UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): December 12, 2024

KRYSTAL BIOTECH, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38210**	**82-1080209**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification Number)**

2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(Address of principal executive offices, including Zip Code)
Registrant's telephone number, including area code: (412) 586-5830

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock	**KRYS**	**Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 12, 2024, Krystal Biotech, Inc. (the "Company") issued a press release announcing an initial clinical update for its rare respiratory disease programs KB408 and KB407, including early clinical evidence of gene delivery to the lung of AATD patients and increase in lung AAT to therapeutic levels. In addition, the press release indicated that the Company would host a conference call and webcast at 8:30 a.m. ET on December 12, 2024, to discuss the interim clinical data and its KB408 and KB407 clinical development programs. For purposes of the call and webcast, the Company provided a slide presentation, which will be available on the "Investors" section of the Company's website at www.krystalbio.com. Copies of the press release and the slide presentation are attached hereto as Exhibit 99.1 and Exhibit 99.2, respectively, and are incorporated by reference herein.

The information in this Item 7.01 of this Current Report on Form 8-K and in Exhibits 99.1 and 99.2 attached hereto shall not be (i) deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, or (ii) incorporated into any registration statement or other document filed with the Securities and Exchange Commission by the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release dated December 12, 2024
99.2	Slide Presentation dated December 2024
104	Cover Page Interactive Data file (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: December 12, 2024

KRYSTAL BIOTECH, INC.

By: /s/ Krish S. Krishnan
Name: Krish S. Krishnan
Title: Chairman and Chief Executive Officer

Krystal Biotech Announces Initial Clinical Update for Rare Respiratory Disease Programs KB408 and KB407 Including Early Clinical Evidence of Gene Delivery to the Lung of AATD Patients and Increase in Lung AAT to Therapeutic Levels

Clear evidence of SERPINA1 gene delivery and AAT expression following KB408 administration in AATD patients

Both KB408 for AATD patients and KB407 for patients with cystic fibrosis were safe and well tolerated at all dosing regimens evaluated to date

Conditional sanctioning of the KB407 Phase 1 CF Study CORAL-1 protocol by CFF TDN

Investor call and webcast to be held December 12 at 8:30 am ET to discuss data update

PITTSBURGH, December 12, 2024 (GLOBE NEWSWIRE) – Krystal Biotech, Inc. (the "Company") (NASDAQ: KRYS), a commercial-stage biotechnology company, announced today clinical data updates for both KB408 and KB407, the Company's clinical-stage, inhaled genetic medicine programs in Phase 1 for the treatment of rare respiratory diseases. Today's updates include molecular data from multiple patients demonstrating *SERPINA1* delivery and alpha-1 antitrypsin (AAT) expression within the respiratory tract following KB408 administration as well as safety and tolerability data for both KB407 and KB408 that, taken together, highlight the potential of the Company's platform to safely deliver genetic cargo to the lung.

"To achieve meaningful AAT expression levels and functionality with the first dose of KB408 is a very exciting development for this program and for our alpha-1 antitrypsin deficiency (AATD) patients," said Robert A. Sandhaus, MD, PhD, FCCP, Professor of Medicine at the National Jewish Health in Denver, Executive Vice President and Senior Medical Director of AlphaNet, as well as Clinical Director of the Alpha-1 Foundation. "Even though the first intravenous augmentation therapy was approved decades ago, we still don't have a good understanding of the impact these therapies are having on lung disease. A safe, effective, non-invasive therapy that is less burdensome on patients and supported by molecular evidence of function in the lung is needed, and we look forward to additional clinical updates on KB408 in the months to come."

The Company will host an investor conference call and webcast today, Thursday, December 12, 2024, at 8:30 am ET, to discuss the clinical data updates. Investors and the general public can access the live webcast at: https://www.webcaster4.com/Webcast/Page/3018/51767. For

those unable to listen to the live webcast, an archived version will also be available on the Investors section of the Company's website for at least 30 days.

KB408 for the treatment of alpha-1 antitrypsin deficiency (AATD) lung disease

KB408 is being evaluated in the Company's Phase 1 SERPENTINE-1 study. SERPENTINE-1 is an open label, single dose escalation study in adult patients with AATD with a Pi*ZZ or a Pi*ZNull genotype. SERPENTINE-1 is designed to include up to three dose escalation cohorts evaluating single administrations of 10^9, 10^{10}, and 10^{11} PFU of KB408 via inhalation. Additional details of the SERPENTINE-1 study can be found at www.clinicaltrials.gov under NCT identifier NCT06049082.

As of the December 6, 2024 data cut-off, a total of seven (7) patients had been enrolled in SERPENTINE-1, including 3 patients in Cohort 1 who had received the 10^9 PFU KB408 dose and 4 patients in Cohort 2 who had received the 10^{10} PFU KB408 dose. One patient in each of Cohort 1 and Cohort 2 were receiving background intravenous (IV) augmentation therapy.

Two patients in Cohort 2 also received bronchoscopies to assess *SERPINA1* delivery and AAT levels in the lung. Both a baseline bronchoscopy and a post-dose bronchoscopy, conducted 24 to 48 hours after KB408 dosing, were completed. One of the two patients who received bronchoscopies was receiving background IV augmentation therapy.

Clear evidence of successful gene delivery was observed in both patients, including high rates of transduction and AAT expression in the conducting airways of both patients as assessed via bronchoscopy. Key molecular findings for each patient are summarized below:

Patient Not on Background IV Augmentation

- A clinically meaningful proportion of conducting airway epithelial cells were transduced following administration of a single dose of KB408, with the percentage of cells positive for AAT expression increasing from 0% at baseline to 39% after KB408 dosing.
- Free AAT levels in lung epithelial lining fluid increased over 8-fold, rising from 85 nM at baseline to 729 nM after KB408 dosing.
- AAT functionality was also confirmed by detection of AAT-NE binding, with the percentage of active, unbound neutrophil elastase in epithelial lining fluid dropping from 97.2% at baseline to 40.2% – an over 50% absolute reduction achieved within 48 hours after dosing.

Patient on Background IV Augmentation

- Again, a clinically meaningful proportion of conducting airway epithelial cells were transduced following administration of a single dose of KB408, with the percentage of cells positive for AAT expression increasing from 3% at baseline to 35% after KB408 dosing.
- Lavage samples could not be successfully collected from this patient, preventing accurate quantification of AAT and neutrophil elastase binding in lung epithelial lining fluid. However, both KB408 genomes and *SERPINA1* RNA transcripts were detected in multiple bronchial brushing samples, with an average of 4 x 10^3 genome copies and 4 x 10^2 transcript copies detected, providing further support of successful gene delivery and expression in the KB408 treated lung.

In addition to evidence of KB408 transduction and AAT expression in the lungs of these two patients, increases in serum AAT levels were also detected in all four Cohort 2 patients after KB408 dosing, suggestive of broad dissemination of KB408-encoded AAT following expression in the lung. Increases in serum AAT relative to baseline ranged from 270 nM to 5.3 µM in the three patients that were not on confounding background IV augmentation, including in one case increases in serum AAT from 4.4 µM at baseline to 9.7 µM after KB408 dosing.

KB408-related adverse events for all seven patients treated in Cohort 1 and Cohort 2 were mild to moderate and transient. No serious adverse events have been reported.

“With clear evidence of gene delivery, including detection of high nanomolar concentrations of AAT in lung epithelial lining fluid, as well as corresponding reductions in the percentage of unbound, active neutrophil elastase by over 50%, today’s initial clinical data is a major step forward towards our goal of developing a safe, effective, and non-invasive therapy for AATD patients to maintain therapeutic AAT levels in the lung,” said Suma Krishnan, President, Research & Development, Krystal Biotech, Inc. “These data, together with the attractive tolerability profile observed to date, also reinforce our conviction in HSV-1 based gene delivery to the lung and our entire inhaled genetic medicines pipeline. We look forward to sharing additional updates on our respiratory programs in 2025.”

The Company will enroll two additional patients in Cohort 2 of SERPENTINE-1 and expects to provide additional data updates in 2025. In parallel, the Company will open Cohort 3 to explore safety and gene delivery at the highest dose of KB408.

KB407 for the treatment of cystic fibrosis (CF)

Based on preclinical data submitted to date by the Company, the Cystic Fibrosis Foundation (CFF) Therapeutic Development Network (TDN) Clinical Research Executive Committee has granted conditional sanctioning of the Company's KB407 Phase 1 CORAL-1 study protocol subject to review of the data monitoring committee charter, if required, to align with CFF TDN standards. No additional preclinical updates for KB407 are required, and the Company expects to be fully sanctioned and open sites within the CFF TDN shortly.

KB407 is being evaluated in the Phase 1 CORAL-1 study. CORAL-1 is an open label, dose escalation study in adult patients with CF. CORAL-1 is designed to include up to three dose escalation cohorts evaluating either one, two, or four daily administrations of 10^9 PFU of KB407 via inhalation. Additional details of the CORAL-1 study can be found at www.clinicaltrials.gov under NCT identifier NCT05504837.

As of the December 6, 2024 data cut-off, a total of five (5) patients had been enrolled in CORAL-1. Three patients received a single 10^9 PFU KB407 dose in Cohort 1 and three patients, including one roll-over from Cohort 1, received two daily 10^9 PFU KB407 doses in Cohort 2. All but one patient was on background modulator therapy.

The initial focus of Cohorts 1 and 2 was safety of single and repeat inhaled administration of KB407 in patients with CF. As observed with KB408, KB407 has been well tolerated in all patients dosed to date. KB407-related adverse events for all five patients treated in Cohort 1 and Cohort 2 were mild to moderate and transient. No serious adverse events have been reported. The Company expects to report data from Cohort 3 in 1H 2025, including data on *CFTR* gene delivery and expression in patients with cystic fibrosis.

About Krystal Biotech, Inc.

Krystal Biotech, Inc. (NASDAQ: KRYS) is a commercial-stage biotechnology company focused on the discovery, development and commercialization of genetic medicines to treat diseases with high unmet medical needs. VYJUVEK® is the Company's first commercial product, the first-ever redosable gene therapy, and the first medicine approved by the FDA for the treatment of dystrophic epidermolysis bullosa. The Company is rapidly advancing a robust preclinical and clinical pipeline of investigational genetic medicines in respiratory, oncology, dermatology, ophthalmology, and aesthetics. Krystal Biotech is headquartered in Pittsburgh, Pennsylvania. For more information, please visit http://www.krystalbio.com, and follow @KrystalBiotech on LinkedIn and X (formerly Twitter).

Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for Krystal Biotech, Inc., including statements about the potential of the Company's platform to safely deliver genetic cargo to the lung; the Company's clinical-stage, inhaled genetic medicines programs in Phase 1 for the treatment of rare respiratory diseases; the Company's plans to enroll two additional patients in Cohort 2 of its SERPENTINE-1 study and provide additional data updates in 2025; the Company's plans to open Cohort 3 of its SERPENTINE-1 study to explore safety and gene delivery at the highest dose of KB408; the Company's expectation to be fully sanctioned and open sites within the CFF TDN shortly; the Company's expectation that it will report data from Cohort 3 of its CORAL-1 study in 1H 2025, including data on *CFTR* gene delivery and expression in cystic fibrosis patients; 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 uncertainties inherent in the initiation and conduct of clinical trials, as well as regulatory review of clinical trials and applications for marketing approvals; and such other important factors as are set forth under the caption "Risk Factors" in the Company's annual and quarterly reports on file with the U.S. Securities and Exchange Commission. The forward-looking statements included in this press release represent the Company's views as of the date of this press release. 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 press release.

CONTACT

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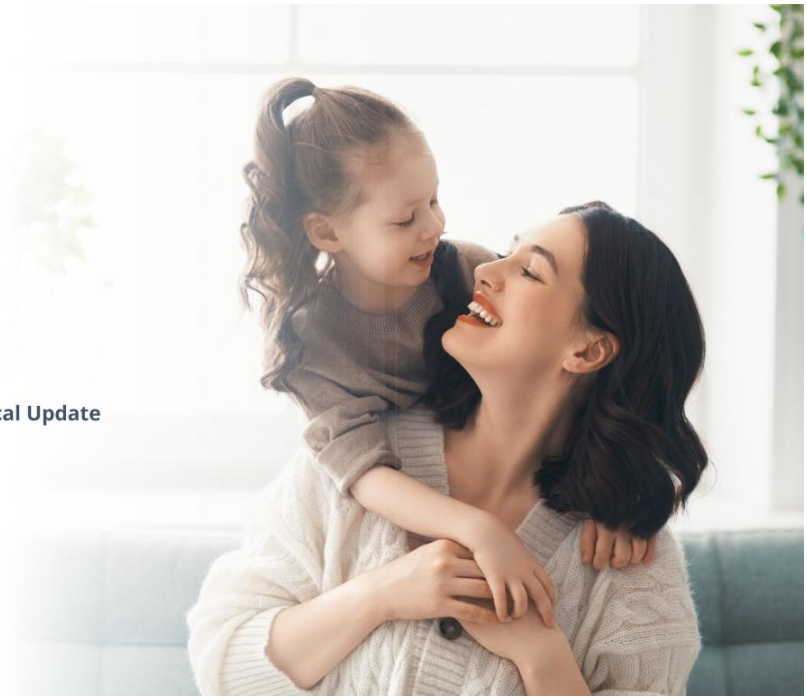


Rare Respiratory Pipeline Interim Clinical Update

December 2024

Forward Looking Statements and Disclosures

Forward Looking Statements

This presentation and the accompanying oral presentation that are collectively referred to as this presentation contain forward-looking statements that involve substantial risks and uncertainties. Any statements about future expectations, plans and prospects for Krystal Biotech, Inc. (the "Company"), including but not limited to statements about the Company's HSV-1-based platform being able to safely and effectively deliver and express genetic cargo when administered to the lung via repeated inhalation; the initial positive clinical data from the Company's rare respiratory disease programs, KB408 and KB407 and the implications thereof for the Company's broader pipeline targeting diseases of the lung; the prevalence and incidence of AATD and cystic fibrosis; the Company's intention to accelerate its clinical study of KB408 and simultaneously enroll confirmatory patients in Cohort 2 and open Cohort 3 to explore safety and gene delivery at the top dose; the Company's belief that the positive initial data from the KB408 study demonstrates a clinically relevant dosing range; the targeted patient segments for KB407 and the estimated number of patients in such segments; the Company's belief that KB407 sanctioning by CFF TDN will accelerate enrollment and shorten time to bronchoscopies and KB407 molecular data; the Company's plans to share molecular data from the KB407 program in 1H 2025; 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: uncertainties associated with regulatory review of manufacturing processes and clinical trials and the content and timing of decisions made by regulatory authorities; the uncertainties inherent in the initiation and conduct of clinical trials; availability and timing of data from clinical trials and utility of such data; and such other important factors as are set forth in the Company's filings with the U.S. Securities and Exchange Commission. The forward-looking statements included in this presentation represent the Company's views as of the date of this presentation and should not be relied upon as representing the Company's views as of any subsequent date.

This presentation may contain estimates and statistical data. These estimates involve assumptions and limitations, and investors are cautioned not to give undue weight to such estimates. Neither the Company nor any other person makes any representation as to the accuracy or completeness of such estimates or data or undertakes any obligation to update such estimates or data. Any projections, assumptions and estimates of the Company's future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

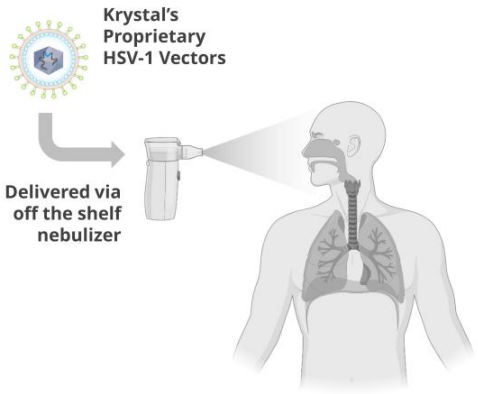
Disclosures

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

The Company is using the Aerogen Solo® Nebulizer System and Aerogen® Ultra in its clinical trials evaluating KB407, KB408, and inhaled KB707.

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

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



Historical Challenges with Inhaled Gene Therapy[1]

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

HSV-1 Platform Has Potential to Overcome Historical Challenges

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

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

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

AAV, adeno-associated virus; *CFTR*, cystic fibrosis transmembrane conductance regulator; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus 1

Alpha-1 Antitrypsin Deficiency (AATD)

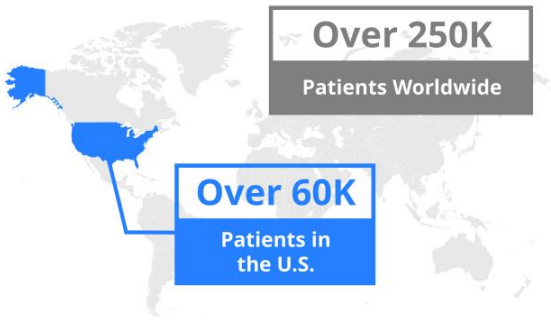
Monogenic disorder that leads to progressive lung disease

- Alpha-1 antitrypsin (AAT) is a key regulator of protease activity, in particular neutrophil elastase in lungs[3]
- AATD is an autosomal co-dominant inherited genetic disorder resulting from mutations in *SERPINA1* gene encoding AAT, misfolding mutations Pi*ZZ and Pi*SZ are the most common
- Genetic deficiency of AAT can result in unopposed neutrophil elastase activity and progressive pulmonary impairment

Unproven and Limited Treatment Options[1,2]

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

Severe AATD Prevalence[3-5]*



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

*Severe AATD defined as patients with Pi*ZZ genotype

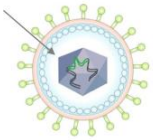
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; IV, intravenous; *SERPINA1*, serpin family A member 1; U.S., United States

Inhaled Candidate KB408 for AATD Lung Disease

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

KB408

2 x *SERPINA1* genes



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

Preclinical Summary

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

Data package strongly supportive of KB408 progression to the clinic

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

KB408 Phase 1 Study SERPENTINE-1

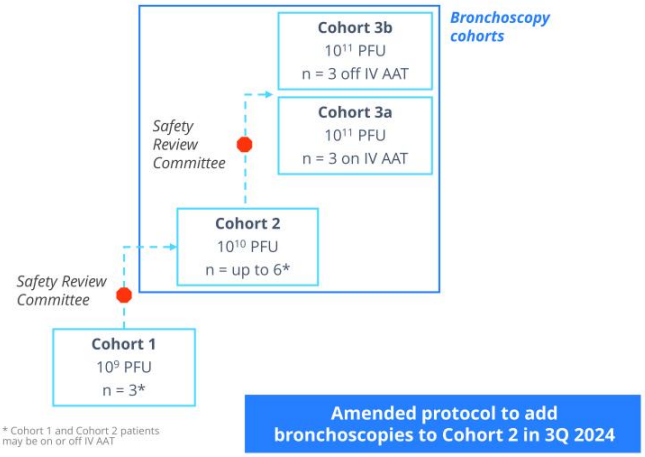
Open-label, single dose escalation study in adult patients with AATD with a PI*ZZ genotype

Study Objectives

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

Key Enrollment Criteria

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



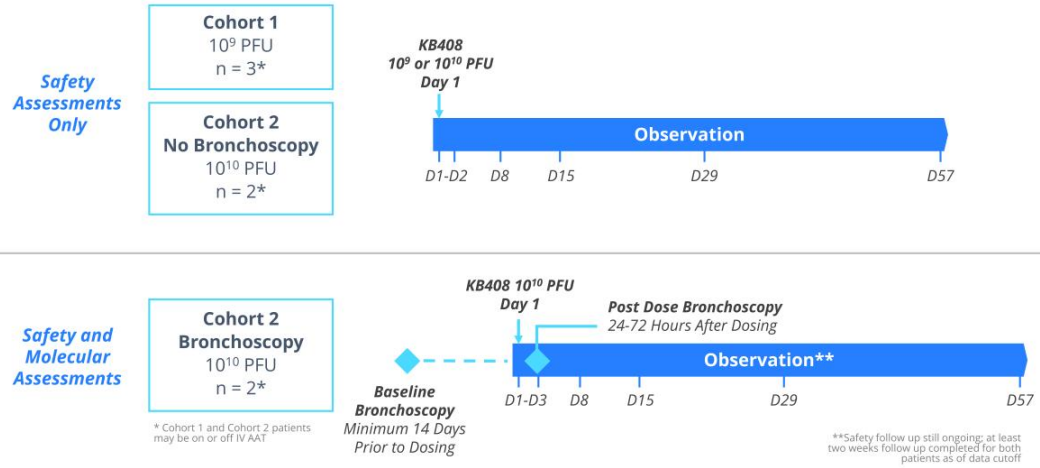
* Cohort 1 and Cohort 2 patients may be on or off IV AAT

Amended protocol to add bronchoscopies to Cohort 2 in 3Q 2024

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

Scope of First SERPENTINE-1 Interim Readout

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



Data cutoff date of December 6, 2024

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

Patient Demographics and Augmentation Therapy Status

Study population predominantly elderly with variable augmentation therapy use, all Pi*ZZ genotype

Safety Assessments Only

Cohort 1
10^9 PFU
n = 3*

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

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

Safety and Molecular Assessments

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

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

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

Data cutoff date of December 6, 2024

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

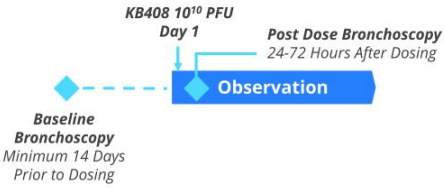
KB408 Well Tolerated in All Patients Dosed To Date

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

Bronchoscopy Sampling Plan and Molecular Data in Interim Readout

Multiple assessments conducted to mitigate inherent variability in sample collection across patients

Cohort 2 Bronchoscopy Timing



Sample Collection at Each Timepoint

- **Tissue Biopsies**
- **Bronchial Brushings**
- **Bronchoalveolar Lavage**

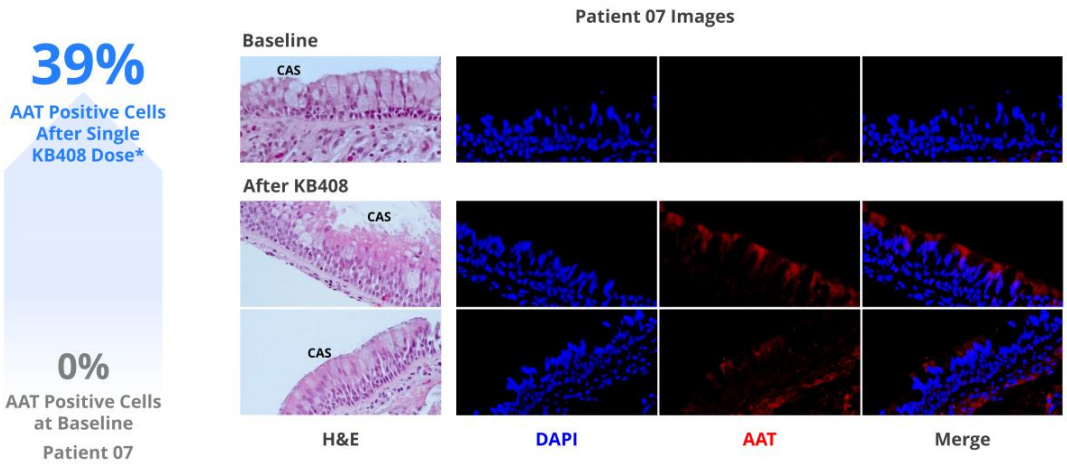
Assessments Included in Interim Readout

1. **Rate of KB408 transduction and AAT expression in cells of the conducting airways:** Assessed by immunofluorescent staining for AAT positive cells in tissue biopsy samples
2. **Secreted free AAT levels and residual active neutrophil elastase in lung ELF:** Free AAT and % unbound neutrophil elastase assessed by ELISA in lung lavage samples, adjusted for lavage dilution factor
3. **Change in *SERPINA1* Expression Levels in Lung Airway Cells:** Assessed by quantification of codon-optimized *SERPINA1* genome copies and transcript levels by qPCR and qRT-PCR in brushings

AAT, alpha-1 antitrypsin; ELISA, enzyme-linked immunosorbent assay; PFU, plaque forming unit; qPCR; quantitative polymerase chain reaction; qRT-PCR, quantitative reverse transcription polymerase chain reaction; *SERPINA1*, serpin family A member 1

Clear Evidence of Transduction and AAT Expression in KB408 Treated Lungs

Patient 07, **no** background augmentation; clinically meaningful proportion of airway cells positive for AAT after single dose



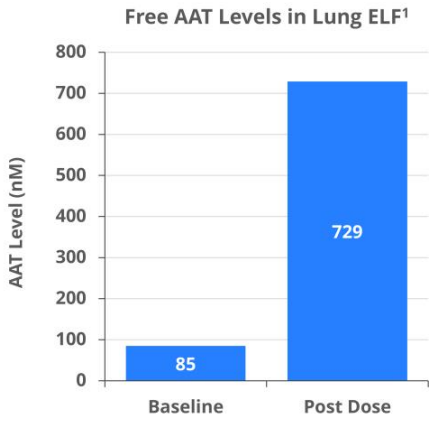
* Based on quantification of DAPI positive and DAPI + AAT co-positive cells lining the conducting airways of the lung by immunofluorescence; three biopsies assessed for post-dose DAPI + AAT co-positive cell quantification, total cell counts > 300

AAT, alpha-1 antitrypsin; CAS, conducting airway surface; DAPI, 4',6-diamidino-2-phenylindole; H&E, hematoxylin and eosin

All imaging conducted at 40× magnification
Post-dose biopsies harvested 48 hours after nebulization
Biopsy locations: Baseline biopsy #1, top: lower lobe, right lung; post-dose biopsy #3, middle: lower lobe, left lung; post-dose biopsy #4, bottom: lower lobe, left lung

Secreted AAT Reached Clinically Meaningful Levels after Single KB408 Dose

Patient 07, **no** background augmentation; increase in AAT to high nanomolar range supports further exploration of mid dose



Over 8-fold increase in ELF AAT with one dose

Achieved target range of 5-10% of systemic levels

% Free Neutrophil Elastase in ELF

97.2%

At Baseline

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

40.2%

After Single KB408 Dose

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

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

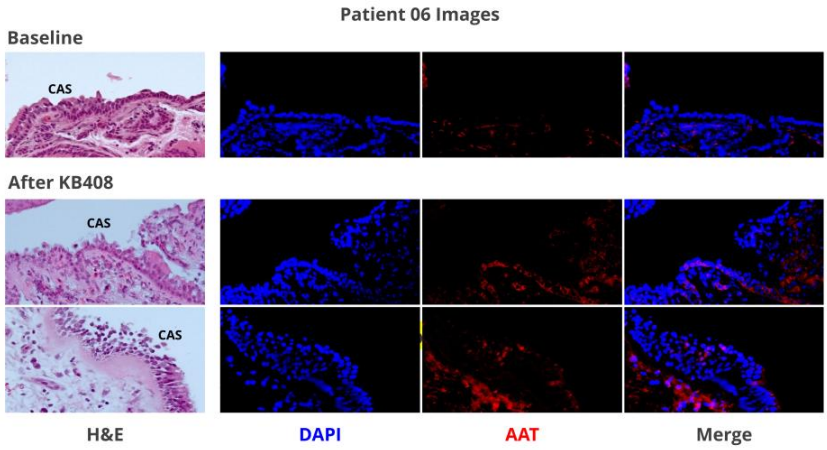
Clear Evidence of Transduction and AAT Expression in KB408 Treated Lungs

Patient 06, on background augmentation; also detected meaningful proportion of airway cells positive for AAT after single dose

35%
AAT Positive Cells After Single KB408 Dose*

3%
AAT Positive Cells at Baseline

Patient 06



* Based on quantification of DAPI positive and DAPI + AAT co-positive cells lining the conducting airways of the lung by immunofluorescence; four biopsies assessed for post-dose DAPI + AAT co-positive cell quantification, total cell counts > 600

AAT, alpha-1 antitrypsin; CAS, conducting airway surface; DAPI, 4',6-diamidino-2-phenylindole; H&E, hematoxylin and eosin

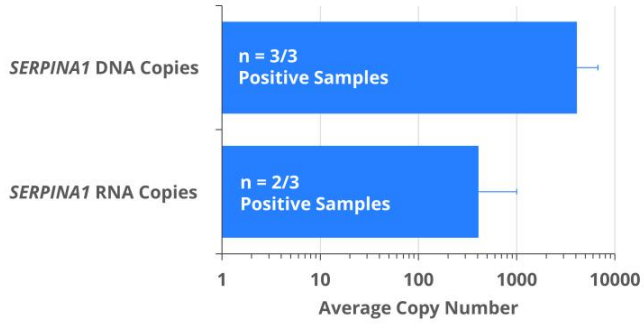
All imaging conducted at 40× magnification
Post-dose biopsies harvested 24 hours after nebulization
Biopsy locations: Baseline biopsy #2, top: lingula (left lung); Post-dose biopsy #2, middle: lower lobe, right lung; Post-dose biopsy #3, bottom: lower lobe, right lung.

Increased *SERPINA1* in Brushings Consistent with KB408 Mechanism

Lavages not successfully collected in Patient 06 but increased *SERPINA1* levels provide further evidence of successful delivery

- Challenges with lavage sample collection prevented evaluation of AAT levels in Patient 06 epithelial lining fluid
- However, KB408 transduction and *SERPINA1* expression was independently confirmed by qPCR and qRT-PCR analysis
- Assays are specific for KB408-encoded, codon-optimized *SERPINA1*
- No signal was detected from baseline samples (n = 3)

***SERPINA1* DNA and RNA Levels After KB408 Dosing**



AAT, alpha-1 antitrypsin; DNA, deoxyribonucleic acid; qPCR; quantitative polymerase chain reaction; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RNA, ribonucleic acid; *SERPINA1*, serpin family A member 1

Clear Evidence of Successful and Safe Gene Delivery with KB408

Positive initial data supports acceleration of KB408 and has positive read-through implications for pipeline

- ✓ **KB408 delivery via inhalation well tolerated at both dose levels tested to date**
- ✓ **Over a third of airway cells positive for AAT in both patients after single 10^{10} PFU KB408 dose**
- ✓ **Free AAT levels in ELF of over 700 nM from first patient are already in clinically relevant range**
- ✓ **Encoded AAT is functional and binds neutrophil elastase; over 50% reduction from single dose**
- ✓ **Increases in *SERPINA1* transcript levels consistent with KB408 mechanism and AAT data**

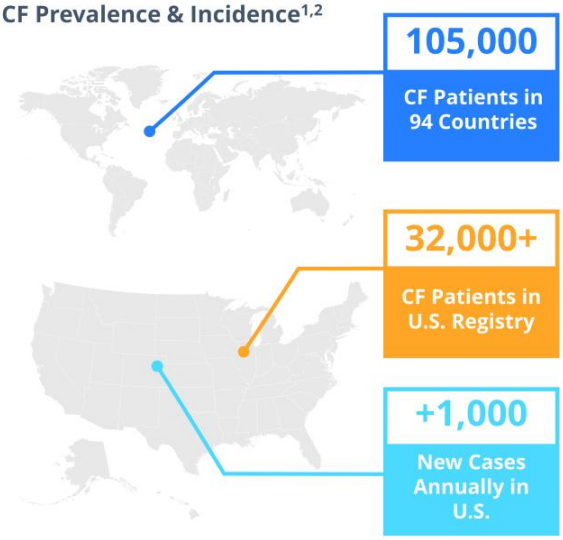
Based on positive data will simultaneously continue enrollment in Cohort 2 and open Cohort 3 to explore higher end of dose range

AAT, alpha-1 antitrypsin; ELF, epithelial lining fluid; PFU, plaque forming unit; *SERPINA1*, serpin family A member 1

Cystic Fibrosis Disease Overview

A life-span shortening progressive disease of the lung

CF Prevalence & Incidence[1,2]



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

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

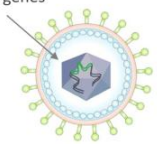
CF, cystic fibrosis; CFTR / *CFTR*, cystic fibrosis transmembrane conductance regulator; GI, gastrointestinal; U.S., United States

KB407 Designed To Address Major Unmet Needs in CF

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

KB407

2x *CFTR* genes



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

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

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

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

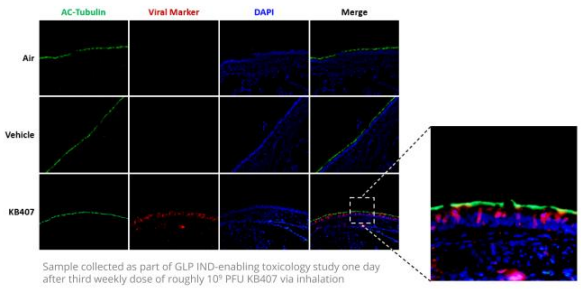
Robust Preclinical Data Package Supports Clinical Evaluation of KB407

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

All Key Preclinical Criteria for KB407 Have Been Met

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

Representative Image from NHP Lung



Sample collected as part of GLP IND-enabling toxicology study one day after third weekly dose of roughly 10^8 PFU KB407 via inhalation

KB407 recently received conditional sanctioning from CFF TDN subject to data monitoring committee charter review – no additional preclinical data requested

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

KB407 Phase 1 Study CORAL-1

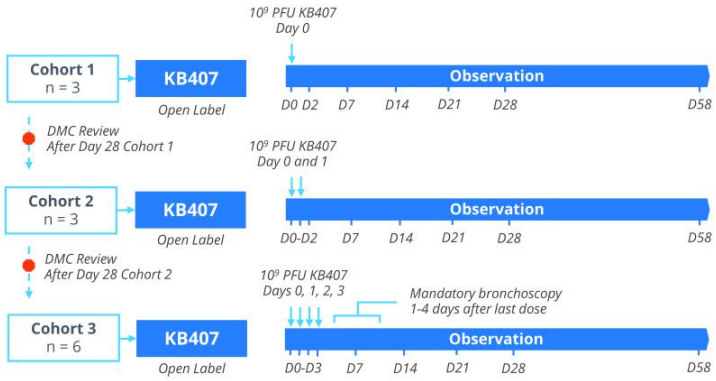
Ongoing study to assess safety and transduction efficiency of ascending doses of KB407 in adults with CF

Study Objectives

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

Key Enrollment Criteria

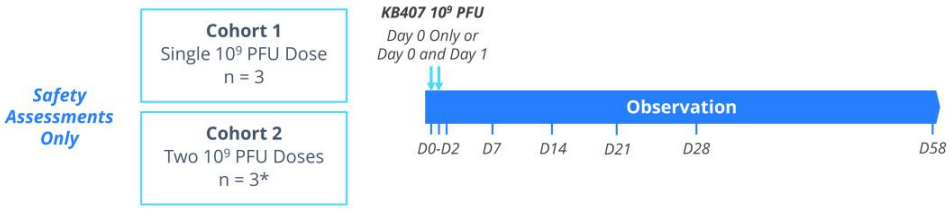
- Age ≥ 18 years with confirmed diagnosis of CF
- $ppFEV_1$ ≥50% and ≤100%
- Resting O_2 saturation ≥92% on room air
- **Cohort 1 and 2:** Participants may receive concurrent modulator therapy, bronchoscopy optional
- **Cohort 3:** No more than 3 out of 6 participants may be on concurrent modulator therapy,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



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

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

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



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

*One patient rolled over from Cohort 1 to Cohort 2

Data cutoff date of December 6, 2024

CFTR / *CFTR*, cystic fibrosis transmembrane conductance regulator; PFU, plaque forming unit; $ppFEV_1$, percent predicted forced expiratory volume in 1 second

KB407 Well Tolerated in All Patients Dosed To Date

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

Working Towards a Highly Differentiated Respiratory Franchise

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

- **First direct clinical evidence of safe gene delivery using HSV-1**
- **Well-tolerated by patient population with underlying lung disease**
- **Delivering full-length genes and demonstrated functionality of KB408-encoded AAT in patients with AATD**
- **Successfully delivered to the lung using commercially available nebulization technology *– off the shelf, non-invasive therapy***
- **Redosability provides opportunity to build on efficacy over time**
- **KB407 sanctioning by CFF TDN will accelerate enrollment and shorten time to bronchoscopies and KB407 molecular data**

Positive read though implications for all of Krystal's inhaled genetic medicines portfolio

KB408

For AATD Lung Disease

KB407

For Cystic Fibrosis

Inhaled KB707

For Solid Tumors of the Lung

+ future pipeline opportunities

AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; CFF, Cystic Fibrosis Foundation; HSV-1, herpes simplex virus 1; IV, intravenous; TDN, Therapeutic Development Network


Krystal®
Developing Genetic Medicines to Treat Diseases with High Unmet Medical Needs
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