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): June 2, 2022

CENTESSA PHARMACEUTICALS PLC

(Exact name of Registrant, as specified in its charter)

England and Wales	**001-04321**	**98-1612294**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

Mailing address:
3rd Floor
1 Ashley Road
Altrincham
Cheshire WA14 2DT
United Kingdom
(Address of principal executive offices) (Zip code)

Registrant's telephone number, including area code: **+44 7391 789784**

Former name or address, if changed since last report:

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 (see General Instruction A.2. below):

☐ 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**
Ordinary shares, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.002 per share	CNTA	Nasdaq Stock Market, LLC

*Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market, LLC.

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 2.05 Costs Associated with Exit or Disposal Activities

On June 2, 2022, Centessa Pharmaceuticals plc (the "Company") announced its strategic decision to discontinue the clinical development of lixivaptan for the treatment of Autosomal Dominant Polycystic Kidney Disease ("ADPKD").

As part of this strategic decision, we expect to incur costs of approximately $6 million to $8 million relating to lixivaptan program wind-down activities and reduction in headcount, all of which are expected to be incurred in 2022. The estimate of costs that we expect to incur and the timing thereof are subject to a number of assumptions, and actual results may differ. We may also incur other charges or cash expenditures not currently contemplated due to events that may occur as a result of, or associated with, the decision to discontinue and wind-down the clinical development of lixivaptan.

Item 8.01 Other Events

On June 2, 2022, we issued a press release announcing, among other things, our decision to discontinue the development of lixivaptan for ADPKD. We expect a significant reduction in annual cash burn and anticipate that the cash runway for our existing programs will now extend into 2026, without drawing on the remaining available tranches under the Oberland credit facility.

The ALERT study was an open-label, non-registrational repeat-dose study designed to assess hepatic and non-hepatic safety of lixivaptan in subjects who previously experienced abnormal liver chemistry test results that met the criteria for drug induced liver injury ("DILI") while undergoing treatment with tolvaptan, and who were permanently discontinued from tolvaptan for that reason. One participant in the ALERT study, who had previously experienced alanine aminotransferase ("ALT") elevations with tolvaptan on two occasions (maximum ALT elevation of 2.2x the ULN), was observed to have an ALT elevation of 3.3x the ULN and an aspartate aminotransferase ("AST") elevation 3.2X ULN on day 104 after first dose of lixivaptan. Lixivaptan dosing was stopped. Subsequently, and upon elevation of ALT to 5.7x the ULN, the subject was hospitalized and then discharged the following day. Highest ALT elevation reported as of May 28, 2022 was 6.9x the ULN. The subject has had no other signs or symptoms, no other implicated drugs, and no lab evidence of viral or autoimmune hepatitis. To date, no alternative plausible causes have been identified for the subject's abnormal ALT and AST findings. The subject remains under close monitoring, and protocol processes are being followed. The Company has started the notification process for the health authorities as well as study sites and investigators.

A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K.

On June 2, 2022, we also updated our Corporate Presentation, including new data from our LockBody LB101 ASCO 2022 abstract. A copy of the presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K.

Cautionary Note Regarding Forward Looking Statements

This report, including the exhibits hereto, contains forward-looking statements. These statements may be identified by words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements, including statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including SerpinPC and ZF874; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; market size and opportunity for our product candidates; our anticipated cash runway; and costs that we expect to incur in connection with our decision to discontinue development of lixivaptan. Any forward-looking statements in this press release are based on our current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to our ability to protect and maintain our intellectual property position; business (including commercial viability), regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oberland, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and/or commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; geo-political risks such as the Russia-Ukraine war and risks related to the ongoing COVID-19 pandemic including the effects of the Delta, Omicron and any other

variants. These and other risks concerning our programs and operations are described in additional detail in our Form 10-K, our Form 10-Q, and our other reports, which are on file with the SEC. We explicitly disclaim any obligation to update any forward-looking statements except to the extent required by law.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Press Release dated June 2, 2022
99.2	Corporate Presentation including LockBody LB101 ASCO Update, dated June 2022

SIGNATURES

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

Date: June 2, 2022

By:	/s/ Saurabh Saha
Name:	Saurabh Saha, M.D., Ph.D.
Title:	Chief Executive Officer

Centessa Pharmaceuticals Makes Strategic Decision to Discontinue Clinical Development of Lixivaptan for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Decision based on reassessment of commercial potential of lixivaptan following recent observation of ALT/AST elevations in ALERT Study -

- Discontinuation of lixivaptan development expected to significantly reduce cash burn and extend cash runway into 2026 -

- Company continues to focus on the development of its innovative high impact rare disease and immuno-oncology pipeline of investigational medicines for patients -

BOSTON and LONDON, June 2, 2022 – Centessa Pharmaceuticals plc (Nasdaq: CNTA), today announced that it has made the strategic decision to discontinue development of lixivaptan for Autosomal Dominant Polycystic Kidney Disease (ADPKD) including both the Phase 3 ACTION Study and the open-label ALERT Study. The decision is based on a thorough reassessment of the commercial potential of lixivaptan as a potential best-in-class therapy for patients with ADPKD, and the incremental development challenges and associated costs, following a recent observation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations in one subject in the ALERT Study.

"The ALERT Study was designed to help provide an early assessment of the safety profile of lixivaptan in ADPKD patients who previously experienced liver chemistry abnormalities while treated with tolvaptan, the only FDA approved therapy for ADPKD. In assessing the recent data from a subject in the ALERT Study, we believe that lixivaptan is unlikely to achieve the differentiated safety and tolerability profile Centessa required for further development of the program. Given the revised commercial potential of lixivaptan and our commitment to being financially disciplined, we made the data-driven decision to voluntarily discontinue development of lixivaptan," said Saurabh Saha, MD, PhD, Chief Executive Officer of Centessa. "As an organization focused on developing best-in-class therapies and innovative medicines for patients, we had hoped lixivaptan would provide patients with ADPKD a safer alternative treatment option to the current approved therapy. We are incredibly grateful to all the patients, their families and the investigators who participated in the lixivaptan trials and contributed to this research."

Dr. Saha continued, "Going forward, we remain focused on continuing to advance our innovative rare disease and immuno-oncology programs with the potential for multiple clinical proof of concept readouts over the next 12 to 24 months. With our decision to discontinue development of lixivaptan, we believe we are well positioned with the capital and resources to execute these programs. We expect a significant reduction in annual cash burn and that our cash runway will now extend into 2026."

About the ACTION Study

The ACTION Study was a Phase 3 trial consisting of a two-arm, double-blind, placebo-controlled, randomized phase ("Part 1") followed by a single-arm, open-label phase ("Part 2"). The ACTION Study was designed to evaluate the efficacy and safety of lixivaptan in subjects with ADPKD. Further

information on the ACTION Study can be found at clinicaltrials.gov at https://clinicaltrials.gov/ct2/show/NCT04064346

About the ALERT Study

The ALERT Study was an open-label, non-registrational repeat-dose study designed to assess liver and non-liver safety in subjects who previously experienced liver chemistry test abnormalities while treated with tolvaptan and were permanently discontinued from the drug for that reason. Further information on the ALERT Study can be found at clinicaltrials.gov at https://clinicaltrials.gov/ct2/show/NCT04152837

About Centessa Pharmaceuticals

Centessa Pharmaceuticals plc ("Centessa") is a clinical-stage pharmaceutical company with a Research & Development ("R&D") innovation engine that aims to discover, develop and ultimately deliver impactful medicines to patients. Our programs span discovery-stage to late-stage development and cover a range of high-value indications in rare diseases and immuno-oncology. We are led by a management team with extensive R&D experience, providing direct guidance to our program teams to rapidly advance our candidates from research through all stages of development. For more information, visit www.centessa.com, which does not form part of this release.

Forward Looking Statements

This press release contains forward-looking statements. These statements may be identified by words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements, including statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including SerpinPC and ZF874; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; market size and opportunity for our product candidates; and our anticipated cash runway. Any forward-looking statements in this press release are based on our current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the safety and tolerability profile of our product candidates; our ability to protect and maintain our intellectual property position; business (including commercial viability), regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our ongoing and

planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oberland, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and/or commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; geo-political risks such as the Russia-Ukraine war and risks related to the ongoing COVID-19 pandemic including the effects of the Delta, Omicron and any other variants. These and other risks concerning our programs and operations are described in additional detail in our Quarterly Report on Form 10-Q for the quarter ended March 31, 2022 and our other reports, which are on file with the U.S. Securities and Exchange Commission. We explicitly disclaim any obligation to update any forward-looking statements except to the extent required by law.

Contact:

Kristen K. Sheppard, Esq.

Senior Vice President Investor Relations

investors@centessa.com

CENTESSA PHARMACEUTICALS

Corporate Overview

JUNE 2022

Disclaimer

This presentation has been prepared by Centessa Pharmaceuticals plc (the "Company") for informational purposes only and not for any other purpose. This presentation does not contain all the information that is or may be material to investors or potential investors and should not be considered as advice or a recommendation to investors or potential investors in respect of the holding, purchasing or selling of securities or other financial instruments and does not take into account any investor's particular objectives, financial situation or needs. The communication of this presentation may be restricted by law; it is not intended for distribution to, or use by any person in, any jurisdiction where such distribution or use would be contrary to local law or regulation. This presentation is not directed to or intended for distribution, or transfer, either directly or indirectly to, or use by, any person or entity that is a citizen or resident or located in any locality, state, country or other jurisdiction where such distribution, transfer, publication, availability or use would be contrary to law or regulation or which would require any registration or licensing within such jurisdiction.

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Statements in this presentation that are not statements of historical fact are forward-looking statements, including, without limitation, statements related to the Company's ability to deliver impactful medicines to patients; the ability of our key executives to drive execution of the Company's portfolio of programs; our asset-centric business model and the intended advantages and benefits thereof; research and clinical development plans; the scope, progress, results and costs of developing our product candidates or any other future product candidates; the development and therapeutic potential of our product candidates, including SerpinPC and ZF874; strategy; regulatory matters, including the timing and likelihood of success of obtaining approvals to initiate or continue clinical trials or market any products; market size and opportunity for our product candidates; and our anticipated cash runway. Words such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," "aim," "seek," and variations of these words or similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Such statements reflect the current views of the Company with respect to future events and are subject to known and unknown risks, including, without limitation, risks related to the safety and tolerability profile of our product candidates; our ability to protect and maintain our intellectual property position; business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing, including through our financing facility with Oberland, to fund our planned clinical trials and other expenses; trends in the industry; the legal and regulatory framework for the industry, including the receipt and maintenance of clearances to conduct or continue clinical testing; future expenditures risks related to our asset-centric corporate model; the risk that any one or more of our product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies; and risks related to the COVID-19 pandemic including the effects of the Delta, Omicron and any other variants, geo-political risks such as the Russia-Ukraine war and other risk factors contained in our filings with the U.S. Securities and Exchange Commission. In light of these risks and uncertainties, the events or circumstances referred to in the forward-looking statements may not occur. The actual results may vary from the anticipated results and the variations may be material. These forward-looking statements should not be taken as forecasts or promises nor should they be taken as implying any indication, assurance or guarantee that the assumptions on which such forward looking statements have been made are correct or exhaustive or, in the case of the assumptions, fully stated in this presentation. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date this presentation is given. All projections, valuations and statistical analyses are provided for information purposes only. They may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, they should not be relied upon as an accurate prediction of future performance.

This presentation discusses product candidates that are under clinical study, and which have not yet been approved for marketing by the U.S. Food and Drug Administration or any other regulatory agency. No representation or warranty, express or implied, is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third party sources and the Company's own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation or warranty, express or implied, as to the adequacy, fairness, accuracy or completeness of, any information obtained from third party sources. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.


We are an **R&D innovation engine** that aims to discover, develop and ultimately deliver **impactful medicines to patients**

Centessa management team with deep R&D experience

CENTESSA PHARMACEUTICALS

Pipeline of innovative, potential best-in-class medicines for patients

REGISTRATIONAL (Programs in registrational trials this year)

SerpinPC in Hemophilia (Hemophilia B for initial registrational trial)

EMERGING (Programs with clinical proof of concept anticipated in next 18 months)

LB101 and LB201 in Solid Tumors
ZF874 in Alpha-1 Antitrypsin Deficiency
MGX292 in Pulmonary Arterial Hypertension
Orexin Agonists in Narcolepsy and other Sleep-Wake Disorders

EXPLORATORY (Programs with proof of concept beyond 18 months)

CBS001 in Inflammatory/Fibrotic Diseases
CBS004 in Systemic Sclerosis, Lupus Erythematosus

Portfolio of rare disease and immuno-oncology programs targeting multi-billion dollar markets

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External market validation for our Registrational and Emerging programs

Asset	Disease	Reason to believe	Market validation
REGISTRATIONAL (Programs in registrational trials this year)			
SerpinPC	Hemophilia A and B	Associated with **promising ABR reduction** and infrequent **subcutaneous** dosing **with limited risk of thrombosis**	CSL Behring uniQure **$2B+** licensing deal in 2020 for Hemophilia B gene therapy in Phase 3 clinical trials
EMERGING (Programs with clinical proof of concept anticipated in next 18 months)			
LB101 / LB201	Solid Tumors	Platform of LockBody® programs designed to **selectively drive effector function activity** while avoiding systemic tox	AMGEN Teneobio **$2.5B** acquisition for pipeline of bispecific / multi-specific antibody technologies
ZF874	AATD	**Small molecule** pharmacological chaperone folding corrector intended to address **lung and liver manifestations** of AATD	VERTEX **$20B** total market cap loss after two clinical failures for small molecule approaches in AATD
MGX292	PAH	**Replacement BMP9 protein** designed to overcome signaling deficiency and directly target underlying disease mechanism	MERCK ACCELERON **$11.5B** acquisition; lead candidate sotatercept indirectly impacts BMPR2 pathway
Orexin Agonists	Narcolepsy	Designed to leverage unique structural insights and to **directly target underlying pathophysiology** of orexin neuron loss	Takeda **$5B** market cap loss after clinical failure of orexin agonist in Narcolepsy Type 1 (NT1)

Source: Otsuka Holdings FY2021 Financial Results Presentation; uniQure 8-K (May 6, 2021); Amgen PR (July 27, 2021); Vertex market cap loss based on share price changes from Oct 14, 2020 ($271.46) to Oct 15, 2020 ($215.28) and June 10, 2021 ($216.77) to June 11, 2021 ($193.02); Acceleron PR (Sept 30, 2021); Takeda market cap loss based on share price changes from Oct 5, 2021 ($16.08) to Oct 6, 2021 ($14.31).

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Upcoming 2022 catalysts with cash runway now into 2026

$544.5 million cash and cash equivalents as of March 31, 2022

2022 data

- ✓ **LB101 in Solid Tumors:** Preclinical data presented at ASCO in June 2022
- **ZF874 in AATD:** Ph 1 data from multiple dose cohorts anticipated in 2H 2022
- **SerpinPC in Hemophilia:** Open-label extension (OLE) data expected in 4Q 2022

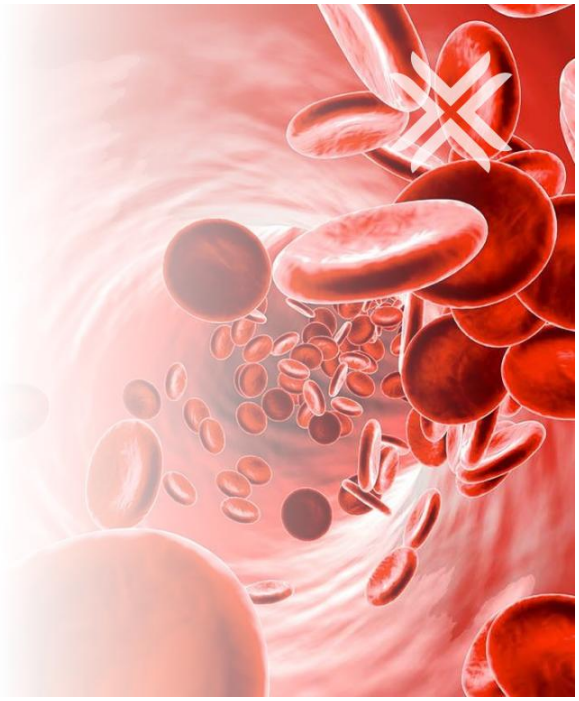
2022 program updates

- ✓ **CBS001 in Inflammatory / Fibrotic Diseases:** Ph1 in Healthy Volunteers commenced in April 2022
- **SerpinPC in Hemophilia B:** Start of Hem B registrational trials planned in 2H 2022
- **LB101 in Solid Tumors:** IND anticipated in late 2022
- **CBS004 in autoimmune diseases:** IND anticipated in late 2022

Potential for multiple clinical proof of concept (PoC) readouts over the next 12-24 months

Note: On June 2, 2022, the Company updated its cash runway estimate following its strategic decision to voluntarily discontinue development of lixivaptan.
Cash runway does not include the remaining available tranches under the Oberland facility. Currently $75m drawn under facility.

SerpinPC in Hemophilia



SerpinPC has the potential to shift Hemophilia B treatment paradigm

GENETIC VALIDATION AND CLINICAL PROOF OF CONCEPT FOR NEW MECHANISM

- Human genetic target validation in individuals who co-inherit Factor V Leiden mutation and either FVIII or FIX mutations reinforced with positive proof-of-concept Phase 2 data

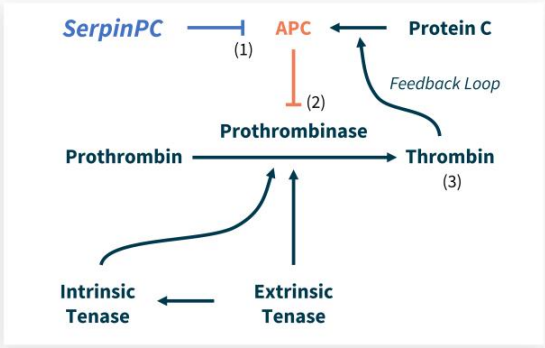
UNIQUE MECHANISM THAT IS NOT BELIEVED TO CONFER RISK FOR THROMBOSIS

- No sustained elevations in D-dimer and no evidence of thrombosis observed in clinical trials in healthy volunteers and persons with hemophilia

PROMISING REDUCTIONS IN BLEEDING WITH INFREQUENT SUBCUTANEOUS DOSING

- Observed a median 88% reduction in all bleed ABR in the highest dose cohort in the Phase 2 study, with PK suitable for an infrequent dosing schedule

SerpinPC is believed to have a unique MoA supported by human genetics



SerpinPC reduces levels of circulating APC (1), thereby prolonging activity of prothrombinase (2) and directly increasing the amount of thrombin (3) at the site of tissue damage

Genetically validated target based on coinheritance of Factor V Leiden mutation with hemophilia

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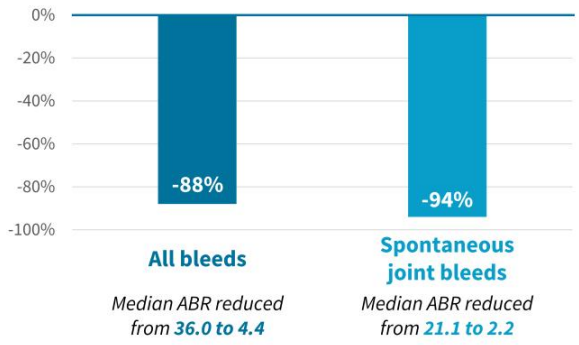
SerpinPC showed promising reductions in bleeding rates and was observed to be well-tolerated in the Phase 2a study

Median ABR reduction for highest dose cohort (1.2 mg/kg)



*Median ABR reduced from **36.0 to 4.4***

*Median ABR reduced from **21.1 to 2.2***

Across all dose levels:

- **No thrombosis**
- **No instances of sustained elevations in D-dimer**
- 1 moderate skin reaction led to withdrawal of a subject with history of a skin disorder
- Two subjects with ADAs, with no apparent impact on ABRs
- No other SerpinPC-related AEs

Initial registration studies focused on Hem B (+/- inhibitors) given high unmet need and market opportunity

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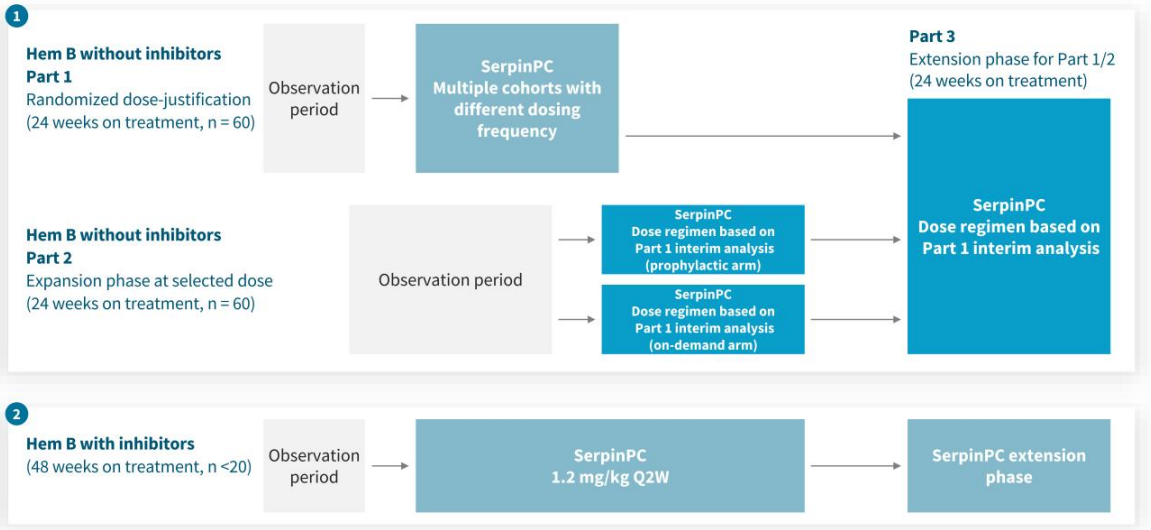
Two registrational trials planned to start in 2H 2022 in Hemophilia B



Note: The first registrational study will also enroll subjects with severe HA, with and without inhibitors, to add to the safety database

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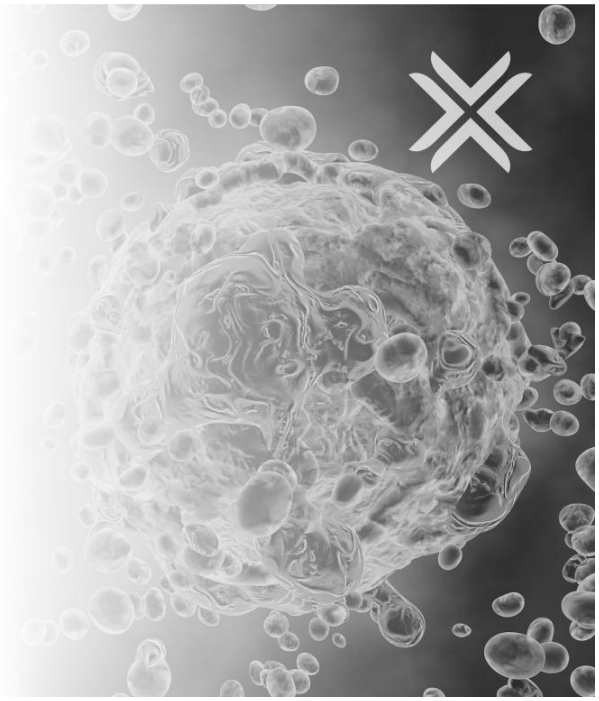
LB101 & LB201 in Solid Tumors



LockBody® platform aims to redefine tumor-specific cell killing

PLATFORM DESIGNED TO ADDRESS IMMUNO-ONCOLOGY THERAPY CHALLENGES

- LockBody® mechanism aims to bypass "sink" effects, minimize peripheral toxicity, and enable tumor-localized effector function activity of contingent domains, such as CD47 or CD3, directly into the tumor

UNIQUE TECHNOLOGY DESIGNED TO UNLOCK CELL KILLING IN THE TUMOR

- Contingent potent effector Fabs, such as CD47 or CD3, are blocked by constitutive Fabs, such as PD-L1 or HER2, until human IgG-derived hinges are naturally degraded in the tumor microenvironment (TME)

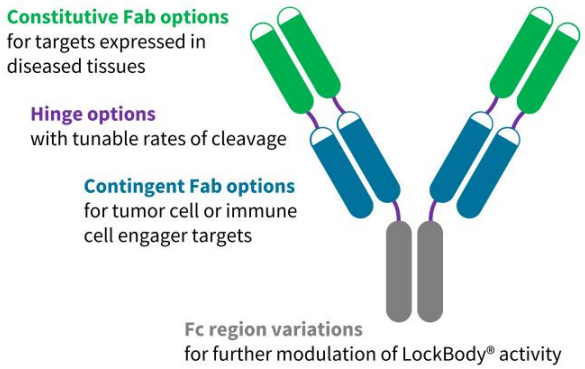
DESIGNED AS SINGLE AGENT SYSTEMIC TREATMENT

- LB101 is designed as a single agent combining PD-L1 targeting, CD47 blockade and a fully functional IgG1 Fc region

Unique, modular platform for multiple LockBody® permutations

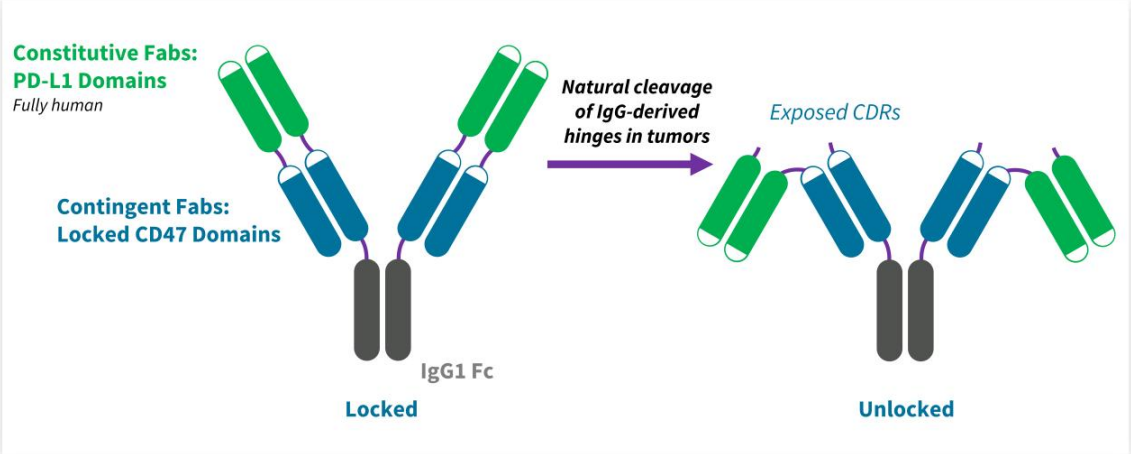
Differentiation of the LockBody® approach:

- ✓ **Single agent** activity, **systemically delivered**, with a **wide therapeutic index**
- ✓ **Tunable**, conditional activation via **natural cleavage** of IgG-derived hinges (not synthetically engineered)
- ✓ **Localized** concentration of the contingent Fabs optimizes bio-distribution and **avoids systemic tox**
- ✓ **'Plug and play'** leads to easy design of new constructs and IgG-like manufacturing



CENTESSA PHARMACEUTICALS

LB101 is designed to provide anti-PD-L1 activity plus CD47-targeted activity in the TME



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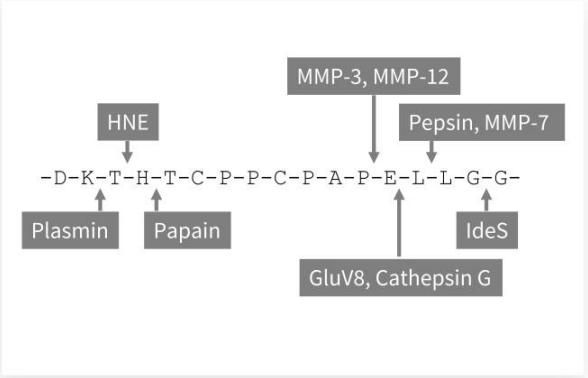
LockBody® mechanism uses human IgG-derived hinges susceptible to multiple proteases in the TME

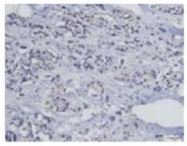
Published work from others showing cleavage of IgG at the hinge in patient tumor

Cleavage sites in IgG hinge sequence

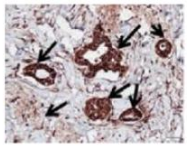


Cleaved hinge detected in Her2+ tumor samples from human patients treated with trastuzumab

No primary Ab



Ab specific for cleaved hinge

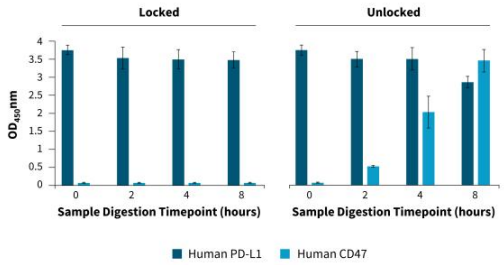


Jordan et al. "Proteinase-nicked IgGs: an unanticipated target for tumor immunotherapy" *Oncoimmunology* 2018

CENTESSA PHARMACEUTICALS

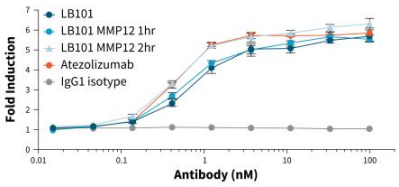
In vitro: LB101 demonstrated expected target binding in locked and unlocked states

LB101 binding to PD-L1 in the locked form, with CD47 binding after activation in the unlocked form

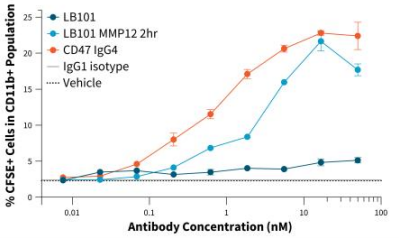


Anti-PD-L1 potency similar to atezolizumab in locked form, and strongly enhanced ADCP in unlocked form

Locked: PD-L1 blockade



Unlocked: CD47 binding



18 Note: The PD-1/PD-L1 cell-based bioassay (Promega, according to manufacturer's instructions) was used to measure the potency of IgG1 isotype, atezolizumab (anti–PD-L1), and LB101 (digested and undigested with MMP12) from 100 nM to 0.01 nM dilutions

CENTESSA PHARMACEUTICALS

In vivo: LB101 showed improved efficacy and durability over control and atezolizumab in a difficult-to-treat mouse model and was well tolerated

Single-agent LB101 delivered systemically resulted in PD-L1 directed, local tumor-specific CD47 effector engagement leading to significant tumor regressions

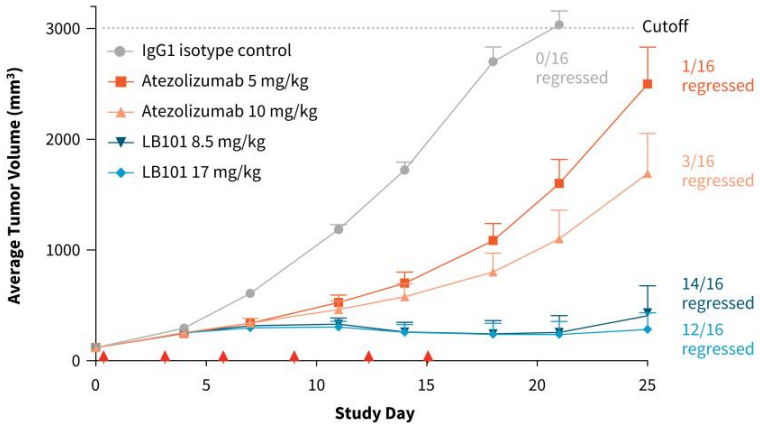
- Single-agent LB101: **26/32 tumors eradicated across both doses**[1]
- Isotype control IgG: 0/16 tumors eradicated
- Atezolizumab: 4/32 tumors eradicated across both doses[2]

In rechallenge studies, none of the mice with prior LB101-induced regressions exhibited tumor growth vs. all naïve mice rapidly established tumors

LB101 exhibited no anemia, weight-loss or overt toxicity at equimolar doses to atezolizumab, while equimolar doses of CD47 are lethal in this mouse model

1. 14/16 eradicated at 8.5 mg/kg dose and 12/16 eradicated at 17 mg/kg dose; 2. 1/16 eradicated at 5 mg/kg dose and 3/16 eradicated at 10 mg/kg dose
Note: MC38 hPD-L1+ syngeneic model in mouse

In vivo: Systemically delivered LB101 exhibited significant tumor regression

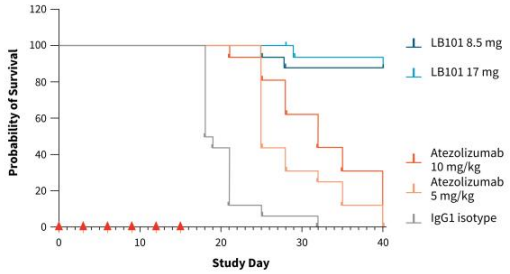


Note: Arrows indicate dosing every 3 days (Q3d x 6) at Days 0, 3, 6, 9, 12, and 15. 5 mg/kg of atezolizumab is equivalent to 8.5 mg/kg of LB101.

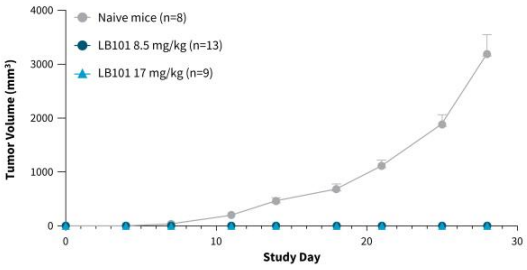
CENTESSA PHARMACEUTICALS

In vivo: LB101 led to higher survival and showed no tumor growth in rechallenge experiment

Higher survival in mice treated with LB101 compared to isotype control and atezolizumab

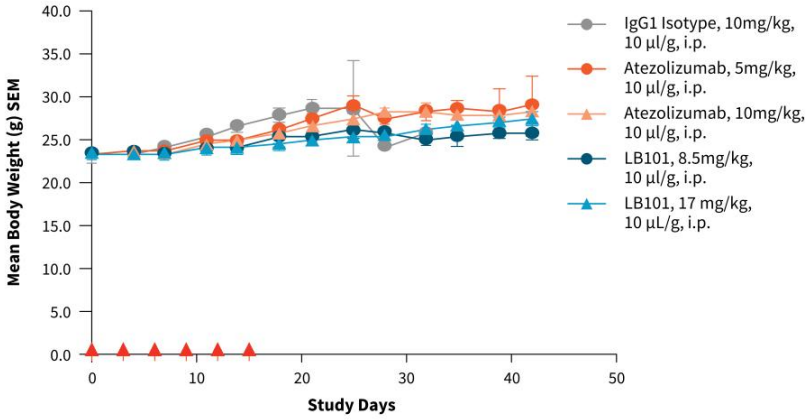


None of the mice from groups with prior LB101-induced regressions exhibited tumor growth



Note: Arrows indicate dosing every 3 days (Q3d x 6) at Days 0, 3, 6, 9, 12, and 15. 5 mg/kg of atezolizumab is equivalent to 8.5 mg/kg of LB101.

In vivo: LB101 was well tolerated with no weight loss



Note: Arrows indicate dosing every 3 days (Q3d x 6) at Days 0, 3, 6, 9, 12, and 15. 5 mg/kg of atezolizumab is equivalent to 8.5 mg/kg of LB101.

CENTESSA PHARMACEUTICALS

LockBody® development plan and upcoming milestones

- Planning to submit an IND for LB101 (PD-L1xCD47 LockBody®) in late 2022
- Planning to submit an IND for LB201 (PD-L1xCD3 LockBody®) in 2023
- Continuing to explore full potential of the technology in improving the therapeutic index of other anticancer biological effectors

ZF874
in AATD

ZF874 has the potential to be a disease-modifying treatment for AATD

DESIGNED AS A CATALYTIC, NON-COVALENT SMALL MOLECULE FOLDING CORRECTOR

- ZF874 is designed to bind to the stalled folding intermediate specific to Z-A1AT with no detectable binding to fully folded Z-A1AT *in vitro*; ZF887 in preclin. development, structurally unrelated to ZF874

POTENTIAL TO INCREASE FUNCTIONAL A1AT LEVELS TO PROTECT THE LUNG

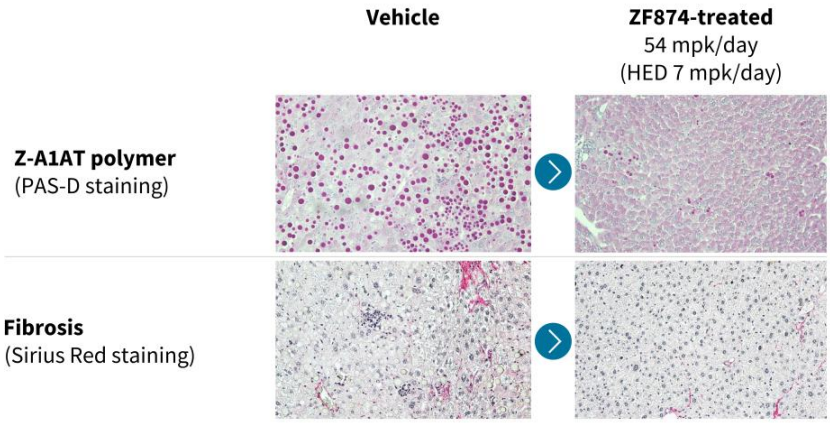
- Initial ZF874 clinical data was the first demonstration that a pharmacological chaperone could provide sufficient functional Z-A1AT increases in serum to potentially achieve >11µm levels in PiZZ individuals

POTENTIAL TO CLEAR POLYMERS FROM THE LIVER

- Preclinical data showed both increased blood levels of Z-A1AT and clearance of Z-A1AT polymer from the liver in mice over-expressing human Z-A1AT at lower doses than in human studies

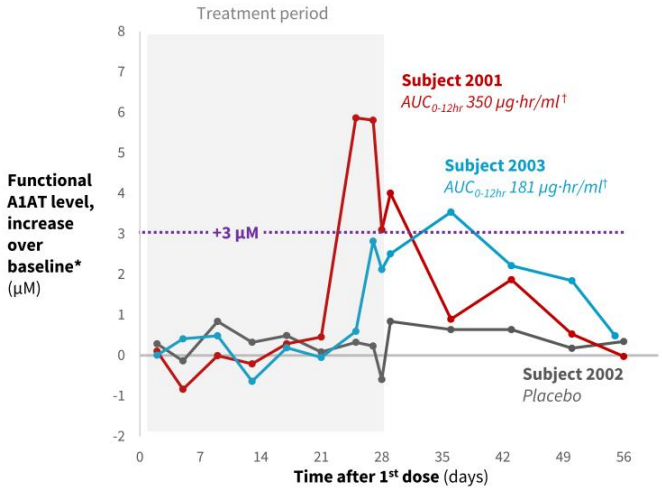
Preclinical data showed low doses of ZF874 clear polymer & reduced fibrosis

Liver histology from 84-day treatment of mice expressing human Z-A1AT (PiZ mice)



Abbreviations: mpk = milligrams per kilogram; PAS-D = Periodic Acid-Schiff staining with diastase; HED = human equivalent dose

Clinical data in PiMZ subjects dosed with placebo or ZF874 15 mpk BID



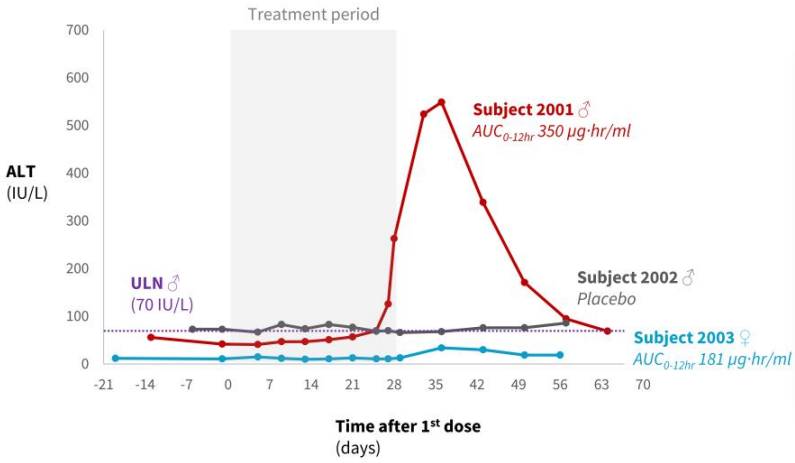
Demographics and data
First 3 subjects in Part B

Subj.	Treatment	Genotype	Baseline A1AT*	Peak A1AT
2001	15 mpk BID (1.6 g BID)	MZ	17.6 µM	23.5 µM
2002	Placebo (N/A)	MZ	12.7 µM	13.5 µM
2003	15 mpk BID (1.1 g BID)	MZ	14.8 µM	18.3 µM

* Activity level equivalent to molar amount of M A1AT reference standard. Baseline for each subject = average of Pre-Screen , Day -1, and Day 1 Pre-Dose values for each subject
† Trapezoidal AUC for the first 12 hours after the first dose on Day 28
* Baseline = average of Pre-Screen, Day -1 and Day 1 Pre-Dose values from A1AT functional assay

CENTESSA PHARMACEUTICALS

Liver signal in one PiMZ subject with highest exposure in Part B



- Subject 2001 showed increases in ALT (8X ULN) and AST (3.5X ULN) after the treatment period
- In the same subject, BILI, GGT and ALP stayed in the reference range throughout the observation period
- No liver signal was observed in SAD with PiMM healthy volunteers in Part A (n = 42, dose range 1.5 mpk to 50 mpk)
- All other observed AEs were mild

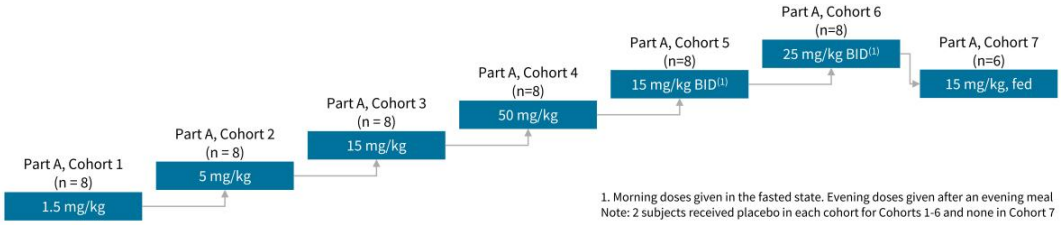
* ULN ♀ (33 IU/L)
† Trapezoidal AUC for the first 12 hours after the first dose on Day 28

Abbreviations: ULN = upper limit of normal; IU/L = international units per liter; BILI = bilirubin; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase

CENTESSA PHARMACEUTICALS

Overview of ongoing Phase 1 trial of ZF874 in AATD

Part A (completed): Single Ascending Dose Study in **Healthy Volunteers**



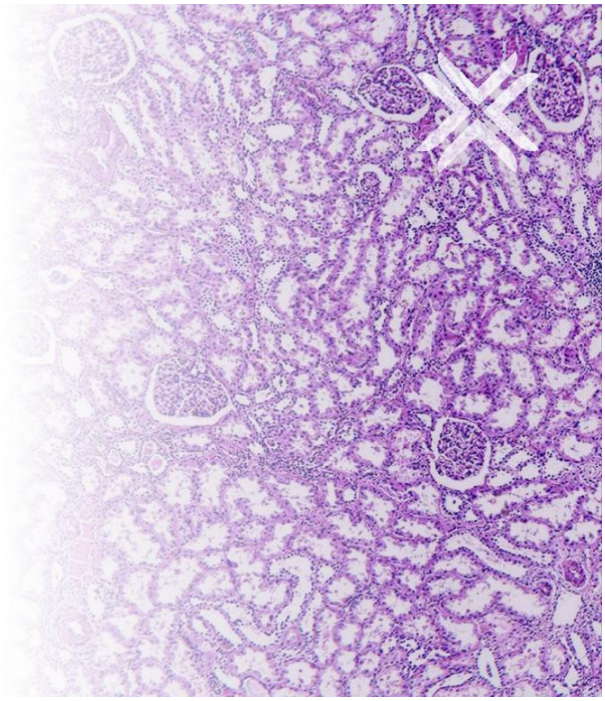
1. Morning doses given in the fasted state. Evening doses given after an evening meal
Note: 2 subjects received placebo in each cohort for Cohorts 1-6 and none in Cohort 7

Part B (ongoing): 28-day Repeat Dosing in **PiXZ Subjects (Including PiZZ and PiMZ Subjects)**

Protocol may be amended to extend duration of dosing in Part B to up to 3 months pending receipt of satisfactory long-term animal tox data

CENTESSA PHARMACEUTICALS

MGX292 in PAH



MGX292 has the potential for disease reversal / modification in PAH

DESIGNED TO DIRECTLY TARGET CENTRAL UNDERLYING DISEASE MECHANISM IN PAH

- Recombinant modified BMP9 replacement protein designed to directly target BMPR2/ALK1 pathway vs. experimental therapies which inhibit Activin signaling with only indirect effects on this pathway

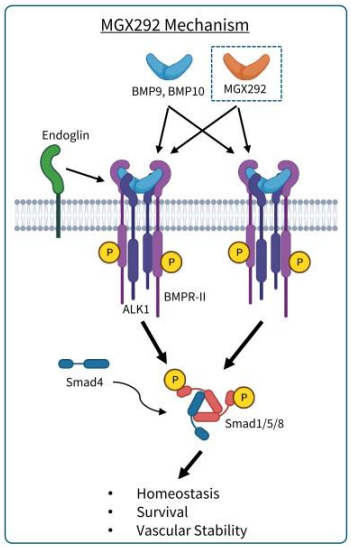
***IN VIVO* DATA DEMONSTRATED POTENTIAL TO RESTORE VASCULAR FUNCTION**

- MGX292 was observed to reverse established advanced pulmonary vascular remodeling in the Sugen-hypoxia rat model, with almost complete reversal of disease at high dose

POTENTIAL FOR RAPID DEVELOPMENT IN GENETICALLY DEFINED PAH

- Potential development plan to address ~25% of idiopathic PAH patients with loss-of-function mutations in the BMP9 signaling axis

MGX292 is designed to directly target central underlying disease mechanism

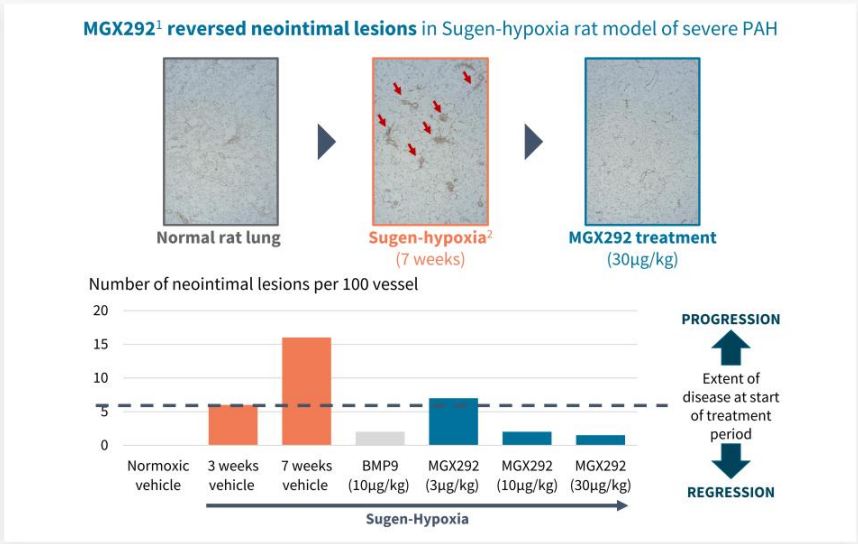


In PAH, reduced **BMP9 signaling** results in the pathological changes underlying PAH.

With MGX292 treatment, supplementation with exogenous recombinant BMP9 protein (MGX292) leads to **restored signaling** and normalization of endothelial cell functions.

CENTESSA PHARMACEUTICALS

MGX292 demonstrated dose-dependent reversal of established lung vascular pathology in Sugen-hypoxia rat model



1. MGX292 treatment was given daily for 4 weeks; 2. Red arrows depict vascular lesions

Development plan for MGX292 in PAH

- Preclinical development ongoing, currently in the IND-enabling stage
- Plan to conduct pre-IND meeting with the FDA in the second half of 2022
- Plan to submit an IND for MGX292 in early 2023

OX2R Agonists in NT1

Our novel orexin agonist approaches have the potential to change the global standard of care in narcolepsy

DESIGNED TO DIRECTLY TARGET UNDERLYING PATHOPHYSIOLOGY OF DISEASE

- Lead molecules are designed to selectively target the Orexin Receptor-2 (OX2R) based on structure-based drug design

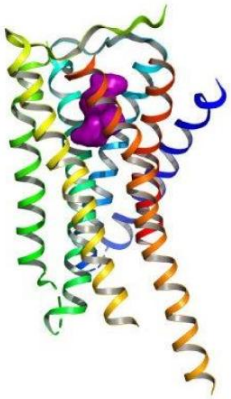
***IN VIVO* DATA DEMONSTRATED DOSE DEPENDENT EFFECTS IN INCREASING WAKEFULNESS**

- Observed significant increases in wakefulness in the NT1 model mice and wild type mice for the exemplar small molecule agonists and in wild type mice for the exemplar peptide agonists

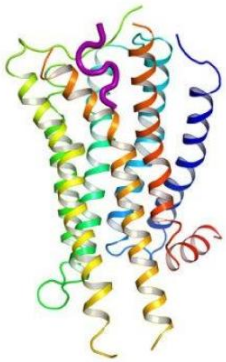
TEAM AND EXCLUSIVE PARTNERSHIPS ENABLE DIFFERENTIATED DRUG DISCOVERY

- Program led by former Takeda orexin team leadership; exclusive license to Sosei Heptares's StaR® technology and exclusive collaboration with Schrödinger to support novel discovery efforts

Our small molecule and peptide orexin agonists are designed to provide a potential replacement therapy approach in NT1



Example X-ray structure of OX2R with small molecule orexin agonist (shown in purple)



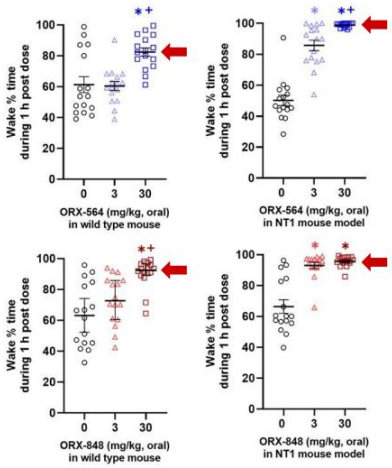
Example Cryo-EM structure of OX2R with peptide agonist (shown in purple)

Our small molecule and peptide orexin agonist molecules have demonstrated **sub-nanomolar potency** in *in vitro* assays *

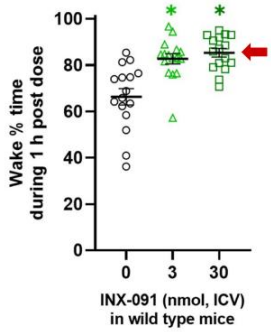
* Based on EC50, *in vitro* functional profiles of exemplar small molecule agonists and exemplar peptide agonists in a calcium mobilization FLIPR assay with cells expressing recombinant human OX2R

Novel small molecule and peptide orexin agonists demonstrated dose-dependent effects in increasing wakefulness in mice

Exemplar small molecule agonists



Exemplar peptide agonist



CENTESSA PHARMACEUTICALS

Development plan for orexin agonists in NT1

- Plan to submit IND / CTA for lead oral program in 2023
- Plan to submit IND / CTA for intranasal program in 2023
- Intend to explore additional indications beyond NT1

Key value drivers

- **Substantial innovative pipeline of rare disease and immuno-oncology assets targeting multi-billion dollar markets**
- **Potential for multiple clinical proof of concept (PoC) readouts over the next 12-24 months**
- **Cash runway into 2026**

Note: Cash runway does not include the remaining available tranches under the Oberland facility

CENTESSA PHARMACEUTICALS