RestorAATion: The First Clinical Program Evaluating an RNA Editing Therapeutic in Humans

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June 20, 2024

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Wave is building the leading RNA medicines company, with RNA editing as a core competency

Multi-modal drug discovery and development platform

- Therapeutic candidates that optimally address disease **biology**
- **RNA editing, siRNA, splicing, antisense**
- Best-in-class oligonucleotide **chemistry**

Differentiated RNA medicines pipeline

- Clinical data updates expected in 2024 from **AATD**, **DMD**, **HD** clinical programs
- INHBE clinical trial initiation for **obesity** expected 1Q 2025
- Initiated first-ever clinical trial in **RNA editing** for AATD

Strategic collaborations (GSK and Takeda)

In-house GMP manufacturing

Strong and broad IP

Well capitalized with cash runway into 4Q 2025*

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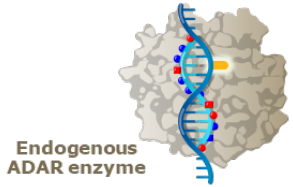
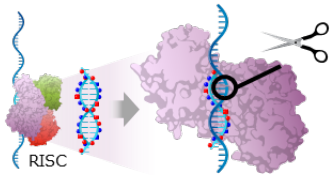
*Cash runway does not include potential future milestones or opt-in payments under GSK and Takeda collaborations
AATD: Alpha-1 antitrypsin deficiency, DMD: Duchenne muscular dystrophy, HD: Huntington's disease

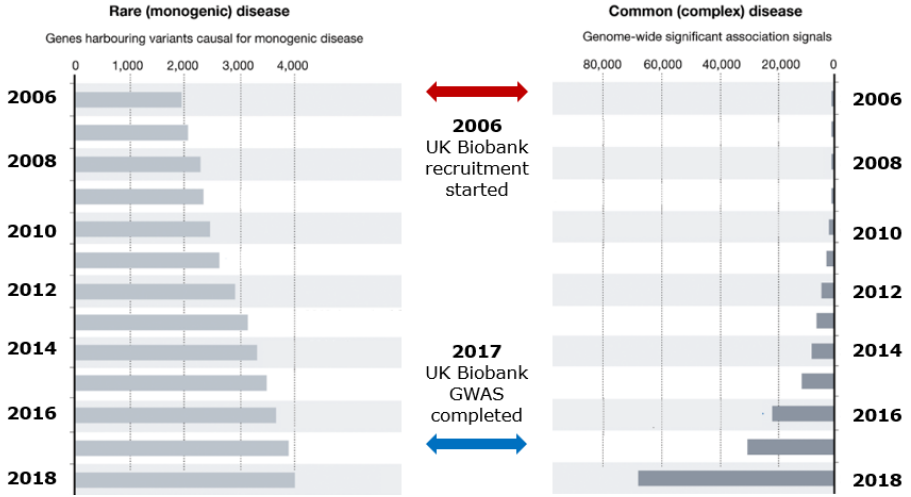
Wave's versatile multimodal RNA medicines platform is ideal for capitalizing on new genetic insights in rare and common diseases

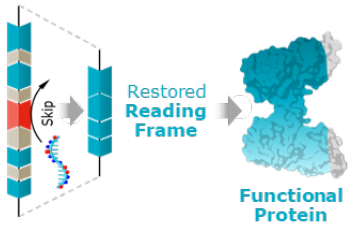


editing

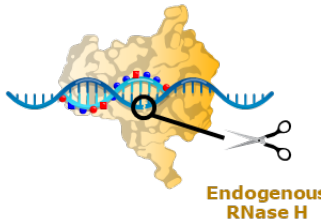


siRNA silencing





splicing

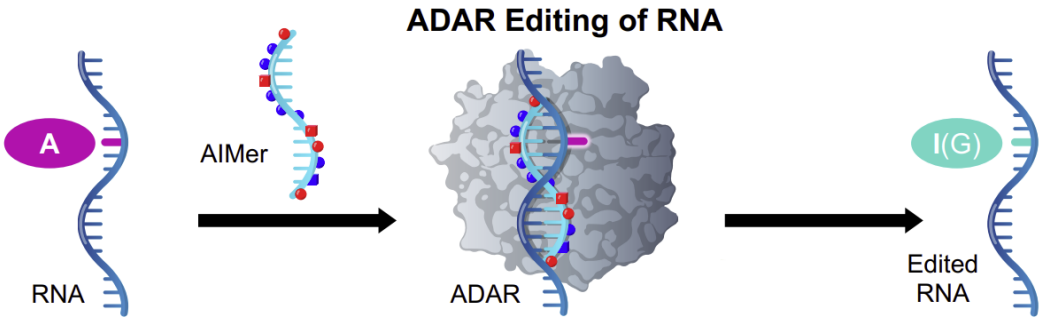


antisense silencing

Accessing UK Biobank and building proprietary machine learning models to generate unique genetic insights

Claussnitzer, et al. Nature (2020) 577, 179; King et al. PLoS Genet (2019) 15, e1008489

Wave's A-to-I RNA editing oligonucleotides (AIMers)



- ✓ Best-in-class, proprietary chemistry yielding superior potency, distribution, durability
- ✓ Efficient and highly specific recruitment of ADAR enzymes
- ✓ Uses GalNAc in the liver and free uptake outside liver; avoids LNPs/other complex delivery vehicles
- ✓ Leveraging ML, AI, large genetic datasets to identify novel insights, targets, target sites
- ✓ First RNA editing clinical candidate will provide proof-of-mechanism for Wave's other AIMer programs

Proof-of-mechanism data from first-ever RNA editing clinical program (RestorAATion) expected in 2024

LNPs: lipid nanoparticles; ML: Machine learning; AI: artificial intelligence

WVE-006: A first-in-class investigational RNA editing therapeutic for AATD

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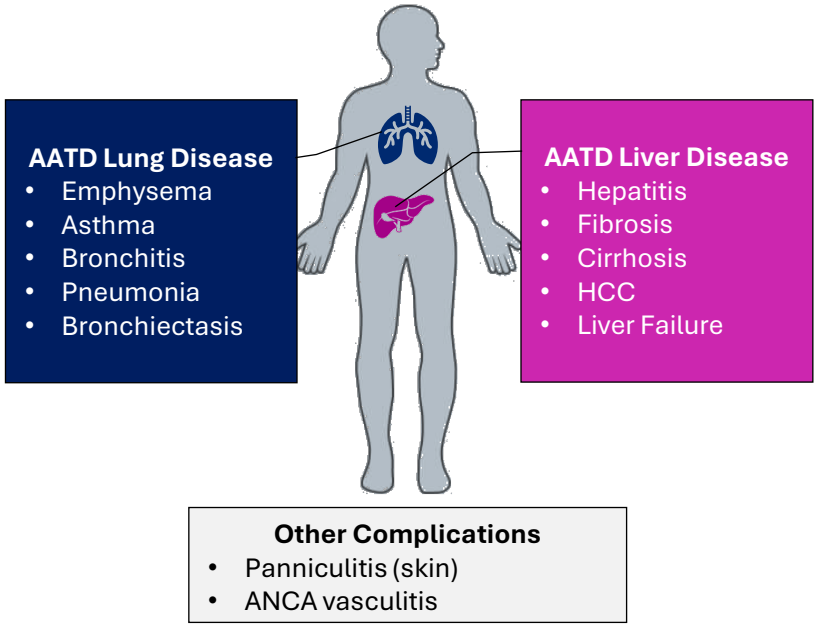
AATD may result in lung and liver disease and has limited treatment options

- **SERPINA1 Z mutation** (E342K) is most common cause of AATD[1]
- **~200,000 Pi*ZZ patients** in US and Europe[2]
- Augmentation therapy is **only treatment option for AATD lung disease** and requires weekly IV infusions
- **No treatment for AATD liver disease**, other than liver transplant
- Average age of diagnosis of AATD lung disease is **46 years**[3] and average age of adult-onset liver disease is **61 years**[4]



1. Greene, C.M., *et al.*, 2016 Nat Rev Dis Primers 2, 16051; 2. Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; 3. Strnad, *et al.* 2020 *N Engl J Med* 382:1443-55; 4. Tanash and Piitulainen 2019 *J Gastroenterol* 54:541-548

Patient insights highlight burden of AATD

> *It's an **invisible disease.** It seems like it tricks you - I look healthy and then I tell someone I can't help them grab something 20 feet away. That's the disconnect.*

> *I used to own a salon and with my lungs going bad so quickly, I had to do away with that…I get **short winded**…I lay around a lot, I'm sick a lot.*

> *It makes it harder for us to travel and go do things, because I have to be home once a week for my infusions. It's definitely an **inconvenience**.*

> *I now have very **high elevated liver enzymes and fatty liver** just in the last year. I get a lot of pain on that side. They believe it is related to AATD.*

> *I have back issues, anytime they do a CAT scan or MRI there is always a notation about fatty liver disease and scarring on my liver. **I know it's there. I know there's a problem.** It's just part of my everyday.*

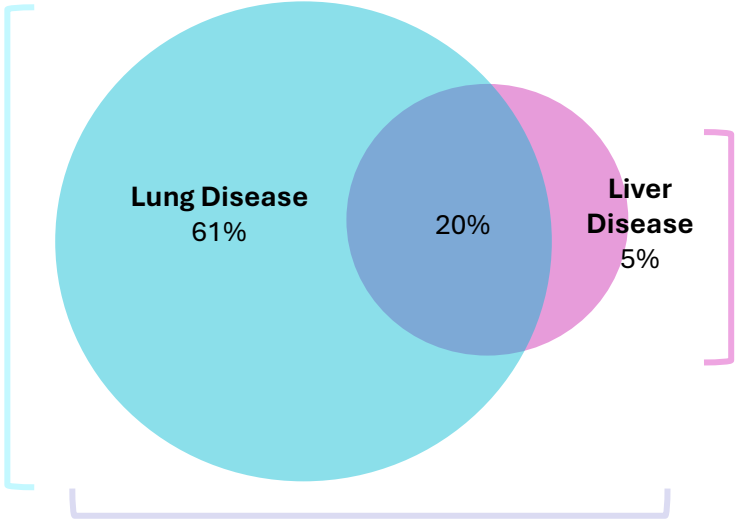
Engaged patient community to inform clinical development plans

AATD landscape is poised to evolve but most approaches focus on lung or liver disease

Selected Therapeutic Strategies in Development for AATD

*Frequency of Lung or Liver Disease of Pi*ZZ Patients at Diagnosis**

- Augmentation therapy (Plasma derived, IV) ***[Approved]***
- Recombinant Fc-AAT (IV)
- Inhaled AAT (nebulized)
- Neutrophil elastase inhibitors (oral)



- RNAi (subcutaneous)

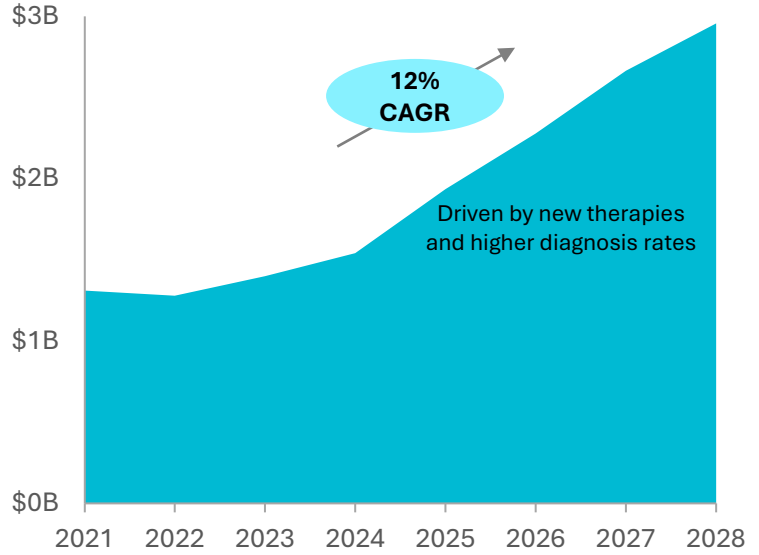
**From Alpha One International Registry (n=3,405)*[3]
(13% reported no disease at diagnosis)

Despite being a rare disease, AATD market estimated to grow to ~$3B by 2028

AATD Market Overview

- **AATD market today is estimated at ~$1.3B worldwide[1] despite limitations of current treatment**
  - Market consists entirely of plasma-derived augmentation therapy for AATD-lung disease
  - Augmentation therapy requires weekly IV and is not reimbursed in some markets
- **Market expected to grow to ~$3B by 2028**
  - Treatment for AATD-liver disease in development
  - Opportunity to improve upon treatments for AATD-lung disease (efficacy, administration)
  - Potential to increase diagnosis (e.g., for liver disease, through direct-to-consumer genetic testing)

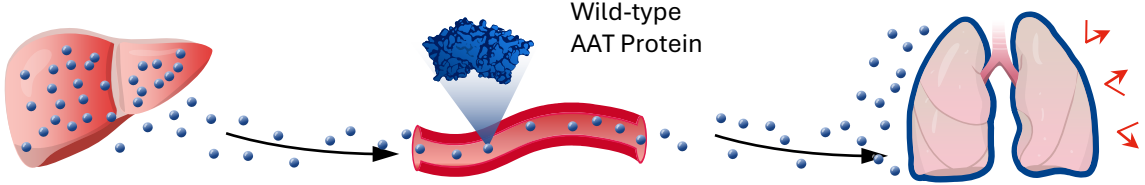
Global AATD Market Value (2021 – 2028)[1]



1. Evaluate Pharma; 2. Lumanity KOL Market Research 2022

AAT protein is predominately produced by the liver, protects the lung

AAT is a **protein** predominately produced by liver cells (hepatocytes)

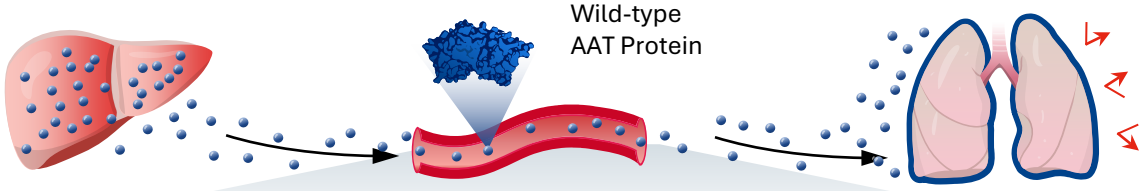


AAT circulating in blood protects lungs against enzymes that breakdown tissue

Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 *Alpha-1 Antitrypsin Deficiency* GeneReviews

The Z mutation is the most common cause of Alpha-1 antitrypsin deficiency (AATD)

AAT is a **protein** predominately produced by liver cells (hepatocytes)

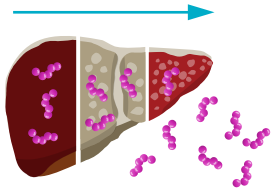


AAT circulating in blood protects lungs against enzymes that breakdown tissue

Gain-of-function and loss-of-function disease

Misfolded Z-AAT protein

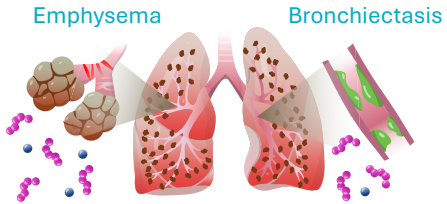
Liver Disease



Misfolded AAT protein trapped in liver can lead to liver disease (fibrosis, cirrhosis, hepatocellular carcinoma)

Low levels of AAT protein in the blood

Lung Disease



Low levels of AAT protein can lead to lung disease

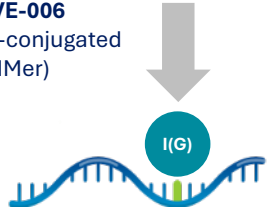
Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 *Alpha-1 Antitrypsin Deficiency* GeneReviews

WVE-006 is designed to correct mutant SERPINA1 transcript to address both liver and lung manifestations of AATD

WVE-006 for AATD

SERPINA1 Z allele mRNA encodes Z-AAT protein with E342K mutation

WVE-006
(GalNAc-conjugated AIMer)



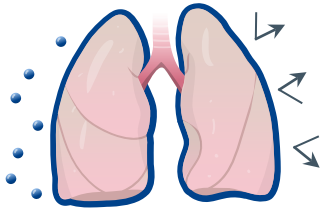
Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

WVE-006 ADAR editing approach to address key goals of AATD treatment:

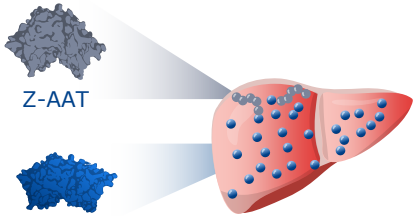
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

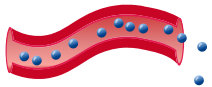
3) Retain M-AAT physiological regulation



M-AAT reaches lungs to protect from proteases



RNA correction replaces mutant Z-AAT protein with wild-type M-AAT protein



M-AAT secretion into bloodstream

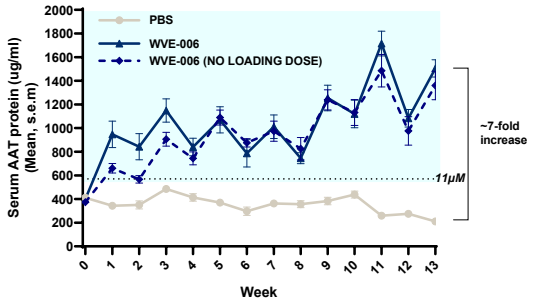
AAT: Alpha-1 antitrypsin Strnad et al., 2020 N Engl J Med 382:1443-55; Blanco et al., 2017 Int J Chron Obstruct Pulmon Dis 12:561-69; Remih et al., 2021 Curr Opin Pharmacol 59:149-56.

Preclinical data demonstrate correction and functionality of AAT protein

Potentially comprehensive approach to address both lung and liver manifestations of AATD

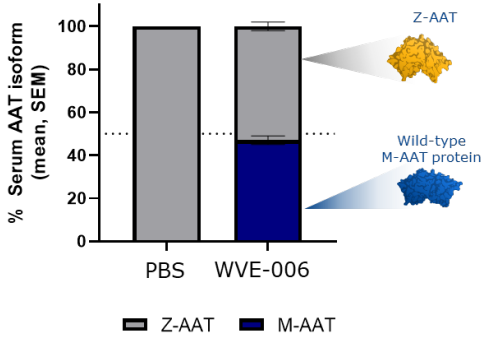
Increased AAT protein in NSG-PiZ mice

WVE-006 treatment results in serum AAT protein levels of up to 30 uM in NSG-PiZ mice



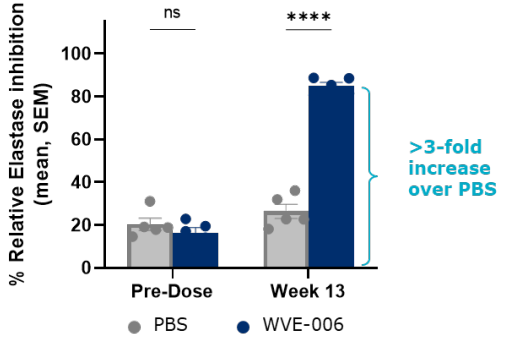
Confirmed restored wild-type M-AAT protein

Overall percentages of serum AAT protein isoforms in NSG-PiZ mice (Week 13)



Demonstrated functionality of M-AAT protein

Serum neutrophil elastase inhibition activity in NSG-PiZ mice



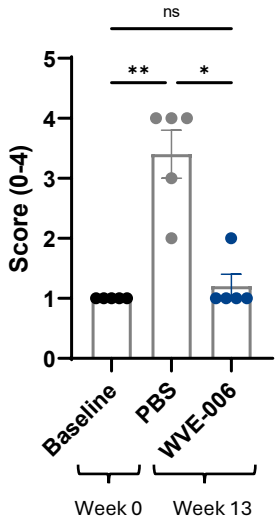
≥50% editing supports restoration of MZ phenotype

AATD: Alpha-1 antitrypsin deficiency; M-AAT protein: wild-type AAT protein; WVE-006 administered subcutaneously (10 mg/kg bi-weekly) in 7-week old NSG-PiZ mice (n=5 per group); Loading dose: 3 x 10 mg/kg at Day 0. Left: Liver biopsies collected at wk 13 (1 wk after last dose) and SERPINA1 editing quantified by Sanger sequencing; Right: Total serum AAT protein quantified by ELISA; Stats: Two-Way ANOVA with adjustment for multiple comparisons (Tukey)

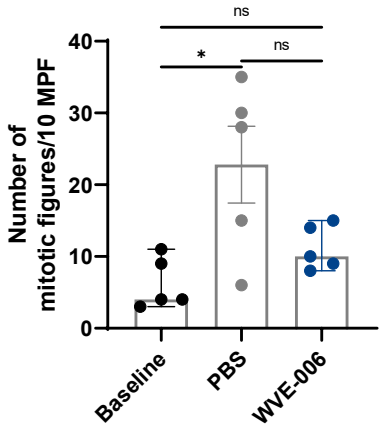
WVE-006 improves several markers of liver disease and prevents increase in hepatocyte turnover, indicating improved hepatocyte survival

Correction of gain-of-function liver phenotypes

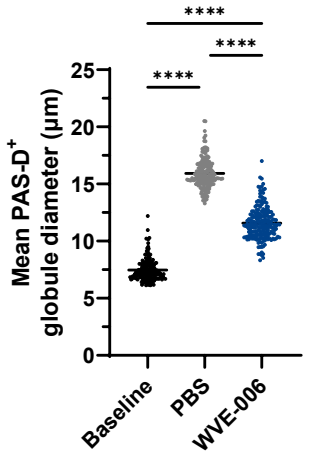
Lobular inflammation
(NSG PiZ mice, week 13)



Mitoses
(NSG PiZ mice, week 13)



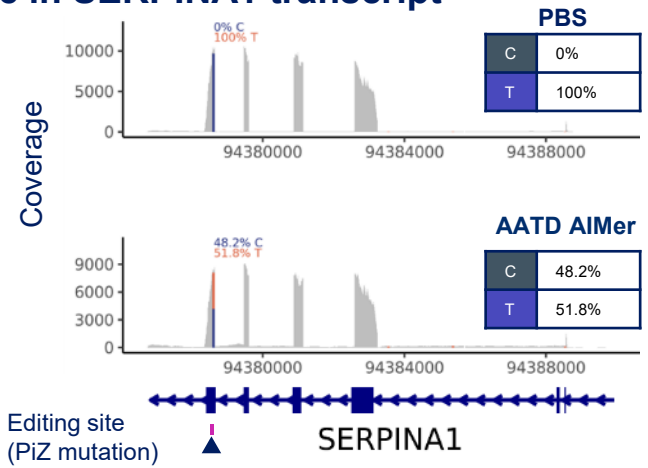
PAS-D-positive globule size
(NSG PiZ mice, week 13)



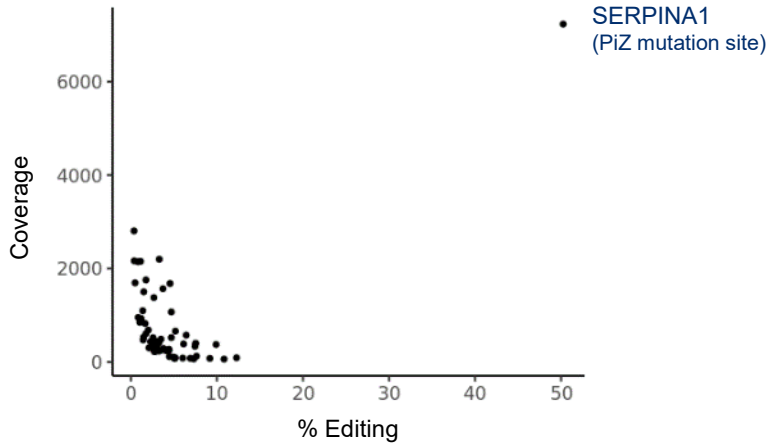
Left (Lobular inflammation) and Middle (Mitoses): Scatter plot showing inflammation grade or mitoses score. Each circle represents an individual mouse, (Mean ± SEM); Right (PAS-D Globule Size): 40 largest globules in each of 5 mice were measured. Each circle represents a single PAS-D globule, (Mean ± SEM). Baseline: week 0 (7 weeks old); Treated week 13 (20 weeks old); Stats: Kruskal-Wallis followed by Dunn's test

AIMer-directed editing is highly specific in mice, as observed in liver biopsy

RNA editing only detected at PiZ mutation site in SERPINA1 transcript



RNA editing across transcriptome



No bystander editing observed on SERPINA1 transcript

Dose 3x10 mg/kg (days 0, 2, 4) SC with AATD AIMer (SA1 – 4). Liver biopsies day 7. RNA-seq to quantify on-target SERPINA1 editing, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4), SERPINA1 edit site is indicated

Data support WVE-006 as best-in-class approach for AATD

Preclinical *in vitro* and *in vivo* datasets demonstrate:

- ✓ **Significant increase in serum AAT of up to 30 uM in NSG-PiZ mice**
  - ~50% editing supports restoration to MZ phenotype
- ✓ **Editing is highly specific, restores wild-type M-AAT protein**
  - No bystander edits leading to protein isoforms
- ✓ **Functionality of M-AAT protein**
  - >3-fold improvement in neutrophil elastase inhibition activity
- ✓ **Improvement in liver phenotype**
  - Decreased lobular inflammation and PAS-D globule size, prevents increase in hepatocyte turnover

WVE-006 potential to address all key treatment goals with durable, subcutaneous delivery

Advancing the first-ever RNA editing candidate in the clinic

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RestorAATion clinical program advancing

- RestorAATion-2 in AATD patients in underway
- Used RestorAATion-1 data in healthy volunteers, as well as preclinical data, to inform dose likely to engage target in AATD patients
- GalNAc pharmacology in healthy volunteers translating as expected
- On track to deliver proof-of-mechanism data (measured by M-AAT restoration) in 2024
- Would be first-ever clinical demonstration of RNA editing
- Would provide proof-of-concept for wholly owned pipeline of RNA editing candidates

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Wave Life Sciences Announces Approval of First Clinical Trial Application for RestorAATion-2 Trial of WVE-006 in Individuals with Alpha-1 Antitrypsin Deficiency (AATD)

April 30, 2024

Proof-of-mechanism data for WVE-006 in individuals with AATD remain on track for 2024

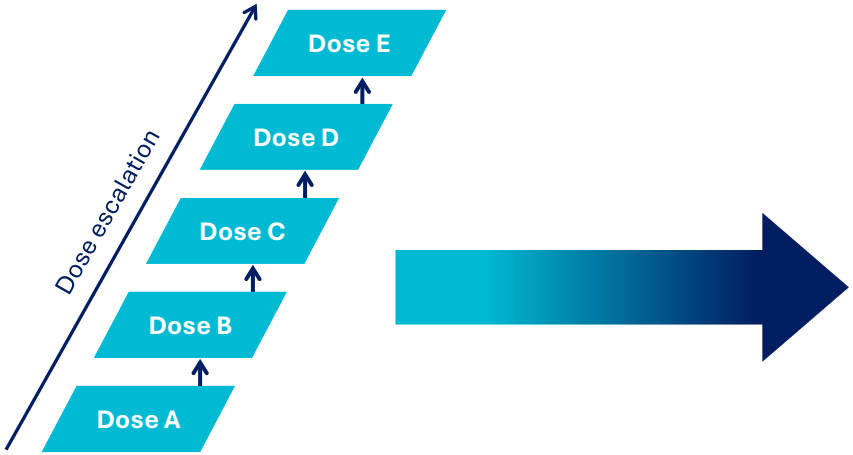
CAMBRIDGE, Mass., April 30, 2024 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage biotechnology company focused on unlocking the broad potential of RNA medicines to transform human health, today announced the approval of its first clinical trial application (CTA) for its RestorAATion-2 clinical trial of WVE-006, the company's first-in-class RNA editing oligonucleotide, which is being developed for the treatment of alpha-1 antitrypsin deficiency (AATD). WVE-006 is GalNAc-conjugated and subcutaneously administered; it does not use a lipid nanoparticle (LNP) delivery system.

"The approval of our first CTA for the RestorAATion-2 clinical trial of WVE-006 marks an important milestone as we continue extending our leadership in RNA editing. It is also important for the alpha-1 community as WVE-006 has the potential to enable correction of the disease-causing RNA mutation and provide a single therapeutic option regardless of whether patients have AATD liver disease, lung disease or both," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "Our rapid progress in dose escalating healthy volunteers enabled us to demonstrate the translation of safety and pharmacokinetics of WVE-006 in humans and quickly identify a starting dose level that, based on preclinical data, is expected to engage the target in patients. With proof-of-mechanism data from RestorAATion-2 expected later this year, we look forward to the opportunity to provide clinical demonstration of RNA editing and proof-of-concept for our wholly owned pipeline of RNA editing candidates."

RestorAATion-2 underway, proof-of-mechanism data expected in 2024

RestorAATion-1: Healthy Volunteers → Informs dose & dose frequency → **RestorAATion-2: AATD Patients**

SAD → MAD cohorts



Up to 7 doses

Cohort 3

Cohort 2

Cohort 1

Multiple assessments of serum AAT throughout cohort

Study key objectives

Safety and tolerability
Pharmacokinetics
Serum M-AAT levels

HV: healthy volunteer; SAD: single-ascending dose; MAD: multi-ascending dose

Wave's collaboration with GSK positions WVE-006 for late-stage development and commercialization from global leader in respiratory medicine

Collaboration Highlights

- $170 million upfront[1]
- Additional research funding
- Potential for up to $3.3 billion in milestones[2]
- Leverage GSK's expertise in genetics and genomics

	Maximize global potential for WVE-006 for AATD	Advance up to eight GSK collaboration programs	Expand Wave's pipeline
	Up to $525 million in total milestones and **tiered royalties on net sales**	**Up to $2.8 billion** in total milestones and **tiered royalties on net sales**	Wave to advance up to **three wholly owned collaboration programs** (or more with GSK's consent)[3]
Recent Highlights	✓ **$20 million milestone** with first individual dosing RestorAATion-2 trial underway (AATD patients)	✓ **$12 million aggregate initiation payment** for GSK's selection of two programs to advance	✓ **INHBE is Wave's first wholly owned program** emerging from GSK collaboration

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1. $120 million in cash and $50 million equity investment 2. Initiation, development, launch, and commercialization milestones for WVE-006 and programs progressed during initial 4-year research term (8 GSK collaboration programs), 3. GSK eligible to receive tiered royalty payments and commercial milestones from Wave


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