Krystal

Developing Genetic Medicines for Rare Diseases

May 2023

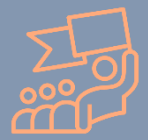
Forward Looking Statements

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. (the "Company"), including but not limited to statements about the Company's technology platform; development of the Company's product candidates, such as the future development or commercialization of beremagene geperpavec (B-VEC) and the Company's other product candidates; conduct and timelines of preclinical and clinical trials; the clinical utility of B-VEC and the Company's other product candidates; plans for and timing of regulatory filings, and efforts to bring B-VEC and the Company's other product candidates to market; the market opportunity for and the potential market acceptance of B-VEC and the Company's other product candidates; plans to pursue research and development of other product candidates; the sufficiency of the Company's existing cash resources; 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; uncertainties associated with regulatory review of clinical trials and applications for marketing approvals; the availability or commercial potential of product candidates; the ability to retain and hire key personnel; the sufficiency of cash resources and need for additional financing; 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 also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. Neither we nor any other person makes any representation as to the accuracy or completeness of such data or undertakes any obligation to update such data after the date of this presentation. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Krystal Biotech Overview

A fully-integrated biotechnology company focused on developing and commercializing genetic medicines for patients with rare diseases



Developing redosable gene therapies – powered by a proprietary HSV-1 vector technology

Initial focus on rare dermatologic diseases established clinical POC and a growing pipeline across Krystal and Jeune[1]

Expanding focus on larger indications, new tissue types and alternative routes of administration

Fully integrated, R&D and commercial-ready company, with in-house GMP manufacturing

Well funded with cash[2] of $355.5 million, providing runway through multiple clinical and commercial milestones

1. Jeune Aesthetics, Inc., a wholly owned subsidiary of Krystal Biotech; 2. Cash, cash equivalents and investments position as of 1Q 2023

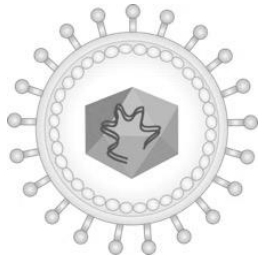
GMP, good manufacturing practice; HSV-1, herpes simplex virus type 1; POC, proof of concept

Technology Platform

HSV-1: A Differentiated Vector

Vector addresses challenges related to host genome integration, neutralizing immunogenicity, and payload capacity

Wild-type HSV-1



HSV-1 has natural affinity for broad cell types with favorable properties

Gene Delivery Platform Comparison

	HSV-1	LV	AAV	LNP
In vivo dosing	**Yes**	No	Yes	Yes
Potential baseline neutralizing immunity	**No**	No (if ex vivo)	Yes	No
Repeat-dose capabilities	**Yes**	Yes (if ex vivo)	No	Yes
Carrying capacity	**>30 kb**	9 kb[7]	<5 kb[7]	~12 kb[8]
Integrates payload into host cell DNA	**No**	Yes	Maybe[9]	No
Efficiency of delivering genetic cargo	**High**	High	Variable	Low
Regulatory precedent	**Yes**	Yes	Yes	Yes

- HSV-1 is a well characterized virus, highly prevalent in the human population, with some estimates suggesting at least 67% of the US population ≥ 12yrs have been exposed to HSV-1[1]
- HSV-1 efficiently infect cells; their genomes remain episomal without integrating into host DNA[2,3], thus avoiding risks of insertional mutagenesis
- Additional benefits of HSV-1 vectors include large payload capacities exceeding 30 kb and natural properties to resist immune clearance[4-6]

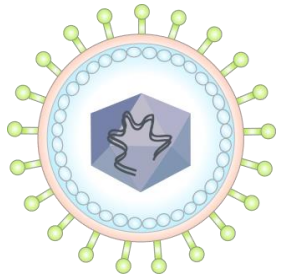
1. Xu F, et al. *J Infect Dis*. 2002;185(8):1019–24; 2. Heldwein EE, Krummenacher C. *Cell Mol Life Sci*. 2008;65(11):1653-68; 3. Goins WF, et al., Engineering HSV-1 Vectors for Gene Therapy, in Herpes Simplex Virus: Methods and Protocols, J.R. Diefenbach and C. Fraefel, Editors. 2014, Springer New York:New York, NY. p. 63-79; 4. Tognarelli EI, et al. *Front Cell Infect Microbiol*. 2019;9:127; 5. Yang L, et al. *Front Immunol*. 2019;10:2196; 6. Oldham ML, et al. *Nature*. 2016;529(7585):537-40; 7. Epstein AL, et al. *Curr Gene Ther*. 2005;5(5):445-58; 8. Generation Bio (GBIO) Prospectus. (2020, June 11); 9. Dalwadi DA, et al. *Mol Ther*. 2021; 29(2):680-690

AAV, adeno-associated virus; HSV-1, herpes simplex virus type 1; LNP; lipid nanoparticle; LV, lentivirus

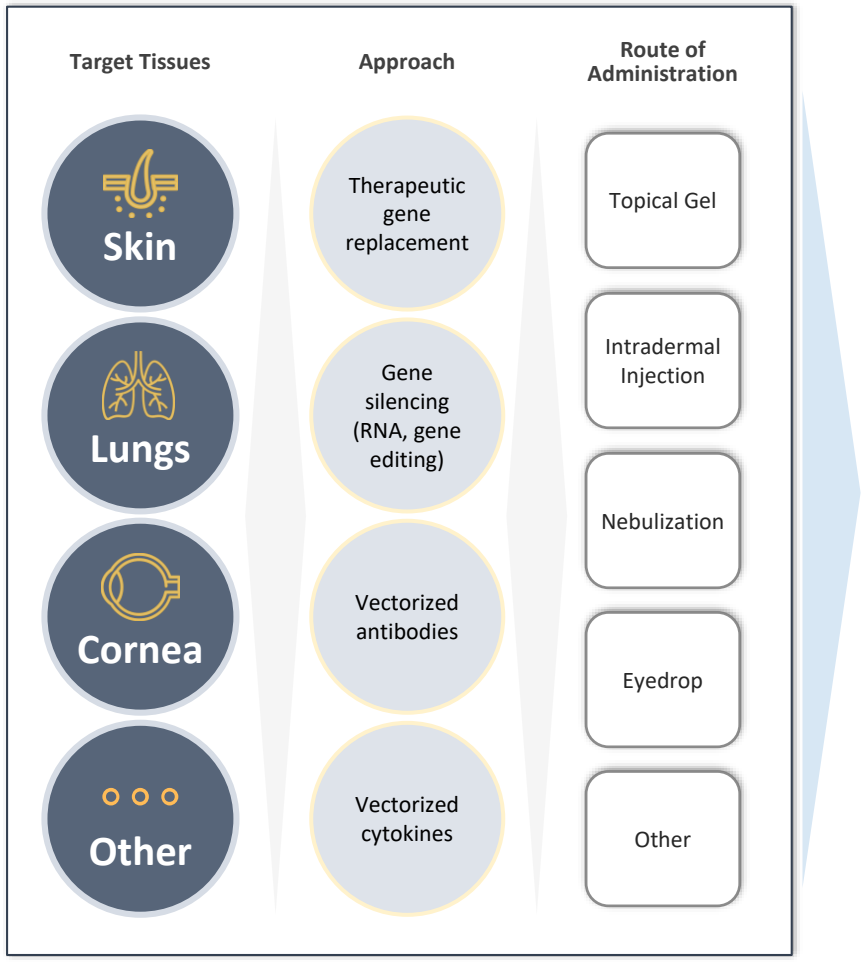
Redosable Gene Delivery Technology Has Broad Potential

Vector can deliver a variety of therapeutic modalities and be administered repeatedly

Engineered HSV-1 platform



The HSV-1 vector is engineered to be replication incompetent, thus further reducing cytotoxicity and the potential for cell to cell spread, while retaining the favorable properties of HSV-1, including immune-evasion, high payload capacity, and broad tropism.



Krystal

Rare diseases / conditions

- ✓ B-VEC (COL7A1) for DEB (PDUFA date of May 19, 2023)
- ✓ KB105 (TGM1) for TGM1-ARCI
- ✓ KB407 (CFTR) for Cystic Fibrosis
- • KB104 (SPINK5) for Netherton Disease
- • KB408 (AAT) for Alpha-1 Antitrypsin Deficiency
- • Undisclosed preclinical candidates

JEUNE

Aesthetic skin conditions

- ✓ KB301 (COL3)
- • KB302 (COL1)
- • KB303 (ELN)
- • KB304 (ELN + COL3)
- • KB305 (COL4)

Collaboration Opportunities

Non-rare diseases / conditions

- • Chronic, non-monogenic diseases
- • Autoimmune skin or lung conditions
- • Vectorized antibodies or cytokines
- • Organ systems outside of Krystal's core focus

✓ In the clinic

AAT, Alpha-1 antitrypsin; ARCI, autosomal recessive congenital ichthyosis; BLA, Biologics License Application; B-VEC, beremagene geperpavec; CFTR, cystic fibrosis transmembrane conductance regulator; COL1, type I collagen; COL3, type III collagen; COL4, type IV collagen; DEB, dystrophic epidermolysis bullosa; ELN, elastin; HSV-1, herpes simplex virus type 1; SPINK5, serine protease inhibitor Kazal-type 5; TGM1, transglutaminase-1

All products described in this presentation are investigational therapies

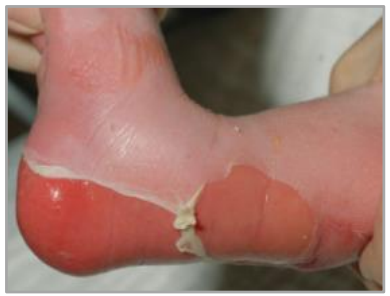
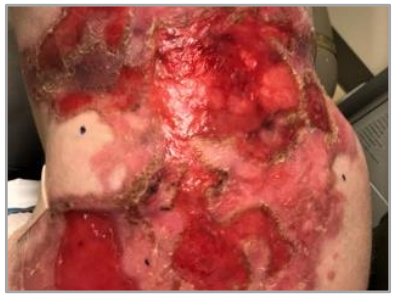
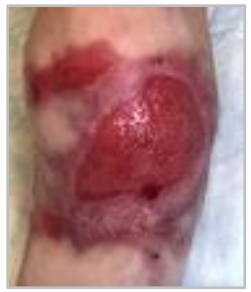
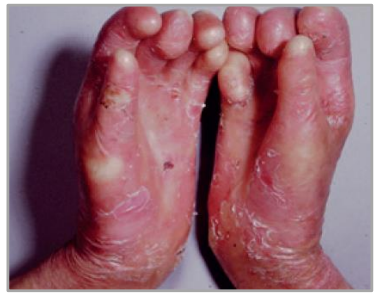
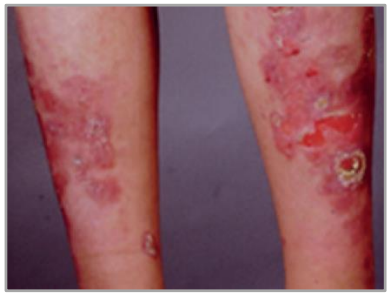
Beremagene Geperpavec (B-VEC)

RMAT/PRIME/Orphan/Voucher*

*RMAT: Regenerative Medicine Advanced Therapy Designation by the FDA; PRIME: PRIority Medicines designation by the EMA; Orphan: Orphan Drug designation by the FDA and Orphan Medicinal Product Designation by the EMA; Voucher: Rare Pediatric Disease designation may qualify for a voucher that can be redeemed to receive a priority review

Dystrophic Epidermolysis Bullosa (DEB)

"Butterfly Children" is often used to describe young DEB patients because their skin is as fragile as a butterfly's wings

Dystrophic Epidermolysis Bullosa

- DEB is a serious, ultra-rare genetic blistering disease caused by mutations in the *COL7A1* gene[1-3]
- Mutations in the *COL7A1* gene lead to absent or dysfunctional COL7 protein, without which the epidermis does not anchor to the dermis[1-3]
- DEB is characterized by a range of symptoms, including blistering (e.g., on the hands, feet, knees, elbows), wounds, scarring, nail, oral, and GI abnormalities. DEB is classified by inheritance pattern into 2 subtypes, the recessive DEB (RDEB), more severe form, and dominant DEB (DDEB)[1,4,5]
- Patients with DEB are at increased risk for serious complications, including aggressive squamous cell carcinoma[6-8]

DEB is a lifelong condition, with clinical features and complications evolving from childhood through late adulthood[2,3]

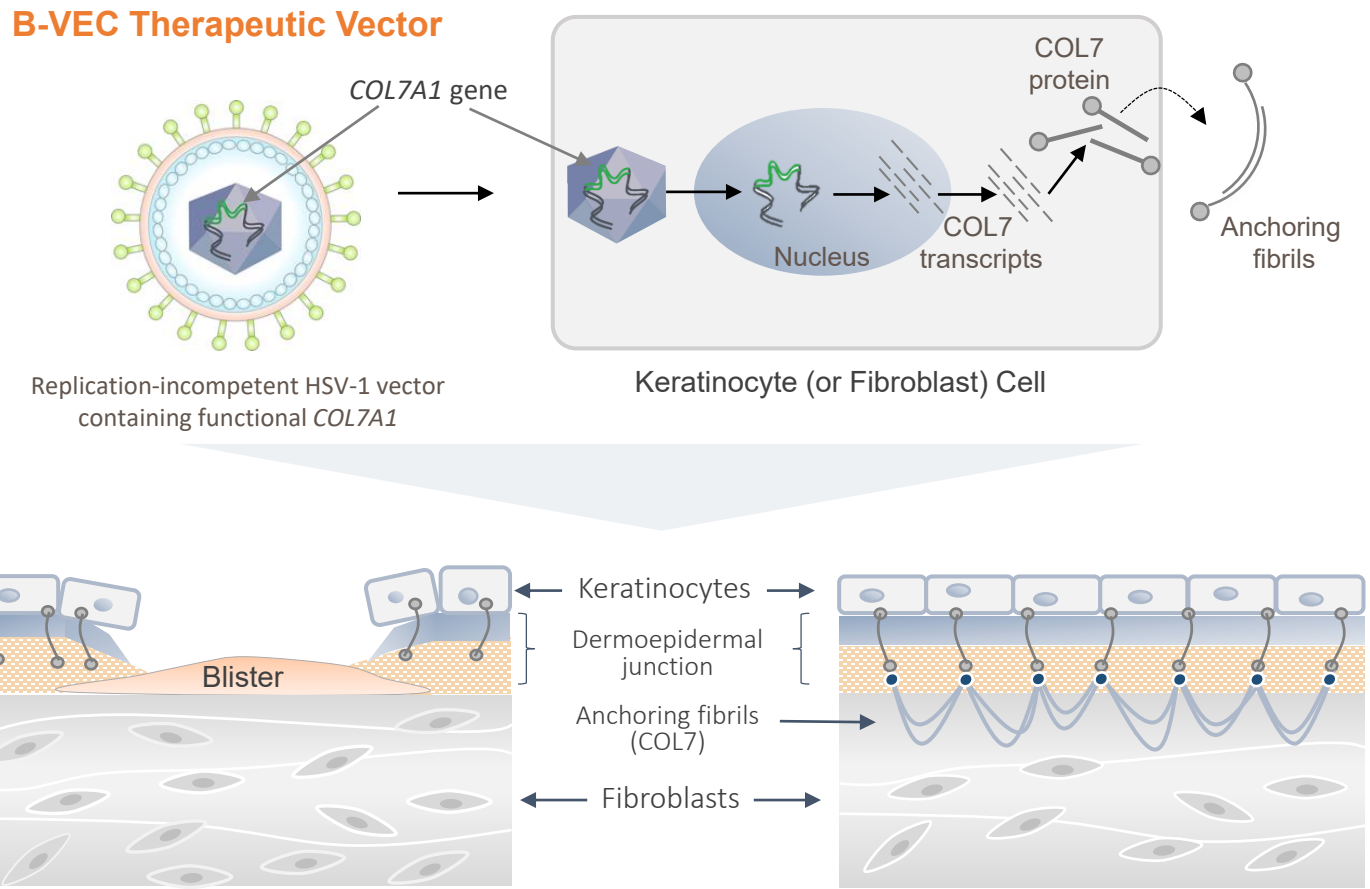
1. Fine J-D, et al. *J Am Acad Dermatol*. 2014;70(6):1103-1126; 2. Fine J-D. *JAMA Dermatol*. 2016;152(11):1231-1238; 3. Bardhan A, et al. *Nat Rev Dis Primers*. 2020 Sep 24;6(1):78; 4. Has C, et al. *Br J Dermatol*. 2020;183(4):614-627; 5. Bardhan A, et al. *Nat Rev Dis Primers*. 2020;6(1):78; 6. Condorelli A, et al. *Int J Mol Sci.* 2019;20(22):5707; 7. Montaudié H, et al. *Orphanet J Rare Dis*. 2016;11(1):117; 8. Fine J-D, Mellerio JE. *J Am Acad Dermatol*. 2009;61:367-384

COL7, type VII collagen; DDEB dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa

All products described in this presentation are investigational therapies

Beremagene Geperpavec (B-VEC) for DEB

Topically applied B-VEC gel designed to induce local COL7 expression and molecular correction



- Topically-administered B-VEC enters the compromised skin of DEB patients and transduces both keratinocytes and fibroblasts[1-2]
- Once inside the nucleus, the vector genome is deposited episomally, allowing the cell to produce and secrete functional COL7 protein without host genomic disruption[1-2]
- The secreted COL7 protein assembles into anchoring fibrils, which holds the epidermis and dermis together[1-2]

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

B-VEC, beremagene geperpavec; COL7, type VII collagen; DEB, dystrophic epidermolysis bullosa

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B-VEC Opportunity

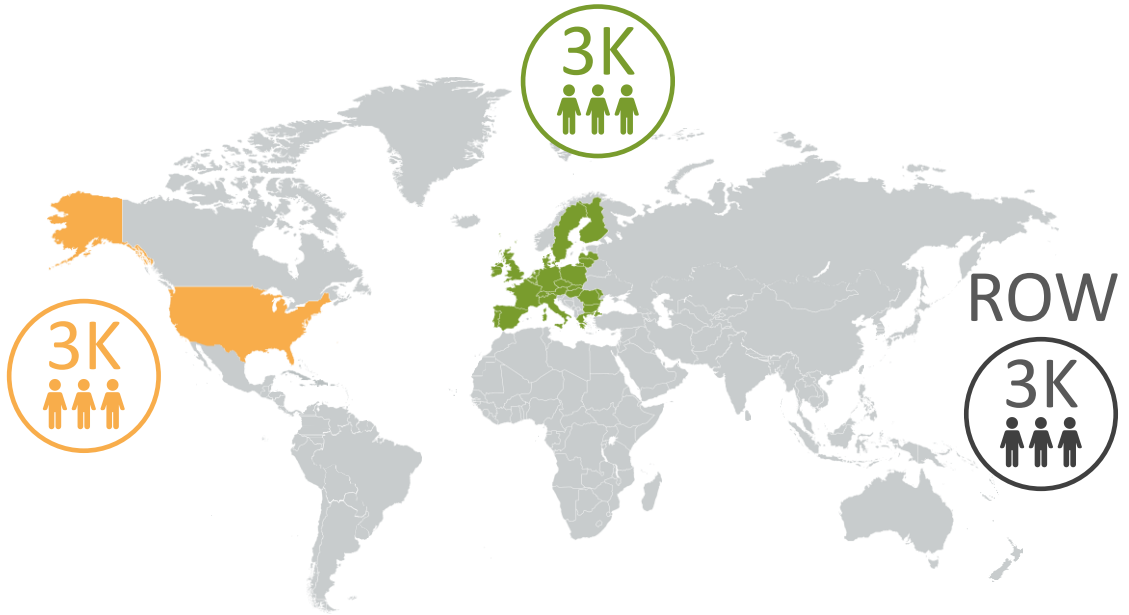
A topical redosable gene therapy intended to treat DEB

DEB is rare: **~9,000** patients across global reimbursable markets and **>2,500** patients diagnosed[1]

High unmet need: DEB has no FDA-approved treatments; current management is limited and supportive in nature[2,3]

Burden of existing treatment: supportive treatments can be time-consuming and costly, **$200k – $400k** annually[4,5]

Significant opportunity: DEB represents a **>$500M** global market



Global commercial & medical teams with deep expertise in rare diseases

1. Internal data on file; 2. Denyer J, et al. Accessed March 16, 2022. https://www.woundsinternational.com/download/resource/5921; 3. Bruckner AL, et al. *Orphanet J Rare Dis*. 2020;15(1):1; 4. 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; 5. GENEGRAFT Report Summary. (2015, February 16). Retrieved December 13, 2016, from http://cordis.europa.eu/result/rcn/156078_en.html

B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; FDA, U.S. Food and Drug Administration

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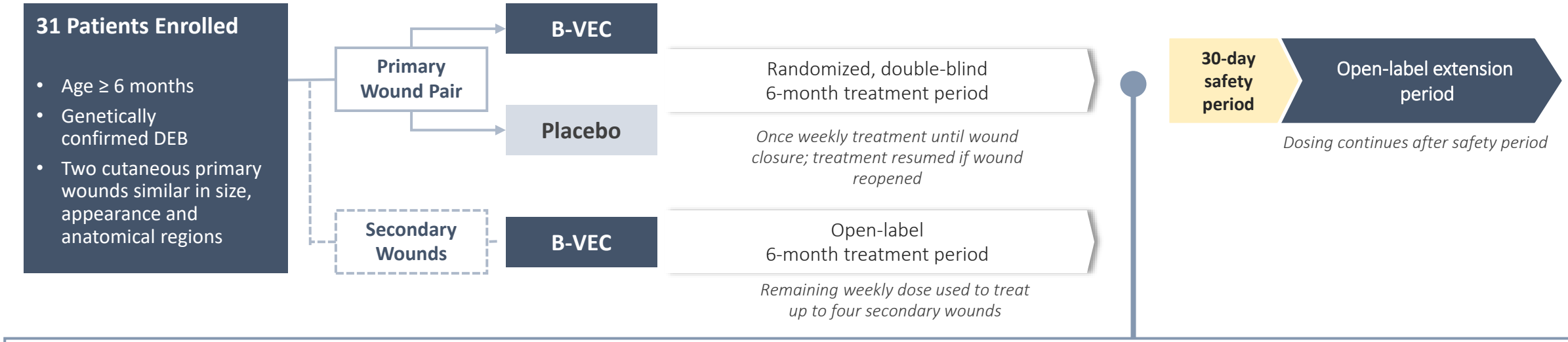
GEM-3 Pivotal Study Evaluated Weekly B-VEC or Placebo in DEB



Demographics

- 31 patients, each with one primary wound pair were enrolled and included in the intent-to-treat (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

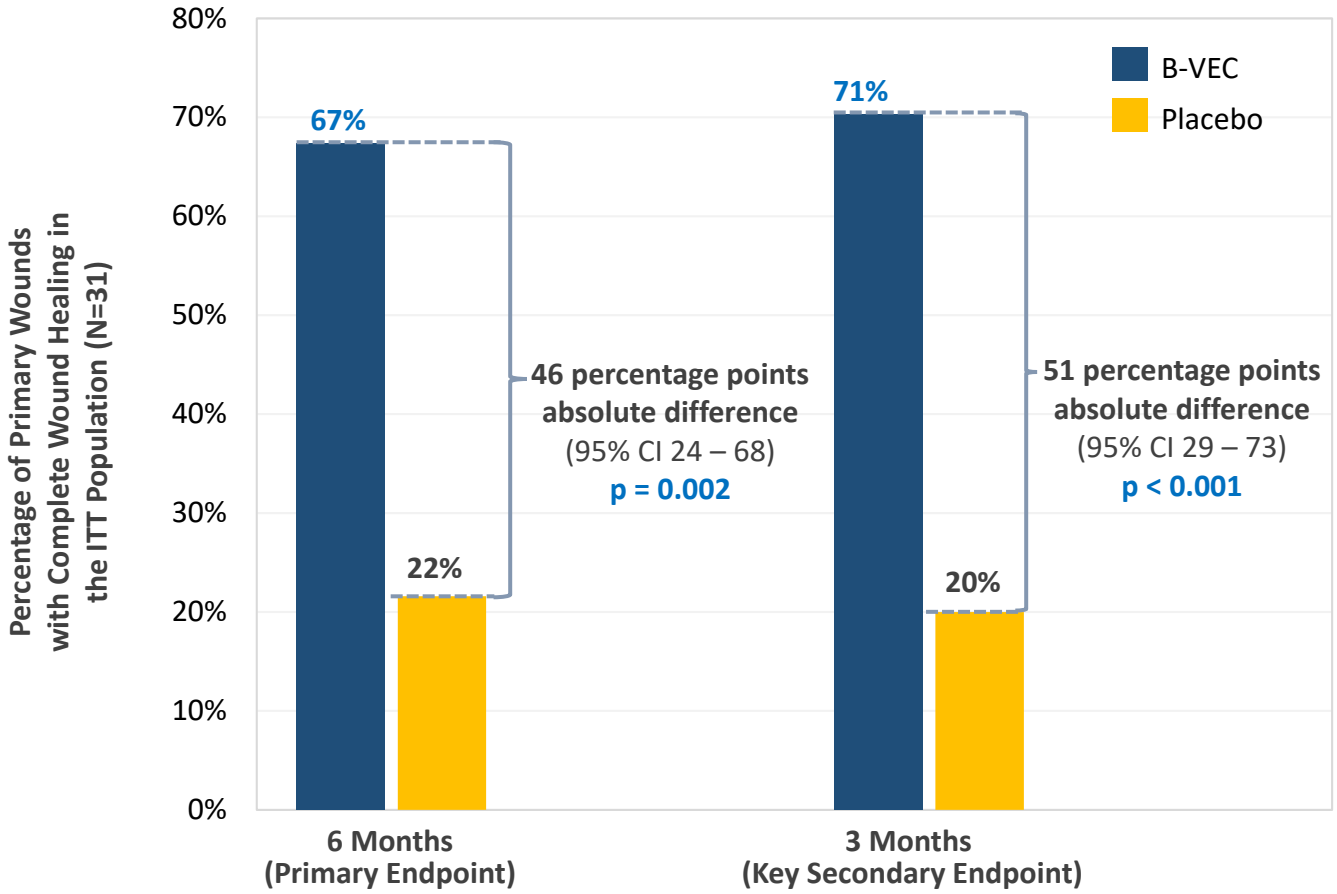
B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa

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

All products described in this presentation are investigational therapies

Significantly Greater Complete Wound Healing with B-VEC Treatment

Proportion of primary wounds with complete healing was significantly greater with B-VEC vs placebo



Durability of wound healing

- 49.7% of B-VEC treated wounds (N = 31) vs 7.1% of placebo treated wounds (N=31) demonstrated durability of response, defined as achieving complete wound healing at both 3 months (key secondary endpoint) and 6 months (primary endpoint)[1]
- Nearly half of all B-VEC treated wounds demonstrated complete wound healing for three consecutive visits[1,2]
- Of the total B-VEC wounds closed at 3 months, 66.7% (14/21) of B-VEC-treated wounds were also closed at 6 months, as compared to 33.3% (2/6) for placebo treated wounds[2]

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

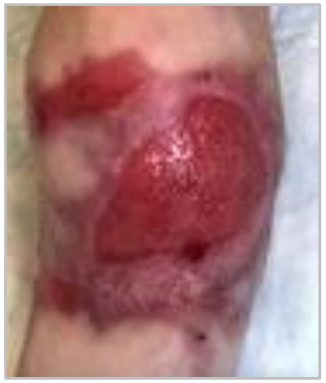
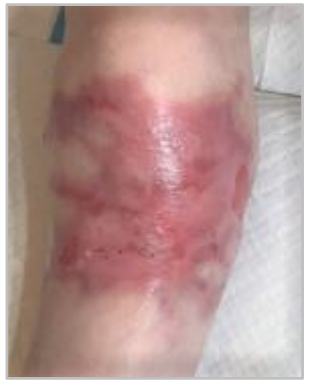
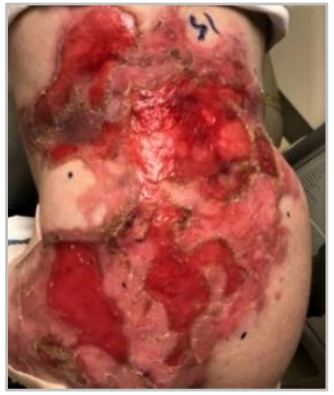
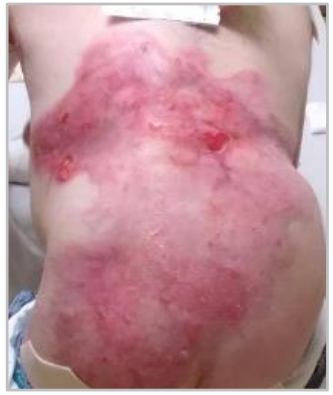
Data in figure based on ITT population (imputed); p-values and CIs are based on exact McNemar's test

B-VEC, beremagene geperpavec; CI, confidence interval; ITT, intent-to-treat

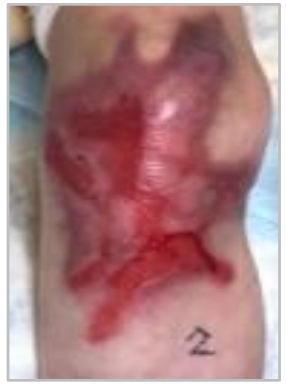
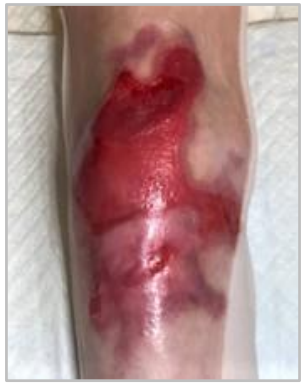
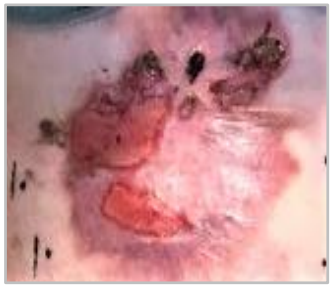
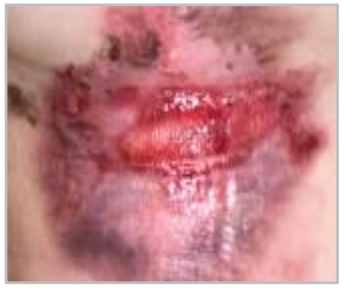
All products described in this presentation are investigational therapies

Wound Healing with B-VEC Treatment (Illustrative)

B-VEC

	Baseline	6 months
Knee[1]		
Back[2]		

Placebo

	Baseline	6 months
Knee[1]		
Sternum[1]		

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

B-VEC, beremagene geperpavec

All products described in this presentation are investigational therapies

Consistent Evidence of a Treatment Response with B-VEC across Subgroups

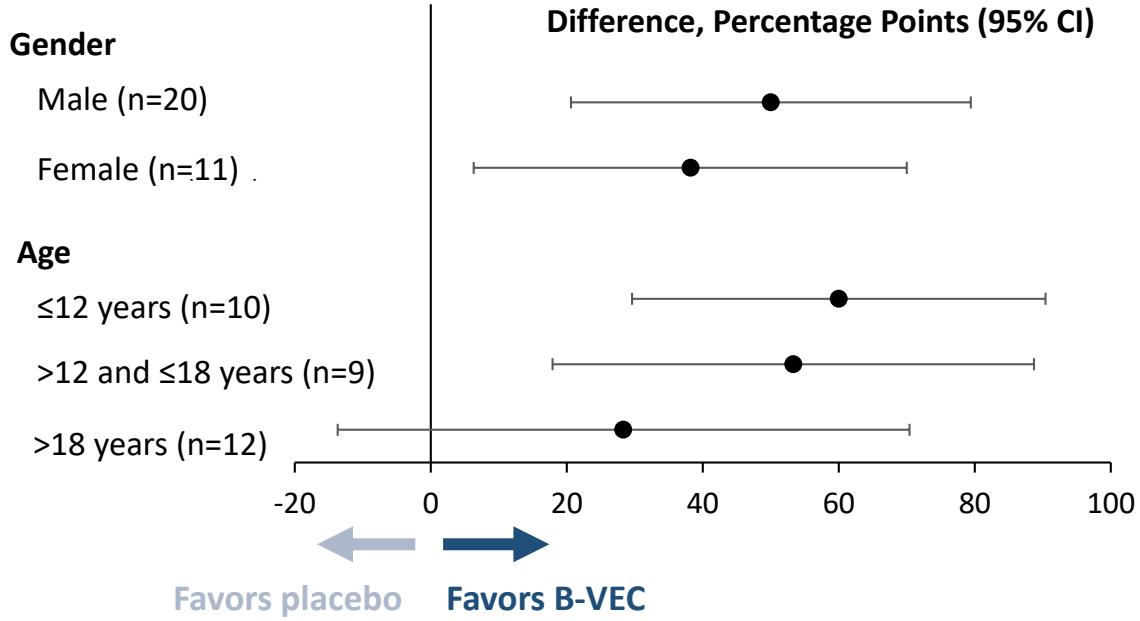
Treatment response was in favor of B-VEC regardless of wound size, gender, and age†

Complete Wound Healing at 6 Months by Baseline Wound Size

Baseline primary wound area/size*	B-VEC		Placebo	
	N	Complete wound healing at 6 months, n (%)	N	Complete wound healing at 6 months, n (%)
<20 cm²	23	14 (60.9)	22	5 (22.7)
20 - <40 cm²	6	4 (66.7)	8	1 (12.5)
40 – 60 cm²	2	1 (50.0)	1	0 (0)

*In a small number of patients, the pre-defined threshold values for wound area/size category fell in between the size of the two wounds

Complete Wound Healing at 6 Months by Gender & Age



†Individual subgroups were not powered to demonstrate statistical significance

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

Data in figures based on ITT population (imputed); CIs are based on exact McNemar's test; gender and age subgroups were pre-specified

B-VEC, beremagene geperpavec; CI, confidence interval; ITT, intent-to-treat

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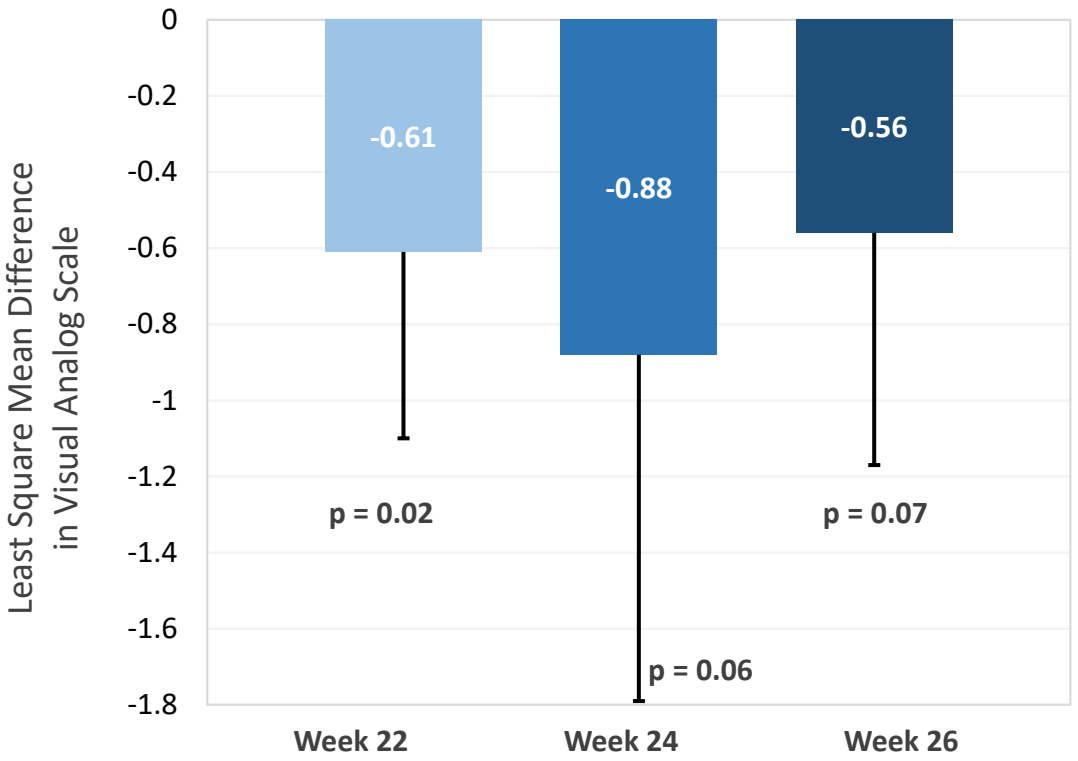
Pain and PRO Improvement Consistent with a Wound Healing Response

Change from Baseline in Pain following B-VEC Treatment



Change from baseline in pain severity associated with wound dressing changes, as measured by Visual Analog Scale, at Weeks 22, 24, and 26 for the ITT population, ages 6 and above.

Least square mean difference, 95% CI (shown as error bars), and p values were generated from analysis of covariance linear model with treatment and subject as the fixed effects and the baseline value as the covariate and change from baseline as the dependent variable.

- Baseline VAS score of enrolled patients were approximately 2 to 3 on average[1]
- A trend towards decreased pain in B-VEC treated versus placebo treated wounds was observed across Weeks 22, 24, and 26; improvement in pain was consistent with wound healing[1,2]
- PRO measures (EQ-5D-5L and Skindex-29) assessed before and after treatment with B-VEC demonstrated improvement across multiple domains directionally, consistent with a wound healing response[1,2]

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

B-VEC, beremagene geperpavec; PRO, patient reported outcomes; VAS, Visual Analog Scale

All products described in this presentation are investigational therapies

B-VEC was Generally Well-Tolerated

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
- 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 B-VEC was not associated with HSV-1 serostatus at baseline or with COL7 seroconversion

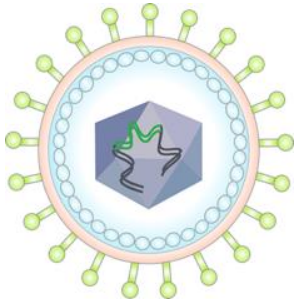
Guide SV, et al. *N Engl J Med.* 2022;387(24):2211-9

AEs, adverse events; B-VEC, beremagene geperpavec; COL7, type VII collagen; HSV-1; herpes simplex virus type 1; SAEs, serious adverse events

All products described in this presentation are investigational therapies

GEM-3 Results Provide Clinical Validation of the Platform

Engineered HSV-1 Vector Platform



GEM-3 Study

Platform fully integrated from research to development to manufacturing to commercialization

1

Demonstrates B-VEC met the primary and secondary efficacy endpoints in complete wound healing for DEB

- Most advanced clinical application of platform

2

Validates therapeutic vector in dermatologic applications

- Skin pipeline covers rare and aesthetic conditions (via wholly owned subsidiary Jeune Aesthetics, Inc.)
- Potential to deliver diverse genetic cargo

3

Validates therapeutic vector for broader redosable gene delivery

- Tropism to lung and additional types under exploration
- Potential to deliver diverse exogeneous genetic materials with a variety of delivery mechanisms

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

All products described in this presentation are investigational therapies

Therapeutic Pipeline

Wholly-Owned Pipeline Spanning Dermatology & Respiratory Diseases

	Product	Protein	Indication	Discovery	Preclinical	Phase 1/2	Phase 3	Commercial
Dermatology	**B-VEC**†¤•Δ‡§	Type VII collagen	Dystrophic Epidermolysis Bullosa					PDUFA May 19, 2023
Dermatology	**KB105**†¤•‡	Transglutaminase 1 (TGM1)	TGM1-deficient ARCI					
Dermatology	**KB104**¤	Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)	Netherton Syndrome					
Dermatology	**KB1XX**	Undisclosed Programs						
Dermatology	**KB5XX**	Vector Encoded Antibodies	Chronic Skin Conditions					
Respiratory	**KB407**†¤‡	Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)	Cystic Fibrosis					
Respiratory	**KB408**	Alpha-1 antitrypsin (AATD)	alpha-1 antitrypsin deficiency					
Respiratory	**KB4XX**	Undisclosed Programs						

All pipeline compounds are investigational. All pipeline compounds are wholly owned.

Rare disease

More prevalent conditions

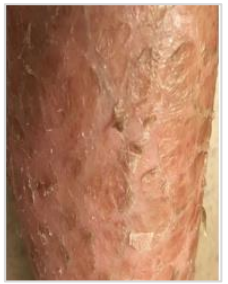
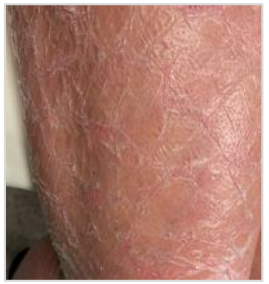
†: FDA Orphan Drug Designation
¤: FDA Rare Pediatric Disease Designation
•: Fast-track Designation
Δ: FDA RMAT designation
‡: EMA Orphan Drug Designation
§: EMA PRIME Designation

Autosomal Recessive Congenital Ichthyosis Associated with TGM1 Mutations

Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period

ARCI Associated with TGM1

- The most common form of ARCI is caused by an inactivating mutation in the TGM1 gene encoding the enzyme transglutaminase-1, a protein that is essential for the proper formation of the skin barrier
- The condition is characterized by thick, dry, scaly skin, increased trans-epidermal water loss (TEWL), risk for dehydration, sepsis, and skin malignancies

High unmet need

- There are no approved treatments for ARCI associated with TGM1
- Topical and systemic retinoids and time-consuming supportive treatments are the most commonly used treatments of care (and can require up to four hours of skin care per day)

2K-6K

Estimated TGM1-ARCI Patients in US and Europe

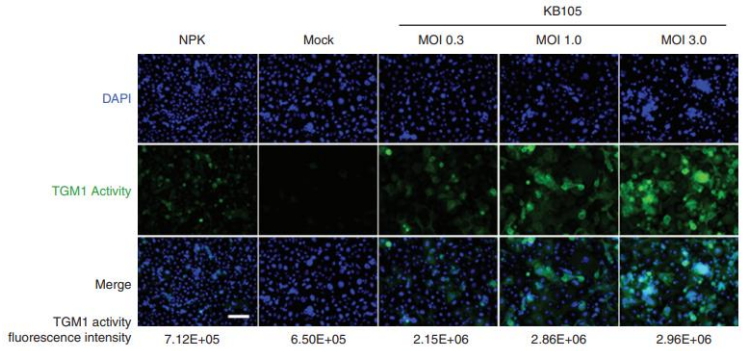
1. Rodriguez-Pazos L, et al. *Actas Dermosifiliogr.* 2013;104(4):270–84; 2. Dreyfus I, et al. *Orphanet J Rare Dis.* 2014;9:1; 3. Hernandez-Martin A, et al. *J Am Acad Dermatol.* 2012;67(2):240–4; 4. Pigg M, et al. *Eur J Hum Genet.* 1998;6(6):589–96; 5. Pigg M, et al. *Acta Derm Venereol.* 2016;96(7):932–37; 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

ARCI, autosomal recessive congenital ichthyosis

KB105 for TGM1 Associated ARCI

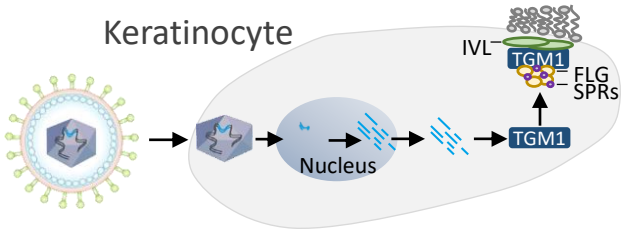
Topically applied gel that delivers functional human TGM1 to keratinocytes

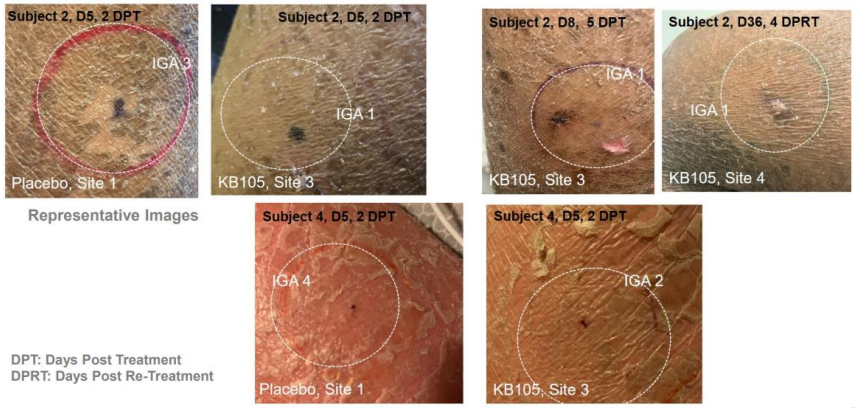
KB105 in immortalized TGM1-deficient patient-derived keratinocytes[1]



- A dose-dependent increase in TGM1 enzymatic activity was observed in KB105-infected cells by immunofluorescence
- TGM1-mediated peptide cross-linking in infected cells surpassed the levels of endogenous TGM1 activity in normal primary keratinocytes

Topical KB105 delivers functional TGM1 locally and preliminary Phase 1/2 results encouraging[2]





- KB105 transduced cells produce functional TGM1 protein that localizes to the cell membrane
- TGM1 catalyzes the covalent cross-linking of different cornified envelope proteins in the stratum corneum, also known as the skin barrier, therefore molecularly correcting the defect
- In Phase 1 study, KB105 treatment restored functional TGM1 protein expression and activity in all treated sites; KB105-expressed TGM1 was correctly localized in the epidermis
- Phenotypic evaluation limited by small treatment areas, but KB105 treated areas showed reduced reversion to ichthyotic scaling phenotype
- No drug-related AEs noted; No HSV or TGM1 antibodies throughout the study

1. Freedman JC, et al. *J Invest Dermatol*. 2021;141(4):874-882; 2. Paller A, et al. Oral presentation at Society for Investigative Dermatology (SID) 2020 Annual Meeting. Virtual. May 13-16, 2020

AE, adverse event; HSV, herpes simplex virus

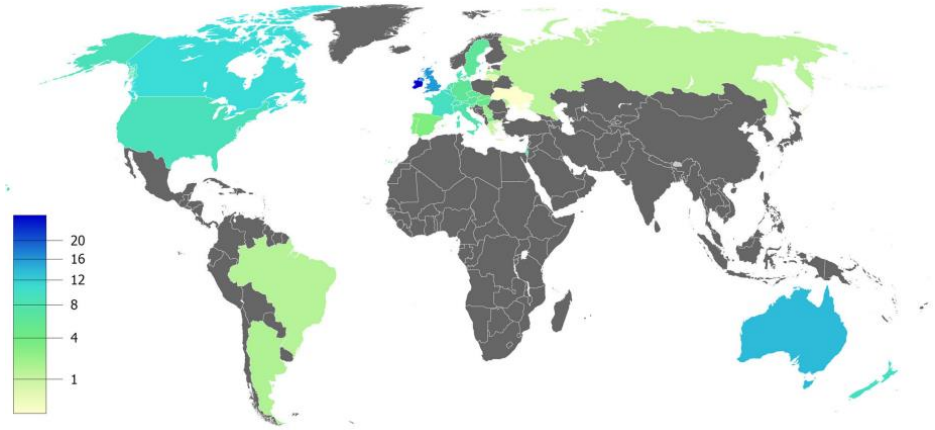
All products described in this presentation are investigational therapies

Cystic Fibrosis: Significant Unmet Need Despite Recent Approvals

Approximately 10% of CF patients have mutations that are not amenable to current small molecule approaches

Cystic Fibrosis

- Known as a life-threatening inherited disease, with an incidence of ~1/2,500 live births, affecting ~80,000 people worldwide[1]
- It is autosomal recessive, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), leading to reduced and/or loss of CFTR function[2-4]
- Progressive lung disease is the primary cause of morbidity and mortality where the loss of CFTR-mediated chloride and bicarbonate transport leads to airway mucus obstruction, recurrent bacterial infection, and inflammation[5]



Estimated prevalence of cystic fibrosis per 100,000 habitants[6]

Unmet need remains significant despite recent approvals

- Small molecule correctors work by improving the functions of mutated CFTR; however, they only restore ~50% of protein function in patients with certain amenable mutations
- These therapies are ineffective in the ~10% patients with mutations that do not produce any CFTR protein (null mutations)
- Suboptimal efficacy or tolerability issues remain even in those responsive to therapies

CF Prevalence & Incidence[1,6,7]

~80,000 patients with CF worldwide

~30,000 patients in US CF registry

~1,000 new cases of CF diagnosed each year in the US

1. Middleton PG, et al. *N Engl J Med.* 2019;381(19):1809-1919; 2. O'Sullivan BP, et al. *Lancet.* 2009;373:1891-904; 3. Elborn JS, et al. *Lancet.* 2016; 388:2519-31; 4. Sanders DB, et al. *Pediatr Clin North Am.* 2016;63:567-84; 5. Stoltz DA, et al. *N Engl J Med.* 2015;372 (4):351-362; 6. Lopes-Pacheco M. *Front Pharmacol*. 2016;7:275; 7. US Cystic Fibrosis Foundation

CF, cystic fibrosis

All products described in this presentation are investigational therapies

KB407 for Cystic Fibrosis (CF)

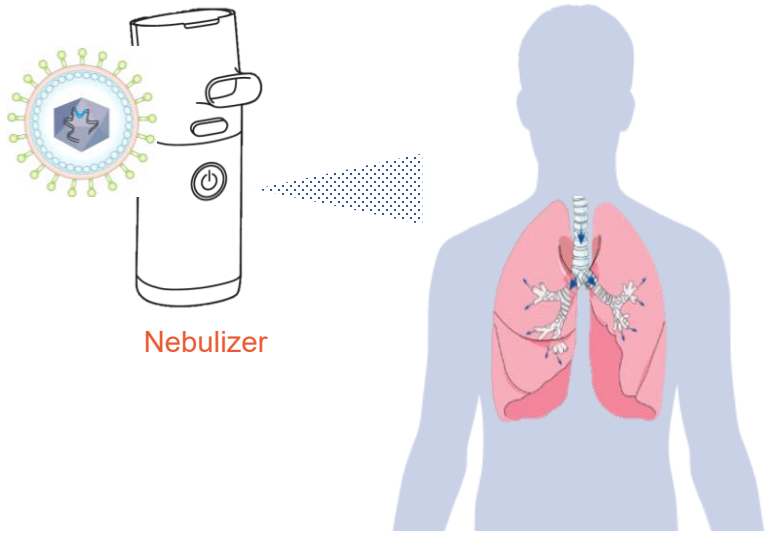
An inhaled gene therapy designed with the ability to redose

Gene therapy targeting CF

- Extensive effort with gene therapies have been explored spanning decades, with both viral (adenovirus and AAV) and non-viral (DNA plasmids and stabilized mRNA) approach
- Late-stage success remains elusive; challenges include physical limitations for large cargo, low efficiency of gene transfer, toxicity, immune intolerance, product instability, and burdensome delivery

KB407 characteristics

- Replication incompetent HSV-1 delivers two copies of full length, human *CFTR*
- Duration of nebulization expected to be <30 minutes, using a commercially available nebulizer
- Episomal delivery of *CFTR* gene does not disrupt cell DNA
- Ability to redose and/or adjust dose over time as lung cells turnover

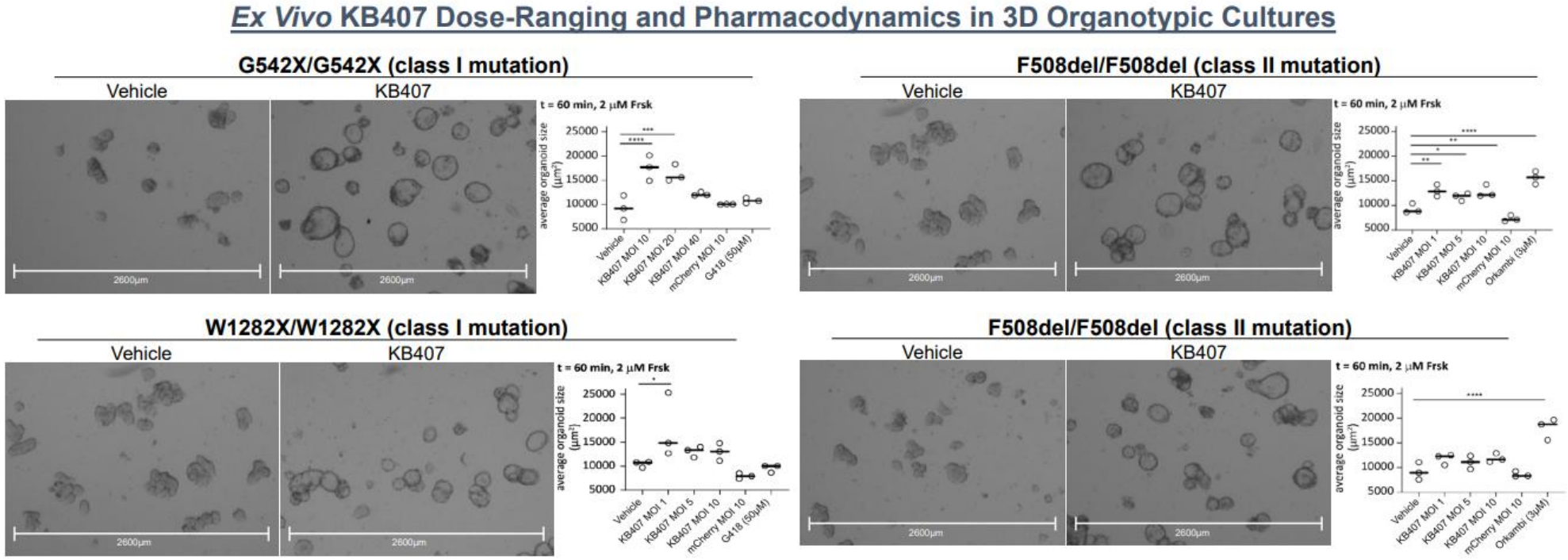


CF, cystic fibrosis

All products described in this presentation are investigational therapies

KB407 Corrected *CFTR* Defect in 3D Patient-Derived Intestinal Organoids

Restoration of normal cystic organoid morphology occurs irrespective of underlying CFTR mutation



- Transduction by KB407 leads to a restoration of normal cystic organoid morphology even at the lowest MOI tested within 24 hours of infection, irrespective of the underlying *CFTR* mutation
- KB407 also found to transduce primary CF patient derived small airway epithelial cells in a dose-dependent manner; the vector efficiently produces functional, full-length CFTR protein that properly traffics to the cell membrane

Freedman C, et al. Poster at the ASGCT 2020 Annual Meeting. Virtual. May 12-15, 2020; Krystal Biotech. Data on file.

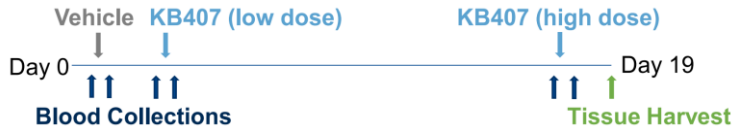
CF, cystic fibrosis; MOI, multiplicity of infection

All products described in this presentation are investigational therapies

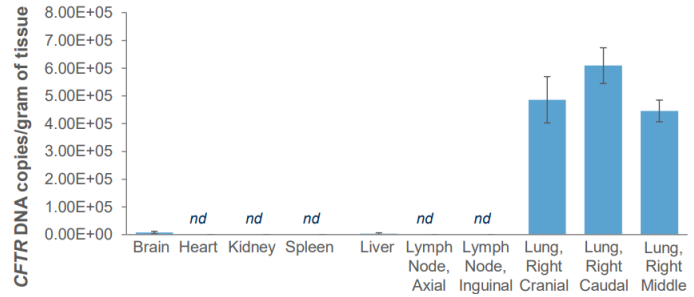
Pilot KB407 Non-Human Primate (NHP) Study: Human *CFTR* ≥ NHP *CFTR*

Confirmed KB407's CFTR payload transcribed in NHP lung with RNA levels at or exceeding endogenous CFTR

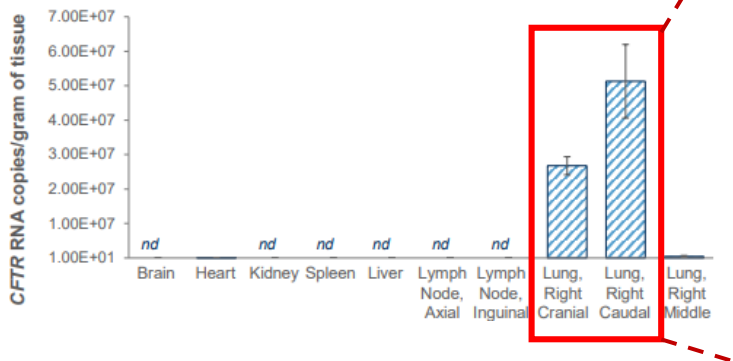
Pilot NHP Study Design



Human *CFTR* DNA Copies / Gram of Tissue

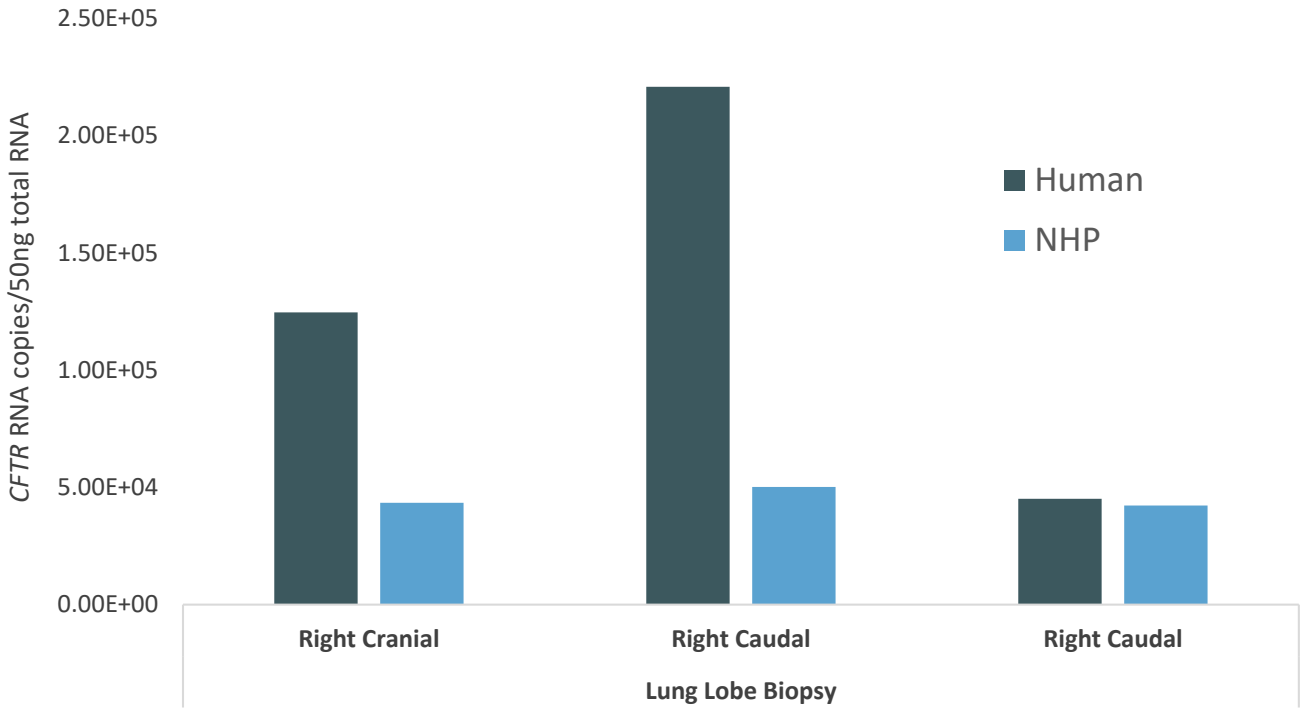


Human *CFTR* RNA Copies / Gram of Tissue



- Absolute quantification of exogenous human *CFTR* transcripts in multiple lung tissue biopsies were found to be 106%-440% of the endogenous levels observed in otherwise healthy primate airways

Absolute *CFTR* Transcription



Parry T, et al. Abstract #655 at the 2022 North American Cystic Fibrosis Conference (NACFC). November 3-5, 2022

NHP, nonhuman primate

All products described in this presentation are investigational therapies

Repeat Dose GLP IND-Enabling Toxicology Study in NHPs

Repeat dose of KB407 well tolerated and broadly distributed throughout lung tissue in NHPs*

Study Design

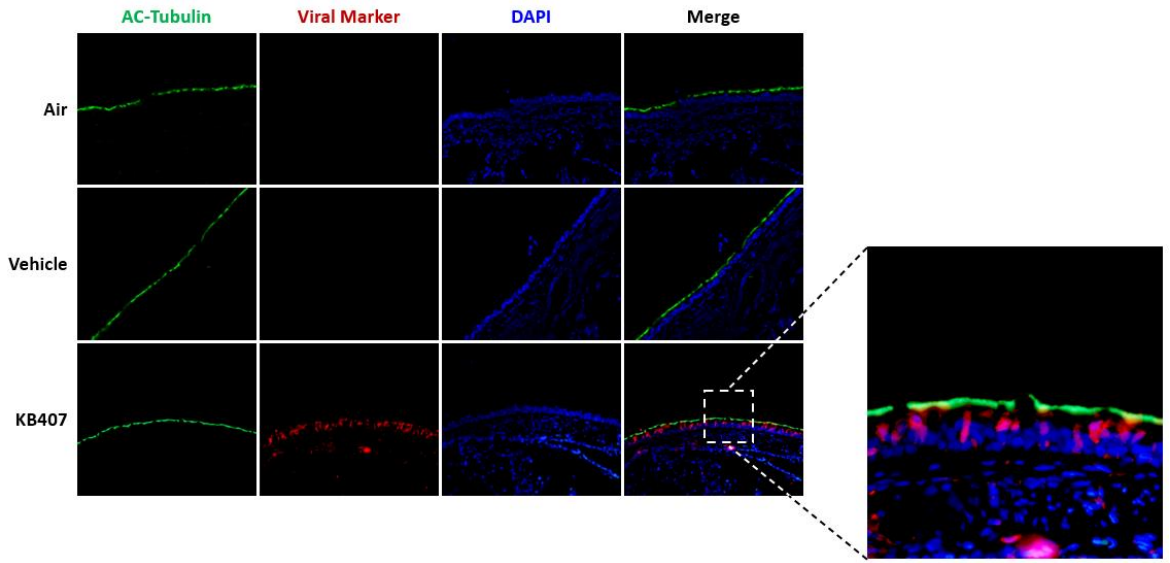
Group	n	Avg. Dose Deposited in Lungs (PFU/administration)	Dosing Days	Necropsy Days
Air	6	-	1, 8, 15	16
Vehicle	10	-	1, 8, 15	16, 43
Low Dose KB407	10	$1.81x10^8$ (male) $2.33x10^8$ (female)	1, 8, 15	16, 43
High Dose KB407	10	$1.43x10^9$ (male) $2.11x10^9$ (female)	1, 8, 15	16, 43

Toxicology: NOAEL determined to be high dose

- No toxicity based on mortality, cage side/clinical observations, body weights, pulmonary function, and pathology
- Effects considered non-adverse due to the mild severity, lack of impact on health, and reversible on recovery

Biodistribution: Broad distribution and sustained expression in NHP lungs

- A significant percentage of airway epithelial cells KB407+ positive by microscopy; quantification based on 10 fields of view, high dose group, lungs collected on Day 16, one day after last dose
  - **59.6%** (n = 298/500) of ciliated cells (AC-Tubulin+) were KB407+ ***representative image below***
  - **17.4%** (n = 38/218) of club cells (SCGB1A1+) were KB407+
  - **8.0%** (n = 8/100) of goblet cells (MUC5AC+) KB407+
  - Only 20.6% of KB407+ cells were also CD163+ suggestive of limited macrophage uptake
- Human *CFTR* expression also detected in lungs harvested on Day 43, 28 days after last dose



* KB407 IND cleared

Parry T, et al. Poster #541 at the 2021 North American Cystic Fibrosis Conference (NACFC). Virtual. November 1-5, 2 file.

GLP, good laboratory practice; IND, Investigational New Drug; NHPs, nonhuman primates; NOAEL, no observed adverse effect level; PFU, plaque forming unit

All products described in this presentation are investigational therapies

Alpha-1 Antitrypsin Deficiency (AATD)

Monogenic disorder that leads to progressive lung disease

AATD

- Alpha-1 Antitrypsin (AAT) is the most abundant serine protease inhibitor in human plasma and regulator of protease activity, in particular neutrophil elastase in lungs
- AATD is an autosomal co-dominant inherited genetic disorder resulting from mutations in *SERPINA1* gene encoding AAT; with misfolding mutations Pi*ZZ and Pi*SZ as the most common
- Genetic deficiency of AAT can result in unopposed neutrophil elastase activity, excessive degradation of elastin, collagen, and fibronectin and progressive pulmonary impairment

Unproven and Limited Treatment Options

- There is no cure available for patients with AATD
- Standard of care is augmentation therapy, consisting of weekly IV infusions of AAT
- Multiple limitations with current treatment options: burdensome on patients and clinical benefit of augmentation therapy on lung function is not well defined

Severe AATD Prevalence[1,2,3*]

*Over **60,000** patients in the US*

*Over **250,000** patients globally*

*Severe AATD defined as patients with Pi*ZZ genotype

Over $1B

Global annual revenues for AAT augmentation therapy[4**]

**Combined 2021 global sales of Prolastin®-C, Glassia®, Zemaira®

KB408 is in development as a redosable, non-invasive, inhaled gene therapy to enable local AAT expression in the lung

1. Aboussouan LS (2009) *Respir Med*. 103: 335-341; 2. Stoller JK (2013*) COPD*. 10: 26-24; 3. Blanco I (2017) *Int J Chron Obstruct Pulmon Dis*. 12: 561-569; 4. Evaluate Pharma, query 'Prolastin-C', 'Glassia', 'Zemaira', accessed June 28 2022; 5. Greene CM (2016) *Nat Rev Dis Primers*. 2: 16051; 6. Brantly ML (2019) *Chronic Obstr Pulm Dis*. 6: 100–114

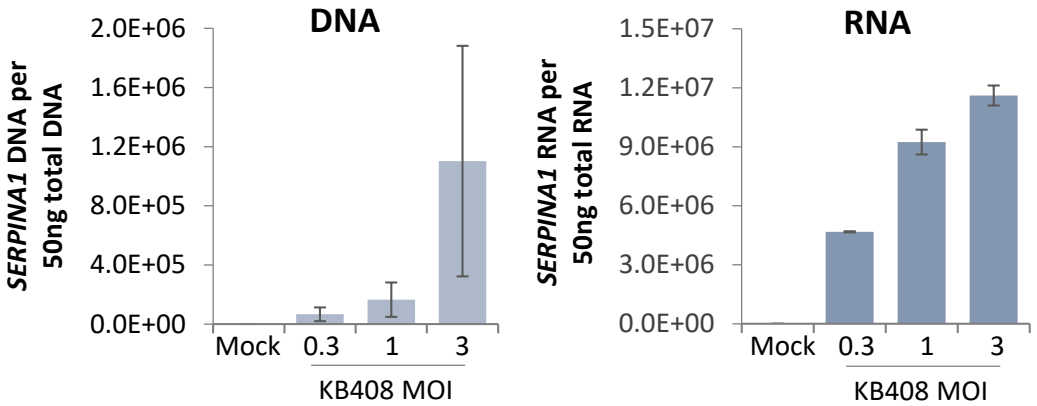
AAT, Alpha-1 Antitrypsin; AATD, Alpha-1 Antitrypsin Deficiency; IV, intravenous

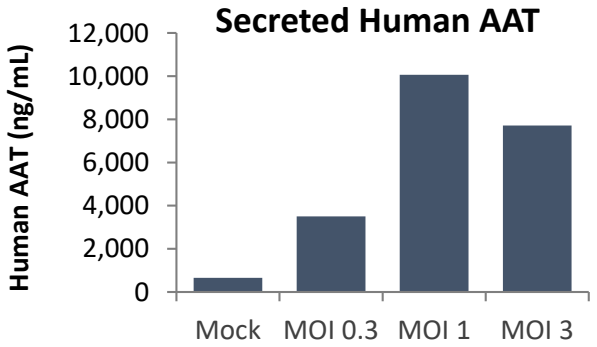
All products described in this presentation are investigational therapies

KB408 for AATD

Dose-dependent expression of human AAT in clinically relevant cells and mouse lungs

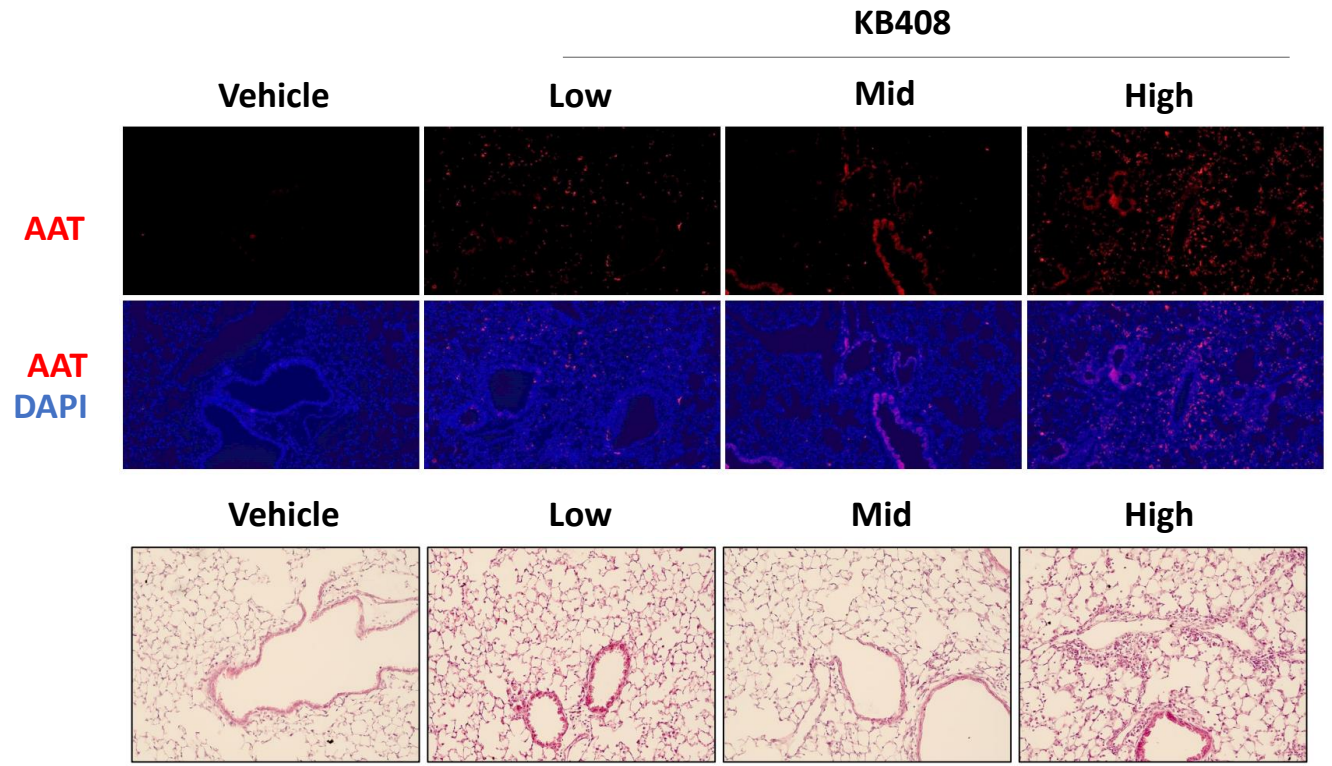
Dose-dependent expression of AAT in primary human small airway epithelial cells





Widespread human AAT expression in mouse lungs without visible toxicity

- C57BL/6 mice received vehicle or KB408 intratracheally on Day 1 and Day 3, three dose levels
- Lungs collected on Day 4 for histology and AAT expression analysis by immunofluorescence
- Similar findings in *SERPINA1* deficient (*Serpina1*^{em3Chmu}) mice



Artusi S et al., Poster # 40. at the 2021 European Society of Gene and Cell Therapy

AAT, alpha-1 antitrypsin; AATD, DAPI, Alpha-1 Antitrypsin Deficiency; 4',6-diamidino-2-phenylindole; MOI, multiplicity of infection

All products described in this presentation are investigational therapies

Krystal

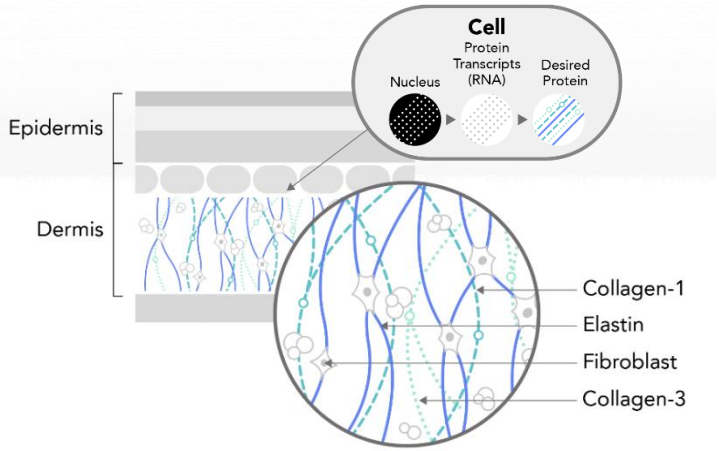
JEUNE

A wholly owned subsidiary of Krystal Biotech, Inc.

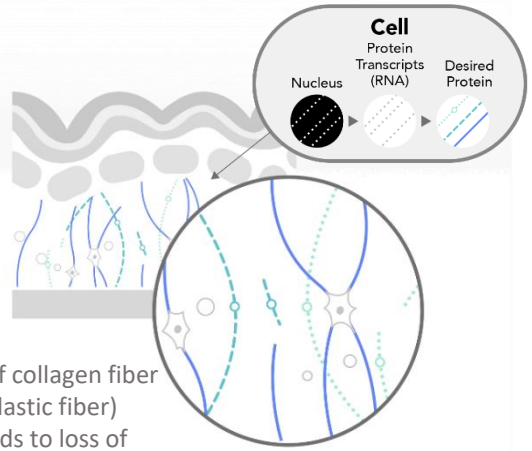
The Characteristic Look of Aging is Caused by Declining Levels of Key Proteins in the Skin's Extracellular Matrix

- Skin aging is a complex process that is caused by intrinsic factors (age) and extrinsic factors (e.g., sun, cigarette smoke, pollutants, diet etc.)
- These factors cause dermal matrix alterations, impaired collagen synthesis, and degradation of extracellular matrix which consequently affects overall quality and function of skin
- 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

Jeune Aesthetics is Creating a New Category of Aesthetic Medicines Designed to Directly Address Underlying Biology

Damage

Using light and sound waves, **energy-based devices damage the skin** triggering a wound healing response

Fill

Whether bovine collagen, hyaluronic acid, or others, **fillers add artificial volume** to decrease the appearance of wrinkles

Paralyze

By inducing temporary denervation **toxins paralyze the underlying muscle** to prevent movement, thereby decreasing the appearance of wrinkles

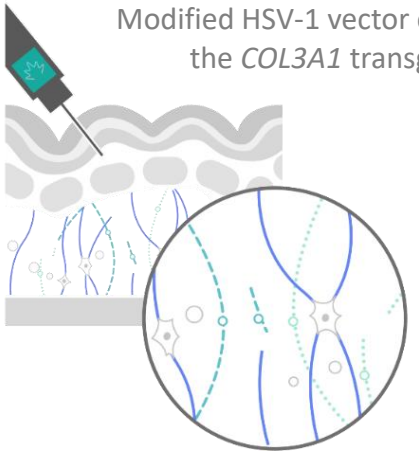
Restore and Rebuild

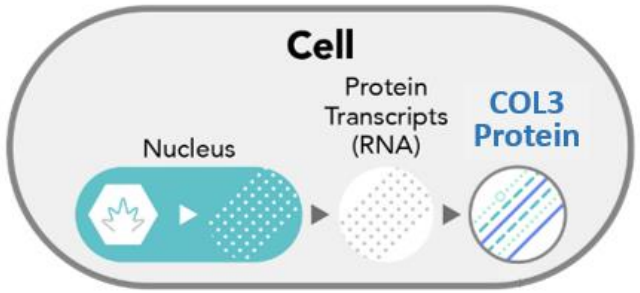
Via targeted gene delivery directly to skin cells Jeune Aesthetics' gene-based treatments are designed to **restore protein production to rebuild** the underlying extracellular matrix structure, to improve skin quality and appearance

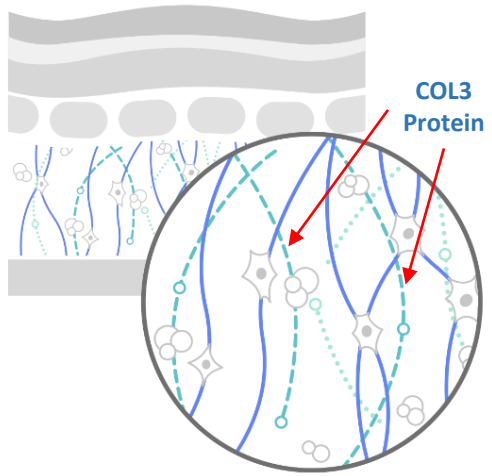
KB301 Mode of Action

KB301

Modified HSV-1 vector containing the *COL3A1* transgene







1 Intradermal Injection

- Delivered via 33G needle
- Treatment area numbed with ice (no topical anesthesia required)

2 Protein Synthesis

- Once in the nucleus, *COL3A1* gene designed to allow normal cell machinery to make COL3 protein*

3 Protein Integration

- Newly made protein is secreted into the extracellular space where it rebuilds and restores the extracellular matrix

*COL3 provides tensile strength, and influences other functions such as cell adhesion, migration, proliferation, and differentiation through its interaction with integrins, which are cell surface receptors[1]

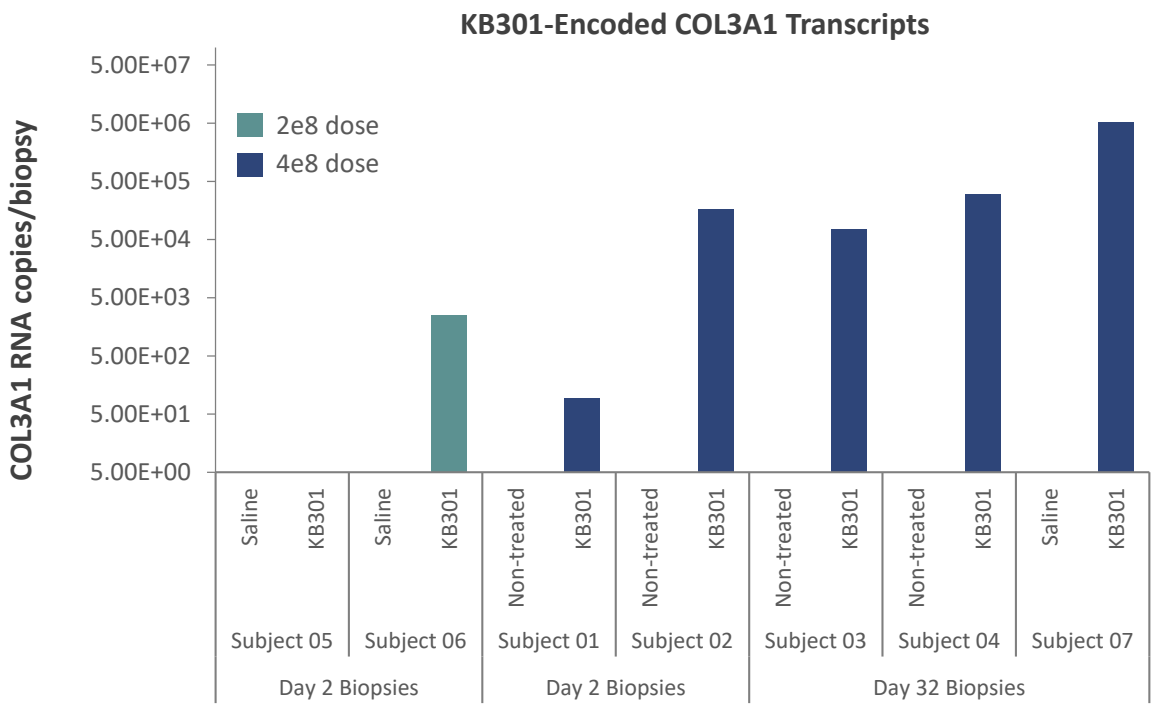
1. Kim JK, et al. *J Biol Chem.* 2005;280(37):32512–20

COL3, type III collagen

All products described in this presentation are investigational therapies

KB301 – PEARL-1 Cohort 1 (Safety)

COL3A1 transcripts were similar following first & second doses



Study Design

- Open label, dose ranging study designed to evaluate safety and repeat dosing after intradermal injections in 7 subjects aged ≥18 and ≤75
- Subjects received two (day 0 and day 30) intradermal bolus injections dosages (1e8, 2e8 and 4e8) in buttocks region; biopsy was taken on day 2 and day 32

Initial data from Cohort 1 (Safety)

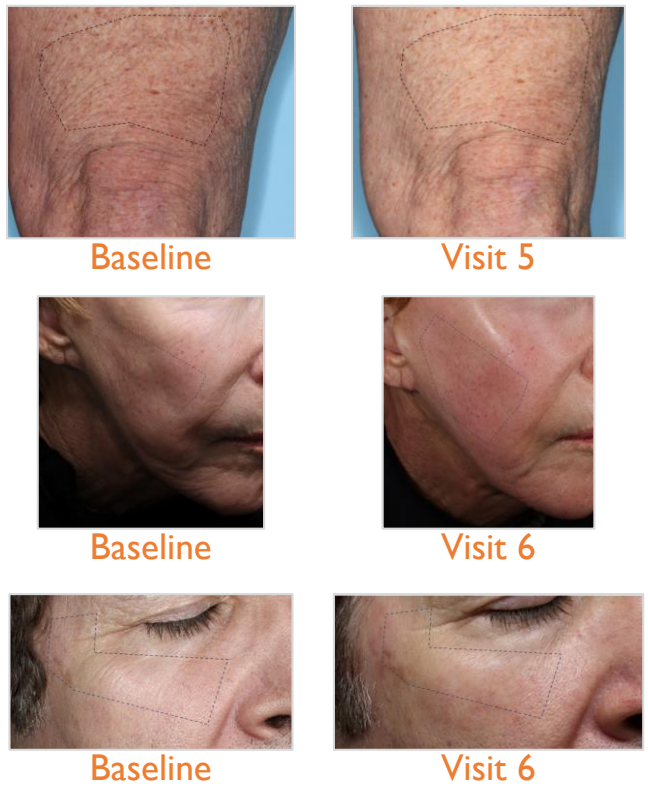
- Repeated intradermal injections of KB301 were well tolerated; adverse events were transient, mild to moderate injection site or biopsy site reactions (e.g., erythema, site pain, purpura, ecchymosis)
- No clinically significant changes in anti-drug antibodies were observed with up to 90-days of follow-up
- KB301-encoded *COL3A1* expression measurable at the mid and high dose; expression was evident by day 2 following the first dose

Krishnan S et al., Society for Investigative Dermatology Annual Meeting 2021

All products described in this presentation are investigational therapies

KB301 – PEARL-1 Cohort 2 (Efficacy)

Illustrative phots before vs after treatment



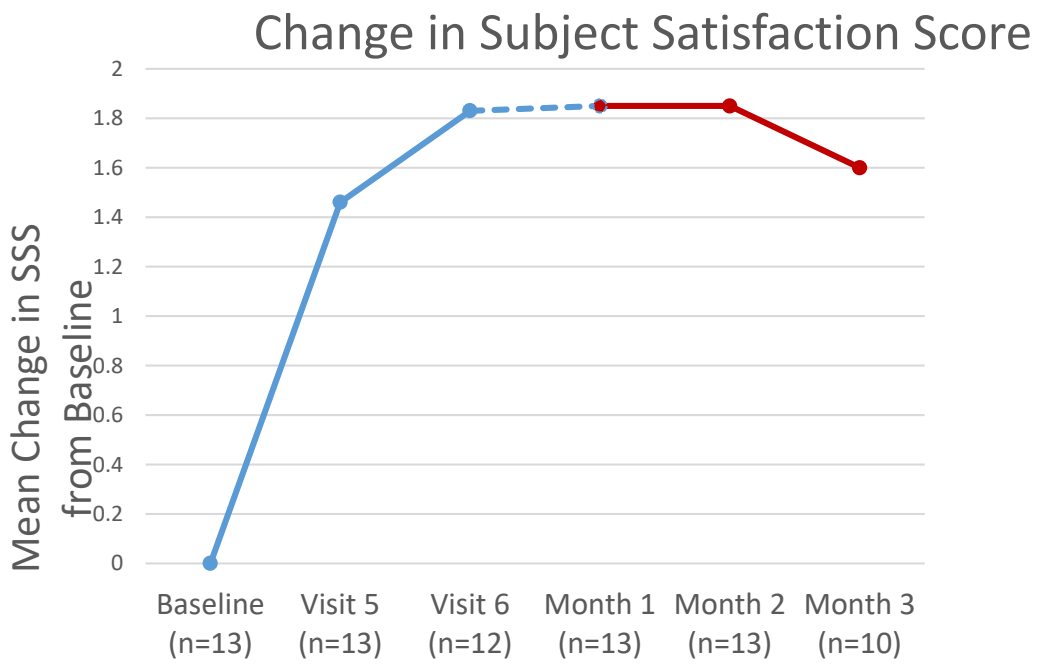
Cohort 2 (Efficacy) Summary

- Repeat administration of KB301 was well tolerated across subjects with minimal injection site reactions; all injection site reactions resolved within 3-5 days post injection
  - Systemic adverse events (drug or placebo related) included: mild body ache (n=4), mild fatigue (n=4), mild headache (n=2), mild chills (n=2); moderate muscle pain on one side of the body (placebo, n=1)
- Treatment of KB301 has demonstrated improved Subject Satisfaction Scores across three areas compared with placebo
- Before/after pictures show improvement in fine lines and skin texture
- The FDA has guided on the fine lines and wrinkle scale for KB301, confirming a path forward for utilization

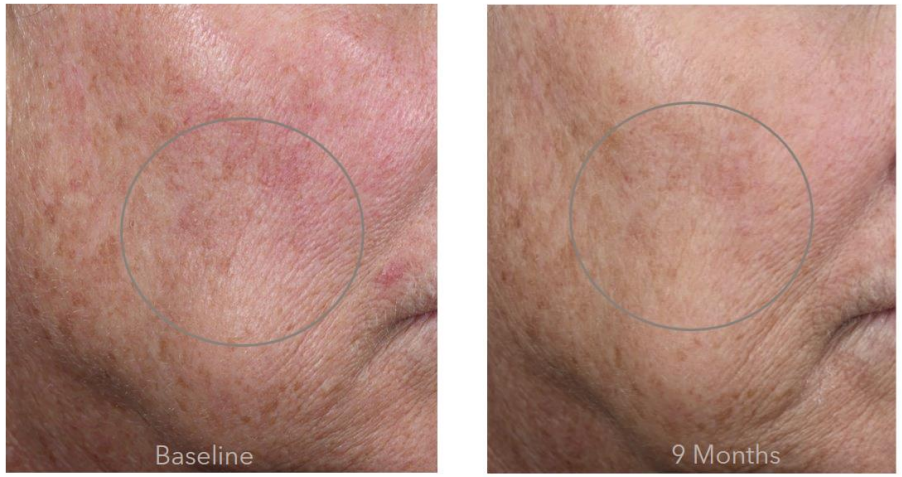
Guide S. American Academy of Dermatology Annual Meeting 2022

All products described in this presentation are investigational therapies

KB301 – PEARL-1 Cohort 2E (Durability)



Subject Age: 65



Cohort 2E (Durability) Summary

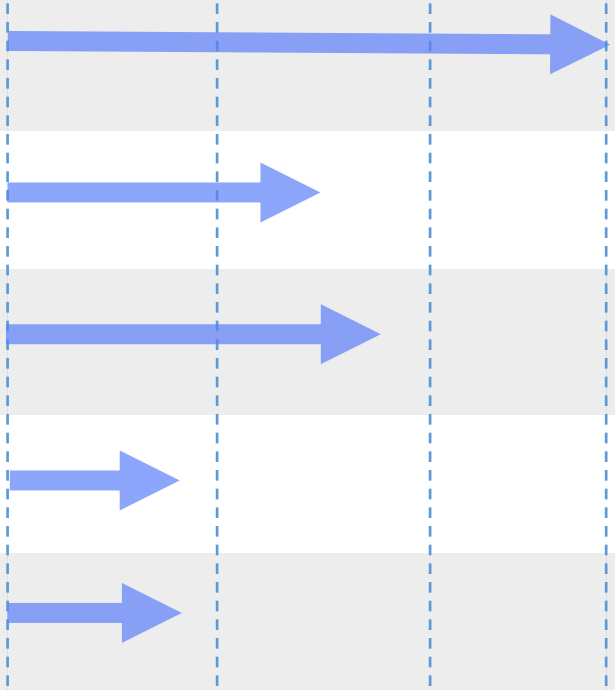
- Subject satisfaction scores collected in Cohort 2E indicate persistent treatment effect out to 9 months after the last dose of KB301
  - Subject Satisfaction Scores remain elevated from baseline approximately 7-9 months after the last dose in Cohort 2
- Investigator Assessment shows high proportion of cheeks with a clinically meaningful difference up to 9 months after last dose

Change in Subject Satisfaction Scores compared to baseline (defined as the beginning of Cohort 2 prior to any treatment with KB301). Visit 5 and 6 correspond to 2 to 4 weeks after the last dose, depending on whether the subject received 3 or 4 doses
Missing data at Visit 6 and Month 3 are due to missed study visits.

All products described in this presentation are investigational therapies

Robust Pipeline Addressing Key Skin Proteins Holds Broad Potential

Product	Gene	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Commercial
KB301	Type III collagen	TBD						
KB302	Type I collagen	TBD						
KB303	Elastin	TBD						
KB304	Type III collagen & Elastin	TBD						
KB305	Type IV collagen	TBD						



All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies. All pipeline compounds are wholly owned.

Fully Integrated

In-house Manufacturing Capacity and Expertise

ANCORIS Facility

- ~21,100 sq. ft. GMP facility
- Capabilities: Drug Substance, Drug Product, GMP Storage, Bulk Packaging, Waste Handling, Environmental Monitoring, and Logistics
- Built to support global B-VEC launch

ASTRA Facility

- ~155,000 sq. ft. GMP facility
- Capabilities: Process Development, MVB, Drug Substance, Drug Product, Packaging, Analytical Testing, Storage, General Office Space, GMP Storage, Bulk Packaging, Waste Handling, Environmental Monitoring, and Logistics
- Operational in 1H 2023

B-VEC, beremagene geperpavec; GMP, good manufacturing practice; MVB, master virus bank

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2023 Milestones

Timing	Program	Event
1H23	B-VEC for Dystrophic Epidermolysis Bullosa	PDUFA Date May 19, 2023
1H23	KB105 for Autosomal Recessive Congenital Ichthyoses	Initiate Phase 2 Study in adults and pediatric populations
1H23	KB407 for Cystic Fibrosis	Initiate dosing in Phase 1 clinical study
1H23	KB301 for treatment of Lateral Canthal lines	Initiate Phase 1c study in adult population
2H23	KB408 for Alpha-1 Antitrypsin Deficiency	Initiate Phase 1 clinical safety and efficacy study
2H23	B-VEC for Dystrophic Epidermolysis Bullosa	File Marketing Authorization Application in EU
2H23	B-VEC for Dystrophic Epidermolysis Bullosa	Initiate clinical study in Japan on small subset of Japanese patients
2H23	KB104 for Netherton Syndrome	File IND
2H23	KB301 for treatment of Lateral Canthal lines	Initiate Phase 2 clinical study

B-VEC, beremagene geperpavec; IND, Investigational New Drug; PDUFA, Prescription Drug User Fee Act

All products described in this presentation are investigational therapies

Krystal

Developing Genetic Medicines for Rare Diseases