Krystal

The Leader in **Redosable Gene Therapy** for Rare Disease

October 2021

Forward looking statements

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Krystal overview

A fully integrated, clinical stage gene therapy company powered by proprietary redosable gene delivery platform

Differentiated viral vector platform enables *in vivo*, repeat dose gene therapies

- Proprietary, engineered *replication incompetent* HSV-1 based platform
- Clinical data shows maintenance of safety and transgene expression after repeat dosing
- Positive external clinical and regulatory precedent with *in vivo* HSV-1 based therapy

Initial focus on rare, dermatologic indications led to rapid clinical proof of concept and pipeline

- Lead program, B-VEC (formerly KB103) went from IND to Phase 3 in less than 3 years; pivotal data anticipated in 4Q21
- Two lead dermatologic pipeline programs, KB104 and KB105, leverage the same vector

Broadening focus to address larger indications and new tissue types

- Ongoing Phase 1 trial in aesthetic skin indications with KB301, under our wholly owned subsidiary Jeune Aesthetics, Inc.
- Positive pre-clinical data from KB407 for cystic fibrosis demonstrates potential to target lung tissue
- Continue to drive innovation by investing in next-gen platform capabilities

In-house GMP manufacturing to support clinical and commercial needs

- Stable producer cell line developed and leveraged across pipeline has cost, scale, and regulatory benefits
- Current GMP facility near company headquarters in Pittsburgh is producing pivotal material at commercial scale; BLA readiness is underway
- Investing in additional capacity via construction of an ~150,000 sqft facility which is expected to be operational in 2022

Upcoming Milestones

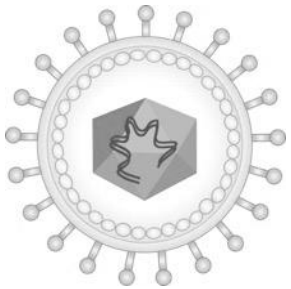
	Timing	Program	Event
☑	1Q21	B-VEC for DEB	Complete enrollment in pivotal GEM-3 study in DEB
☑	1Q21	KB301 for aesthetic indications	Announce Initial safety data from cohort 1 of Phase 1 study in facial wrinkles and acne scars
☑	1Q21	KB301 for aesthetic indications	Provide update on strategy for KB301 and aesthetic pipeline (under Jeune Aesthetics, Inc.)
☑	2Q21	KB407 for CF	Announce data from IND enabling toxicology study in nonhuman primates
☑	2Q21	Respiratory pipeline	Announce new development candidate KB408 for alpha-1 antitrypsin deficiency (AATD)
☑	2Q21	B-VEC	Present detailed Phase 1/2 safety summary at SID (May 3-8)
☑	2Q21	KB301	Present detailed Phase 1 (cohort 1) safety summary at SID (May 3-8)
☑	2Q21	KB5XX	Present preclinical proof-of-concept from vectorized antibody platform at ASGCT (May 11-14)
☑	2Q21	KB105 for TGM1-ARCI	Announce initial Phase 2 data and update on next Phase 2 cohorts
☑	3Q21/4Q21	KB407 for CF	Initiating Phase 1/2 study
☑	3Q21	B-VEC for DEB	Multiple abstracts at DEBRA International (Sept 16-19) including preclinical data on delivery to the eye
	4Q21	KB408 for AATD	Present preclinical pharmacology data for KB408 at ESGCT (Oct 19-22)
	4Q21	KB407 for CF	Present in vivo data, including nonhuman primate GLP tox data at NACFC (Nov 2-5)
	4Q21	KB301 for aesthetic indications	Initial efficacy data from Phase 1 study
	4Q21	**B-VEC for DEB**	**Announce top line data from the pivotal GEM-3 study**
	2022	KB105 for TGM1-ARCI	Initiate dosing in next Phase 1/2 cohort
	2022	KB104 for Netherton	File IND and initiate clinical trial

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

Our technology platform enables noninvasive, redosable gene therapy

HSV-1 is positively differentiated vs. other gene therapy technologies

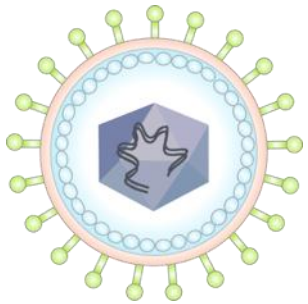
Wild-type HSV-1



HSV-1 has natural affinity for epithelial cells (in addition to several other cell types) with favorable immune-evasion mechanisms

Targeted mutagenesis resulting in platform that is both safe and effective for localized, repeat delivery of genetic payload

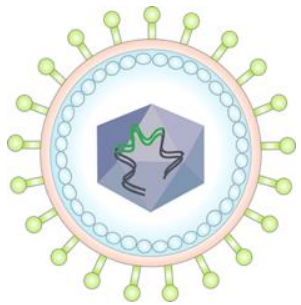
Krystal's Modified HSV-1 Platform



Replication incompetent HSV-1 vector that can be administered repeatedly for chronic dosing

Insertion of one or more therapeutic effectors of interest into the vector

Therapeutic Vector



Large carrying capacity allows insertion of large transgenes, multiple copies of the transgene of interest and/or multiple different transgenes

Vector Platform Comparison

	LV	AAV	HSV-1	LNP
In vivo dosing?	No	Yes	**Yes**	Yes
Baseline antibody exclusion criteria?	No (if *ex vivo*)	Yes	**No**	No
Repeat-dose capabilities?	Yes (if *ex vivo*)	No	**Yes**	Yes
Carrying capacity?	8 kb[1]	<4 kb[1]	**>30 kb**	~12 kb[2]
Integrates payload into host cell DNA?	Yes	No	**No**	No
Regulatory precedent?	Yes	Yes	**Yes**	Yes

1. Lundstrom, K. Viral Vectors in Gene Therapy. *Diseases* 2018, 6, 42.
2. Generation Bio (GBIO) Prospectus. (2020, June 11). Retrieved September 4, 2020, https://www.sec.gov/Archives/edgar/data/1733294/000119312520167812/d924849d424b4.htm

LV = lentivirus
AAV = adeno-associated virus
LNP = lipid nanoparticle

Therapeutic pipeline

	Product	Protein	Indication	Discovery	Preclinical	Phase 1/2	Phase 3	Key Upcoming Milestone	Ownership
Dermatology	**B-VEC**†¤•Δ‡§	Type VII collagen (COL7)	Dystrophic EB					Top line Phase 3 data in 4Q21	Wholly owned
Dermatology	**KB105**†¤•‡	Transglutaminase 1 (TGM1)	TGM1-deficient ARCI					Initiate next Phase 2 cohort in 2022	Wholly owned
Dermatology	**KB104**¤	Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)	Netherton Syndrome					File IND in 2022	Wholly owned
Dermatology	**KB1XX**	Undisclosed programs							Wholly owned
Dermatology	**KB5XX**	Vectorized antibodies	Chronic conditions						Wholly owned
Respiratory	**KB407**†¤‡	Cystic fibrosis transmembrane conductance regulator (CFTR)	Cystic fibrosis					Initiating Phase 1 study in 3Q21/4Q21	Wholly owned
Respiratory	**KB408**	Alpha-1 antitrypsin (AAT)	Alpha-1 antitrypsin deficiency						Wholly owned
Respiratory	**KB4XX**	Undisclosed programs							Wholly owned

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

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

Aesthetics pipeline

Program	Indication	Gene	Discovery	IND Enabling	Clinical Development	Next Milestone
KB301	Skin quality	type III collagen (COL3)				Phase I efficacy data in 4Q21
KB302	TBA	type I collagen (COL1)				
KB303	TBA	elastin (ELN)				
KB304	TBA	COL3 + ELN				

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

Platform supported by in-house manufacturing capacity and expertise

Established process conducted at Krystal's end-to-end GMP facility (Ancoris)

- Maintains control of IP/trade secrets relating to manufacturing process
- Adheres to internal process and production schedules, avoiding use of high demand gene therapy CMOs

Upstream process using stable producer cell lines has cost and regulatory benefits

- Stable complementary cell lines developed in-house are used in established methods for production of consistent batches
- Eliminates the need for multiple cGMP qualifications of plasmids and variability in transfection efficiency from batch to batch
- Scalable from clinical phase to commercial

We have successfully developed a robust and reproducible downstream process

- Work conducted in an aseptic closed system process
- The same process is leveraged across pipeline with minimal redevelopment effort between product candidates
- Compliant with global regulatory requirements

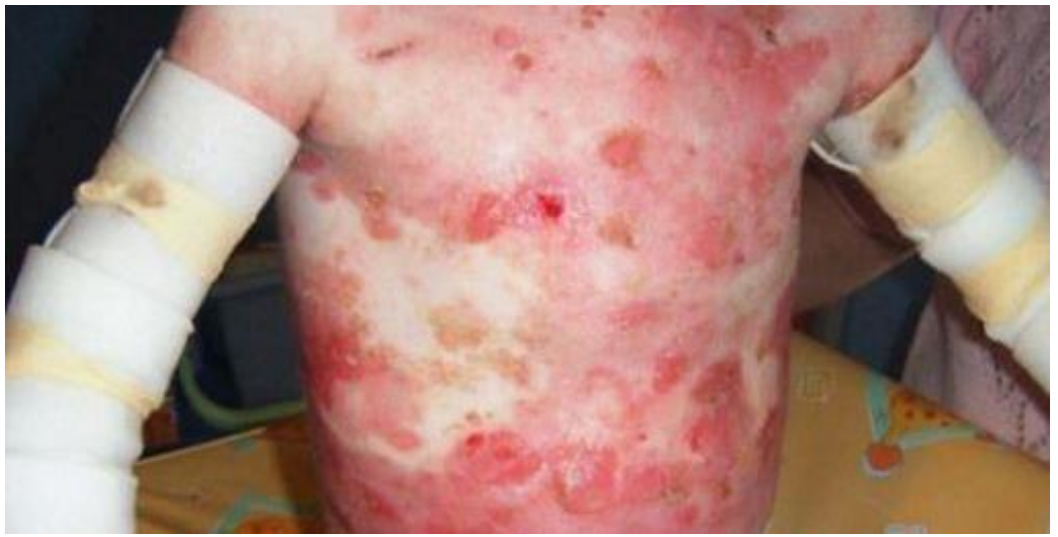
Initial focus on rare skin diseases led to rapid clinical POC and pipeline

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

- A rare, genetic skin disease that causes skin to tear or blister from minor contact
- Mutations in the *COL7A1* gene lead to absent or dysfunctional COL7 protein, without which the epidermis does not anchor to the dermis
- The recessive form (RDEB) is the classic, most severe form of the condition. Dominant DEB (DDEB) has a broader range in severity and is often characterized by blistering on the hands, feet, knees, and elbows



Epidemiology

- **Prevalence**: Up to 125,000 people are affected by DEB worldwide[1]
- We believe that there are, at present, approximately 3,000 DEB patients in the US
- **Incidence:** The incidence of DEB is 6.5 per million births in the US[2]

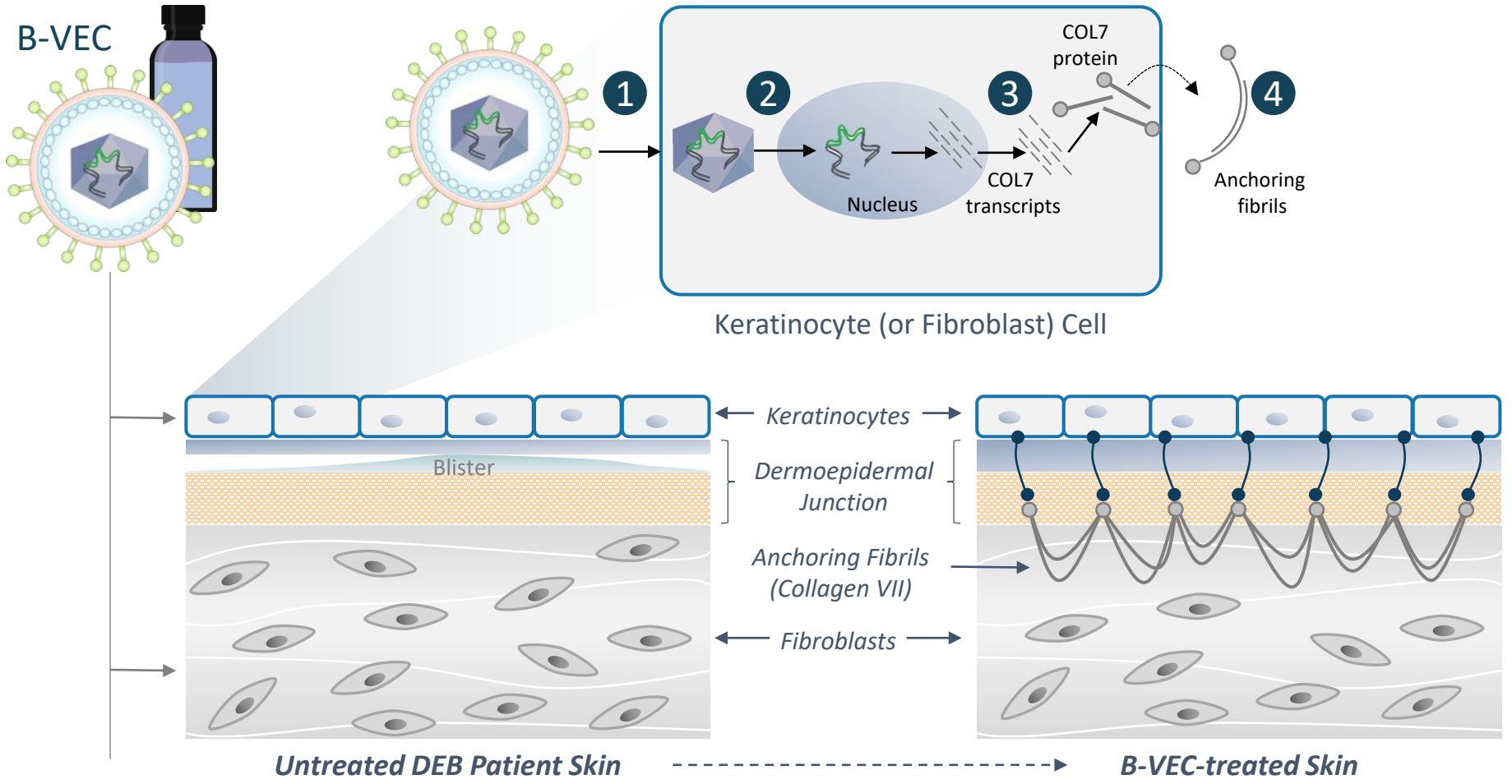
Current Standard of Care

- There are no approved treatments for DEB
- Existing therapies limited to expensive and time-consuming palliative treatments
- Palliative treatments cost $200k – $400k annually[3,4]

1. DEBRA International, http://www.debra-international.org/epidermolysis-bullosa/causes-and-subtypes.html; http://www.debra-international.org/what-is-eb/causes-and-subtypes/deb.html
2. Pfendner EG, Lucky AW. Dystrophic Epidermolysis Bullosa. 2006 Aug 21 [Updated 2015 Feb 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet].
3. 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
4. GENEGRAFT Report Summary. (2015, February 16). Retrieved December 13, 2016, from http://cordis.europa.eu/result/rcn/156078_en.html

Beremagene geperpavec (B-VEC) for DEB

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



1. B-VEC enters the compromised skin of DEB patients and transduces both keratinocytes and fibroblasts
2. Once in the nucleus of transduced cells the vector genome is deposited (episomally)
3. As a result, *COL7A1* transcripts are generated, allowing the cell to produce and secrete functional COL7 protein
4. The secreted COL7 protein assembles into anchoring fibrils which hold the epidermis and dermis together

B-VEC is an investigational therapy being studied in clinical trials

Topical B-VEC was evaluated in a Phase 1/2 study

Design

- GEM1/2 (NCT03536143) was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo.
- Each patient on-study for ~6 months; 3 months of on-site visits followed by 3-month at-home imaging period
- *Study PI: Dr. Peter Marinkovich (Stanford University)*

Enrollment

- A total of 9 RDEB patients (adult and pediatric) were enrolled in the study; 3 subjects re-enrolled later in the study and were re-randomized for a total of 12 subjects

Dosing

- In the Ph1 portion (n=2) one wound was administered B-VEC and one wound was administered placebo at a dose of 1e8 PFU/wound with varying frequency throughout the study period
- In Phase 2 portion (n=10) 2 wounds were administered B-VEC and one wound was administered placebo (except 1 patient who was 1:1) at doses of either 2e8, 3e8, 6e8 or 8e8 PFU/wound with varying frequency throughout the study period

Key Endpoints

Safety measures

- AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings
- Viral shedding was analyzed through the collection of blood, urine, and skin swabs, and antibodies to HSV and COL7 were analyzed through collection of serum

Efficacy measures

- Level of collagen VII (COL7) in B-VEC-administered skin as measured by immunofluorescence; presence of anchoring fibrils as measured by immunoelectron microscopy
- Wound closure (change in wound surface area relative to baseline), time to wound closure, and duration of wound closure, all relative to placebo

B-VEC is an investigational therapy being studied in clinical trials

Repeat doses of topical B-VEC were well tolerated; COL7 expression and molecular correction established

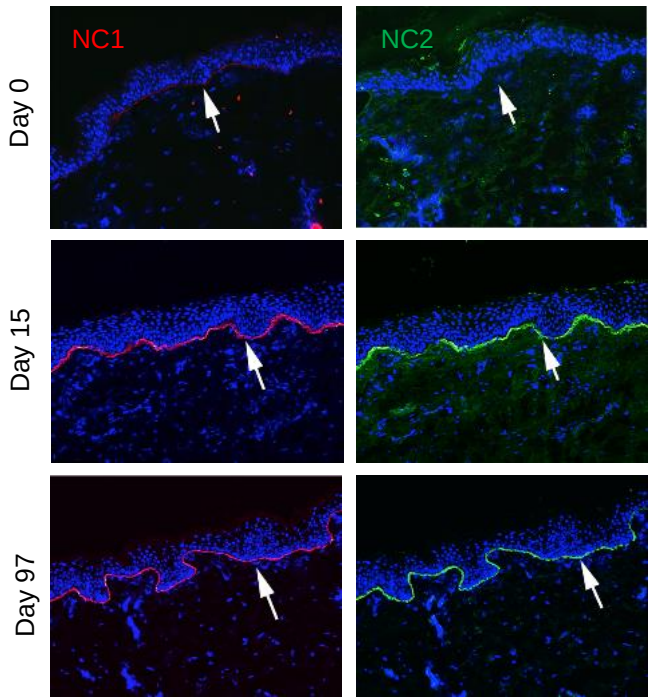
Increasing doses and dosing frequency were well tolerated

- In the Ph1/2 trial, the number of repeat doses per wound ranged from 4 to 41; the PFU per wound ranged from 1e8 to 8e8
- No treatment-related serious AEs were reported; AEs deemed possibly related were mild (n=20) or moderate (n=1)
- No immune response or blistering observed around the sites of administration following first and repeat doses
- Blood and urine samples collected throughout the study revealed:
  - No systemic viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
- Some patients had baseline COL7 and/or HSV-1 antibodies which did not impair efficacy or impact tolerance of therapy

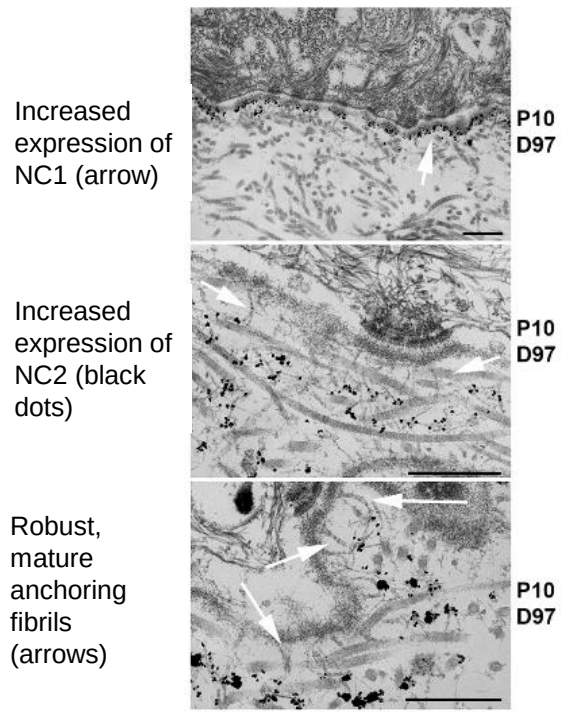
Molecular correction established and correlated with wound healing

- Expression and correct localization of full-length COL7 was observed following B-VEC therapy, evidenced by presence of *both* NC1 and NC2 domains and visible anchoring fibrils on IEM.

Baseline, Days 15 and 97 collagen VII expression using NC1 and NC2 specific antibodies (patient 10)



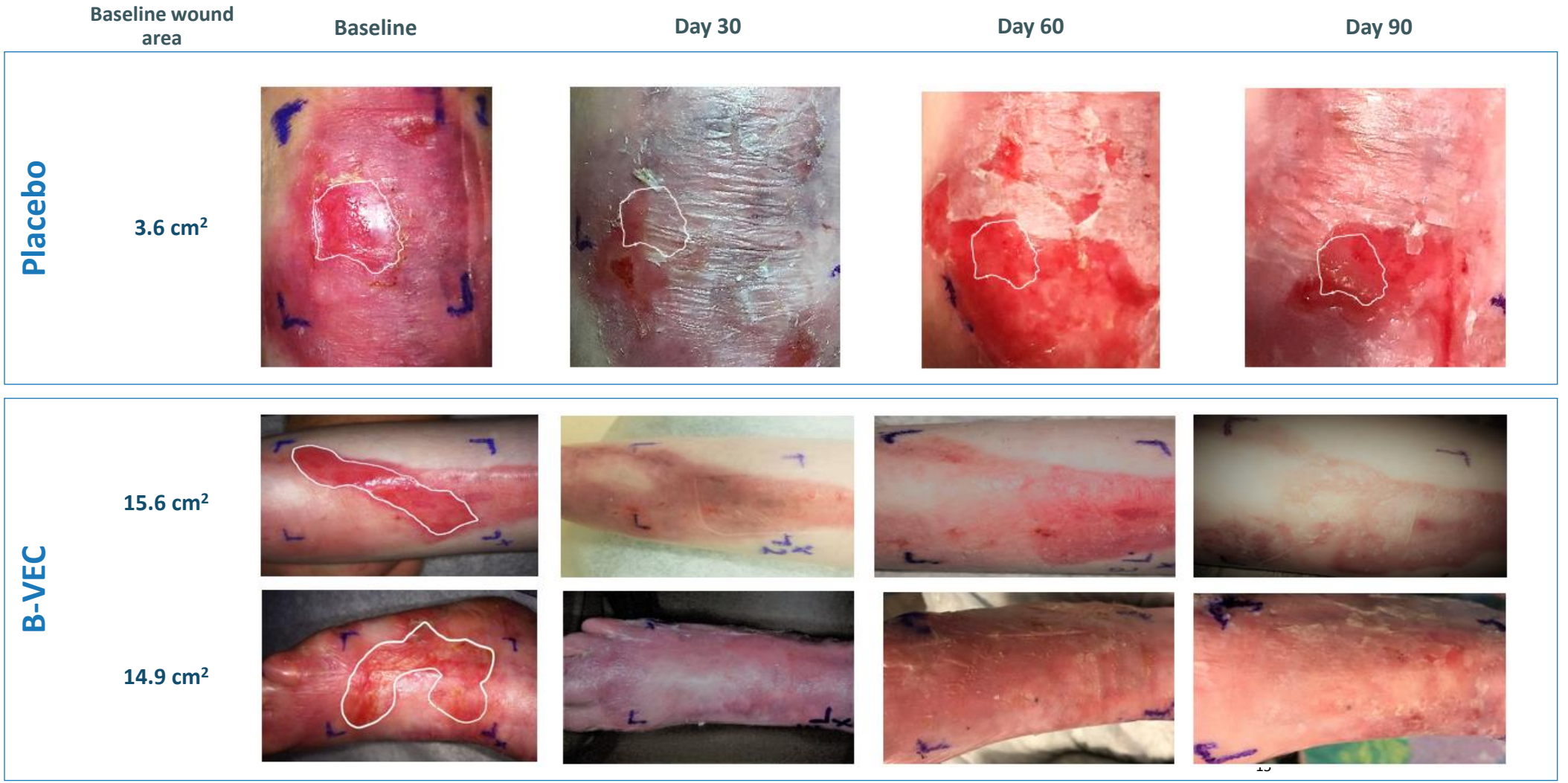
Immunoelectron microscopy shows mature anchoring fibrils at day 97 (patient 10)



Arrows indicate basement membrane zone

B-VEC is an investigational therapy being studied in clinical trials

Time course of B-VEC vs. placebo treated wounds - patient 5 (age 13)

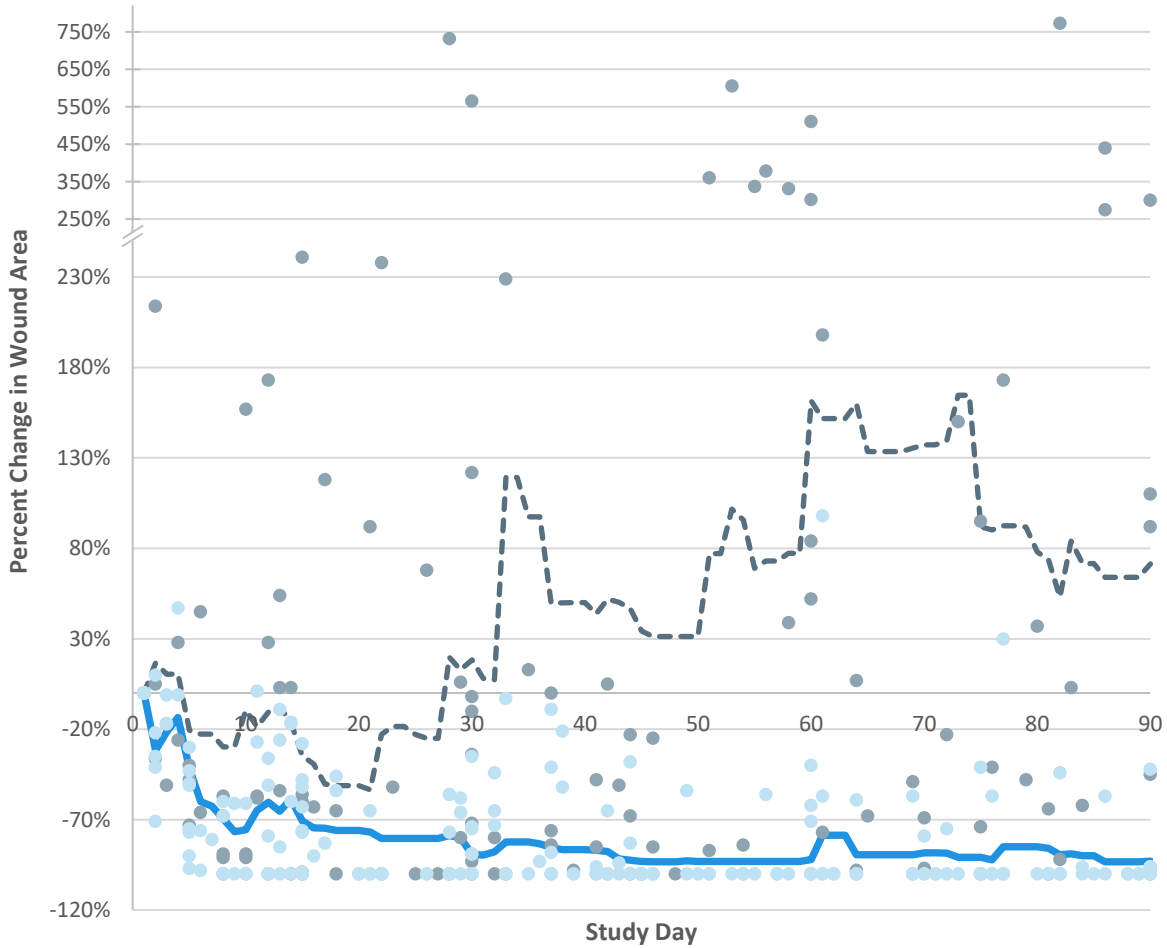


Dose: $3x10^8$ PFU per dose
Dosing days: 1, 2, 3, 4, 5, 36

B-VEC is an investigational therapy being studied in clinical trials

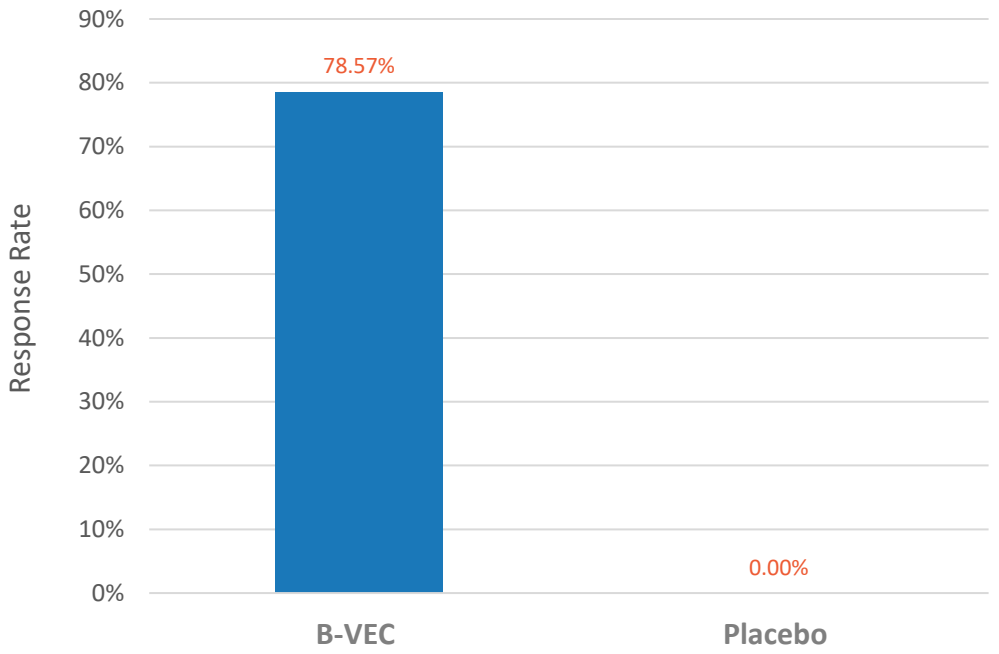
B-VEC showed statistically significant benefit in wound healing relative to placebo

Percent change in wound area from (individual measurements and average) from Day 0 to 90¤



¤ excluding patient 12

78.6% of B-VEC treated wounds vs. 0% of placebo treated wounds were completely closed at weeks 8 and 10 *or* weeks 10 and 12 ¤



B-VEC	78.57% (11/14)	0.00% (0/7)
p-value*	0.00257	

*based on McNemar test

¤ analysis based on all wounds that had measurements at weeks 8 and 10 or weeks 10 and 12

B-VEC is an investigational therapy being studied in clinical trials

The pivotal GEM-3 study is ongoing; top line data expected in 4Q21

Design

- GEM-3 (NCT04491604) is a randomized, double-blind, intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo
- Each patient on-study for approximately 7 months: the 6-month dosing period followed by a 30-day safety follow up

Enrollment

- 31 DEB subjects (adult and pediatric) were enrolled in US
- Ages ranged from 1 to 44 years old, 61% of patients were 18 years old or younger
- Each subject provided at least 1 pair of primary target wounds, one wound of the pair was randomized to B-VEC and the other to placebo
- In addition to the primary target wound pair(s), additional wounds (secondary wounds) may be selected to be treated with B-VEC in an open-label manner

Efficacy Endpoints

Primary

- Complete wound healing determined by the Investigator in B-VEC treated wounds versus placebo. A positive response is defined as:
  - Complete wound healing at Week 22 and Week 24; or
  - Complete wound healing at Week 24 and Week 26

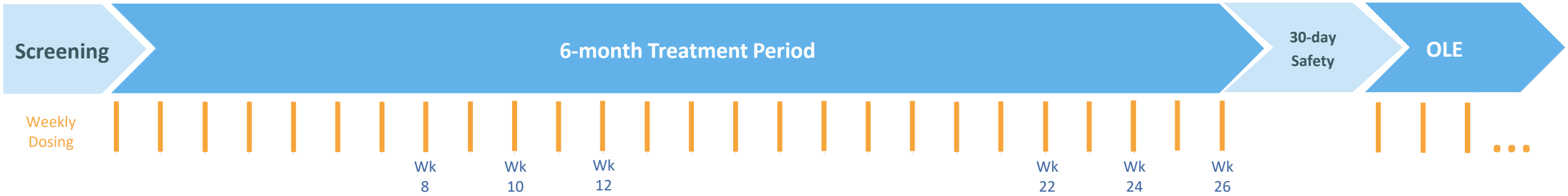
Secondary

- Complete wound healing, determined by the Investigator, as compared to baseline in B-VEC treated wounds versus placebo at weeks 8 and 10, or 10 and 12
- Mean change in pain severity (using either a VAS or FLACC-R Scale) per primary wound site associated with wound dressing changes
- Mean Change in Quality of Life in addition to Skindex score as compared to baseline at week 26

B-VEC is an investigational therapy being studied in clinical trials

Phase 3 trial is well powered and inclusive of a broad patient population

*The trial is designed to maximize chances of success while maintaining potential for a broad label, inclusive of **chronic and recurring wounds of any size** in RDEB or DDEB patients*



Dosing:

- Primary wounds will be treated once weekly with a fixed dose until wound closure; should a wound re-open, weekly dosing will resume at the assigned dose until wound closure
- Each patient is allowed a maximum weekly dose of B-VEC; if that maximum is not reached in dosing primary wounds, additional secondary wounds may be chosen and treated with B-VEC in an open label manner

Key Design Elements:

- No restriction on chronic or recurring wounds
- Maximum weekly dose allows for flexibility to treat multiple and / or larger wounds
- Inclusive of RDEB *and* DDEB patients

Primary Endpoint:

- A positive response is defined as complete wound healing at weeks 22 and 24 *or* weeks 24 and 26
- The study has greater than 90% power to detect a 50% difference in response rate between B-VEC and placebo with two-sided Type 1 error rate of 5% using the McNemar test

Dose Per Wound	
Wound Area	**Dose**
<20cm^2	4x10^8 PFU
20-40cm^2	8x10^8 PFU
40-60cm^2	1.2x10^9 PFU

Maximum Weekly Dose Per Subject:	
Age	**Max Weekly Dose**
≥ 6 months to < 3 years	1.6x10^9 PFU/week
≥ 3 years to < 6 years	2.4x10^9 PFU/week
≥ 6 years	3.2x10^9 PFU/week

B-VEC is an investigational therapy being studied in clinical trials

Autosomal Recessive Congenital Icthyosis associated with TGM1 mutations

Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life

Autosomal Recessive Congenital Ichthyosis (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, skin malignancies, etc

Epidemiology[1-8]

- **Prevalence:** There are approximately 20,000 people affected by TGMI related icthyosis worldwide (~1,800 US; 3,000 EU; 18,000 ROW)
- **Incidence:** It is estimated that around 350-400 babies are born with the condition each year, worldwide

Current Standard of Care

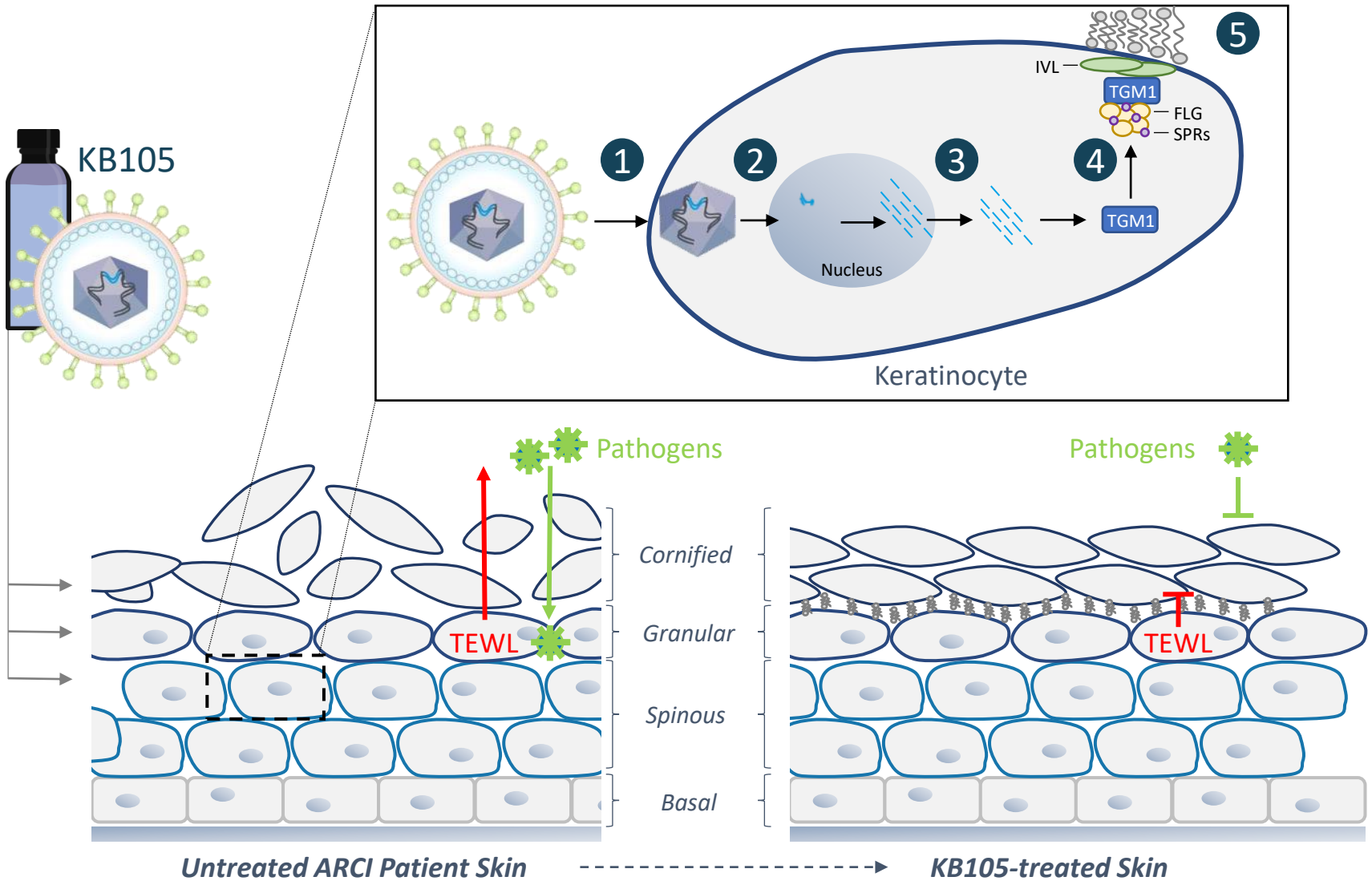
- There are no approved treatments for ARCI associated with TGM1
- Topical and systemic retinoids and time-consuming supportive treatments (up to 4 hours a day of skin care) are most often used

1. Rodriguez-Pazos et al. *Actas Dermosifiliogr.* 2013 May;104(4):270–284;
2. Dreyfus et al. *Orphanet J Rare Dis.* 2014 Jan 6;9:1;
3. Hernandez-Martin et al. *J Am Acad Dermatol.* 2012 Aug;67(2):240–244;
4. Pigg et al. *Eur J Hum Genet.* 1998 Nov-Dec;6(6):589–596.
5. Pigg et al. *Acta Derm Venereol.* 2016 Nov 2;96(7):932–937;
6. Orphanet;
7. Foundation for Ichthyosis & Related Skin Types (FIRST);
8. National Organization for Rare Disorders (NORD).

KB105 for TGM1 associated ARCI

Topically applied KB105 delivers multiple copies of the human transglutaminase 1 ("TGM1") gene

1. KB105 enters permeabilized skin and transduces keratinocytes (native TGM1-producing cells)
2. KB105 is transported into the nucleus of transduced cells and the vector genome is deposited (episomally)
3. *TGM1* transcripts are generated, which allows the cell to produce functional TGM1 protein that localizes to the cell membrane
4. TGM1 crosslinks target proteins (*e.g.*, filaggrin (FLG), involucrin (IVL), small proline-rich proteins (SPRs)) to aid in the formation of the cornified cell envelope
5. This layer, known as the stratum corneum, acts as a mechanical barrier to protect against transepidermal water loss (TEWL) and entry of infectious agents



KB105 is an investigational therapy being studied in clinical trials

KB105 is being evaluated in a Phase 1/2 study

Design

- The Ph1/2 trial (NCT04047732) is an open label, intra-patient comparison of KB105 and placebo
- Each patient on-study for four to six months
- *Study PI: Dr. Amy Paller (Northwestern University)*

Enrollment

- 4 TGM1-ARCI subjects were enrolled across 2 sites; three Ph1 patients were enrolled at Paddington Testing Company (Philadelphia); one Ph2 subject was enrolled at Northwestern (Chicago)

Dosing

- In the Ph1 portion (n=3) one or two ~20cm^2 target areas were administered placebo, and 3 target areas were administered 2x10^9 PFU with varying frequency over ~60 days
- In Ph1, topical and microneedle administration was evaluated; in Ph2 topical administration will be utilized
- In the Phase 2 portion (n=1) four ~100cm^2 treatment areas were administered KB105, either 4x10^9 PFU or 1x10^{10} at either a high or low dosing frequency

Key Endpoints

Safety measures

- AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings
- Viral shedding analyzed through the collection of blood, urine, and skin swabs; antibodies to HSV and TGM1 analyzed through collection of serum

Efficacy measures

- Level of transglutaminase 1 in KB105-administered skin as measured by immunofluorescence microscopy (Ph1)
- Improvement of disease severity in the treatment area assessment through Investigator's Global Assessment (IGA)

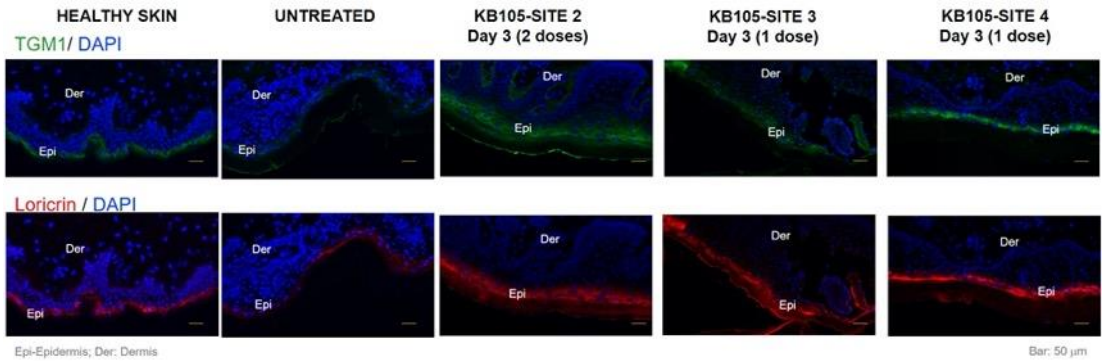
KB105 is an investigational therapy being studied in clinical trials

Phase 1/2 data shows repeat dosing of KB105 to be well tolerated; molecular and phenotypic improvement evident

KB105 Was Well Tolerated and Generated Functional TGM1 protein

- Repeat dosing with KB105 was well tolerated with no drug related AEs and no immune response to HSV or TGM1
- No vector shedding detected in swabs, blood or urine in all three patients
- Biopsies assessed in the Phase 1 portion of the study show:
  - KB105 treatment restored functional TGM1 protein expression and activity in all treated sites
  - KB105-expressed TGM1 was correctly localized in the epidermis, colocalizing with Loricrin, and was functionally active
  - qPCR, IF, and in situ analyses demonstrated similar delivery efficacy of TGM1 DNA from single and repeat administration

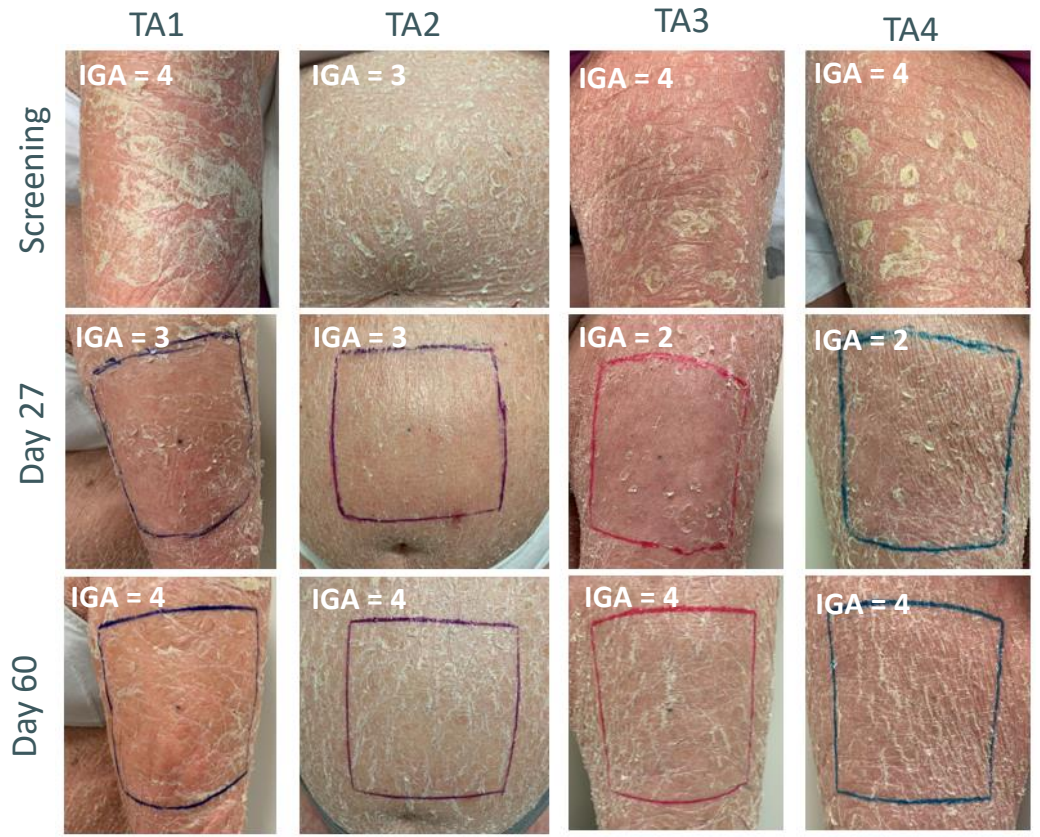
Subject 1: Treatment Restored TGM1 Expression to Normal Levels



- TGM-1 turnover was observed to be variable and rapid, and pharmacokinetic data suggested that the optimal dosing frequency may be more frequent

Maximum 2-point Improvement in IGA Scale as Compared to Screening Observed at Day 27 at High Dose

- In the Phase 2 portion (n=1) four ~100cm2 treatment areas (TAs) were administered KB105, either $4x10^9$ PFU or $1x10^{10}$ at either a high or low dosing frequency

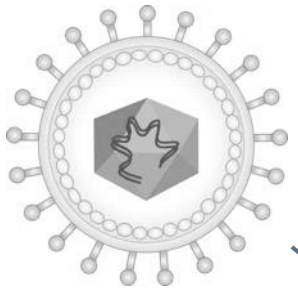


KB105 is an investigational therapy being studied in clinical trials

Leveraging platform to target new tissues and larger indications

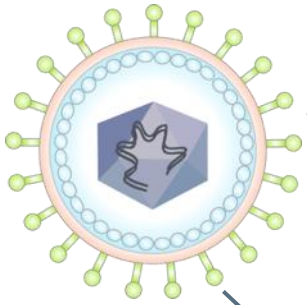
HSV-1 has potential beyond rare skin diseases

Wild-type HSV-1



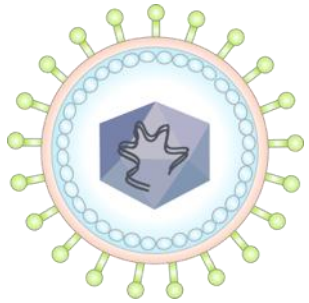
HSV-1 has natural affinity for **epithelial cells,** in addition to several other cell types, with favorable immune-evasion mechanisms

Krystal's Current Platform



- Skin
  - Rare Skin Disease
    - ✓ B-VEC (COL7) for DEB
    - ✓ KB105 (TGM1) for TGM1-ARCI
    - • KB104 (SPINK5) for Netherton's Disease
    - • Additional preclinical candidates
  - Aesthetics (Jeune Aesthetics)
    - ✓ KB301 (COL3) for Acne Scars and Wrinkles
    - • Additional preclinical candidates
  - Different Diseases
  - Different Effectors (e.g. antibodies, RNAi)
- Lung
  - Rare Lung Disease
    - • KB407 (CFTR) for Cystic Fibrosis
    - • KB408 (AAT) for alpha-1 antitrypsin deficiency
    - • Additional preclinical candidates
  - Different Diseases
  - Different Effectors (e.g. antibodies, RNAi)

Investing in Next Gen Technology to Maintain Leadership in HSV-1 Space



KB407 for cystic fibrosis

Gene therapy approaches have been tried and failed in their attempts to replace CFTR protein

- Viral (adenovirus and AAV) and non-viral (DNA plasmids and stabilized mRNA) approaches have been tested in more than 25 clinical trials enrolling >470 patients
- Past approaches suffer from some combination of physical limitations for large cargo, low efficiency of gene transfer, toxicity, immune intolerance, product instability, and burdensome delivery

We are developing KB407 as an inhalable, repeat dose gene therapy that delivers the full human CFTR gene

- ✓ Replication incompetent HSV-1
- ✓ Delivers two copies of full length, human CFTR protein (mutation agnostic approach)
- ✓ Duration of nebulization expected to be under 30 minutes, using a commercially available nebulizer
- ✓ Episomal delivery of CFTR gene does not disrupt cell DNA
- ✓ Ability to re-dose and/or adjust dose over time as lung cells turnover

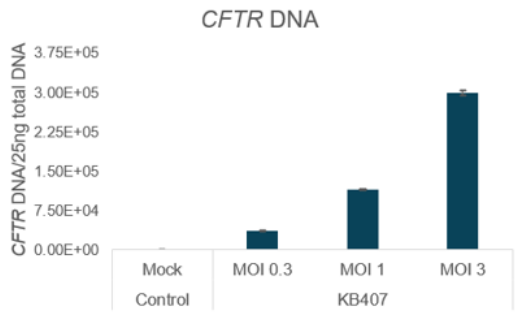
Our vector can be formulated and delivered via nebulizer with no significant change in activity

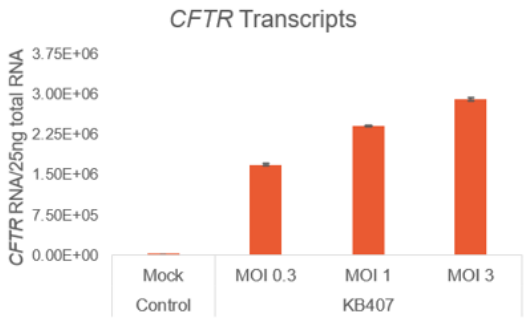
- In vitro data shows KB407 can be nebulized, successfully transduce target lung cells and induce expression of fully functional and properly localized CFTR

KB407 is an investigational therapy being studied in preclinical trials

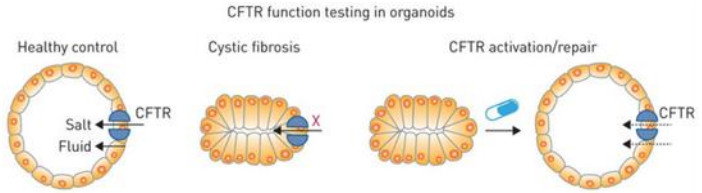
Preclinical data supports KB407 in CF and broader development in lung disease

Robust, dose-dependent CFTR expression and functional correction in 2D airway epithelial cell culture

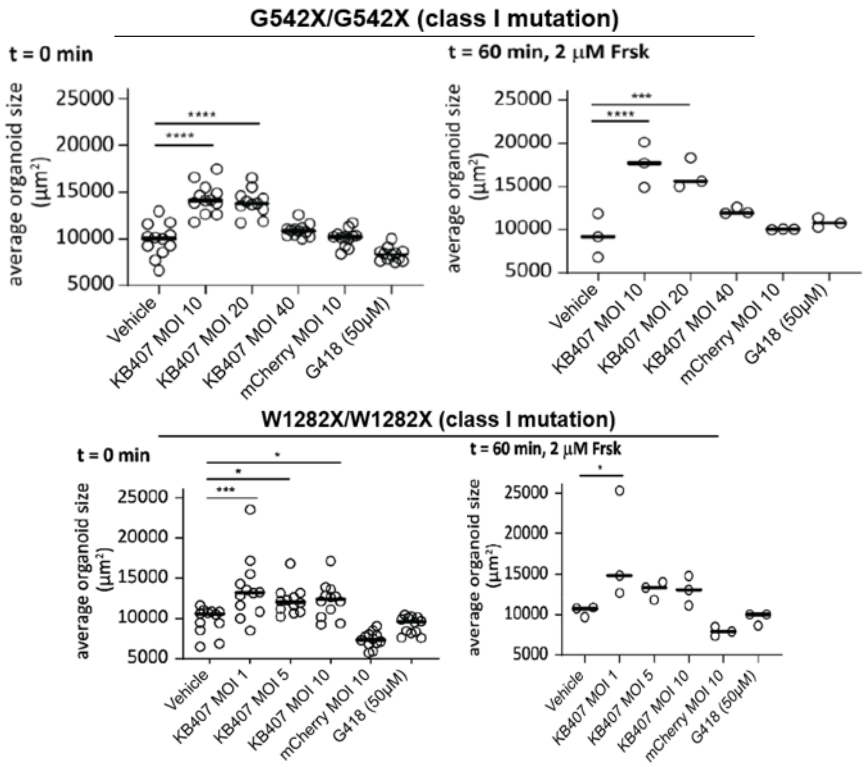




KB407-mediated functional correction of CF phenotype in clinically relevant 3D organotypic system (HUB)



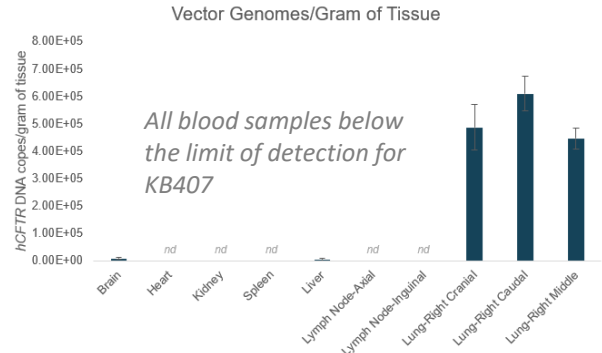
*Van Mourik *et al.* (2019). "Intestinal organoids to model cystic fibrosis".



KB407 is an investigational therapy being studied in preclinical trials

Two repeat doses of KB407 in a nonhuman primate were well tolerated and distributed broadly throughout the lung

- No abnormal cage-side/clinical observations throughout study
- No gross findings noted at time of necropsy



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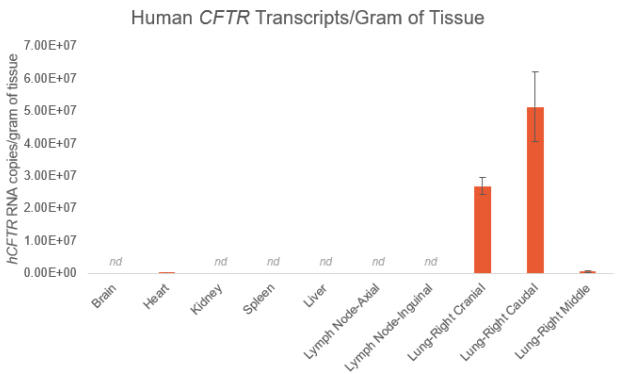


KB301 for aesthetic indications

KB301 and other discovery programs in Aesthetics, are housed in our wholly owned subsidiary, Jeune Aesthetics, Inc.

KB301 aims to increase neocollagenesis, thereby correcting the underlying molecular defect of the aged phenotype

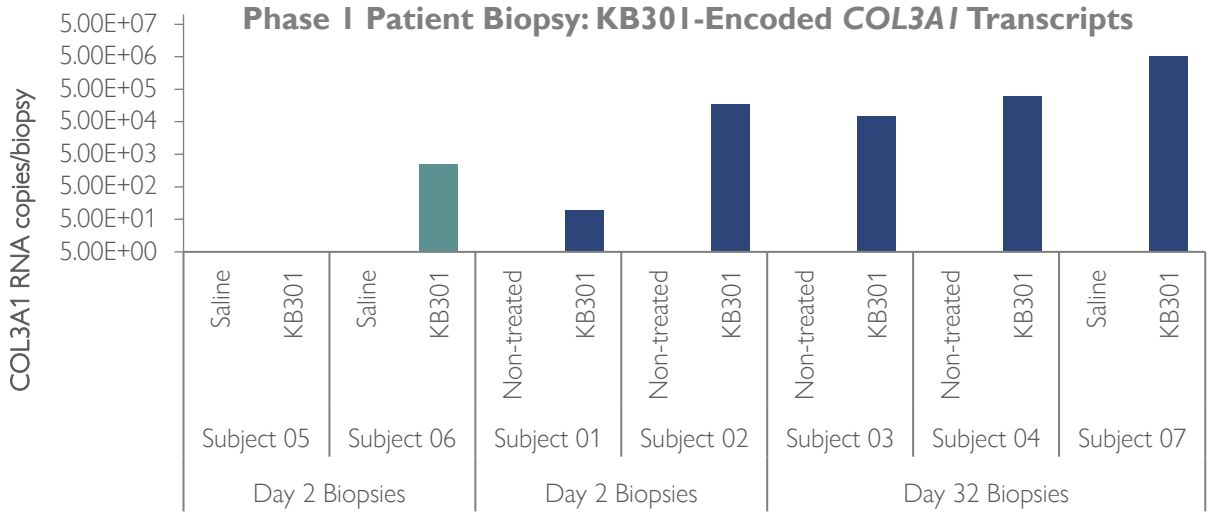
- Dermal collagen, composed primarily of types 1 and 3 collagen fibrils, represents >90% (dry weight) of human skin
- Declining levels of collagen are caused by reduced collagen biosynthesis and increased collagen fibril fragmentation resulting from both intrinsic (e.g., passage of time, genetics) and extrinsic (e.g., chronic light exposure, pollution) pressures
- KB301 is designed to deliver the gene for full-length type III collagen (COL3)
- It is injected directly into the area of interest, with the goal of targeted collagen production by the body's own cells

KB301 is currently being evaluated in a Phase 1 trial (NCT04540900)

- The open label, dose ranging study will evaluate repeat dosing of KB301 injections
- Safety data from Cohort 1 (repeat KB301 injections into the buttock region) was reported at SID 2021
- Cohort 2 is currently enrolling and will evaluate efficacy of repeat doses of KB301 on the face and knees
  - ~30 subjects will be enrolled; bilateral treatment areas on the neck behind the ear, on the cheek below and above the zygomatic arch, and around the knee will be chosen and randomized 2:1 to receive low dose KB301, high dose KB301, or saline administered via in multiple micro depot injections over the selected treatment area
  - Change in skin quality from baseline will be assessed via the Skin Roughness Score (SRS), Fine Lines Score (FLS), and the Subject Satisfaction Score (SSS). Skin calipers will be used to measure the change in skin thickness over the knee

Initial data from Cohort 1 of the Phase 1 study shows safety and tolerability of repeat KB301 injections

- Repeated intradermal injections of KB301 were well tolerated.
- Recorded adverse events were transient and limited to expected mild or moderate injection site or biopsy site reactions (e.g. erythema, site pain, purpura, ecchymosis)
- For all subjects who have completed follow up through day 90 (subjects 1-6; subject 7 follow up ongoing) no clinically significant changes in anti-drug antibodies were observed



- KB301-encoded COL3A1 expression measurable at the mid and high dose, with no detectable expression in control samples
- Expression was evident by day 2 following the first dose; expression levels were similar following the first and second dose

KB301 is an investigational therapy being studied in preclinical trials

Financials and Milestones

Krystal summary

A fully integrated, clinical stage gene therapy company powered by proprietary HSV-1 vector technology

Current Status and Milestones

Rare Skin

- **B-VEC:** Pivotal GEM-3 trial ongoing with topline data expected 4Q21. Commercial planning in US and EU underway
- **KB105:** Phase 2 study ongoing; Initiation of dosing in next Phase 2 cohort in 2022
- **KB104:** IND filing in 2022

Jeune Aesthetics, Inc

- **KB301:** Phase 1 trial in aesthetic skin indications ongoing; initial Phase 1 efficacy data anticipated in 4Q21

Rare Lung

- **KB407:** Phase 1 trial being initiated in Australia

Platform

- **Manufacturing:** Ancoris facility currently supplying all clinical material and will supply initial phase of B-VEC launch; Astra facility (150,000 sqft) construction underway, completion anticipated in 2022
- **Next Gen Tech:** Evaluation of novel effectors, routes of administration, and tissue tropism underway

June 30, 2021 cash balance of $389.1M

- B-VEC, KB105, KB104 and KB407 are PRV eligible

Krystal

The Leader in Redosable Gene Therapy for Rare Disease

October 2021