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): November 1, 2021

CENTESSA PHARMACEUTICALS PLC

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

England and Wales	**001-04321**	**Not applicable**
(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))

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 7.01 Regulation FD Disclosure.

On November 1, 2021, Centessa Pharmaceuticals plc (the "Company" or "Centessa") issued a press release titled "Centessa Pharmaceuticals Demonstrates Proof-of-Mechanism from First Three PiMZ Subjects Dosed in Part B of Phase 1 Study Evaluating ZF874". A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Following the issuance of the press release, the Company will host a webcast and conference call to discuss interim results from Part B of the Study. A copy of the presentation to be used on the webcast and conference call is furnished as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information under this Item 7.01, including Exhibits 99.1 and 99.2 hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	
99.1	Press Release dated November 1, 2021
99.2	Centessa Pharmaceuticals slide presentation

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: November 1, 2021

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

Exhibit 99.1

Centessa Pharmaceuticals Demonstrates Proof-of-Mechanism from First Three PiMZ Subjects Dosed in Part B of Phase 1 Study Evaluating ZF874

~ First demonstration that a pharmacological chaperone can provide sufficient functional Z-A1AT increases to potentially achieve greater than 11 micromolar levels in individuals with PiZZ genotype ~

~ One subject with two-fold higher exposure experienced reversible ALT and AST elevations ~

~ Several actions underway to accelerate enrollment to refine dose and regimen for Phase 2 study expected to start in 2Q 2022 ~

~ Conference call and webcast scheduled for today at 8:30 a.m. EDT ~

BOSTON & LONDON, November 1, 2021 – Centessa Pharmaceuticals plc (“Company”) (Nasdaq: CNTA), together with subsidiary Z Factor Limited (“Z Factor”), today announced proof-of-mechanism data from the first three subjects dosed in the ongoing repeat dose Phase 1 Part B study of ZF874 in subjects carrying at least one Z-mutated alpha-1-antitrypsin allele (PiXZ). This is the first demonstration that a pharmacological chaperone can provide sufficient functional Z-A1AT increases to potentially achieve greater than 11 micromolar levels in individuals with the PiZZ genotype.

ZF-0101 is a Phase 1 study evaluating ZF874 (the “Study”), a novel, catalytically acting pharmacological chaperone designed to rescue the folding of the Z variant of alpha-1-antitrypsin (“A1AT”) to address Alpha-1 Antitrypsin Deficiency (“AATD”). AATD is an autosomal recessive disorder frequently caused by missense mutations in the A1AT gene, resulting in the misfolding of A1AT. Individuals with AATD regularly suffer from chronic obstructive pulmonary disease and/or liver disease.

Part A of the Study was comprised of a single ascending dose study in 7 cohorts of healthy volunteers. Part B of the Study was initially designed to be a 28-day repeat dose study in up to 14 PiXZ patients (including 2 placebo), assessing the safety, tolerability and pharmacokinetics of ZF874. Increase in serum A1AT levels was an exploratory outcome.

In both PiMZ subjects dosed with 15 mg/kg BID of ZF874, the observed increase in functional A1AT was between 3.5 and 6 micromolar for these subjects with one Z-gene copy. The A1AT levels began to increase rapidly in the last week of dosing. After only 28 days of dosing the amount of A1AT was equivalent to achieving 12 to 17 micromolar in individuals with two Z- gene copies (PiZZ). In pre-clinical PiZ mouse models treated with ZF874, A1AT continues to rise with dosing beyond 28 days. A1AT plasma levels of 11 micromolar have been the basis for approval of the existing A1AT augmentation therapies. A1AT levels in the placebo-treated subject were not observed to change significantly.

Consistent with a pharmacological effect for ZF874, and as expected based on the circulating half-life of A1AT, levels returned to baseline by 28 days after completion of dosing.

Pharmacokinetic analysis showed a two-fold higher exposure to ZF874 in one subject. This subject showed a two-fold higher increase in functional A1AT as well as a delayed, reversible increase in ALT (8x ULN) and AST (3.5x ULN). All other liver function tests including bilirubin, GGT, and ALP remained in the

normal range. All other adverse events reported in the Study were classified as mild. Due to ongoing enrollment challenges at the single clinical site, and following the observation of elevated liver enzymes in one Study participant, the Company elected to unblind the Study prior to completing Part B enrollment.

“With only two subjects of data, we have established proof of mechanism for ZF874 and show, for the first time, the promise of a catalytic small molecule corrector to restore A1AT to clinically significant levels,” said Saurabh Saha, M.D., Ph.D., Chief Executive Officer of Centessa. “This now becomes a drug development exercise as we refine a dose and regimen for our planned global six-month Phase 2 study.”

"These are exciting new findings. I look forward to hearing about further development of this novel approach, which has potential to treat both the lung and the liver in this complex disease,” said Jeffrey Teckman, M.D., Patricia and James Monteleone Endowed Chair, Director, Pediatric Gastroenterology and Hepatology, Professor of Pediatrics and Biochemistry, Saint Louis University School of Medicine.

The Company is undertaking a number of actions to accelerate enrollment and facilitate dose exploration in PiXZ subjects, including opening additional sites in the UK and expanding the Study to the EU. In addition, the run-in portion of the expected Phase 2 study will be designed to further refine dose and regimen ahead of the start of 6-month dosing.

Conference Call and Webcast
Centessa Pharmaceuticals will host a webcast and conference call today, November 1, 2021, at 8:30 a.m. EDT to discuss interim results from Part B of the Study. To access the audio webcast with slides, please visit the "Events & Publications" page in the Investors & Media section of the Company's website at https://investors.centessa.com/events-presentations. The call can also be accessed by dialing (855) 493-3565 (domestic) or +1 (929) 517-9002 (international) with conference ID 3574786. An archive of today's webcast will be available on the Company's website.

About Centessa Pharmaceuticals
Centessa Pharmaceuticals plc aims to bring impactful new medicines to patients by combining the strengths of an asset-centric model with the benefits of scale and diversification typical of larger R&D organizations. The asset-centric model refers to a highly specialized, singular-focused company that is led by a team of well-recognized subject matter experts. Centessa’s asset-centric companies’ programs range from discovery-stage to late-stage development and include diverse therapeutic areas such as oncology, hematology, immunology/inflammation, neuroscience, hepatology, pulmonology and nephrology. For more information, visit www.centessa.com.

About Z Factor Limited (Z Factor)
Z Factor is a clinical-stage biotechnology company founded in 2015 to identify and develop therapeutic agents to treat alpha-1-antitrypsin deficiency (“AATD”), a common genetic disorder where a single mistake in the DNA encoding the protein alpha-1-antrypsin (“A1AT”) causes both liver and lung disease.

Z Factor’s lead product candidate, ZF874, is a novel compound that acts as a pharmacological chaperone, allowing the Z variant of A1AT to fold correctly, thereby simultaneously relieving the liver burden of polymer accumulation and providing functional Z-A1AT in circulation to protect the lungs.

Forward Looking Statements
This press release has been prepared by Centessa Pharmaceuticals plc (the “Company”) for informational purposes only and not for any other purpose. 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 regarding our product candidates, including ZF874, its therapeutic potential and our development plans therefor, strategy, regulatory matters, including the timing and designed of planned clinical trials and our ability to complete certain milestones. Words such as "believe," "anticipate," "plan," "expect," "intend," "will," "may," "goal," "project," "estimate," "potential" and 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, business, regulatory, economic and competitive risks, uncertainties, contingencies and assumptions about the Company, risks related to our ability to protect and maintain our intellectual property position; risks inherent in developing products and technologies; future results from our ongoing and planned clinical trials; our ability to obtain adequate financing 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 business 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 variant and the 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.

Contacts:

Investors:
Jennifer Porcelli, Head of Investor Relations
Centessa Pharmaceuticals
jennifer.porcelli@centessa.com

Media:
1AB Media
Dan Budwick
dan@1abmedia.com

CENTESSA PHARMACEUTICALS

Update for ZF874 Phase 1 Part B

November 1, 2021

Disclaimer

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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 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 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.

ZF874 Phase 1 Part B interim results

TODAY'S SPEAKERS

SAURABH SAHA, MD PhD
Chief Executive Officer

JIM HUNTINGTON, PhD
Co-founder & Chief Executive Officer of Z Factor

AVAILABLE FOR Q&A

DAVID GRAINGER, PhD
Co-founder of Z Factor
Chief Innovation Officer of Centessa

GREG WEINHOFF, MD MBA
Chief Financial Officer

ANTOINE YVER, MD MSc
Chief Medical Officer

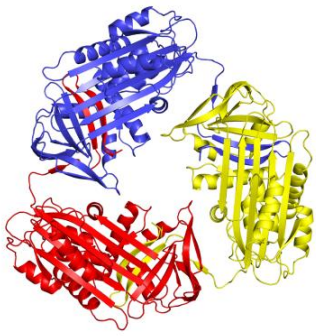
First demonstration that a pharmacological chaperone has the potential to achieve levels greater than 11 μM of functional A1AT in PiZZ subjects

- ZF874's potential to increase functional levels of A1AT to levels >11 μM in individuals with PiZZ genotype is consistent with data from two PiMZ subjects dosed for 28 days
- The current Phase 1 Part B will be expanded to accelerate enrollment and explore dose-exposure-response with lower doses
- Reversible ALT and AST elevations were observed in one subject, similar to other A1AT investigational treatments
- Centessa plans to follow-up this proof-of-mechanism data by launching a global Phase 2 study in Q2 2022

Abbreviations: A1AT = alpha-1 antitrypsin; PiMZ = heterozygote with one wild-type allele of A1AT (M) and one mutant allele of A1AT with a glutamate 342 to lysine mutation (Z); PiZZ = homozygote with two Z mutant alleles; ALT = alanine transaminase; AST = aspartate aminotransferase

Introduction to ZF874 – Folding corrector of Z-A1AT

- **Small molecule folding corrector of the Z variant of A1AT (Z-A1AT).** Catalytic, non-covalent and orally bioavailable
- **Insights from a proprietary crystal structure of a Z-A1AT polymer** led to targeting of a specific pocket
  - ZF874 is designed to bind to the stalled folding intermediate specific to Z-A1AT with the potential to accelerate the final folding step to the native, monomeric form and reduce polymer formation
  - ZF874 was observed to improve folding/secretion of Z-A1AT in cell lines and to have no effect on folding/secretion of wild-type A1AT or a different polymerigenic mutant
  - ZF874 acts catalytically because it is not observed to bind to folded Z-A1AT *in vitro*
- **Preclinical data showed increased blood levels of Z-A1AT *and* clearance of Z-A1AT polymer from liver** in mice over-expressing human Z-A1AT

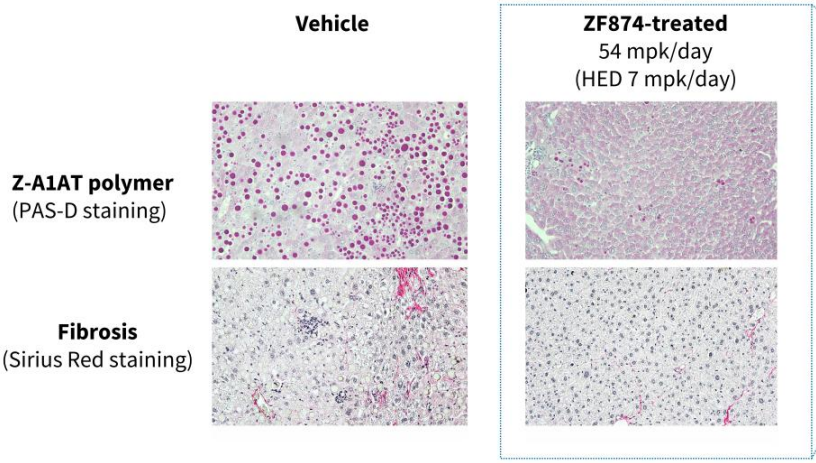


Abbreviations: Z-A1AT = alpha-1 antitrypsin with the Z mutation; M-A1AT = wild-type alpha-1 antitrypsin

Liver pathology is a key feature of A1AT deficiency

Preclinical data shows ZF874 clears polymer and reduces fibrosis

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



In addition to increasing functional A1AT levels, ZF874 improved liver pathology in the PiZ mouse

- Response in mouse liver observed at 54 mpk/day (HED 7 mpk/day or 3.5 mpk BID)
- Active mouse dose of 54 mpk/day (HED 3.5 mpk BID) is 4-fold less than 15 mpk BID dose for first subjects in Phase 1 Part B

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

Schematic of Phase 1 clinical trial for ZF874

Part A (completed, n=54)
SAD Healthy Volunteers

- 15 mpk, high fat meal (n=6)
- 25 mpk, 2 doses (n=6)
- 15 mpk, 2 doses (n=6)
- 50 mpk (n=6)
- 15 mpk (n=6)
- 5 mpk (n=6)
- 1.5 mpk (n=6)
- Placebo (n=12)

Part B (ongoing, n=3)
28-day repeat dosing in PiXZ

- Additional doses TBD
- 15 mpk BID (n=2)
- Placebo (n=1)

Demographics
First 3 subjects in Part B

Subj.	Treatment	Age	Sex	Genotype	Baseline A1AT*
2001	15 mpk BID (1.6 g BID)	47	M	MZ	17.6 µM
2002	Placebo (N/A)	23	M	MZ	12.7 µM
2003	15 mpk BID (1.1 g BID)	47	F	MZ	14.8 µM

* Baseline = average of Pre-Screen, Day -1 and Day 1 Pre-Dose values from A1AT functional assay
Acronyms: SAD = single ascending dose study; PiXZ = patient with one unspecified allele (X) and one mutant allele (Z); TBD = to be determined; BID = twice daily

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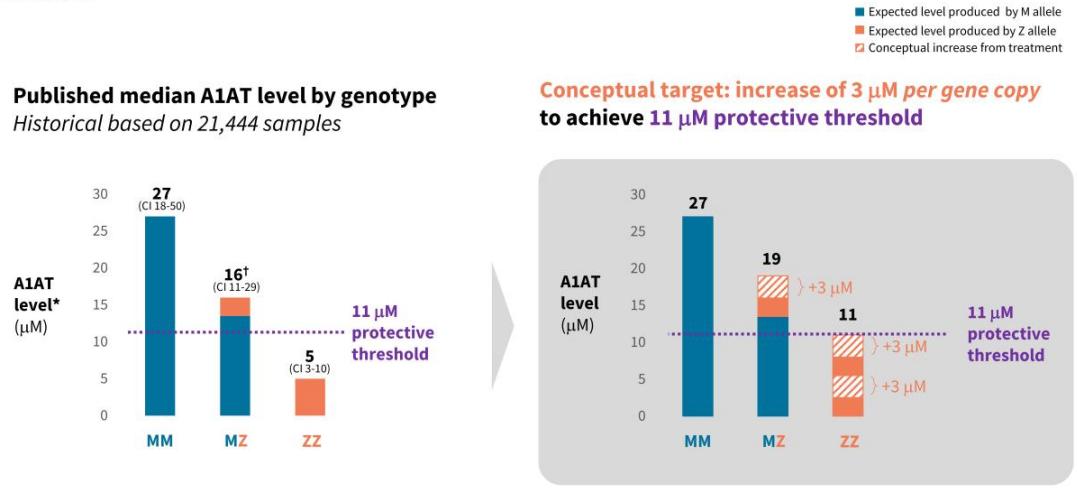
A1AT levels for different genotypes and conceptual target for an effective folding corrector



* Median level from Donato et al. 95% confidence intervals shown.
† M level estimated as half of MM and Z level estimated as half of ZZ
Source: A1AT levels - Donato et al. "Reference and Interpretive Ranges for α_1-Antitrypsin Quantitation by Phenotype in Adult and Pediatric Populations, *Am. J. Clin. Pathol.* 2012; 138:398-405; Protective threshold as basis for replacement therapy – Wewers et al. "Replacement Therapy for Alpha 1 – Antitrypsin Deficiency Associated with Emphysema, *NEJM; 1987 316:1055-1062*

Abbreviations: CI = confidence interval; MM = genotype with two wild-type alleles of A1AT; MZ = genotype with one wild-type and one Z mutant allele of A1AT; ZZ = genotype with two Z mutant alleles of A1AT

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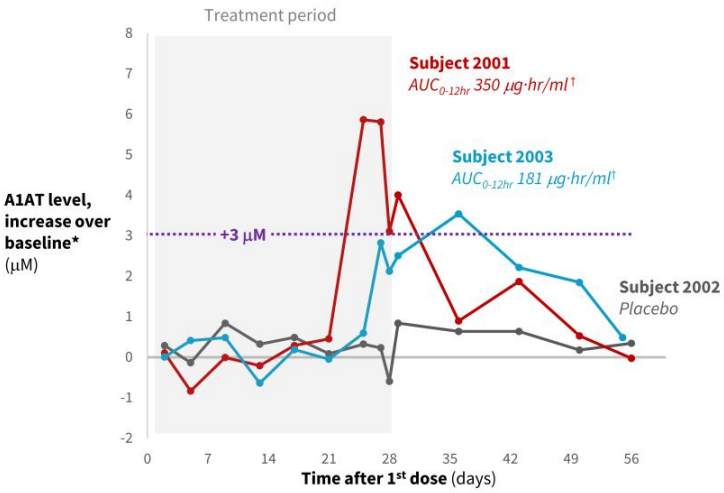
Change in A1AT functional activity for three PiMZ subjects dosed with placebo or ZF874 15 mpk BID



Magnitude of response consistent with feasibility of achieving >11 µM in PiZZ patients

* 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

Abbreviations: AUC = area under the curve

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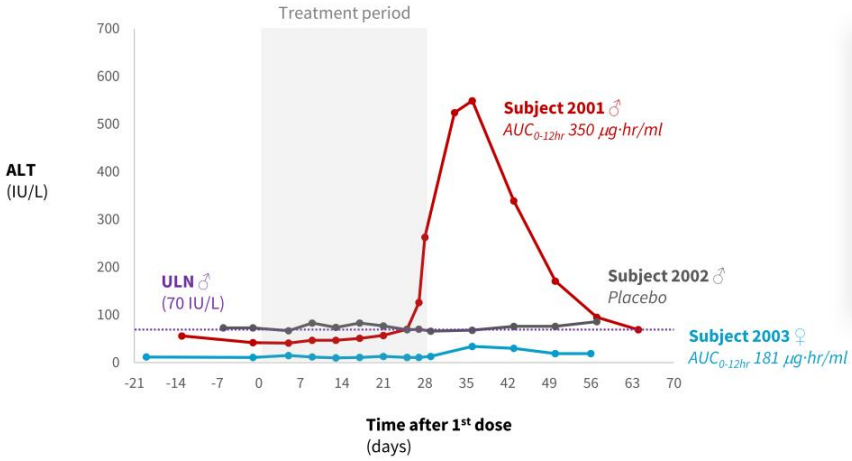
Liver signal in one PiMZ subject with highest exposure in Part B



- 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)

* 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

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Adverse Events for subjects in Part B

Subject 2001 (ZF874)

- Moderate AE of elevated AST/ALT - *possibly drug related*
- Mild AEs of splenomegaly, headache and diarrhea - *unlikely drug related*

Subject 2002 (placebo)

- Mild AE of drowsiness - *possibly drug related*

Subject 2003 (ZF874)

- Mild AEs of headache – *possibly drug related*
- Mild AEs of tiredness and nausea – *unlikely drug related*

Abbreviations: AE = adverse event

Next steps for ongoing Phase 1: Accelerate recruitment to establish Phase 2 dose

- **Additional clinical trial sites**
  - 4 more U.K. sites expected to open this month
  - Expansion to the E.U. underway. Includes a site in Ireland with a large database of PiMZ, PiSZ and PiZZ subjects
- **Exploration of dose-exposure-response in ZF874 in PiMZ/PiSZ and PiZZ subjects**
  - Test 2.5 mpk BID and escalate as appropriate
  - Clear total of 3 PiMZ and/or PiSZ subjects at each dose level before dosing a PiZZ subject
  - Switch to open label without placebo

Updates will be provided as the study progresses to PiZZ subjects

Abbreviation: PiSZ = patient with one allele of S mutant A1AT (glutamate 264 to valine) and one allele of Z mutant A1AT

Commitment to a new global Phase 2 study expected to launch in Q2 2022

- **Two phases**
  - **Run-in.** Additional duration and doses to complement ongoing Phase 1
  - **Six-month portion.** Gated by chronic animal tox available in Q3 2022
    - Assesses magnitude of A1AT response over time. Data from first Phase 1 Part B subjects and preclinical data suggest A1AT levels continue to increase through at least 28-days
    - Includes paired liver biopsy to assess liver pathology. Long-term preclinical studies show clearance of PAS-D staining in liver
- **Principal Investigators.** Agreement to lead trial from experienced U.S. and E.U. Principal Investigators with access to large numbers of PiZZ subjects
- **CRO.** Global CRO is engaged, and Phase 2 planning is underway

6-month Phase 2 allows assessment of both serum A1AT levels over time *and* liver clearance

Abbreviations: CRO = contract research organization

Recap: First demonstration that a pharmacological chaperone has the potential to achieve greater than 11 μM levels of functional A1AT in PiZZ subjects

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- The current Phase 1 Part B will be expanded to accelerate enrollment and explore dose-exposure-response with lower doses
- Reversible ALT and AST elevations were observed in one subject, similar to other A1AT investigational treatments
- Centessa plans to follow-up this proof-of-mechanism data by launching a global Phase 2 study in Q2 2022