Krystal®

Genetic Medicines for High Unmet Medical Needs

March 2025

Forward Looking Statements and Disclosures

Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. Any statements in this presentation about future expectations, plans and prospects for Krystal Biotech, Inc. (together with its subsidiaries, the "Company"), including, but not limited to, statements about commercialization of VYJUVEK® in the United States; efforts and timelines to bring VYJUVEK to market in Europe and Japan; estimated numbers of DEB patients; the market and revenue growth opportunities for VYJUVEK; the opportunity for B-VEC to address DEB ocular complications; the Company's in-house manufacturing capacity and expertise; the Company's technology platform, including its unique attributes, expected advantages, and potential to overcome historical challenges with inhaled gene delivery; the development and commercialization of the Company's product candidates and pipeline expansion opportunities, including the conduct and timelines of clinical trials and data readouts; the preclinical and clinical utility of the Company's product candidates; the market opportunities for and the potential market acceptance of the Company's product candidates; and other statements containing the words "anticipate", "believe", "estimate", "expect", "intend", "may", "plan", "predict", "project", "target", "potential", "likely", "will", "would", "could", "should", "continue" and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the content and timing of decisions made by the U.S. Food and Drug Administration, European Medicines Agency, and other regulatory authorities; the uncertainties inherent in the initiation and conduct of clinical trials; availability and timing of data from clinical trials; whether results of early clinical trials or studies in different disease indications will be indicative of the results of ongoing or future trials; manufacturing uncertainties or disruptions and the availability of VYJUVEK or product candidates; the ability to retain and hire key personnel; and such other important factors as are set forth in the Company's annual and quarterly reports and other filings on file with the U.S. Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company's views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this presentation.

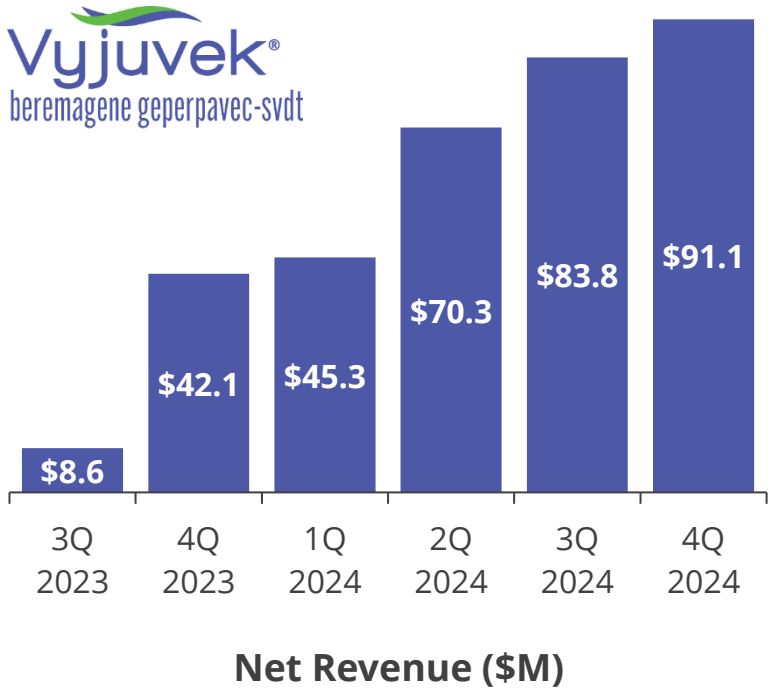
This presentation contains estimates and other statistical data made by independent parties and by the Company relating to market size and growth and other industry data. This data involves several assumptions and limitations, and you are cautioned not to give undue weight to such estimates. No representation as to the accuracy or completeness of such data is made, and the Company does not undertake any obligation to update such data after the date of this presentation. In addition, projections, assumptions and estimates of the Company's future performance and the future performance of the markets in which it operates are necessarily subject to a high degree of uncertainty and risk.

Disclosures

The Company is using the Aerogen Solo® Nebulizer System and Aerogen® Ultra in its studies of inhaled product candidates.

Other than VYJUVEK, all products described in this presentation are investigational therapies.

Building a Global Leader in Redosable Genetic Medicines



Net Revenue ($M)

Over $341M

VYJUVEK Net Revenue Since Launch

✓ **First and only FDA-approved corrective therapy for dystrophic epidermolysis bullosa (DEB)**

- Approved May 2023, U.S. launch August 2023
- Indicated for the treatment of wounds in patients 6 months of age and older with DEB

✓ **Significant global expansion underway**

- Positive EU CHMP opinion in February 2025
- On track for first EU launch in Germany mid 2025
- Approval decision in Japan expected 2H 2025

5

Active Clinical Programs

+

JEUNE

175K+ sq ft

Combined size of Krystal's two cGMP manufacturing facilities

6

Consecutive quarters of positive EPS

Over $749M

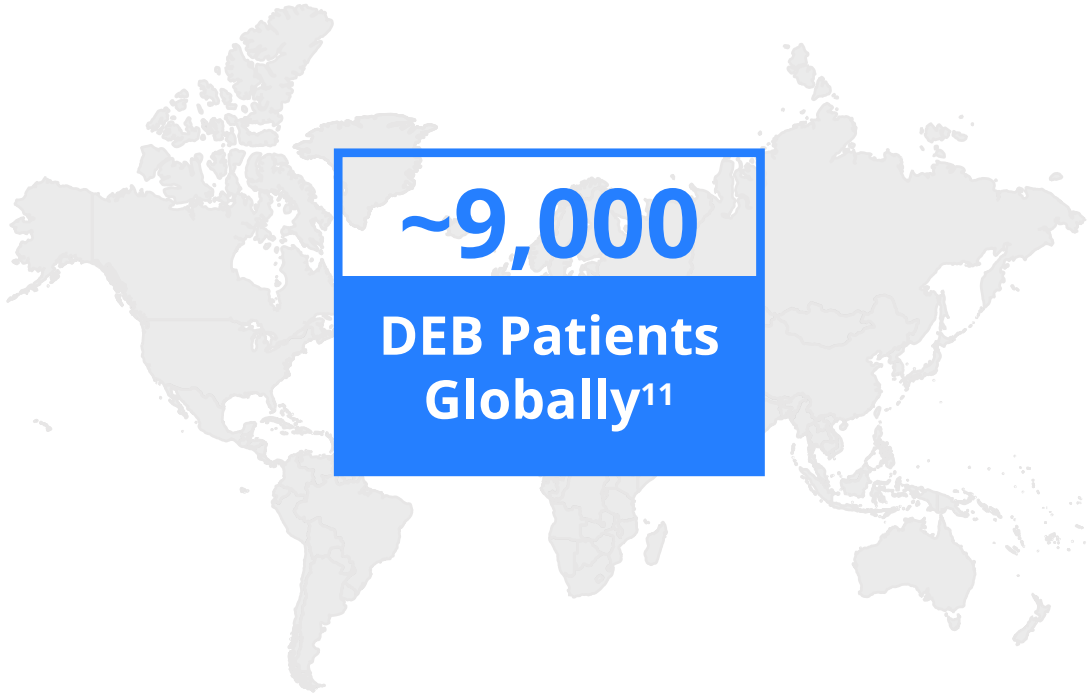
Cash and investments as of 4Q 2024

cGMP, current good manufacturing practices; CHMP, Committee for Medicinal Products for Human Use; EPS, earnings per share; EU, European Union; FDA, U.S. Food and Drug Administration; U.S., United States

VYJUVEK® for Dystrophic Epidermolysis Bullosa

Dystrophic Epidermolysis Bullosa

An ultra-rare genetic disease characterized by fragile skin, recurring and chronic wounds and serious complications



Monogenic Disease Caused by Mutations in *COL7A1* Gene

Mutations lead to absent or dysfunctional COL7 protein, without which the epidermis does not anchor to the dermis[1-3]

Heavy, Lifelong Burden on Patients and Caregivers

Recurring and chronic wounds are hallmarks of DEB causing significant pain, scarring, deformity, loss of function, limited mobility, and other complications with the oral cavity, eye, and gastrointestinal tract[1,4,5]

Costly and Time-Consuming Wound Care

Chronic wound management, bandages, pain and infection control, as well as surgical interventions lead to estimated **annual care costs of $200K-$400K**[6,7]

Increased Risk for Serious Complications and Cancers

DEB patients are at significantly higher risk of developing aggressive forms of squamous cell carcinoma[8-10]

Until VYJUVEK, Only Supportive Care for DEB Patients Available in the U.S.

1. Fine J-D, et al. *J Am Acad Dermatol*. 2014;70(6):1103-1126; 2. Fine J-D. *JAMA Dermatol*. 2016;152(11):1231-1238; 3. Bardhan A, et al. *Nat Rev Dis Primers*. 2020 Sep 24;6(1):78; 4. Has C, et al. *Br J Dermatol*. 2020;183(4):614-627; 5. Bardhan A, et al. *Nat Rev Dis Primers*. 2020;6(1):78; 6. Rashidghamat E., Mellerio J.E., Management of chronic wounds in patients with dystrophic epidermolysis bullosa: challenges and solutions, Chronic Wound Care Management and Research Volume 2017:4, 45-54; 7. GENEGRAFT Report Summary. (2015, February 16). Retrieved December 13, 2016, from http://cordis.europa.eu/result/rcn/156078_en.html 8. Condorelli A, et al. *Int J Mol Sci.* 2019;20(22):5707; 9. Montaudié H, et al. *Orphanet J Rare Dis*. 2016;11(1):117; 10. Fine J-D, Mellerio JE. *J Am Acad Dermatol*. 2009;61:367-384; 11. Krystal Biotech. Data on file

COL7, type VII collagen; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; U.S., United States

VYJUVEK Approved and Launched in U.S.

Strong commercial launch for the first and only corrective therapy for DEB

Vyjuvek®
beremagene geperpavec-svdt

- ✓ ***First* FDA-approved treatment for DEB, approved on May 19, 2023**
  - Indicated for the treatment of wounds in patients 6 months of age and older with DEB
  - Approved for recessive and dominant DEB with no restrictions on use by wound type
- ✓ **Successfully securing broad access and reimbursement**
  - Over 510 reimbursement approvals as of February 2025
  - Positive coverage for 97% of commercial and Medicaid covered lives
  - Reimbursement approvals across all ages and for both dominant and recessive DEB
- ✓ **Expanding the prescriber base and starting to grow the patient pool**
  - Over 65% first-time prescribers in 4Q 2024
  - New prescriptions from previously unknown DEB patients organically expanding pool
- ✓ **Site of care flexibility enabling high compliance**
  - Approved for HCP administration irrespective of care setting, including home or clinic
  - 97% patients opting for treatment at home
  - Patient compliance at 85% through end of 4Q 2024

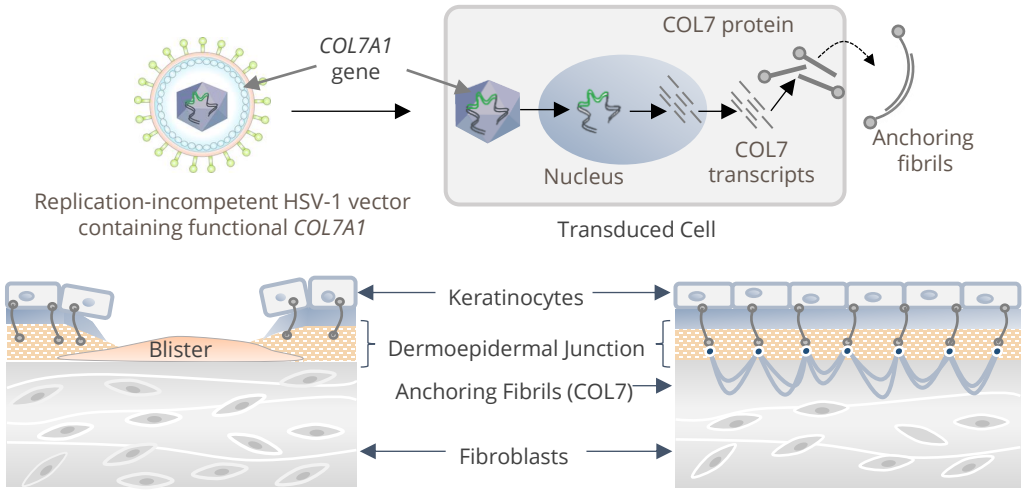
DEB, dystrophic epidermolysis bullosa; FDA, U.S. Food and Drug Administration; HCP(s), healthcare professionals; U.S., United States

VYJUVEK is the First Corrective Therapy for DEB

Topically applied, VYJUVEK, is a gel designed to induce local COL7 expression and replace defective or missing gene

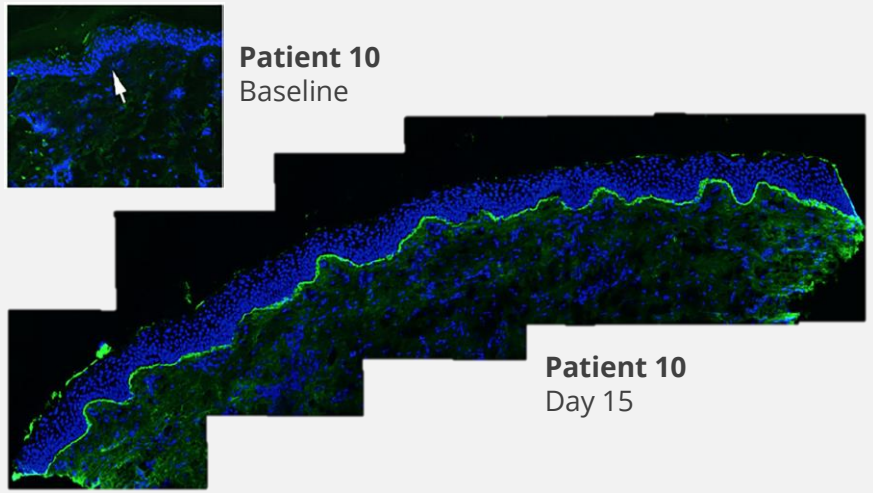
VYJUVEK Mechanism of Action

- When applied topically to the wound, VYJUVEK transduces local keratinocytes and fibroblasts and delivers *COL7A1* to the nucleus[1-3]
- The *COL7A1* payload then persists episomally, enabling the transduced cell to produce and secrete functional COL7 protein without host genomic disruption[1-3]
- Secreted COL7 assembles into anchoring fibrils, holding skin together[1-3]



Clinical Evidence of Molecular Correction in Phase 1/2

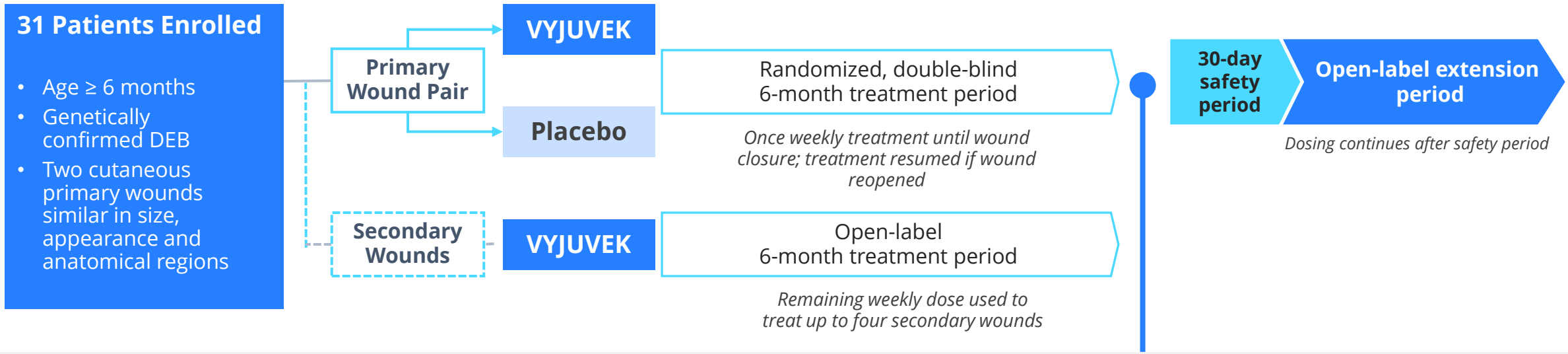
- Representative data from patient in Phase 1/2 study assessing COL7 deposition in the skin by immunofluorescence (in green)[3]
- Strong, properly localized COL7 signal detected in treated skin
- Anchoring fibril formation also detected by electron microscopy



1. Marinkovich MP, et al. Oral presentation at 2022 American Academy of Dermatology (AAD) Annual Meeting; 2. Guide SV, et al. *N Engl J Med.* 2022;387(24):2211-9; 3. Gurevich I et al. *Nat Med* 2022; 28:780-788

COL7, type VII collagen; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa

GEM-3 Pivotal Study Evaluated Weekly Dose of VYJUVEK or Placebo in DEB



Demographics

- 31 patients, each with one primary wound pair were enrolled and included in the ITT analysis
- Enrolled patients ranged from 1 year old to 44 years old at baseline; 61% of the patients enrolled were pediatric (≤18 years old)

Study conducted across 3 sites

Primary Efficacy Endpoints

- Complete wound healing† at Week 22 and Week 24; or at Week 24 and Week 26 (6-months)

Secondary Efficacy Endpoints

- Complete wound healing† at Week 8 and Week 10, or at Week 10 and Week 12 (3-months)
- Mean change in pain severity (VAS or FLACC-R Scale) associated with wound dressing changes

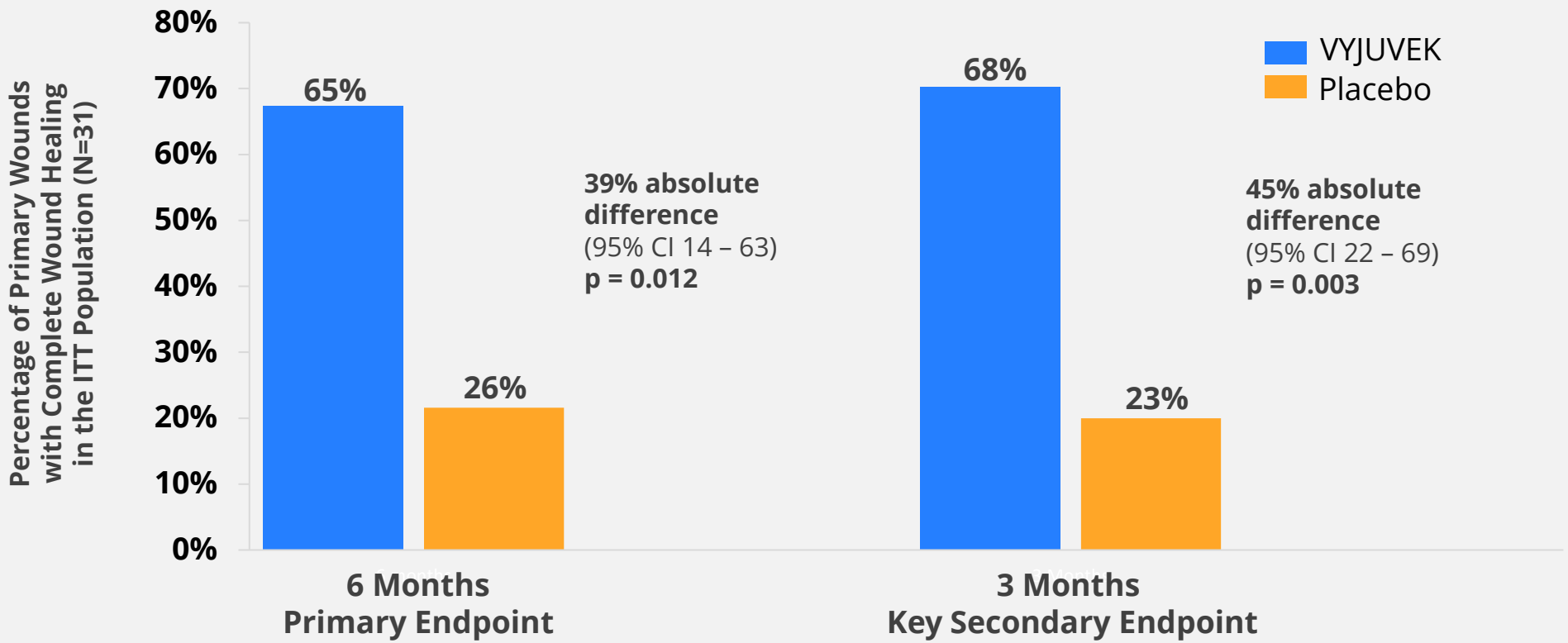
Guide SV, et al. *N Engl J Med.* 2022; 387(24):2211-9

DEB, dystrophic epidermolysis bullosa; FLACC-R Scale, Face, Legs, Activity, Cry and Consolability Revised scale; ITT, intent-to-treat; VAS, Visual Analogue Scale

†Complete wound healing defined as 100% wound closure from the exact wound area at baseline, specified as skin re-epithelialization without drainage

Significantly Higher Proportion of Wounds Closed with VYJUVEK

VYJUVEK impact on closure rates similar at both primary endpoint of 6 months and secondary endpoint of 3 months



Krystal Biotech. Data on file

Data shown on this slide is based on the data handling methodologies requested by FDA during labeling negotiations, with missing data for 1 subject replaced with remote assessments captured during COVID-19 pandemic and worst-case scenario* applied for other 2 subjects with missing data. In the *New England Journal of Medicine* (Guide SV, et al. *N Engl J Med.* 2022; 387(24):2211-9), missing data for 3 subjects was handled with multiple imputation method as prespecified in Statistical Analysis Plan for Phase 3. *Worst-case scenario assumes that the placebo-treated wound achieved complete wound closure whereas the VYJUVEK-treated wound did not.

CI, confidence interval; ITT, intent-to-treat

VYJUVEK Well-Tolerated and Demonstrated Strong Safety Profile

Safety profile consistent across all studies to date

Adverse Events	Total Patients (n=31)
Total number of adverse events (AEs)	45
Patients with ≥ 1 AE, n (%)	18 (58.1)
Serious AEs	3 (9.7)
Severe AEs	2 (6.5)
Drug-related AEs	1 (3.2)
AE leading to treatment discontinuation	0 (0)
Death	0 (0)

- Majority of AEs were mild or moderate; no AEs led to treatment discontinuation or death
- The most common side effects (>5%) were itching, redness, rash, cough, and runny nose
- One AE, mild erythema, was considered possibly related to study drug as assessed by the investigator
- Three patients experienced a total of five SAEs during the study: cellulitis, anemia (two events), diarrhea, and positive blood culture
  - ✓ None were considered related to study drug
- No clinically significant immunologic reactions were reported during the study
- Treatment response to VYJUVEK was not associated with HSV-1 serostatus at baseline or with COL7 seroconversion

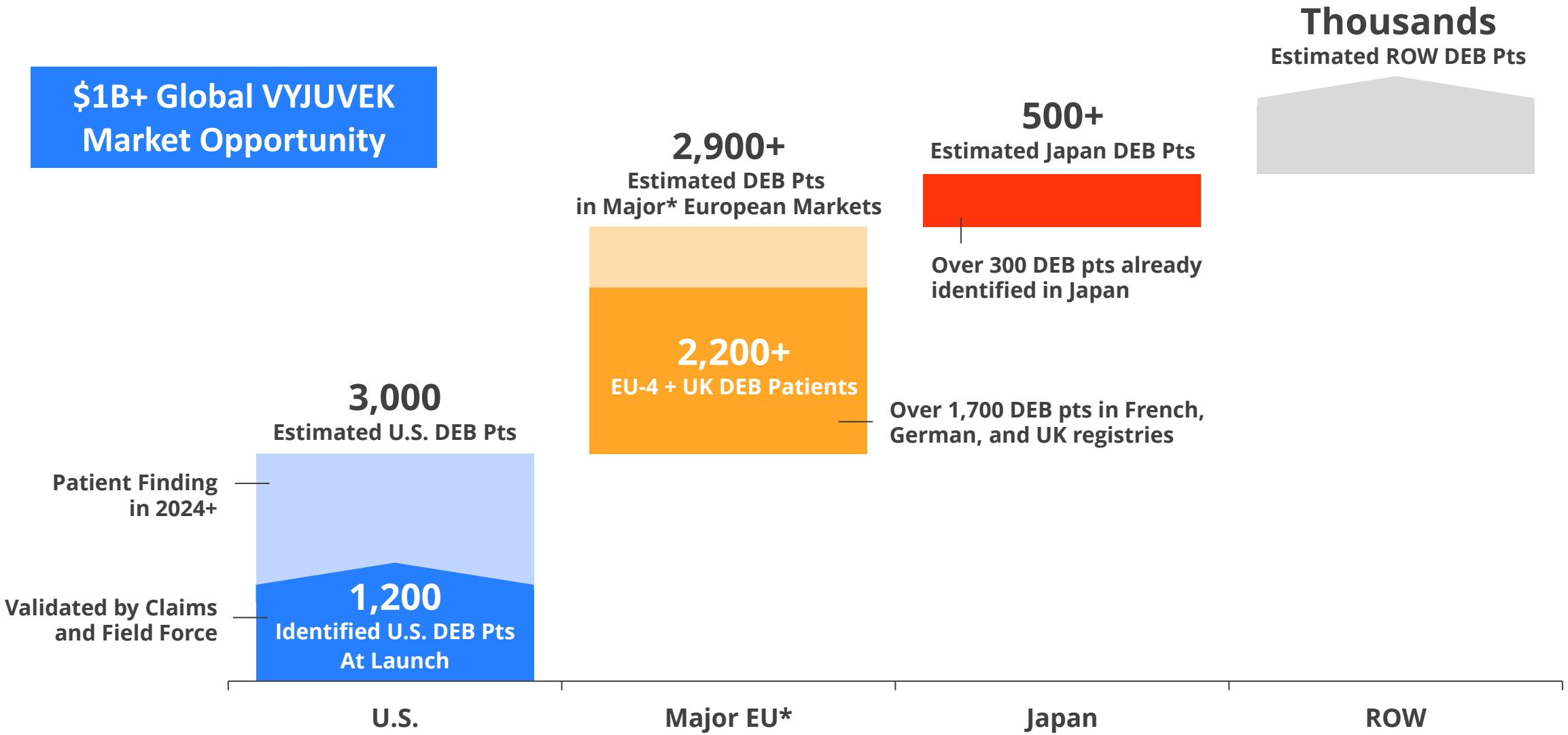
Guide SV, et al. *N Engl J Med.* 2022;387(24):2211-9

AE(s), adverse event(s); COL7, type VII collagen; HSV-1; herpes simplex virus type 1; SAEs, serious adverse events

VYJUVEK is Changing the Treatment Paradigm in DEB

Significant Revenue Growth Opportunities Outside of the United States

$1B+ Global VYJUVEK Market Opportunity



* Refers to European target markets of EU-4 (France, Germany, Spain, Italy), UK, Ireland, Benelux, Switzerland, Austria, Nordics

DEB, dystrophic epidermolysis bullosa; EU, European Union; UK, United Kingdom; ROW, rest of world; U.S., United States

Positive EU CHMP Opinion Issued in February 2025

Broad label recommended by CHMP

- ✓ Recommended approval for treatment of wounds in DEB patients from birth
- ✓ Included option for home administration by either a trained caregiver or a patient, if deemed appropriate by the prescribing healthcare professional
- ✓ No post-approval efficacy study requirements

Final approval decision anticipated in 2Q 2025

+ first launch in Germany mid 2025

Over 1,000

Diagnosed DEB Patients in France and Germany Alone

CHMP, Committee for Medicinal Products for Human Use; DEB, dystrophic epidermolysis bullosa; EU, European Union;

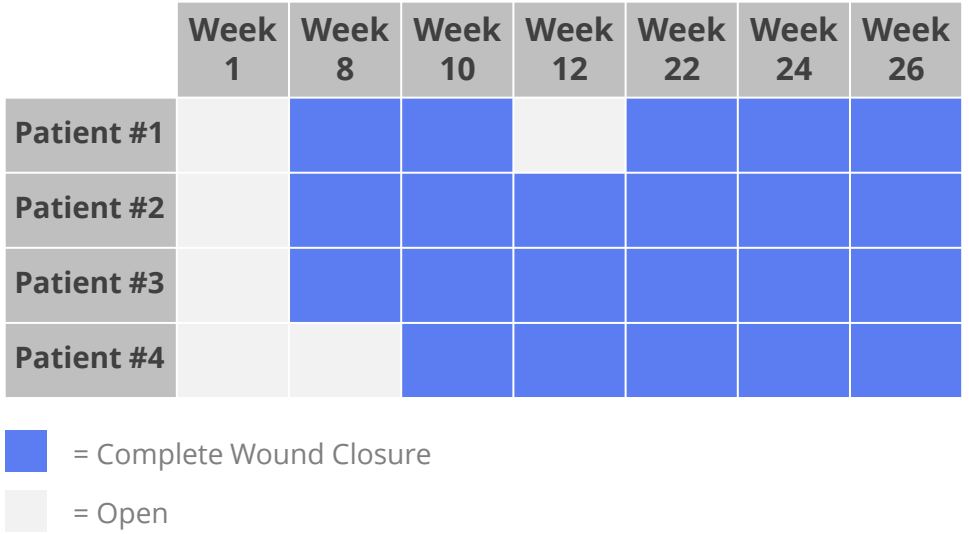
J-NDA Filing Under Review in Japan, Supported by Japan OLE Study

Japan OLE Study

- Multicenter, open-label extension study in Japanese subjects with DEB
- The primary objective was to evaluate wound healing at 6 months, defined as complete closure of primary wound, similar to U.S. registrational Phase 3 design
- Key inclusion criteria
  - Diagnosis of DDEB or RDEB confirmed by genetic testing including *COL7A1*
  - Age of 2 months or older
- Weekly dosing with max weekly dose varying by age
  - 2×10^9 PFU from 2 months up to 3 years
  - 4×10^9 PFU at and above 3 years
- Five subjects enrolled, one dropped out due to scheduling challenges
  - Median 22.3 years of age (range = 12.8 to 68.5)
  - All RDEB subtype, 80% female

Study design previously aligned with Japanese regulatory authorities to support J-NDA submission

Summary of Primary Wound Assessments Per Protocol Population



100%

Wound Closure at Six Month Primary Endpoint (Per Protocol; n = 4/4)

B-VEC well-tolerated in Japanese population and safety profile was consistent with previous U.S. studies

On track for PMDA decision in 2H 2025

B-VEC, beremagene geperpavec; (D/R)DEB, (dominant / recessive) dystrophic epidermolysis bullosa; J-NDA, Japanese New Drug Application; OLE, open label extension; PFU, plaque forming unit; PMDA, Pharmaceuticals and Medical Devices Agency; U.S., United States

Follow-On Opportunity to Address DEB Ocular Complications

A cause of progressive vision loss with no specific therapy available

Ocular Complications of Dystrophic Epidermolysis Bullosa (DEB)[1-3]

- A significant proportion of DEB patients suffer from ocular complications related to local COL7 deficiency in the eye
- Corneal abrasion, scarring, and pannus are among the most commonly cited issues, as well as eyelid ectropion, blisters
- Can lead to progressive vision loss and even blindness

No Specific FDA-Approved Therapy[1-3]

- There is no corrective therapy available to treat ocular complications of DEB
- Standard of care is recurring surgical intervention to separate eyelid from the eye and clear occlusions from cornea; burdensome and no assurance of durable benefit

Over 50%

Proportion of RDEB patients with ocular complications[1,2]

750

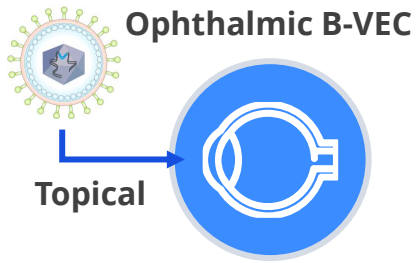
Estimated Patients in U.S.*

2K+

Estimated Patients WW*†

* Assuming 50% of DEB patients have RDEB of which at least 50% have ocular complications[1-4]

† Reimbursable markets only



KB803, a new ophthalmic formulation of B-VEC, is in development to restore local *COL7A1* expression and eye function in DEB patients

1. Tang JY, et al. *Orphanet J Rare Dis.* 2021;16(1):175; 2. Tong L, et al. *Br J Ophthalmol.* 1999; 83(3):323-326; 3. Chen VM, et al. *Ocul Surf.* 2020; 18(4):912-919; 4. Krystal Biotech. Data on File

B-VEC, beremagene geperpavec; COL7, type VII collagen; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; FDA, U.S. Food and Drug Administration; RDEB, recessive dystrophic epidermolysis bullosa; U.S., United States; WW, worldwide

Significant Improvement in Eye of DEB Patient Treated with B-VEC

Well-tolerated and associated with full corneal healing and visual acuity improvement to 20/25

Compassionate Use of Ophthalmic B-VEC in Eye of DEB Patient

- 13-year-old male with DEB and bilateral cicatrizing conjunctivitis
- History of repeated symblepharon lysis surgeries with posterior recurrence, and bilateral limbal stem cell deficiency
- Surgical symblepharon lysis of right eye was performed followed with regular topical applications of B-VEC (5 × 10^9 PFU/mL)
- Regular applications eventually declining to weekly frequency were performed until corneal epithelium was healed, followed by monthly topical applications

Treated Eye

Baseline

6 Months

Visual Acuity in Treated Eye

Time		Visual Acuity
Baseline / Prior to Surgery		HM
After Surgery	1 Week	20/400
	1 Month	20/200
	2 Months	20/150
	3 Months	20/100
	4 Months	20/80-2
	5 Months	20/80-1
	6 Months	20/70
	7 Months	20/40
	8 Months	20/25

Ophthalmic B-VEC well-tolerated and associated with corneal healing, epithelization, and continuing visual acuity improvement

Registrational study to start 1H 2025; natural history study underway

Sabater A et al., Poster # 787 - C0388. at the 2023 Association for Research in Vision and Ophthalmology Annual Meeting; Vetencourt AT, et al. *N Engl J Med*. 2024;390:530-535

B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; HM, hand motion; PFU, plaque forming unit

Technology Platform

HSV-1: A Differentiated Vector Platform

Unique properties of HSV-1 overcome capacity, immunogenicity, and potential safety issues of other commonly used vectors

Krystal's Engineered Replication Deficient HSV-1 Platform

Large genetic payload capacity well in excess of other viral vectors

HSV-1 has a large genome, theoretical cargo capacity > 30 kb significantly exceeds capacity of AAV (< 5 kb) and lentiviruses (~9 kb); VYJUVEK contains over 19 kb genetic cargo

Efficient transduction of wide range of cell types

HSV-1 employs multiple mechanisms to gain cell entry and majority of cell types are permissive; Krystal vectors shown to transduce keratinocytes, fibroblasts, and various cells of the eye and lung so far

Evades host immunity allowing for repeat dosing and reducing immunotoxicity

The ability of HSV-1 to block innate and adaptive immune responses is retained in Krystal vectors; no evidence of significant or persistent neutralizing immunity in clinical studies to date

DNA payload enables durable expression without integration risk

HSV-1 delivers genome to nucleus where it persists episomally; no reports of integration with wild-type virus or Krystal constructs

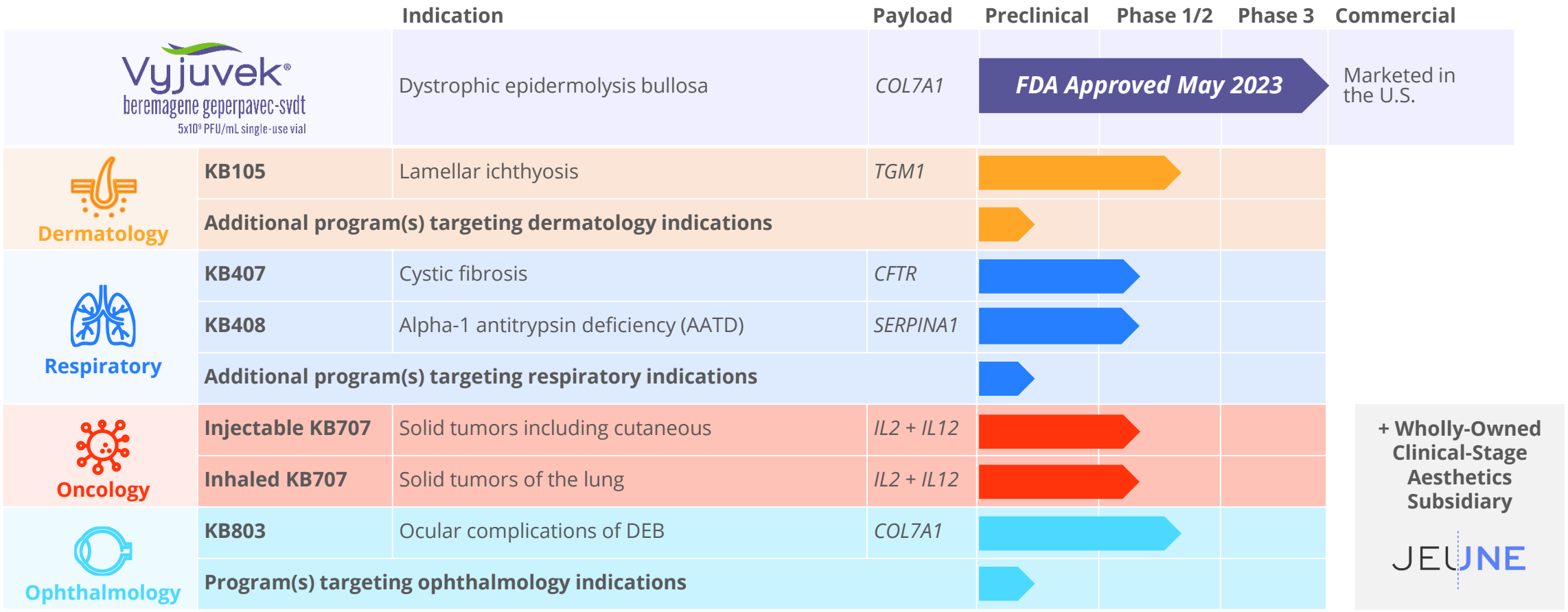
Scalable manufacturing of viral gene therapies

Capable of increasing manufacturing in a streamlined manner because of in-house capabilities

AAV, adeno-associated virus; DNA, deoxyribonucleic acid; HSV-1, herpes simplex virus type 1

Pipeline

Robust pipeline with five active clinical programs



CFTR, cystic fibrosis transmembrane conductance regulator; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; FDA, US Food and Drug Administration; IL-12, interleukin-12; IL-2, interleukin-2; SERPINA1, serpin family A member 1; TGM1, transglutaminase-1; U.S., United States

In-House Manufacturing Capacity and Expertise

Two U.S. GMP facilities with capacity to support global VYJUVEK product needs and future growth

ANCORIS Facility

- ~21,100 sq. ft. GMP facility
- Capabilities: Virus Banks, Cell Banks, Pilot Scale Process Development, Drug Substance, Drug Product GMP Storage, Clinical and Commercial Packaging, Analytical Development, Analytical Testing, Waste Handling, Environmental Monitoring, and Logistics
- Fully equipped AD/QC labs
- Validated methods for titering/release
- Built to support global VYJUVEK launch

ASTRA Facility

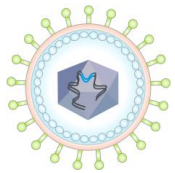
- ~155,000 sq. ft. GMP facility
- Capabilities: Virus Banks, Cell Banks, Drug Substance, Drug Product, Packaging, Storage, General Office Space, GMP Storage, Bulk Packaging, Waste Handling, Environmental Monitoring, and Logistics
- Able to scale up and scale out

GMP, good manufacturing practice; U.S., United States

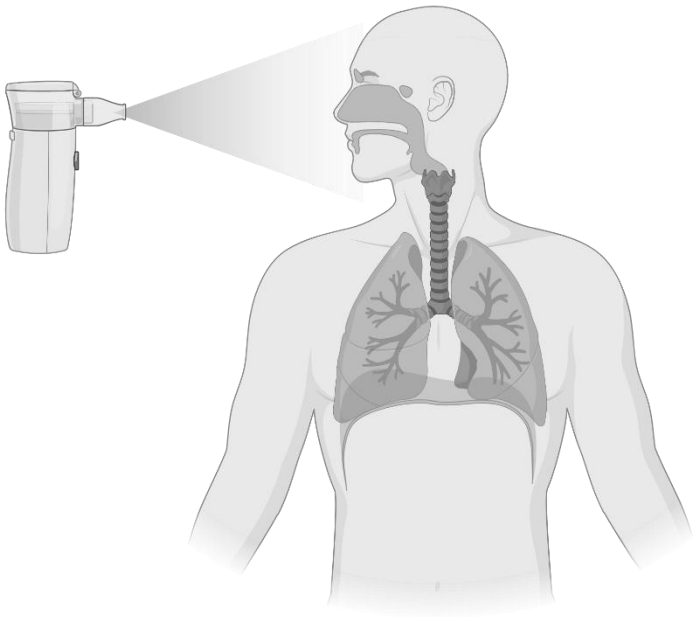
Respiratory Pipeline

Krystal's HSV-1 Based Approach for Lung Gene Delivery

Developing redosable, non-invasive, inhaled gene therapies to address monogenic disorders of the lung



Krystal's Proprietary HSV-1 Vectors



Delivered via off the shelf nebulizer

Historical Challenges with Inhaled Gene Therapy[1]

- Inhaled gene therapy has been explored for decades, with little success
- Focus to date has been on adenovirus, AAV, and non-viral approaches
- Multiple challenges including cargo limitations, low efficiency of gene transfer, toxicity, product instability, and burdensome delivery

HSV-1 Platform Has Potential to Overcome Historical Challenges

- Clinically validated vector; tolerated and redosable in Phase 3 for DEB
- Large cargo capacity to load in full genes, including *CFTR* for cystic fibrosis
- Ability to redose and/or adjust dose over time as lung cells turnover
- Broad cellular tropism and efficient transduction of airway epithelium
- Expected nebulization time is under 30-minutes using off-the-shelf nebulizer

Growing clinical dataset demonstrating that Krystal's inhaled candidates are well-tolerated and distribute broadly in the lung

1. Vu A, et al. *Human Gene Therapy* 2020;31(17-18):921-939

AAV, adeno-associated virus; CFTR, cystic fibrosis transmembrane conductance regulator; DEB, dystrophic epidermolysis bullosa

Alpha-1 Antitrypsin Deficiency (AATD)

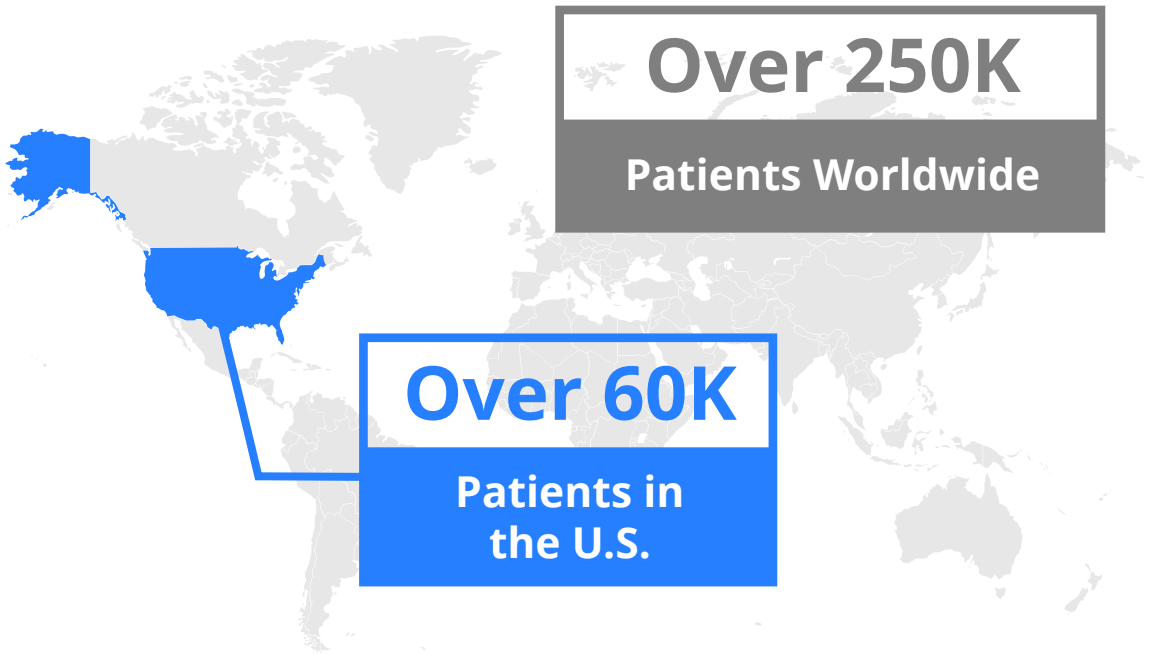
Monogenic disorder that leads to progressive lung disease

- Alpha-1 antitrypsin (AAT) is a key regulator of protease activity, in particular neutrophil elastase in lungs[1]
- AATD is an autosomal co-dominant inherited genetic disorder resulting from mutations in *SERPINA1* gene encoding AAT, misfolding mutations Pi*ZZ and Pi*SZ are the most common
- Genetic deficiency of AAT can result in unopposed neutrophil elastase activity and progressive pulmonary impairment

Unproven and Limited Treatment Options[1,2]

- There is no cure available for patients with AATD
- Standard of care is weekly IV infusions of AAT but treatment is burdensome on patients and clinical benefit not well defined

Severe AATD Prevalence[3-5]*



1. Greene CM, et al. *Nat Rev Dis Primers* 2016;2:16051; 2. Brantly ML, et al. *Int J Chron Obstruct Pulmon Dis.* 2019;6:100–114; 3. Aboussouan LS, et al. *Respir Med.* 2009;103:335-341; 4. Stoller JK, et al. *Int J Chron Obstruct Pulmon Dis.* 2013;10:26-24; 5. Blanco I, et al. *Int J Chron Obstruct Pulmon Dis.* 2017;12:561-569;

*Severe AATD defined as patients with Pi*ZZ genotype

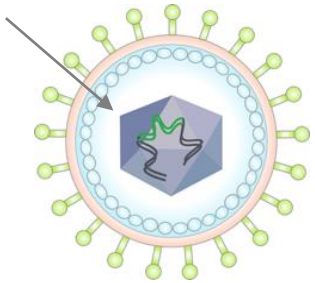
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; IV, intravenous; SERPINA1, serpin family A member 1; U.S., United States

Inhaled Candidate KB408 for AATD Lung Disease

Genetic medicine designed to achieve sustained, local AAT expression is supported by robust preclinical data package

KB408

2 x *SERPINA1* genes



Replication-incompetent HSV-1 vector containing functional human *SERPINA1*

Preclinical Summary

- ✓ **Transduces human airway cells *in vitro* leading to dose-dependent expression and secretion of functional AAT**
- ✓ **AAT secreted from KB408 transduced cells is functional as demonstrated by binding to target neutrophil elastase**
- ✓ **Airway administration to wild-type or *SERPINA1* deficient mice yielded robust AAT expression detected by multiple independent assessments**
- ✓ **Vector platform shown to be amenable to nebulization with broad airway transduction and tolerability in non-human primates *– KB407 data***
- ✓ **Repeat KB408 dosing well-tolerated in murine GLP IND-enabling toxicology study with only mild findings and NOAEL of top dose**

Data package strongly supportive of KB408 progression to the clinic

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; GLP, good laboratory practices; HSV-1, herpes simplex virus 1; IND, investigational new drug; NOAEL, no observed adverse effect level; SERPINA1, serpin family A member 1

KB408 Phase 1 Study SERPENTINE-1

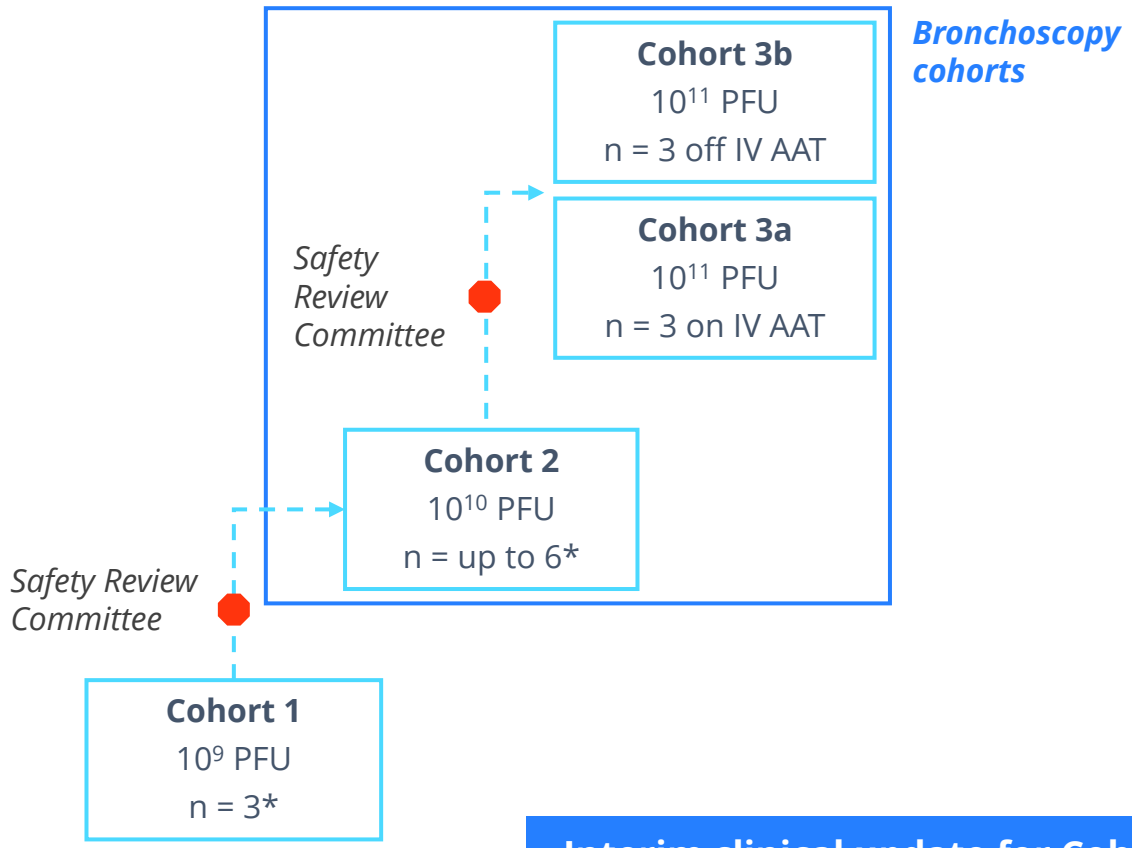
Open-label, single dose escalation study in adult patients with AATD with a PI*ZZ genotype

Study Objectives

- Evaluate safety and tolerability, including
  - Frequency and severity of adverse events
  - Changes in vital signs, spirometry, ECGs, and clinical labs
- Measure AAT and neutrophil elastase concentration in serum, sputum, and bronchoalveolar lavage fluid
- Evaluate transgene expression in lung tissue
- Exploratory evaluation of impact on inflammatory biomarkers, quality of life measures, and pharmacodynamic markers

Key Enrollment Criteria

- Key Inclusion Criteria
  - Age ≥18 to ≤70
  - PI*ZZ or Pi*ZNull genotype
  - Serum AAT < 11µM ***- Cohort 3b only***
- Key Exclusion Criteria
  - $ppFEV_1$ <50%
  - IV AAT within 6 weeks ***- Cohort 3b only***



* Cohort 1 and Cohort 2 patients may be on or off IV AAT

Interim clinical update for Cohorts 1 and 2 provided in 4Q 2024

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; ECG, electrocardiogram; $ppFEV_1$, percent predicted forced expiratory volume in 1 second; IV, intravenous; PFU, plaque forming unit

Scope of First SERPENTINE-1 Interim Readout and Patient Demographics

Safety data from seven patients across two dose levels, and initial molecular data from two Cohort 2 patients

Safety Assessments Only

Cohort 1
10^9 PFU
n = 3*

Cohort 2
No Bronchoscopy
10^{10} PFU
n = 2*

Cohort	Patient ID	*SERPINA1* Genotype	Age	Sex	Background Augmentation
1	01	Pi*ZZ	60	Female	No
	02	Pi*ZZ	66	Female	**Yes**
	03	Pi*ZZ	67	Female	No
2	04	Pi*ZZ	31	Male	No
	05	Pi*ZZ	56	Female	No

Safety and Molecular Assessments

Cohort 2
Bronchoscopy
10^{10} PFU
n = 2*

Cohort	Patient ID	*SERPINA1* Genotype	Age	Sex	Background Augmentation
2	06	Pi*ZZ	60	Male	**Yes**
	07	Pi*ZZ	58	Male	No

* Cohort 1 and Cohort 2 patients may be on or off IV AAT

Safety follow up still ongoing; at least two weeks follow up completed for both patients as of data cutoff

Baseline bronchoscopy conducted at least 14 days prior to dosing, post KB408 bronchoscopy conducted 24-48 hours after dosing

Data cutoff date of December 6, 2024

AAT, alpha-1 antitrypsin; IV, intravenous; PFU, plaque forming unit

KB408 Safely Delivers *SERPINA1* Cargo to the Lung

Clear evidence of transduction and AAT expression in KB408 treated lungs

Well tolerated in all patients to date

- ✓ No serious adverse events or dose-limiting toxicities observed
- ✓ All KB408-related adverse events reported have been mild-to-moderate and transient
- ✓ No evidence of significant neutralizing antibody response following KB408 administration
- ✓ No systemic vector distribution after inhalation, based on blood and urine analysis

* On background augmentation; **Based on quantification of DAPI positive and DAPI + AAT co-positive cells lining the conducting airways of the lung by immunofluorescence; 3-4 biopsies assessed for post-dose DAPI + AAT co-positive cell quantification, total cell counts > 300 per patient

AAT, alpha-1 antitrypsin; DAPI, 4',6-diamidino-2-phenylindole; SERPINA1, serpin family A member 1

Over a third of airway cells in both patients were positive for AAT after a single KB408 dose

Patient 06*

3% AAT Positive Cells At Baseline

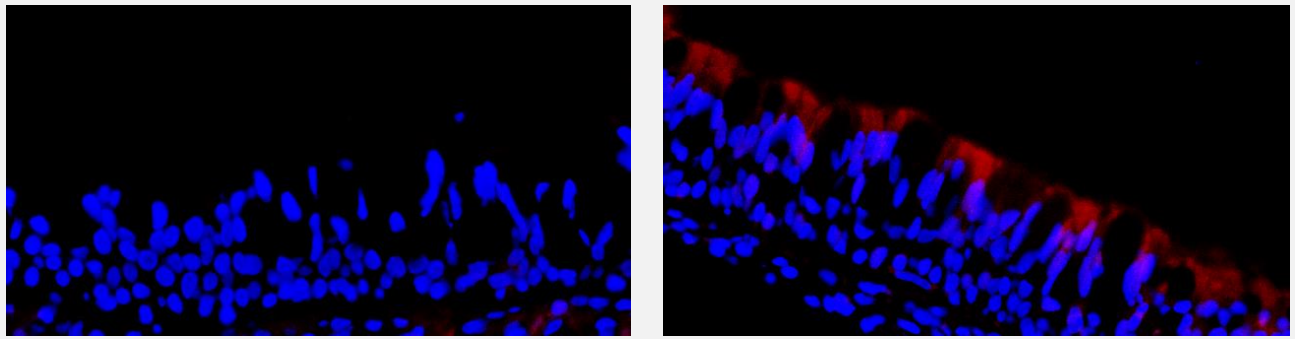
35%
AAT Positive Cells After KB408**

Patient 07

0% AAT Positive Cells At Baseline

39%
AAT Positive Cells After KB408**

Representative Patient 07 Images



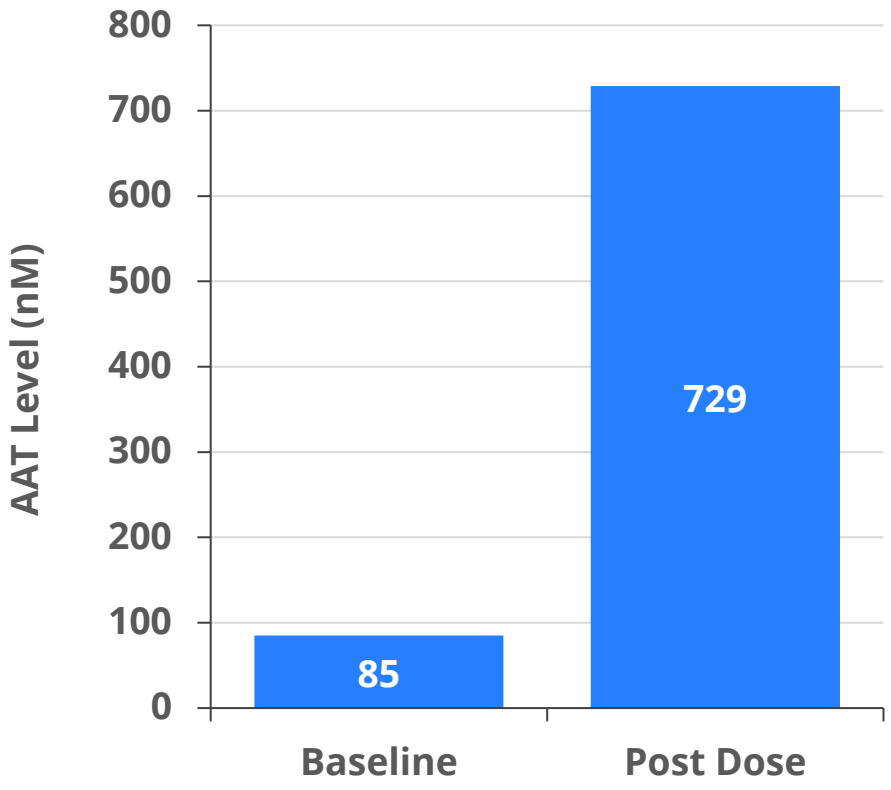
Baseline **After KB408**

All imaging conducted at 40× magnification
Post-dose biopsies harvested 24-48 hours after nebulization

Secreted AAT Reached Clinically Meaningful Levels after Single Dose

Data from Patient 07; increase in AAT to high nanomolar range supports further exploration of mid dose

Free AAT Levels in Lung ELF[1]



Over 8-fold increase in ELF AAT with one dose

Achieved target range of 5-10% of systemic levels

% Free Neutrophil Elastase in ELF

97.2%

At Baseline

Over 50% reduction in % unbound NE within 48 hours of first dose

40.2%

After Single KB408 Dose

Based on positive data Krystal expanded enrollment in Cohort 2 and opened Cohort 3 to explore higher end of dose range, data expected 2H 2025

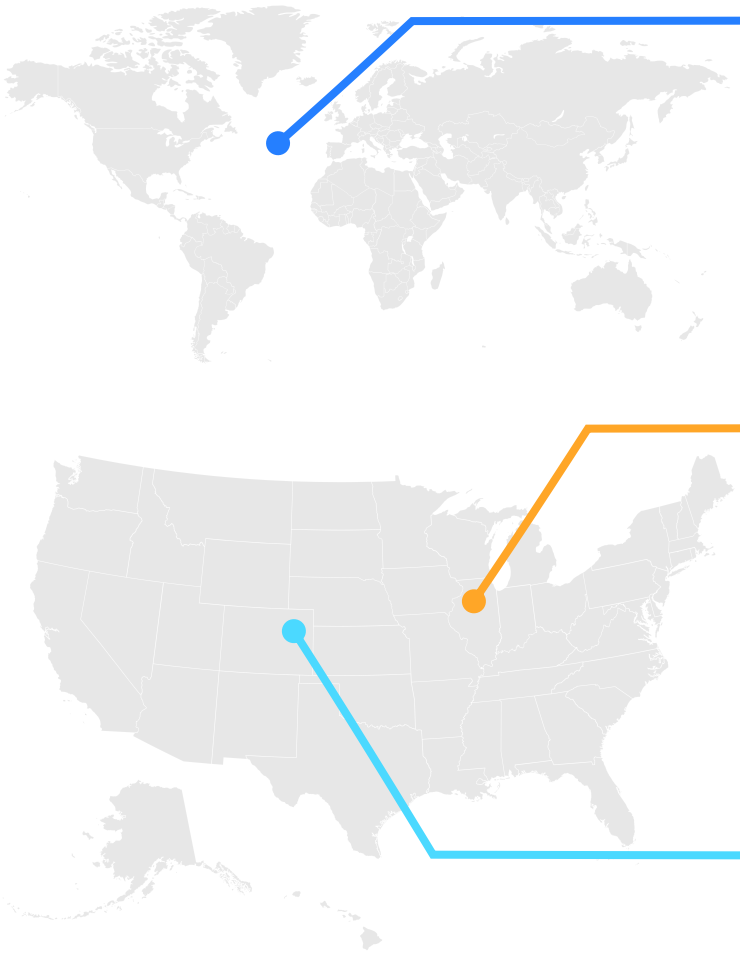
1. Average values from 2 lobes (pre-dose samples). Only 1 post-dose sample was evaluable due to low return from second lobe (<10%)

AAT, alpha-1 antitrypsin; ELF, epithelial lining fluid; NE, neutrophil elastase

Cystic Fibrosis Disease Overview

A life-span shortening progressive disease of the lung

CF Prevalence & Incidence[1,2]



105,000

CF Patients in 94 Countries

32,000+

CF Patients in U.S. Registry

+1,000

New Cases Annually in U.S.

- Cystic fibrosis (CF) is a life-threatening inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), leading to reduced and/or loss of CFTR function[3,4,5]
- Progressive lung disease is the primary cause of morbidity and mortality with loss of CFTR-mediated ion transport leading to[6]
  - Airway mucus obstruction
  - Recurrent bacterial infection
  - Inflammation
- According to the U.S. Cystic Fibrosis Foundation, the median age at death for patients with CF in the United States was 36.6 years in 2022[7]
- CFTR modulators, first approved in 2012 and now used in combination, are emerging as standard of care for eligible patients[8]
- **Limitations of CFTR Modulators:** Not effective for all CFTR mutation types, heterogeneous patient response, GI / liver tolerability, frequent dosing[8]

1. U.S. Cystic Fibrosis Foundation – About Cystic Fibrosis, accessible at: About Cystic Fibrosis | Cystic Fibrosis Foundation (cff.org); 2. U.S. Cystic Fibrosis Foundation – 2022 CFF Patient Registry Highlights; 3. O'Sullivan BP, et al. *Lancet* 2009;373:1891-904; 4. Elborn JS, et al. *Lancet* 2016; 388:2519-31; 5. Sanders DB, et al. *Pediatr Clin North Am.* 2016;63:567-84; 6. Stoltz DA, et al. *N Engl J Med*. 2015, 372 (4): 351-362; 7. Cystic Fibrosis Foundation (2022) Patient Registry Annual Data Report; 8. Hapnadak SG, et al. *J Cyst Fibros.* 2020;19(3):344-354

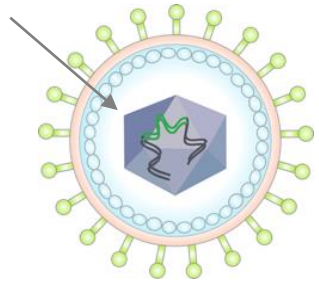
GI, gastrointestinal; U.S., United States

KB407 Designed To Address Major Unmet Needs in CF

Multiple opportunities for KB407 to improve CF patient outcomes as mutation agnostic, redosable gene therapy

KB407

CFTR gene



Replication-incompetent HSV-1 vector containing functional human *CFTR*

Target Segments for KB407	Estimated Patients
1 **Patients ineligible for CFTR modulator therapy including CFTR null patients** 10%+ of all CF patients[1]	**10K**
2 **Patients either weakly or non-responsive to TRIKAFTA®, ppFEV$_1$ increase < 5%** 15-25% of patients otherwise eligible for TRIKAFTA[2]	**19K**
3 **Alternate regimen for patients that poorly tolerate TRIKAFTA** 5% of patients otherwise eligible for TRIKAFTA[2]	**5K**
+ **Upside: Combination therapy or direct competition with TRIKAFTA if demonstrating superior dosing, efficacy, and/or safety**	**All 105K**

1. Krystal estimates based on CFF Patient Registry 2019, ECFS Patient Registry 2018; 2. Krystal estimates based on Middleton PG, et al. *N Engl J Med*. 2009;381:1809-1819; Heijerman HG, et al. *Lancet* 2019;394:1940-1948; Trikafta® FDA Label, Revised 10/2021

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; HSV-1, herpes simplex virus type 1; ppFEV$_1$, percent predicted forced expiratory volume in 1 second

Robust Preclinical Data Package Supports Clinical Evaluation of KB407

Studies across multiple models have shown KB407 is amenable to lung delivery, well tolerated, and encodes functional CFTR

All Key Preclinical Criteria for KB407 Have Been Met

1. **Cellular Tropism:** KB407 efficiently transduces human primary airway epithelial cells leading to dose dependent *CFTR* expression
2. **Full-Length Payload:** CFTR protein expressed in KB407 transduced cells is full-length, properly localized, and glycosylated
3. **Functionality:** Encoded CFTR has shown functionality in both *in vitro* CF patient model and *in vivo* rodent model
4. **Tolerability:** KB407 well tolerated in multiple preclinical studies including in GLP IND-enabling repeat dose toxicology study in NHPs ***– adverse level was not reached and NOAEL was top dose***
5. **Broad and Sustained *In Vivo* Expression:** KB407 was broadly disseminated in NHP lungs after delivery via inhalation and *CFTR* detected out to at least 28 days after last dose

KB407 Phase 1 CORAL-1 Protocol Now Fully Sanctioned by CFF TDN

CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator; GLP, good laboratory practices; IND, investigational new drug; NHP, non-human primate; NOAEL, no observed adverse effect level; TDN, Therapeutic Development Network

KB407 Phase 1 Study CORAL-1

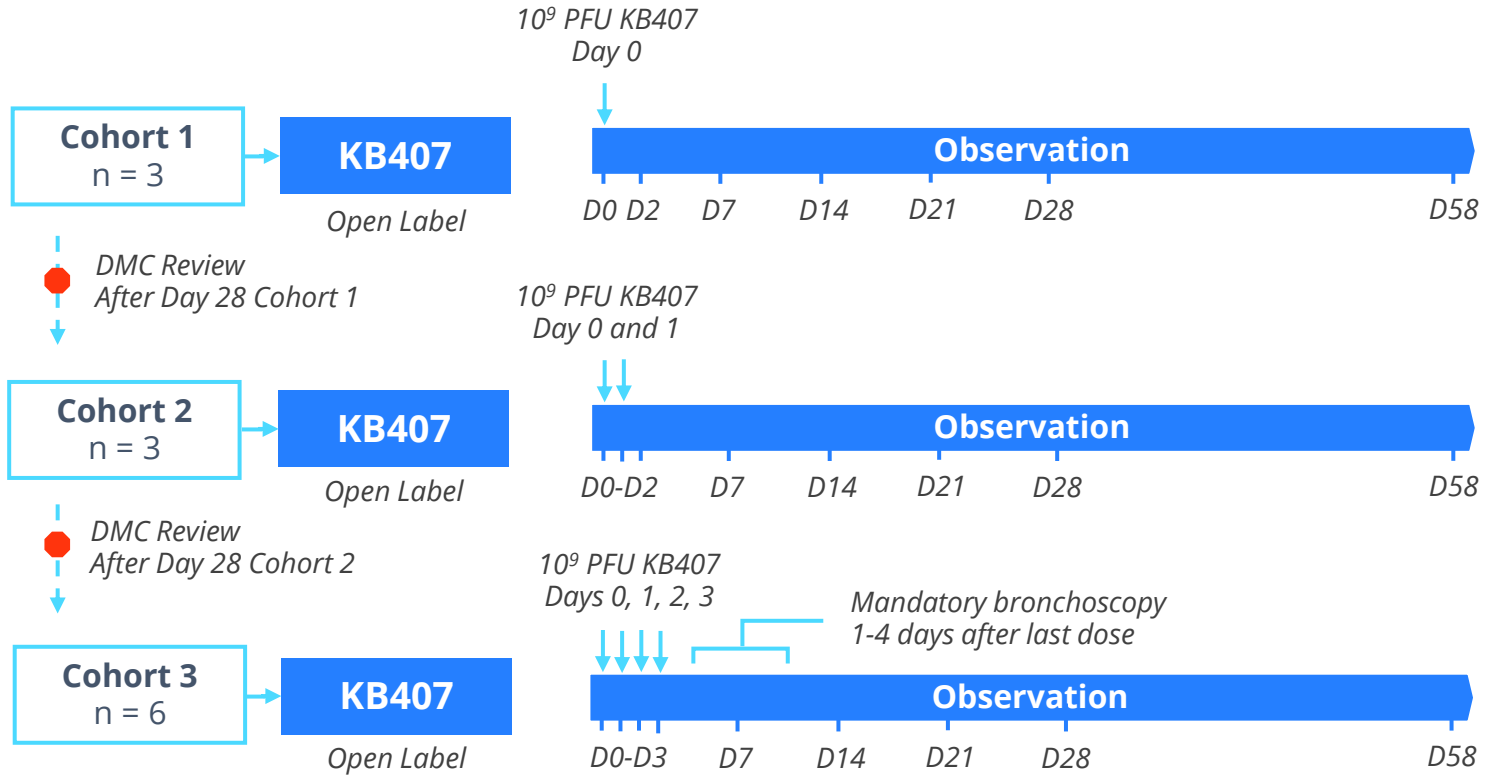
Ongoing study to assess safety and transduction efficiency of ascending doses of KB407 in adults with CF

Study Objectives

- Evaluate safety and tolerability of **ascending doses** of nebulized KB407, as well as preliminary efficacy evaluation
  - KB407 transduction and *CFTR* transgene expression in lung (bronchoscopy sub-study only)
  - Effects of KB407 on pulmonary function ($ppFEV_1$)
  - Effects of KB407 on lung-specific quality of life (CFQ-R respiratory domain)
- Vector shedding and biodistribution will also be assessed in blood, urine, buccal, and sputum samples

Key Enrollment Criteria

- Age ≥ 18 years with confirmed diagnosis of CF
- $ppFEV_1$ ≥50% and ≤100%
- Resting O_2 saturation ≥92% on room air
- **Cohort 1 and 2:** Participants may receive concurrent modulator therapy, bronchoscopy optional
- **Cohort 3:** No more than 3 out of 6 participants may be on concurrent modulator therapy, bronchoscopy mandatory



Interim clinical safety update for Cohorts 1 and 2 provided in 4Q 2024

CF, cystic fibrosis, CFTR, cystic fibrosis transmembrane conductance regulator; DMC, data monitoring committee; PFU, plaque forming unit; $ppFEV_1$, percent predicted forced expiratory volume in 1 second

Scope of CORAL-1 Interim Safety Data Update and Patient Demographics

Safety data available from five patients dosed once or twice with KB407*

Safety Assessments Only

Cohort 1
Single 10^9 PFU Dose
n = 3

Cohort 2
Two 10^9 PFU Doses
n = 3*

KB407 10^9 PFU
Day 0 Only or
Day 0 and Day 1

Cohort	Patient ID	*CFTR* Genotype	Age	Sex	Modulator Therapy
1	01-01	F508del/F508del	35	Male	**Yes**
	01-02	F508del/F508del	28	Female	**Yes**
	01-03	G551D/E60X	34	Female	**Yes**
2	02-01*	F508del/F508del	36	Male	**Yes**
	02-02	F508del/F508del	27	Male	**Yes**
	02-03	F508del/F508del	29	Male	No

*One patient rolled over from Cohort 1 to Cohort 2

Data cutoff date of December 6, 2024

CFTR, cystic fibrosis transmembrane conductance regulator; PFU, plaque forming unit

KB407 Well Tolerated in All Patients Dosed To Date

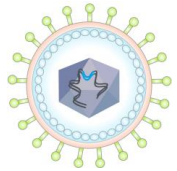
- ✓ No serious adverse events or dose-limiting toxicities observed
- ✓ All KB407-related adverse events reported have been mild-to-moderate and transient
- ✓ No evidence of significant neutralizing antibody response following KB407 administration
- ✓ No systemic vector distribution after inhalation, based on blood and urine analysis

Interim readout from Cohort 3 including bronchoscopy data expected mid 2025

Working Towards a Highly Differentiated Respiratory Franchise

Safe delivery of genetic cargo in Phase 1 is a key derisking event for the platform with read-through to broader pipeline

- **Well-tolerated by patient population with underlying lung disease**
- **Delivering full-length genes and demonstrated functionality of KB408-encoded AAT in patients with AATD**
- **Successfully delivered to the lung using commercially available nebulization technology *– off the shelf, non-invasive therapy***
- **Redosability provides opportunity to build on efficacy over time**
- **KB407 sanctioning by CFF TDN will accelerate enrollment and shorten time to bronchoscopies and KB407 molecular data**



Clinical data updates including molecular data expected for both of Krystal's rare respiratory disease programs in 2025

KB408

For AATD Lung Disease

KB407

For Cystic Fibrosis

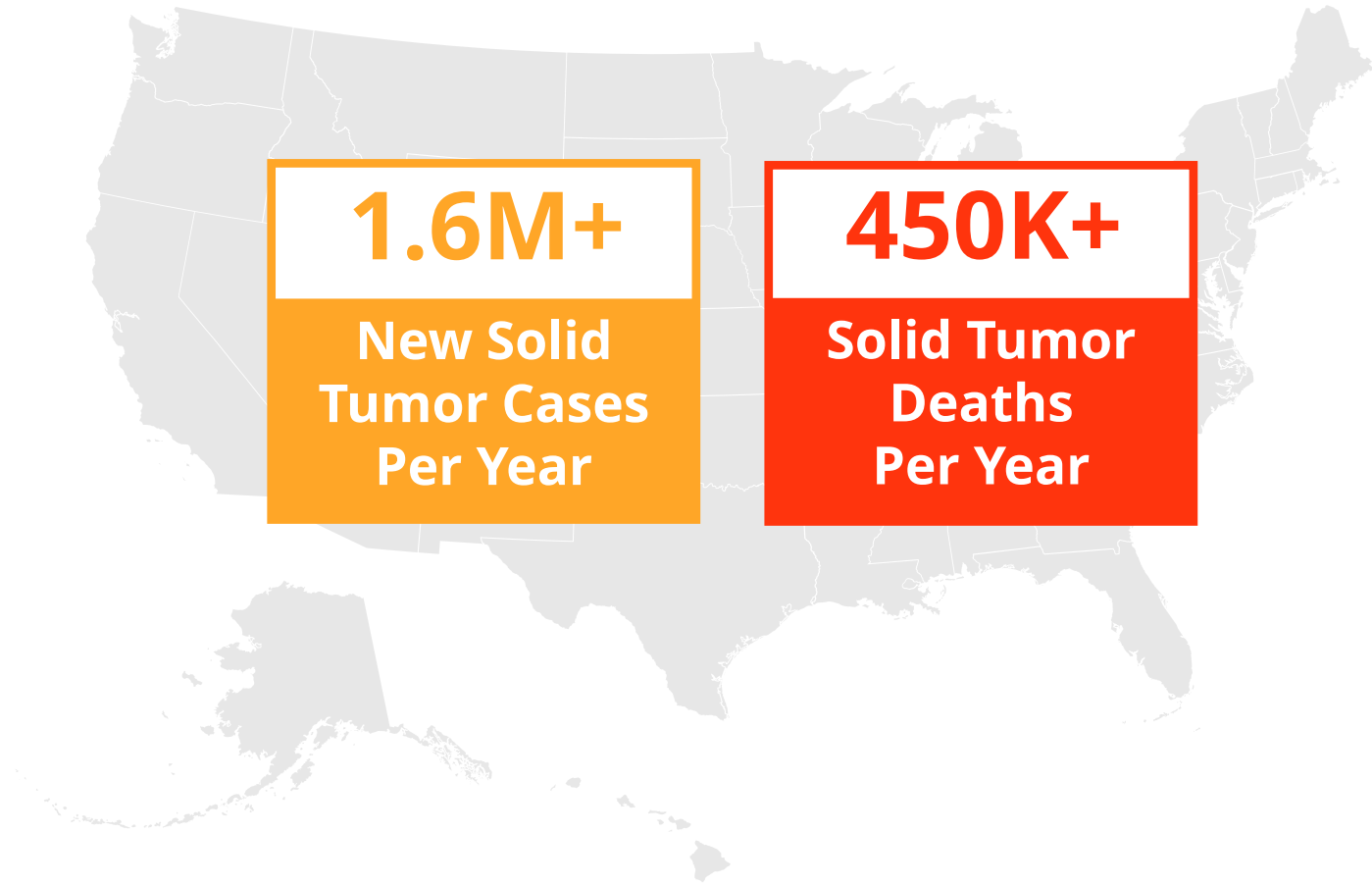
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CFF, Cystic Fibrosis Foundation; TDN, Therapeutic Development Network

Oncology Pipeline

Major Unmet Needs in Checkpoint Inhibitor (CPI) Refractory Solid Tumors

Solid Tumor Incidence and Mortality in U.S.

2023 SEER Estimates[1]



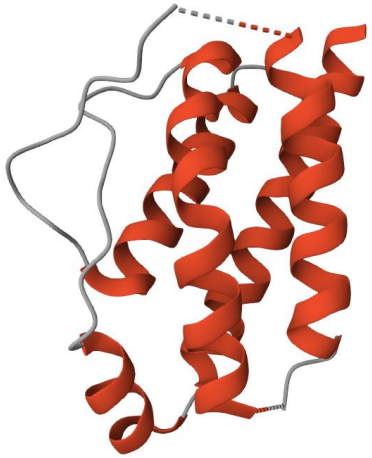
1. NCI SEER. 2023; https://seer.cancer.gov/statfacts/html/common.html [accessed July 20, 2023], combined estimates for incident cases and deaths from cancers of the anus, bladder, bone and joint, brain and nervous system, breast, cervix uteri, colon and rectum, esophagus, kidney and renal pelvis, larynx, liver and intrahepatic bile duct, lung and bronchus, melanoma, oral cavity and pharynx, ovary, pancreas, prostate, small intestine, stomach, testis, thyroid, uterus, and vulva

SEER; Surveillance, Epidemiology, and End Results Program; U.S., United States

HSV-1 Based Vector Coded for the Local Delivery of Both IL-2 and IL-12

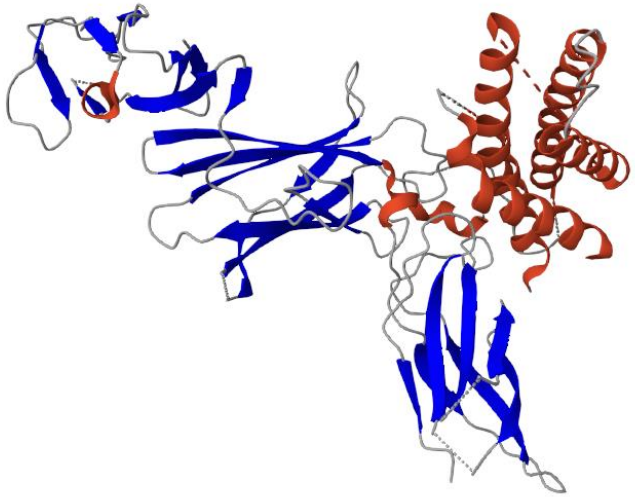
Cytokines with synergistic functions and therapeutic potential

IL-2



+

IL-12



Expand and Activate Lymphocyte Population[1-3]

Well-characterized NK and T cell activator with known roles inducing T cell proliferation and promoting NK and T cell cytotoxic functions

Reinforce Cytotoxic Effector Functions[4,5]

Complementary cytokine known to promote lymphocyte effector functions and IFN-gamma secretion

1. IL-2 image from the RCSB PDB (RCSB.org) of PDB ID 1M47 [image generated July 20 2023]; 2. Jiang T, et al. *OncoImmnuology*. 2016; 5(6):e1163462; 3. Morgan DA, et al. *Science*. 1976; 193(4257):1007-1008; 4. IL-12 image from the RCSB PDB (RCSB.org) of PDB ID 1F45 [image generated July 20 2023]; 5. Lasek W, et al. *Cancer Immunol Immunother*. 2014; 63:419-35

IL-12, interleukin-12; IL-2, interleukin-2; NK, natural killer

Advantages of Replication-Defective HSV-1 Based Cytokine Delivery

Platform well suited to accomplish dual goals of targeted but sustained delivery of IL-2 and IL-12 to the tumor

Optimal vector platform to maximize cytokine expression and immune activation

- ✓ Efficiently transduces a wide variety of cell types maximizing reach within tumor
- ✓ DNA payload persists in transduced cells extending the window of cytokine expression
- ✓ Lack of replication avoids premature lytic cell death or host cell shutdown
- ✓ Redosability to further boost local cytokine expression
- ✓ Safety profile suitable for both **inhaled** or **intratumoral** administration

Krystal Biotech, Data on File.

DNA, deoxyribonucleic acid; HSV-1, herpes simplex virus type 1; IL-12, interleukin-12; IL-2, interleukin-2

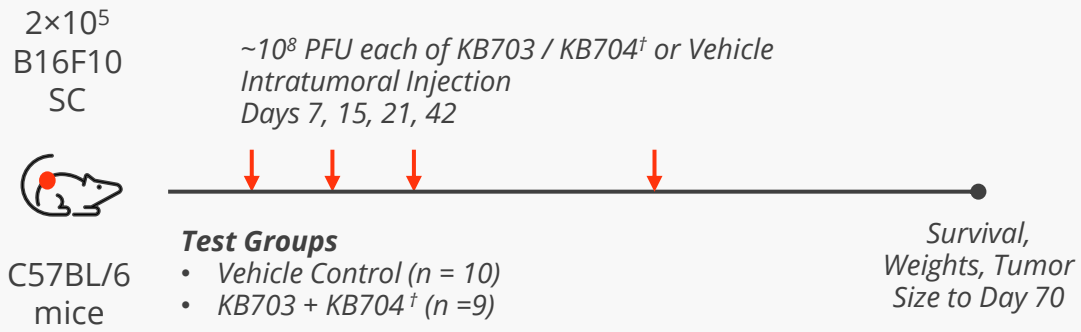
Intratumoral IL-12 and IL-2 Effective in Cold Syngeneic Mouse Tumor Model

Clear antitumor effect and survival benefit in checkpoint inhibitor refractory B16F10 tumor model

Single Flank B16F10 Melanoma Model

- B16F10 is a subclone of the B16 cancer cell line originally derived from the skin of a C57BL/6 mouse with melanoma
- B16F10 tumors are highly aggressive and minimally responsive to immunotherapy, including refractory to PD-1 targeting CPI
- Among the most stringent melanoma cell lines for the evaluation of candidate immunotherapeutics

Study Design

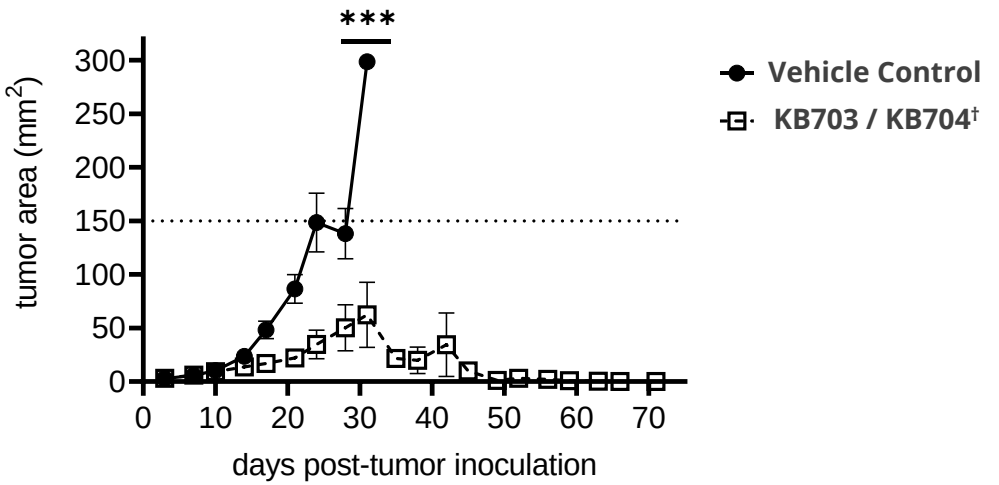


Krystal Biotech, Data on File.

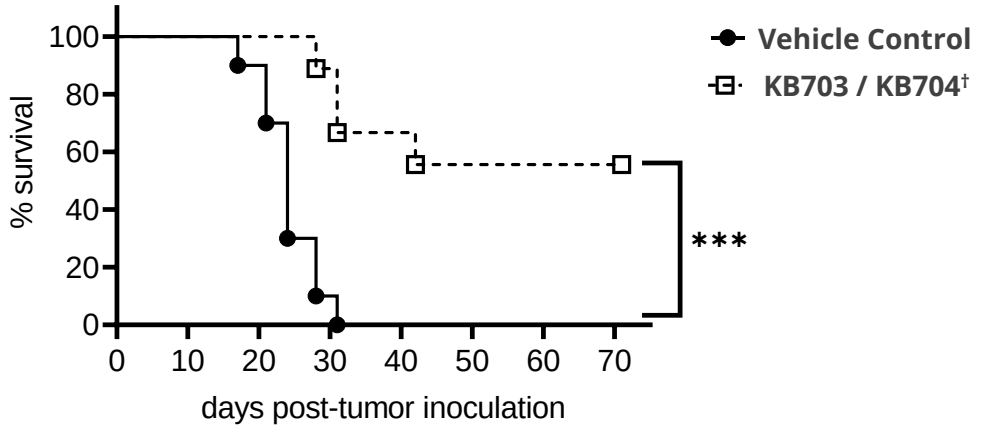
† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

CPI, checkpoint inhibitor; IL-12, interleukin-12 ;IL-2, interleukin-2; PD-1, programmed cell death protein; PFU, plaque forming unit; SC, subcutaneous

Injected Tumor Size



Survival



***p<0.001

Evidence of Systemic Immune Response with Intratumoral IL-12 and IL-2

Antitumor effect and survival benefit in dual flank B16F10 tumor model

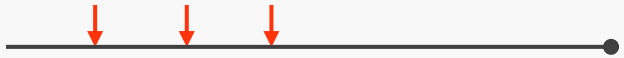
Dual Flank B16F10 Melanoma Model

- Dual flank model mimics metastatic, checkpoint refractory melanoma seen in late line clinical treatment setting
- Only tumor in first flank is injected to evaluate impact of systemic response on secondary tumor outgrowth

Study Design

Day 0
2×10^5 B16F10
First Flank SC

~10^8 PFU each of KB703 / KB704† or Vehicle
Intratumoral Injection First Flank Only
Days 7, 15, 21



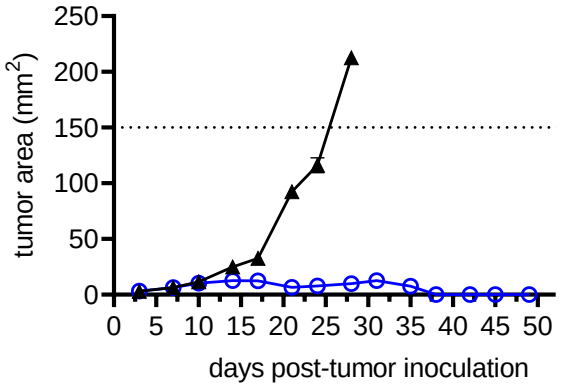
Survival, Weights, Tumor Size to Day 49

Day 4
1×10^5 B16F10
Second Flank SC

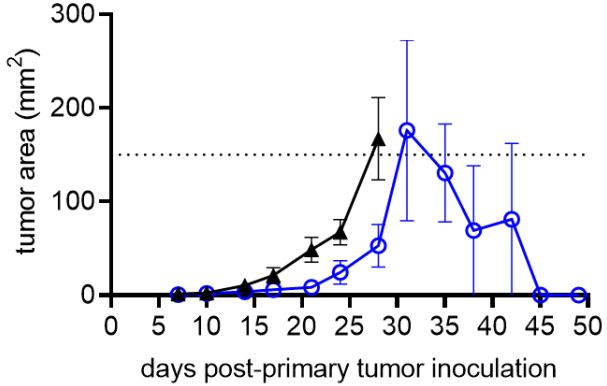
C57BL/6 Mice

Test Groups
- *Vehicle Control (n = 5)*
- *KB703 + KB704† (n =5)*

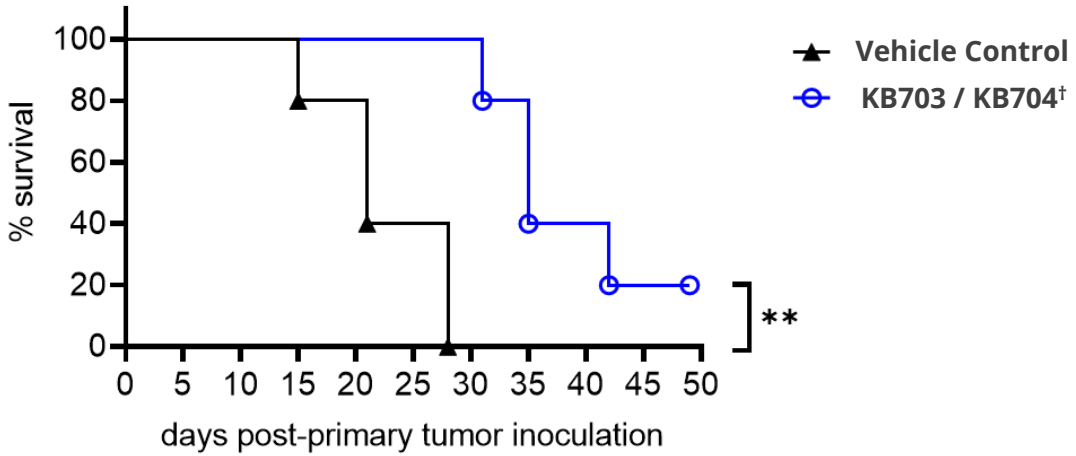
Injected Tumor Size



Secondary Tumor Size



Survival



Krystal Biotech, Data on File.

† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

IL-12, interleukin-12; IL-2, interleukin-2; PFU, plaque forming unit; SC, subcutaneous

**p<0.01

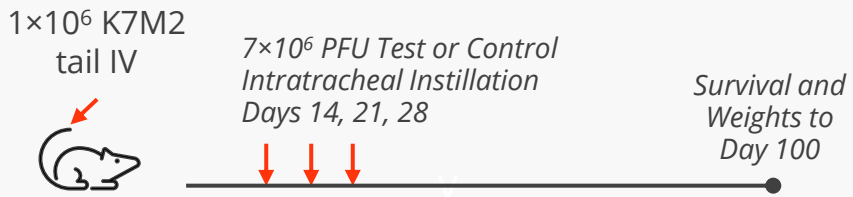
Lung Delivery Effective in Metastatic Osteosarcoma Model

Local delivery of IL-12 and IL-2 confers clear survival benefit in otherwise lethal, metastatic osteosarcoma

Metastatic K7M2 Osteosarcoma Model

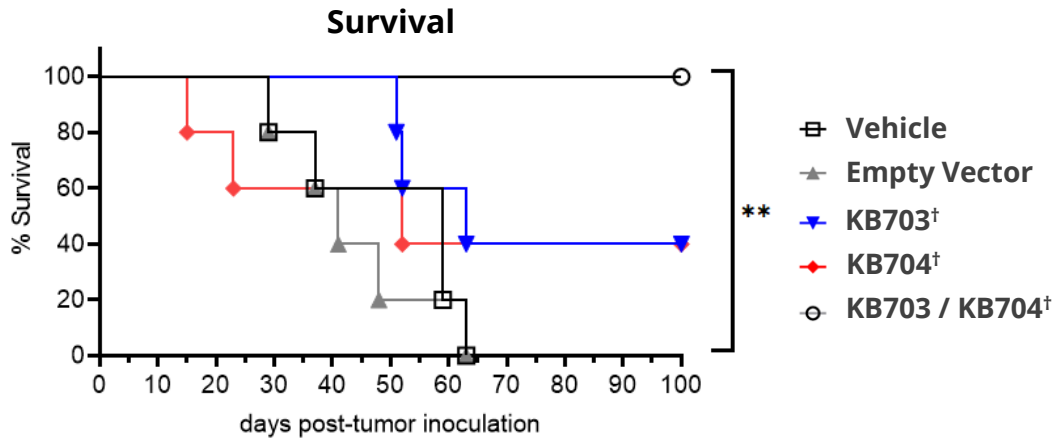
- K7M2 is an osteoblast cell line derived from bone of mouse with spontaneous osteosarcoma[1]
- Considered highly aggressive with pulmonary metastatic rate of over 90% in mice[1]
- Previously shown to be non-responsive to PD-1/PD-L1 targeting therapies, partial benefit from combo therapies[2]

Study Design

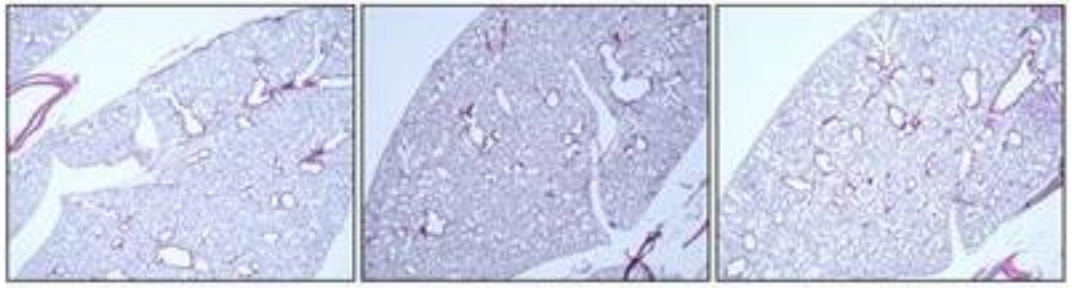


Test Groups

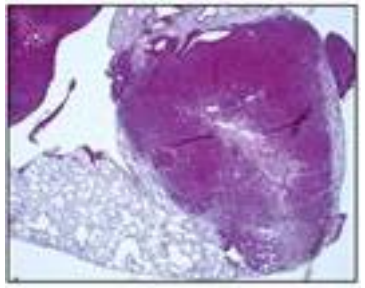
- *KB703 Alone† (n = 5)*
- *KB704 Alone† (n = 5)*
- *KB703 + KB704† (n = 5)*
- *Vehicle Control (n = 5)*
- *Naïve Control (n = 5)*



Lung H&E, Day 100



KB703 / KB704†
Representative images
from n = 3 of 5 survivors



KB703 Alone†
Representative image
from n = 1 of 2 survivors

1. Khanna C, et al., *Clin Exp Metastasis*. 2000;18(3):261-271; 2. Lussier DM et al. *J Immunother Cancer* 2015;3(21);

Krystal Biotech, Data on File.

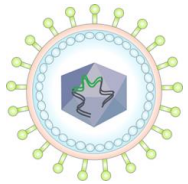
† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

H&E, hematoxylin and eosin; IL-12, interleukin-12; IL-2, interleukin-2; IV, intravenous; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFU, plaque forming unit

**p<0.01

Both Intratumoral and Inhaled KB707 Under Evaluation in the Clinic

Both formulations have also received Fast Track and Rare Pediatric Disease Designations from FDA



KB707

Replication-incompetent HSV-1 vector encoding functional human IL-12 and IL-2

Inhaled ***Intratumoral***

KYANITE-1

- Open-label, multicenter, dose escalation and expansion study evaluating inhaled KB707, as monotherapy or in combination, for treatment of **solid tumors of the lung**
- Broad initial enrollment criteria including patients with primary lung cancers (*e.g.* NSCLC) or lung metastases, heavily pre-treated
- KB707 administered via inhalation weekly for first three weeks, then once every three weeks
- Doses of 10^8 PFU and 10^9 PFU inhaled KB707 were evaluated in dose escalation and 10^9 PFU selected for dose expansion
- Trial objectives include evaluation of safety, tolerability, and tumor response measured using RECIST v1.1 criteria

OPAL-1

- Open-label, multicenter, dose escalation and expansion study evaluating intratumoral KB707, as monotherapy or in combination, for treatment of **injectable solid tumors**
- Patient population also heavily pre-treated, more varied tumor types including various cutaneous cancers
- KB707 administered via direct intratumoral injection to accessible tumors, weekly for first three weeks, then once every three weeks
- Doses of 2 x 10^8 PFU, 2x $10^{8.5}$ PFU and 2 x 10^9 PFU were evaluated in dose escalation and top dose 2 x 10^9 PFU selected for dose expansion
- Trial objectives include safety and efficacy assessments per RECIST v1.1

Reported interim clinical update on monotherapy dose escalation and expansion cohorts in 4Q 2024

NSCLC, non-small cell lung cancer; PFU, plaque forming unit; RECIST, response evaluation criteria in solid tumors

Inhaled KB707 Monotherapy Interim Clinical Update

Promising early evidence of monotherapy activity that was most pronounced in patients with advanced NSCLC

Safe and generally well tolerated across diverse, heavily pre-treated patient population (n = 37)

- Treatment-emergent adverse events have been predictable and manageable in outpatient setting
- Adverse events consistent with underlying disease and known profiles of IL-2 and IL-12
- Majority of treatment-related adverse events have been mild to moderate in severity and transient
- No Grade 4 or 5 adverse events observed

Monotherapy responses detected in patients with advanced NSCLC (n = 11)*

27%
Objective Response Rate

73%
Disease Control Rate

- Three partial responses achieved, two still ongoing as of data cutoff
- Duration of treatment for patients included in the analysis ranged from 10.3 to 33.3 weeks
- Seven patients remained on therapy as of data cutoff
- All patients included in analysis had received at least one prior line of immunotherapy, median four lines prior therapy

Data cutoff date of December 6, 2024

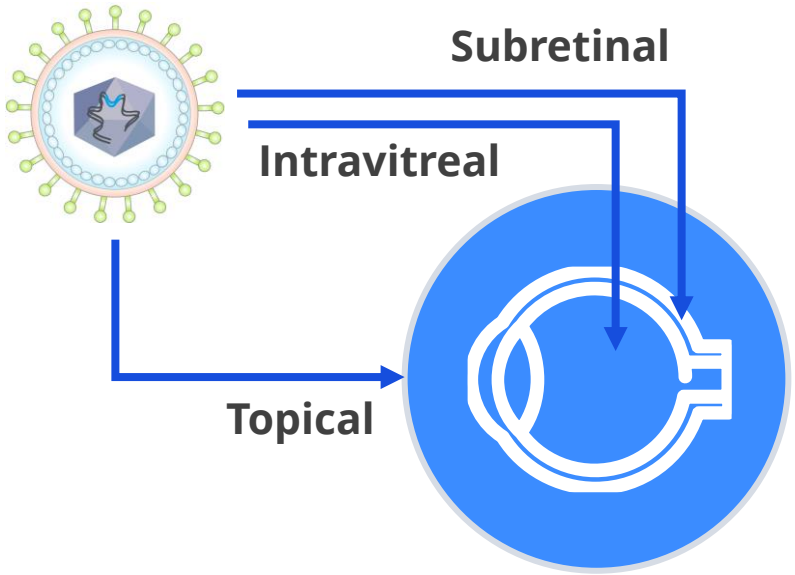
NSCLC, non-small cell lung cancer

* Efficacy analysis conducted in all evaluable NSCLC patients with at least one radiographic scan and RECIST v1.1 evaluation as of data cutoff

Ophthalmology Pipeline

Potential for Pipeline Expansion in Ophthalmology

Pursuing opportunities to leverage unique attributes of HSV-1 platform including large cargo capacity



Current Gene Therapy Pipeline Dominated by Single Vector

- AAVs have had success delivering small genes to back of the eye but many challenges remain
- Small cargo capacity is biggest limitation of AAVs; unable to address many large gene inherited retinal disorders (IRDs) and limits potential to deliver more complex gene editing machinery or regulatory elements
- Clinical applications of AAV have also been primarily focused on the retina; new vectors needed to target all clinically relevant cells of the eye
- Immunotoxicity a persistent concern with AAVs

HSV-1 is a Highly Differentiated, Large Cargo Alternative

- HSV-1 exhibits natural tropism for epithelial and neuronal cells of the eye
- Cargo capacity to address the most common large gene IRDs
- Currently exploring both front and back of the eye delivery, repeat dosing
- Topical, repeat application to the front of eye both safe and effective in clinic under compassionate use

Near-term opportunity to expand utility for ophthalmic B-VEC in DEB followed by potential pipeline expansion to target unmet needs in front and back of eye

Ghobara HH, et al. *Clin Ophthalmol.* 2022;16:1753–1771; Vetencourt AT, et al. *N Engl J Med*. 2024;390:530-535

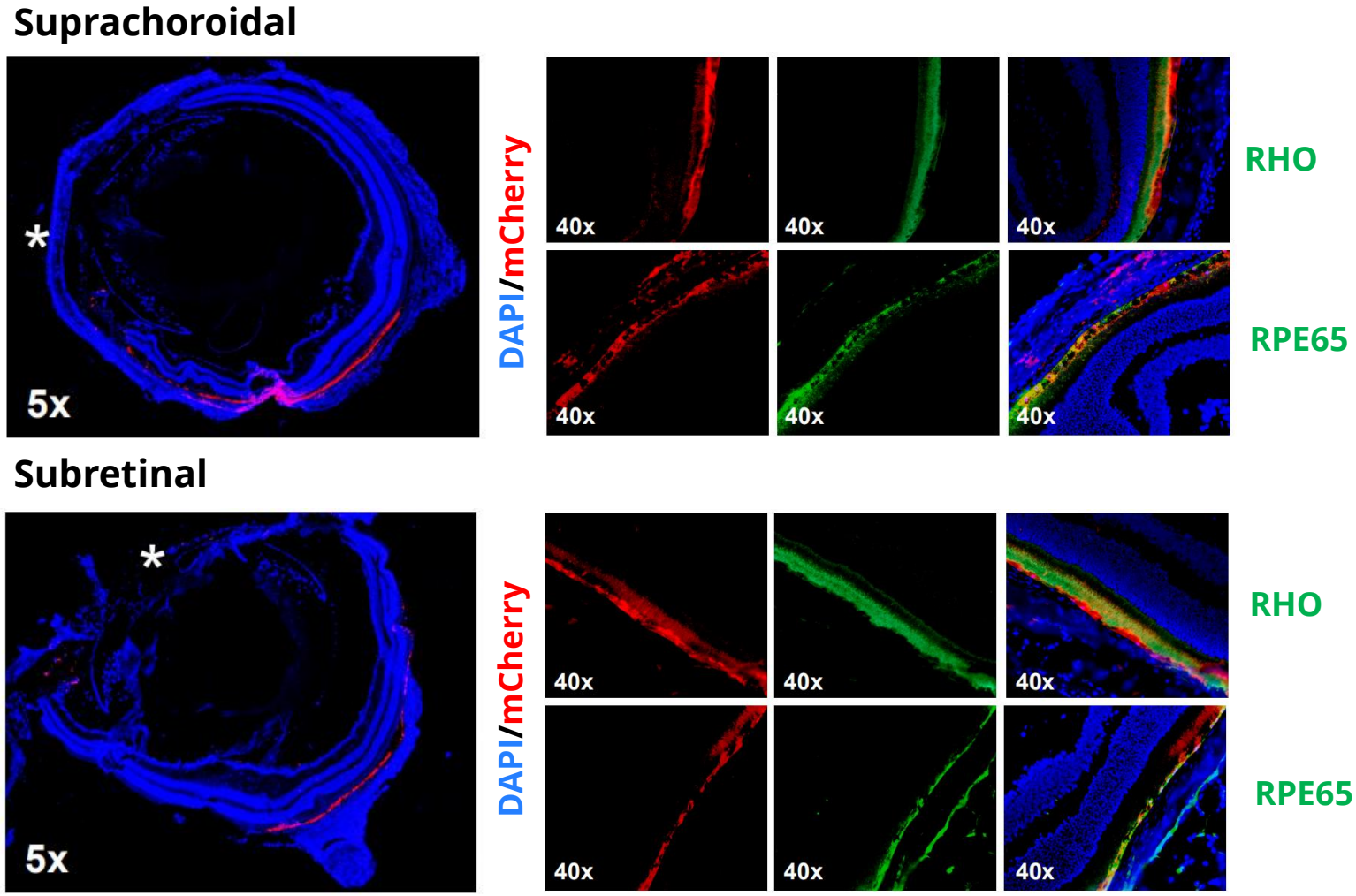
AAV, adeno-associated virus; B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1

Back of the Eye Gene Delivery Using Krystal's HSV-1 Platform

Broad expression of reporter payload across retina following subretinal or suprachoroidal administration

Pilot Eye Injection Study

- Single injection study in mice, data for suprachoroidal and subretinal routes shown
- Mice received single injection of Krystal mCherry reporter virus and eyes collected at 24 hours for immunofluorescence
- Minimal inflammation observed following injection via any route
- No mCherry signal in control treated eyes
- Previously reported reporter virus colocalization with RPE65+ cells in rat subretinal injection study



Reporter virus signal colocalized to both RPE65+ and RHO+ cells

Cartwright HN et al., Poster # 3978 at the 2024 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting

* Denotes cornea

DAPI, 4',6-diamidino-2-phenylindole; HSV-1, herpes simplex virus type 1; RHO, rhodopsin; RPE65, retinal pigment epithelium-specific 65 kDa protein

Next Steps in Ophthalmology

Expedite clinical development of KB803 while building data to support pipeline expansion

Ophthalmic B-VEC Formulation KB803 for Ocular Complications of DEB

- On track to initiate registrational Phase 3 study in 1H 2025

Pipeline Expansion

- Evaluating multiple, preclinical-stage genetic medicine candidates for the treatment of diseases of the front and back of the eye

Sample Indication: Stargardt Disease[1-4]

- Inherited retinal disorder primarily caused by mutations in *ABCA4*
- Leads to progressive vision loss and blindness, no FDA approved therapy
- *ABCA4* is a large gene that does not fit in currently used AAV vectors

26K
Estimated Patients in U.S.*

37K
Estimated Patients in EU Major Markets**

1. Cicinelli MV, et al. *Clin Optom (Auckl).* 2019;11:151-165; 2. Runhart EH, et al. *Acta Ophthalmol.* 2022;100:395-402; 3. Bauwens M, et al. *Genet Med.* 2019;21:1761-1771; 4. Schulz H, et al. *Investig Ophthalmol Vis Sci.* 2017;58:394-403

*Assumed U.S. population of 330M, 1:10K prevalence, 80% *ABCA4;* ** Assumed EU population of 457M focused on major markets only (includes EU-4 + UK, Nordics, Benelux, Ireland, Portugal, Switzerland, Poland, Austria), 1:10K prevalence, 80% *ABCA4*

ABCA4, ATP-binding cassette, sub-family A, member 4; AAV, adeno-associated virus; B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; EU, European Union; FDA, U.S. Food and Drug Administration;

Dermatology Pipeline

KB105, Krystal's Next Clinical Stage Asset in Dermatology

Complementary product for rare disease of the skin significantly derisked by VYJUVEK clinical success

Lamellar Ichthyosis Associated with TGM1 Mutations (TGM1-LI)[1-8]

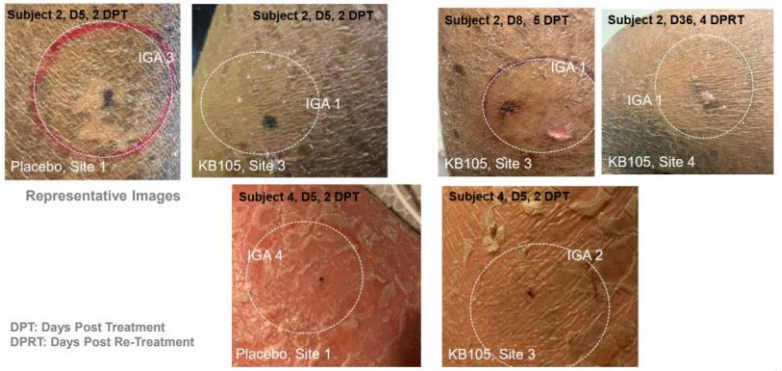
- LI is a form of autosomal recessive congenital ichthyosis (ARCI) and severe, life-long monogenic skin disease
- The most common cause of LI is an inactivating mutation in the *TGM1* gene encoding a protein that is essential for the proper formation of the skin barrier
- LI is characterized by thick, dry, scaly skin, increased trans-epidermal water loss, dehydration, sepsis, and skin malignancies
- There are **no** approved treatments for TGM1-LI
- Topical and systemic retinoids and time-consuming supportive treatments are the most commonly used treatments of care

2K-5K

Estimated TGM1-LI Patients in U.S. and Europe

KB105: Clinical Stage Asset in Phase 1/2[9,10]

- In Phase 1 study in TGM1-ARCI patients, KB105 treatment restored functional TGM1 protein expression and activity in all treated sites
- Phenotypic evaluation limited by small treatment areas, but KB105 treated areas showed reduced reversion to scaling phenotype
- No drug-related AEs noted and no HSV-1 or TGM1 antibodies



Next Step: Initiate Phase 2 cohort in 2026

1. Rodriguez-Pazos L, et al. *Actas Dermosifiliogr.* 2013;104(4):270–84; 2. Dreyfus I, et al. *Orphanet J Rare Dis.* 2014;9:1; 3. Hernandez-Martin A, et al. *J Am Acad Dermatol.* 2012;67(2):240–4; 4. Pigg M, et al. *Eur J Hum Genet.* 1998;6(6):589–96; 5. Pigg M, et al. *Acta Dermato-Venereologica.* 2016;96(7):932–37; 6. Foundation for Ichthyosis & Related Skin Types (FIRST); 7. National Organization for Rare Disorders (NORD); 8. Richard G. Autosomal Recessive Congenital Ichthyosis. In: Adam MP, et al. *GeneReviews® [Internet].* Updated 2017 May 18; 9. Milstone LM, et al. *Arch Dermatol.* 2012;148(9):1080-1; 10. Paller A, et al. Oral presentation at Society for Investigative Dermatology (SID) 2020 Annual Meeting. Virtual. May 13-16, 2020.

AE(s), adverse event(s); HSV-1, herpes simplex virus type 1; TGM1, transglutaminase 1; U.S., United States

Aesthetics Pipeline

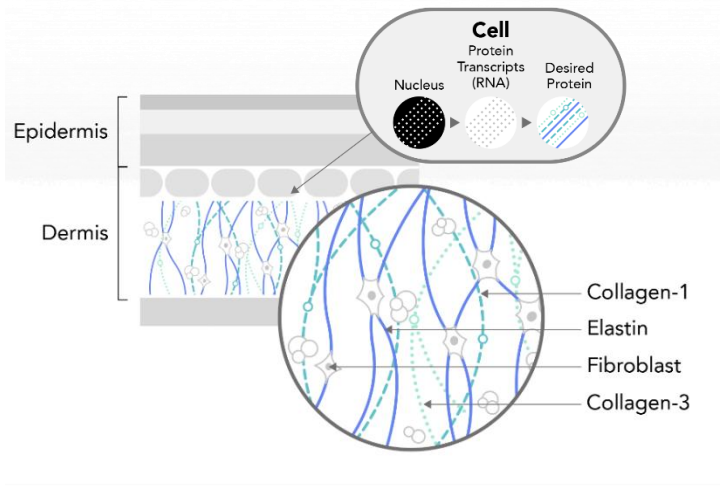
JEUNE

A wholly owned subsidiary of Krystal Biotech, Inc.

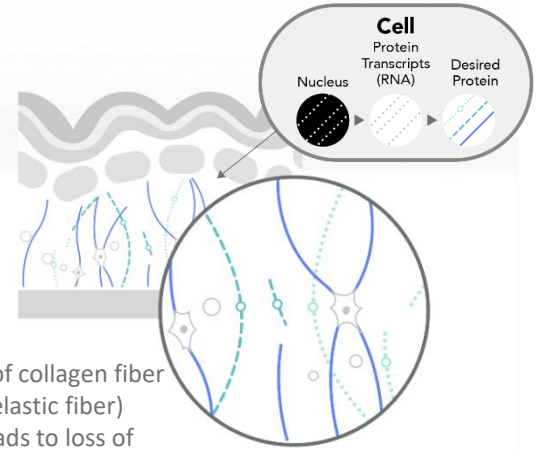
Characteristic Look of Aging Caused by Declining Levels of Key Proteins in Skin's Extracellular Matrix

- Skin aging is caused, in part, by a reduction of the skin's key proteins: collagen and elastin
- Impaired collagen and elastin synthesis leads to the degradation of the extracellular matrix, affecting overall skin quality and function
- The primary function of the extracellular matrix is to give skin its mechanical and biochemical properties

YOUNGER / HEALTHY

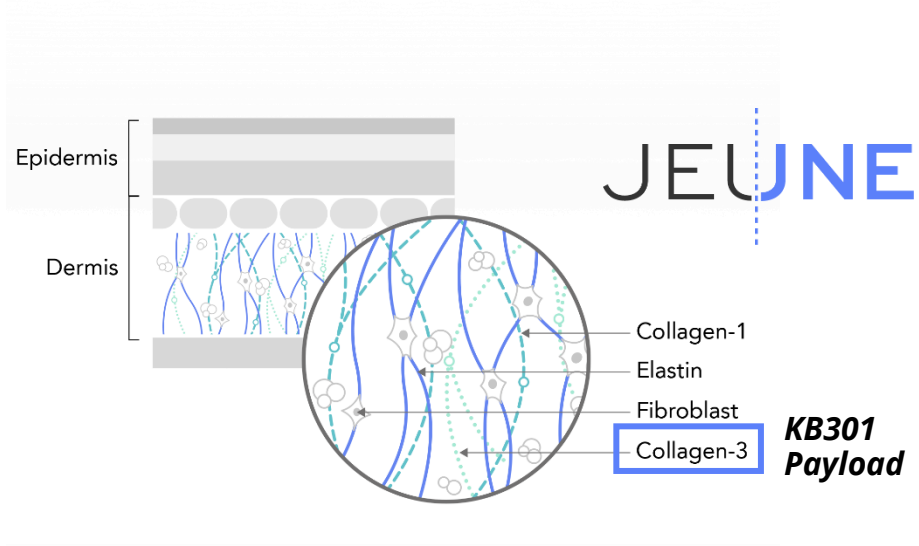


AGED / PHOTODAMAGED



Declining levels of collagen fiber and elastin (elastic fiber) production leads to loss of extracellular matrix integrity

Lead Program KB301 Designed to Increase Type III Collagen in Aging Skin



- Type III collagen (COL3) is the second most abundant protein in the skin but levels decline significantly with age
- COL3 has been implicated in both new collagen fibril formation as well as regulation of collagen fibril diameter, organization, and elasticity

Jeune's lead program KB301 is designed to increase COL3 expression from an individual's own skin cells, restoring youthful collagen levels and rejuvenating the skin

KB301 Phase 1 Program PEARL-1

- ✓ **Cohort 1:** Established single dose safety and confirmed *COL3A1* delivery by biopsy*
- ✓ **Cohort 2:** Repeat KB301 well tolerated in face and knee; clear evidence of aesthetic improvement and pharmacodynamic effect**
- ✓ **Cohort 2 Extension:** Subject reported aesthetic improvements durable for at least 9 months in long-term follow-up***
- ✓ **Cohort 3/4:** Positive safety and efficacy in two aesthetic priority injection areas enabled selection of décolleté indication for Phase 2ǂ

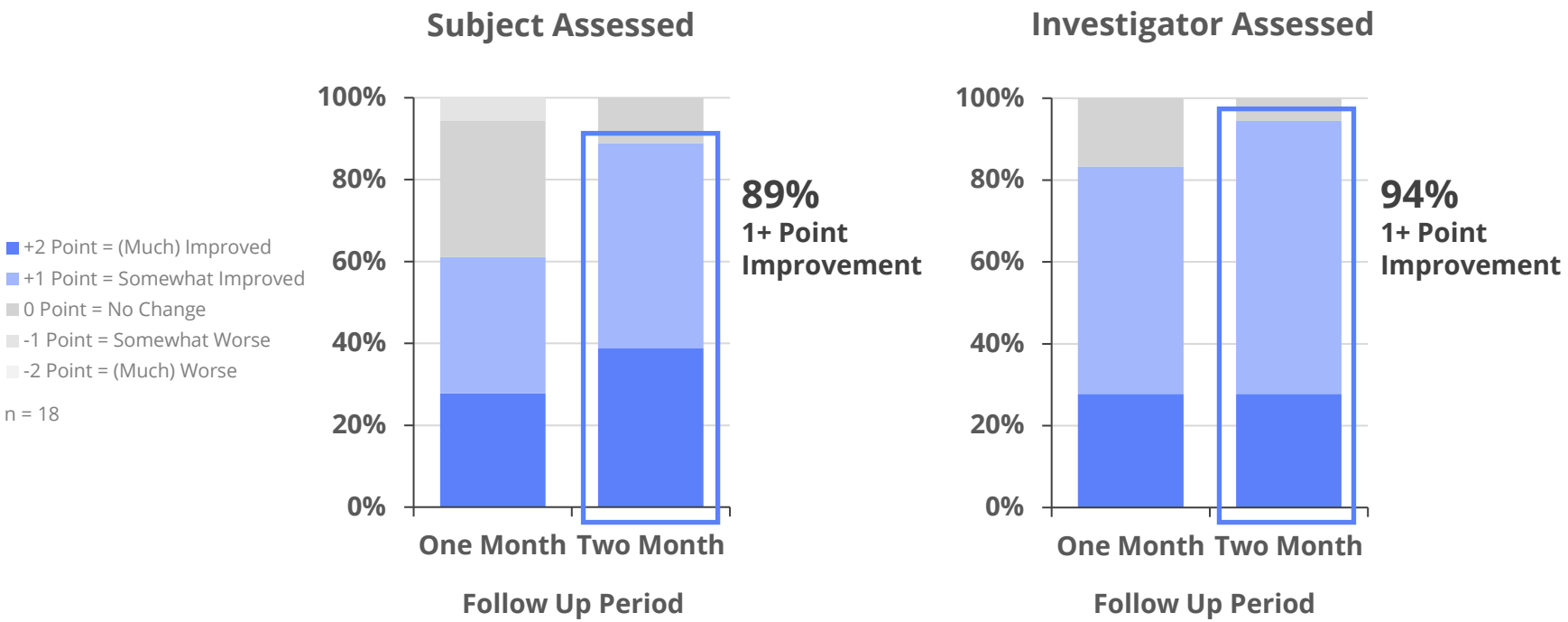
PK, pharmacokinetics

Fleischmajer R 1990 Ann N Y Acad Sci 580: 161-175; Fleischmajer R 1990 J Struct Biol 105: 162-169; Asgari M 2017 Sci Rep 7: 1392; Liu X 1997 Proc Natl Acad U S A 94: 1852-1856; Shuster S 1975 Br J Dermatol 93: 639; Wang P 2018 J Chin Med Assoc 81: 94-101; Yutsovskaya Y 2014 J Drugs Dermatol 13: 1047-1052; Xue M 2015 Adv Wound Care 4: 119-136; Hayakawa T 1979 Clin Chim Acta 93: 119-125

* Results presented at SID 2021 in May 2021
** Results presented March 2022
*** Results presented November 2022
ǂ Results presented August 2024

Dynamic Wrinkles of the Décolleté Selected as KB301 Phase 2 Indication Based on Compelling Phase 1 Efficacy Data

Décolleté Wrinkle Assessments by GAIS



94%

Subjects Reporting Improved Satisfaction with Décolleté Wrinkles*

Two Month Follow Up
n = 18

Improvements also reported for many additional skin attributes including crepiness, hydration, radiance

GAIS, Global Aesthetic Improvement Scale

Subjects received three weekly treatments; assessments one month and two months after completing treatment were included in the interim data readout presented August 2024

*Defined as subject satisfaction increase of one or more points

Phase 2 evaluating KB301 in décolleté to start 2025

Deep Pipeline Targeting Priority Skin Proteins Including Elastin

Jeune Aesthetics Pipeline

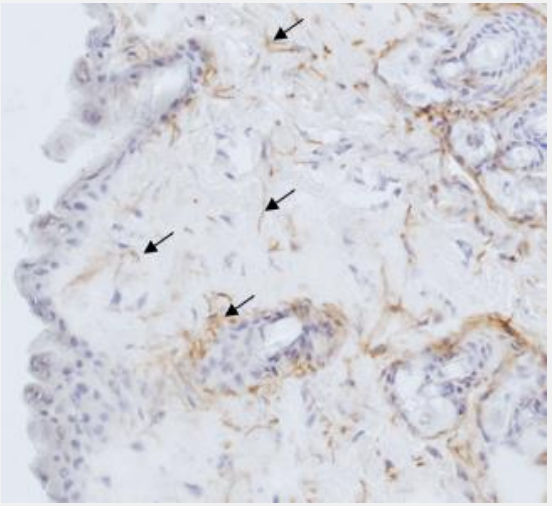
PROGRAM	INDICATION	PAYLOAD	PRE-CLINICAL	PHASE 1	PHASE 2
KB301	Dynamic Wrinkles of the Décolleté	Type III collagen (COL3)			
KB303	TBD	elastin (ELN)			
KB304	TBD	COL3 + ELN			
KB302	TBD	Type 1 collagen (COL1)			
KB305	TBD	Type IV collagen (COL4)			

JEUNE

Two Programs for Elastin Delivery: KB303 and KB304

- Designed to deliver elastin either alone or in combination with type III collagen
- Potential to target skin elasticity loss and supplement benefits from type III collagen delivery
- Expression and elastin fiber formation confirmed in both young and aged mice treated with KB303

KB303 Treated Mouse Skin



Human Elastin Immunohistochemistry

Arrows denote human elastic fibers

KB304 currently being evaluated in Phase 1 study with clinical data update expected later this year

Developing Genetic Medicines to Treat Diseases with High Unmet Medical Needs