First-in-Human Safety and Mechanism of Action (MOA) Analyses of Repeatedly Dosed In Vivo Gene Delivery for Directed Human Type III Collagen (COL3) Expression in Aesthetics

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Introduction

- Due to the essential role collagen plays in the process of skin biorejuvenation, and the diminution of dermal collagen being a significant contributor to the aged phenotype, direct and indirect collagen stimulation/supplementation/replacement has been a focus of cosmetic product development[1-3]
- However, directed supplementation of functional full-length human type III collagen (COL3), produced by and secreted from the patient's own dermal cells, has not previously been explored clinically
  - To this end, we engineered KB301, a replication-defective gene therapy vector, for the targeted delivery of human COL3
  - Preclinically, KB301 was shown to transduce clinically relevant skin cells and express and secrete mature human COL3 *in vitro*, as well as to confirm proper tissue localization of the transgene without toxicity or systemic vector distribution *in vivo*
- Results from these *in vitro* and *in vivo* proof-of-concept studies and safety assessments supported the initiation of a phase I clinical trial of KB301 for the treatment of superficial skin depressions

Methods

Study Design

- An open-label, intra-patient phase 1 study is underway to assess the safety and preliminary efficacy of repeat-dose KB301
- Dosing of cohort 1, the safety cohort, is complete and results are presented herein (**Figure 1**)

Inclusion Criteria (Cohort 1)

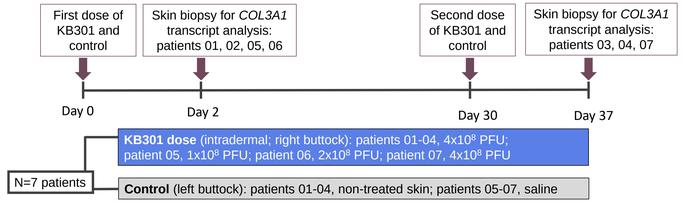
- Male or female in good general health aged ≥18 and ≤75 at the time of consent
- Regions of suitable skin to be selected as Target Area(s), as determined by a physical examination during a screening visit:
  - Patients 01-04: region of healthy buttock skin
  - Patients 05-07: two bilaterally symmetrical regions of healthy buttock skin at least 6 cm apart
- A Fitzpatrick skin phototype score of I-IV
- A negative pregnancy test at the Study Day 0 Visit for patients of child-bearing potential
- Signed and dated informed consent and willingness to attend all study visits and complete all procedures required by this protocol

Exclusion Criteria (Selected)

- Any transient or chronic skin condition, disorder, or infection within 20 cm of the Target Area(s) that may confound study results
- History of laser treatment or chemical peels to the Target Area(s) within six months of the Study Day 0 Visit
- History of surgical procedures to Target Area(s), including removal of benign or malignant skin cancers that may confound study results

Methods (Cont'd)

Figure 1. Phase I, Cohort 1, Open-Label, Intra-Patient Evaluation of KB301 Trial Design (N=7)



Primary end point (safety): Assessment of adverse events, physical examinations, vital signs, and clinical laboratory test results
Secondary end point (MOA): *COL3A1* transgene expression via qRT-PCR analysis

Results

Table 1. Patient Demographics

Patient	Visit	Age at Informed Consent, y	Sex	Ethnicity	Race
01	Screening	56	Female	Not Hispanic or Latino	White
02	Screening	48	Female	Not Hispanic or Latino	White
03	Screening	74	Female	Not Hispanic or Latino	White
04	Screening	52	Male	Not Hispanic or Latino	White
05	Screening	63	Female	Not Hispanic or Latino	White
06	Screening	51	Male	Not Hispanic or Latino	White
07	Screening	71	Female	Not Hispanic or Latino	White

Table 2. Adverse Events

Treatment	Adverse Event	Severity (No. of Events)			
		Grade 1	Grade 2	Grade 3	Grade 4
KB301	Treatment site erythema	2	11		
KB301	Treatment site pain	1	4		
KB301/Control	Purpura at bilateral biopsy sites	1			
KB301/Control	Ecchymosis at bilateral biopsy sites	2			
KB301	Treatment site edema	1	1		
KB301	Treatment site induration	1			

- All reported AEs were expected treatment site reactions of mild to moderate severity, and no SAEs or clinically significant lab results were reported for any study patients at any time point. None of the AEs required a pause in the study or alteration of dosing frequency (**Table 2**)

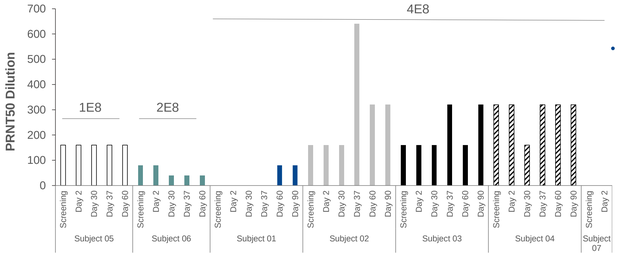
Results (Cont'd)

Table 3. Vector Shedding by Site Visit

		Site Visit					
	Sample Type	Screening	Day 2	Day 30	Day 37	Day 60	Day 90
Subject 01	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 02	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 03	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 04	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 05	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 06	Whole Blood	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Urine	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
	Skin Swab	BLOD	BLOD	BLOD	BLOD	BLOD	BLOD
Subject 07	Whole Blood	BLOD	BLOD	BLOD	BLOD		
	Urine	BLOD	BLOD	BLOD	BLOD		
	Skin Swab	BLOD	BLOD	BLOD	BLOD		

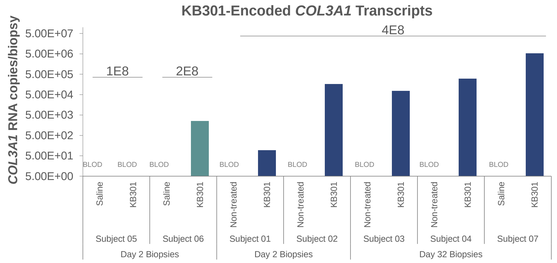
BLOD: below limit of detection

Figure 2. Anti-HSV Antibody Response



- No clinically significant increases (defined as a 4-fold sustained increase in anti-HSV antibody titer) in ADAs were detected in any patient (**Figure 2**)

Figure 3. *COL3A1* Transcript Analysis



- Equivalent transgene expression levels were observed in biopsies from patients having received one or multiple KB301 administrations (**Figure 3**)

BLOD: below limit of detection (defined as 100 copies/5 µL).

CONCLUSIONS

KB301 was shown to be well tolerated for *COL3A1* supplementation in healthy human subjects, supporting clinical progression of KB301 for the treatment of aesthetic skin conditions

- **AEs were limited to expected, transient treatment site reactions**
- **No severe (grade 3) or life-threatening (grade 4) AEs; no SAEs were reported**
- **No clinically significant changes in lab results were observed**
- **No vector shedding was detected in blood, urine, or skin swabs**
- **No clinically significant changes in anti-HSV antibodies were observed**
- **Similar KB301-encoded transgene expression levels were observed at first and second dose**
- **No apparent impact on transgene expression in patients with pre-existing anti-HSV antibodies at enrollment was observed**

Abbreviations

ADA, anti-drug antibody; AE, adverse event; BLOD, below limit of detection; COL3, human type III collagen; HSV, herpes simplex virus; MOA, mechanism of action; PFU, plaque-forming unit; qRT-PCR, quantitative reverse transcription–polymerase chain reaction; SAE, serious adverse event

References

1. Kontis & Rivkin 2009. *Facial Plast Surg.* 25(2): 67-72.
2. Liu *et al.* 2005. *Semin Plast Surg.* 19(3): 241-50.
3. Yutskovskaya *et al.* 2014. *J Drugs Dermatol.* 13(9): 1047-52.

Acknowledgments

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Disclosures

S. Krishnan, N. Angeloff, N. Reitze, N. Sarma, and T. Parry are employees of Krystal Biotech, Inc. Dr. Nestor is the principal investigator of this study.

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