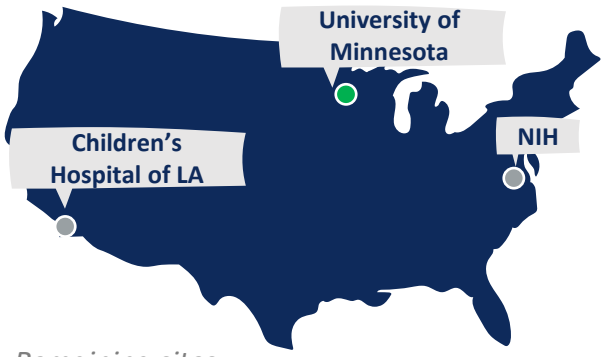
Dose level 3: N=3 | 6.0×10^{13} vg/kg → *Follow-up*

Expectations for Phase 1/2 data 2H 2022

- Safety and tolerability
- 12-week cortisol and hormone data
- Goal is to see improvement from baseline of >50% in ACTH-stimulated endogenous cortisol

Progress in site activation

First site active and enrolling with first patient dosed January 2022



Remaining sites expected to be fully activated by 1H22

KRAS mutant-driven cancers

- Prevalence (US & EU): **>500K**
- Stage: **Lead optimization**
- Next Catalyst: **Development candidate selection 2H22**

Basia

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

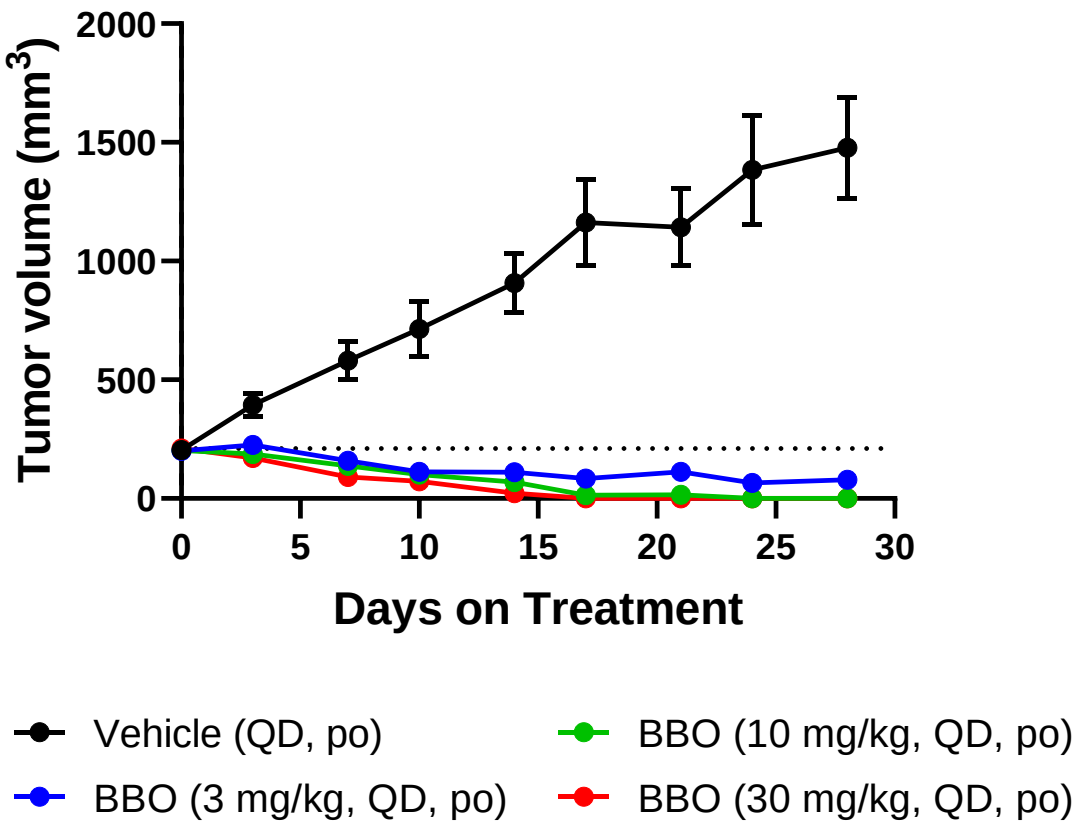
BridgeBio G12C inhibitors modify both GTP (active) and GDP (inactive) forms of $KRAS^{G12C}$

			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

	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	✓	

Note: Conclusions based on preclinical models

BBO KRAS^{G12C} inhibitor demonstrates potent efficacy in MIA PaCa-2 xenograft model

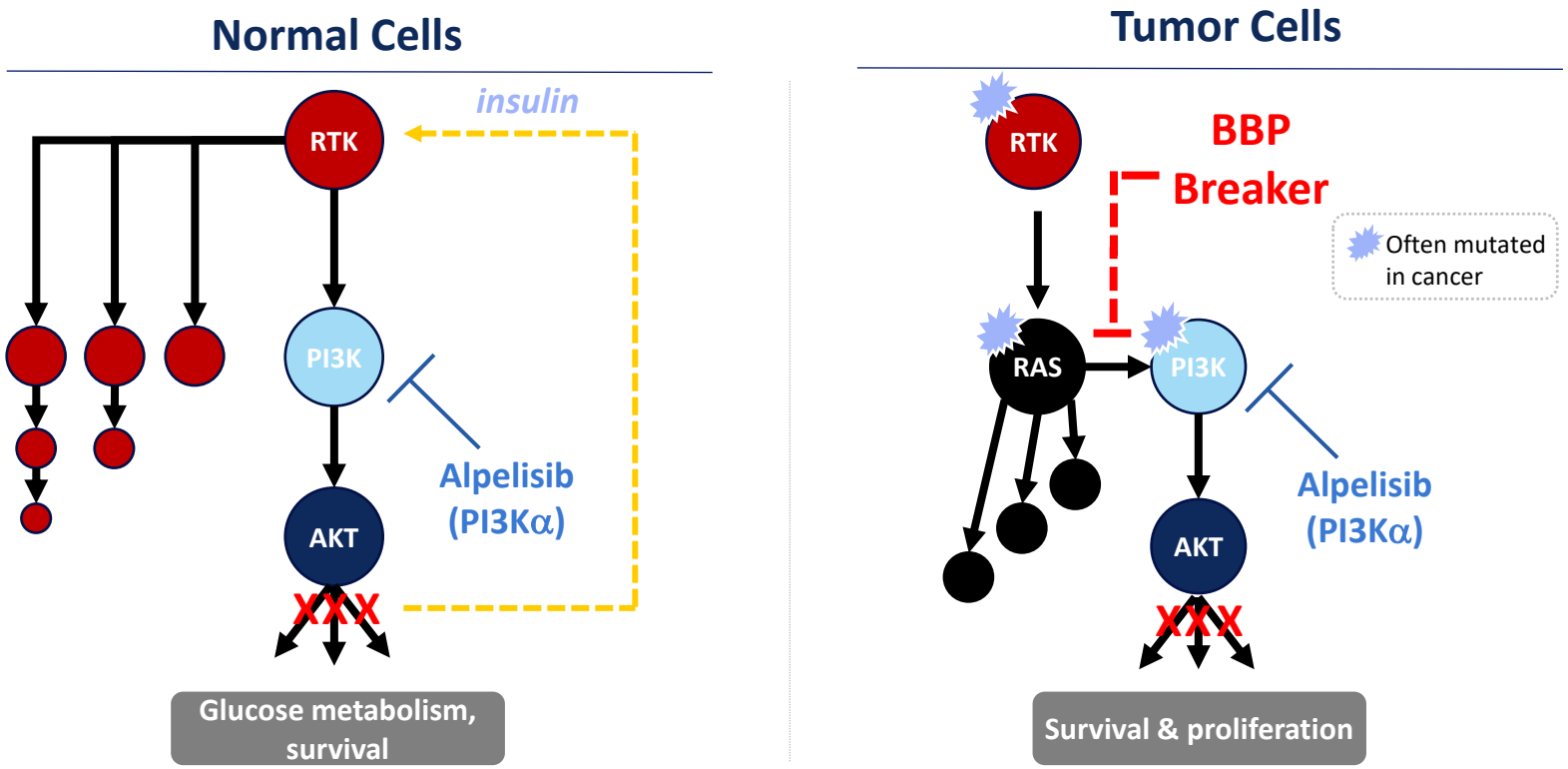


Group (n=10)	Day 28			
	Mean tumor regression	Complete regressions	P value vs vehicle	Body weight change
Vehicle	-	1/10	-	+10.4%
BBO (3 mg/kg)	60%	1/10	<0.0001	+7.1%
BBO (10 mg/kg)	100%	9/10	<0.0001	+4.7%
BBO (30 mg/kg)	100%	10/10	<0.0001	+5.6%

Two-way repeated measures ANOVA performed with Dunnett's multiple comparison test for statistical analyses (day 3 to 28)

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

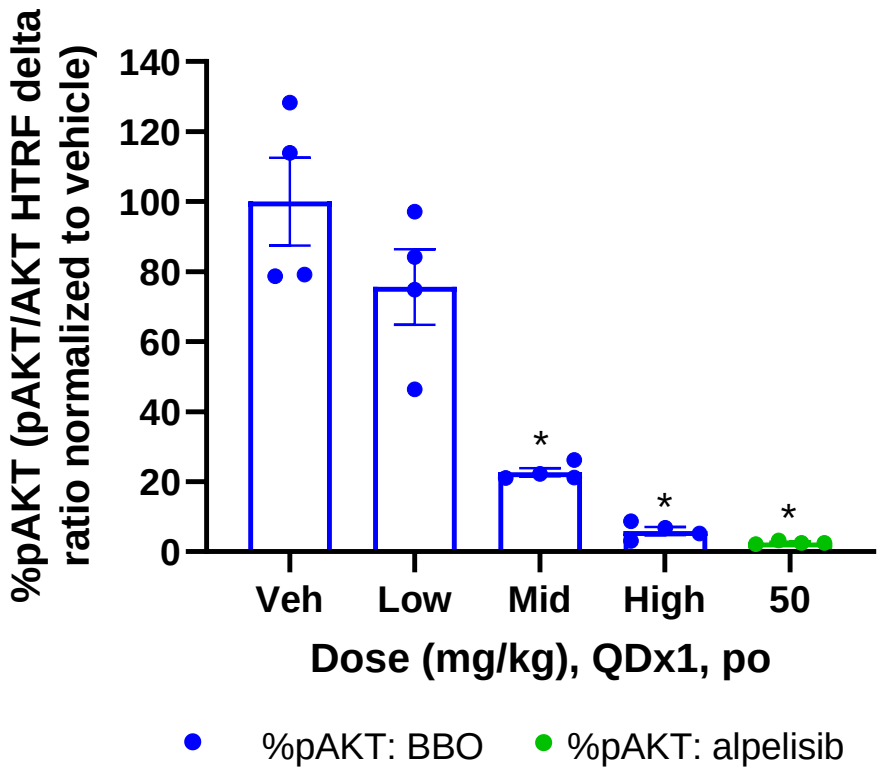
- PI3Kα kinase inhibitors ***block normal cell signaling*** as well as RAS-driven PI3Kα pathway activation in tumor cells, resulting in ***dose-limiting hyperglycemia and insulin-driven resistance***
- Our novel approach of inhibiting PI3Kα:RAS PPI with a ***"PI3Kα Breaker"*** should avoid hyperglycemia 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)***



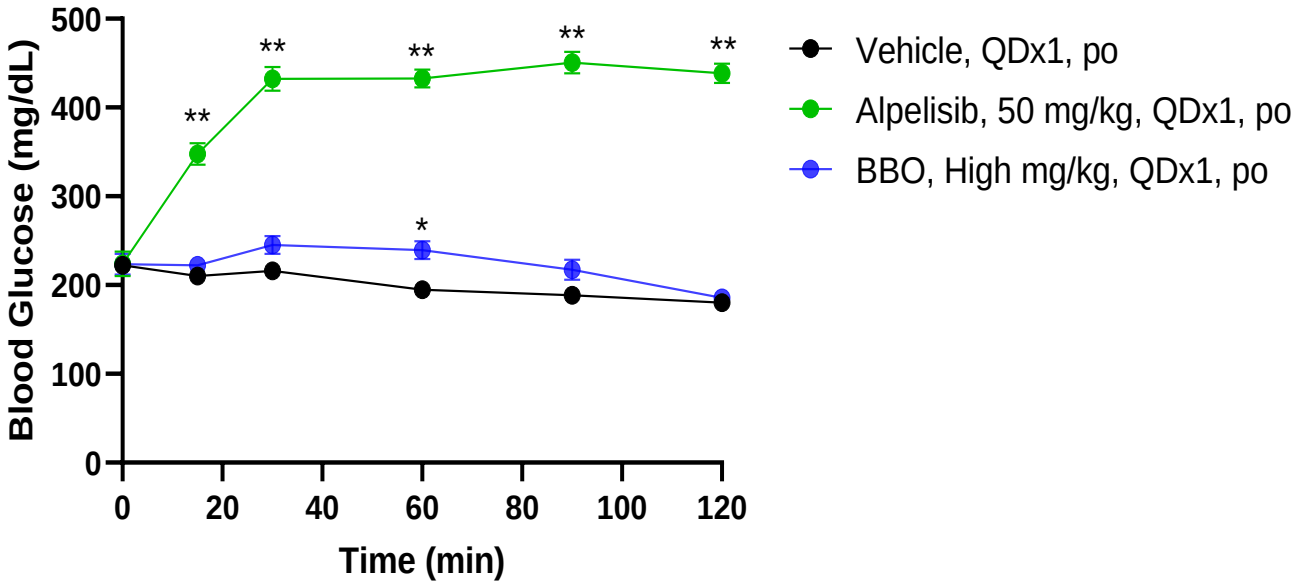
- Structural insights provide a novel approach to develop PI3Kα:RAS breakers
- PI3Kα:RAS breakers selectively bind to PI3Kα
  - PI3Kα amino acid sequence in the region of the binding pocket is unique amongst all the isoforms
  - No binding affinity to KRAS
- PI3Kα:RAS breakers do not affect kinase activity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

BBO induces strong pAkt inhibition in tumor xenograft model but does not induce hyperglycemia in non-tumor-bearing mice

Dose response



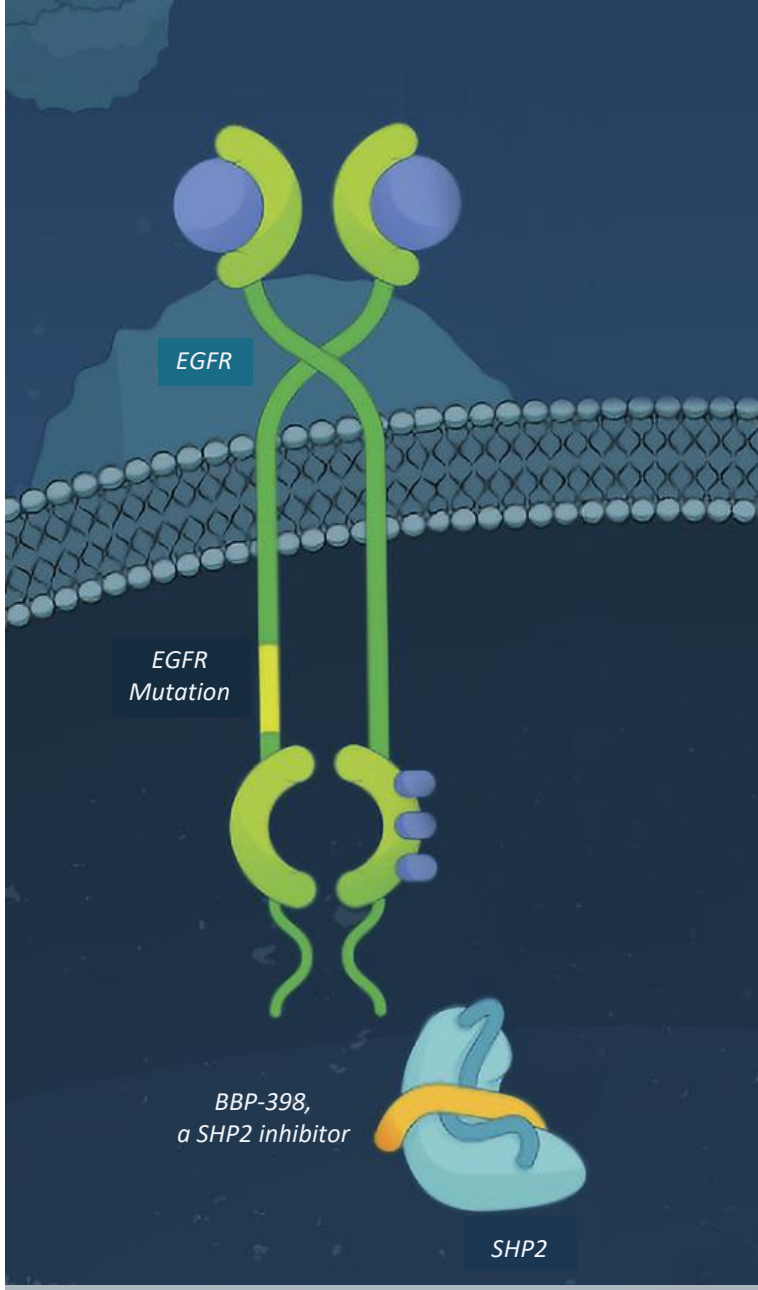
Blood glucose levels



Dose response: One-way ANOVA with Tukey's test vs vehicle *p<0.0001. Blood glucose levels: One-way ANOVA with Dunnett's multiple comparisons test vs vehicle: *p<0.01, **p<0.0001

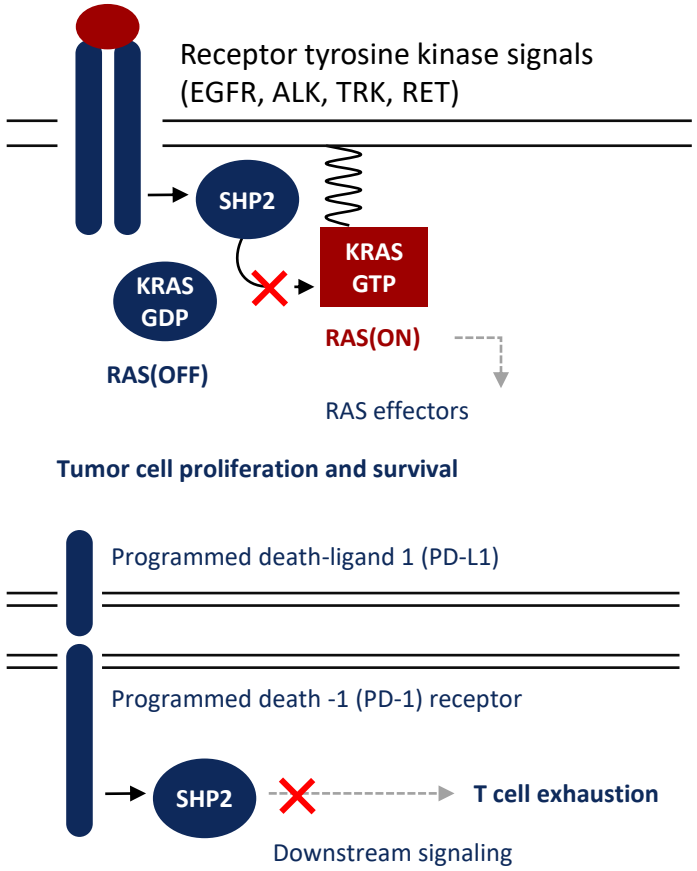
BBP-398: SHP2 inhibitor for treatment resistant cancer

- Prevalence (US & EU): **>500K**
- Stage: **Phase 1**
- Next Catalyst: **Phase 1 monotherapy data 2022**



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

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

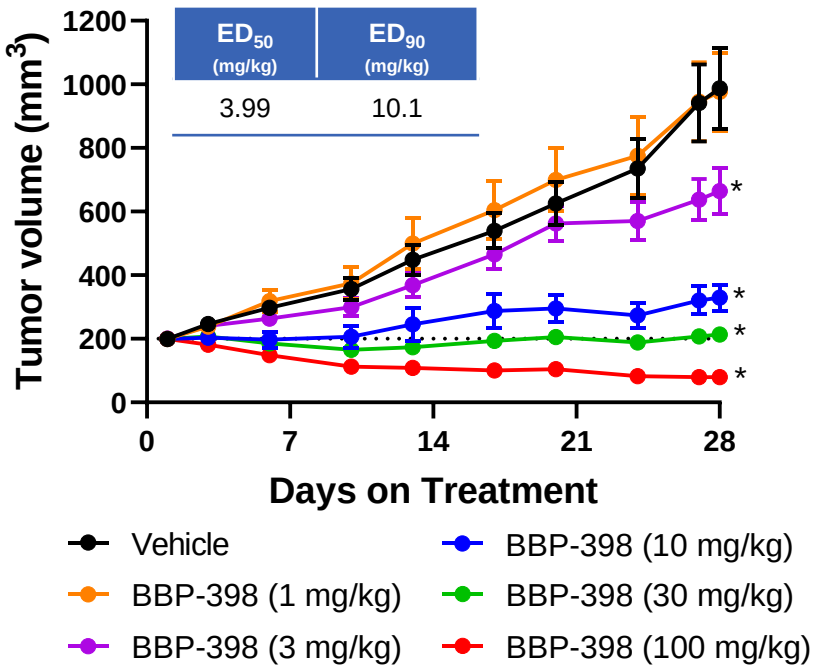
Initial clinical combinations of focus based on SHP2i preclinical data

Combination Agent	Patient Population[1]
KRAS G12Ci AMGEN	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

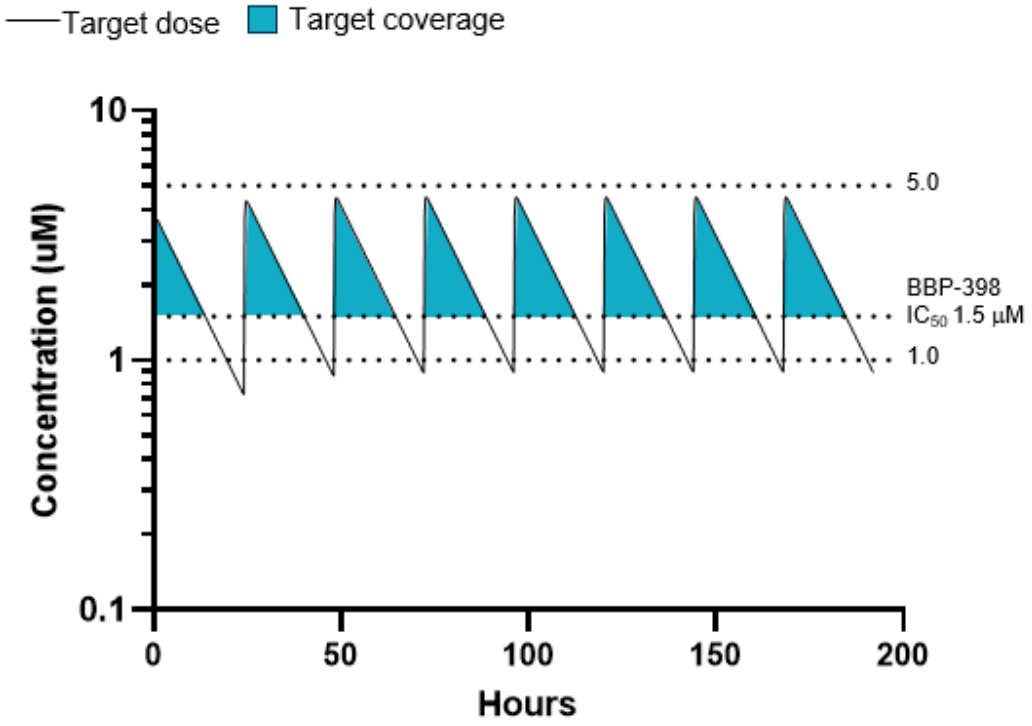
Predicted BBP-398 pharmacokinetics support once daily oral administration to achieve target coverage

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

Precision oncology summary

BridgeBio Oncology

- ✓ 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)