CENTESSA PHARMACEUTICALS

Update for ZF874 Phase 1 Part B

November 1, 2021

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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

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Chief Medical Officer

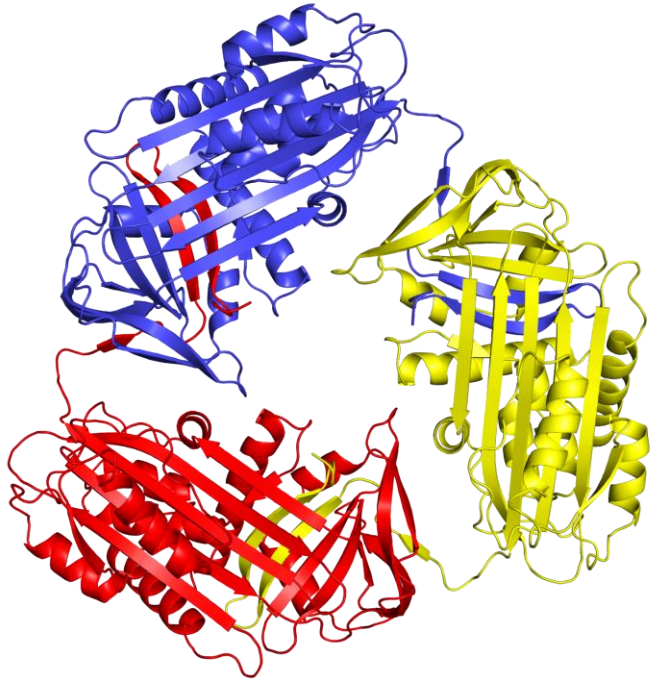
First demonstration that a pharmacological chaperone has the potential to achieve levels greater than 11 μM of functional A1AT in PiZZ subjects

- 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

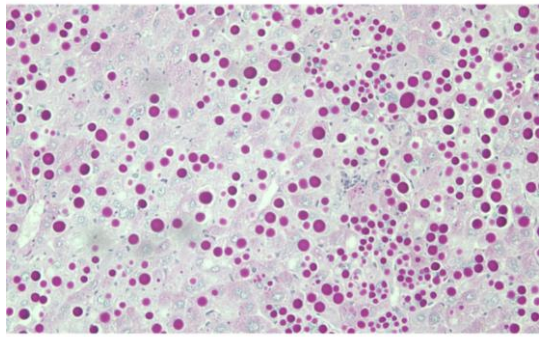
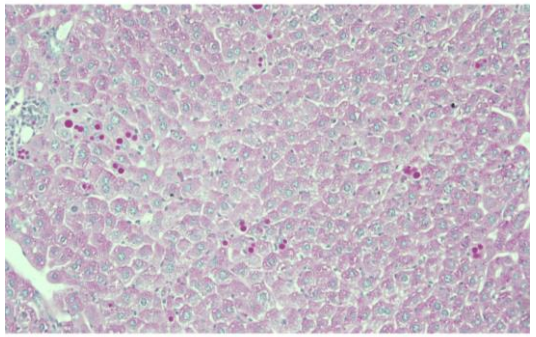
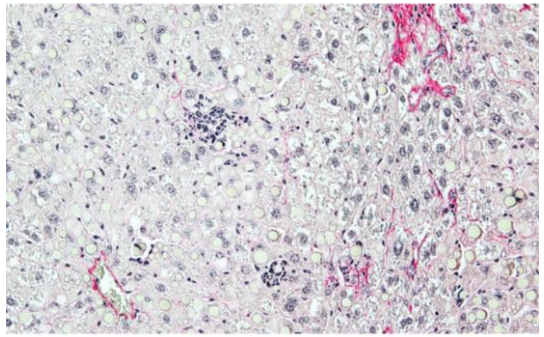
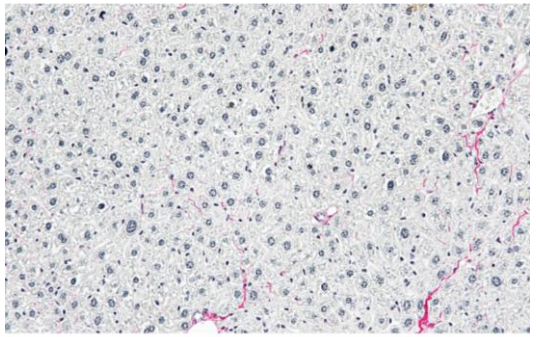


Abbreviations: Z-A1AT = alpha-1 antitrypsin with the Z mutation; M-A1AT = wild-type alpha-1 antitrypsin

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)

	Vehicle	ZF874-treated 54 mpk/day (HED 7 mpk/day)
Z-A1AT polymer (PAS-D staining)		
Fibrosis (Sirius Red staining)		

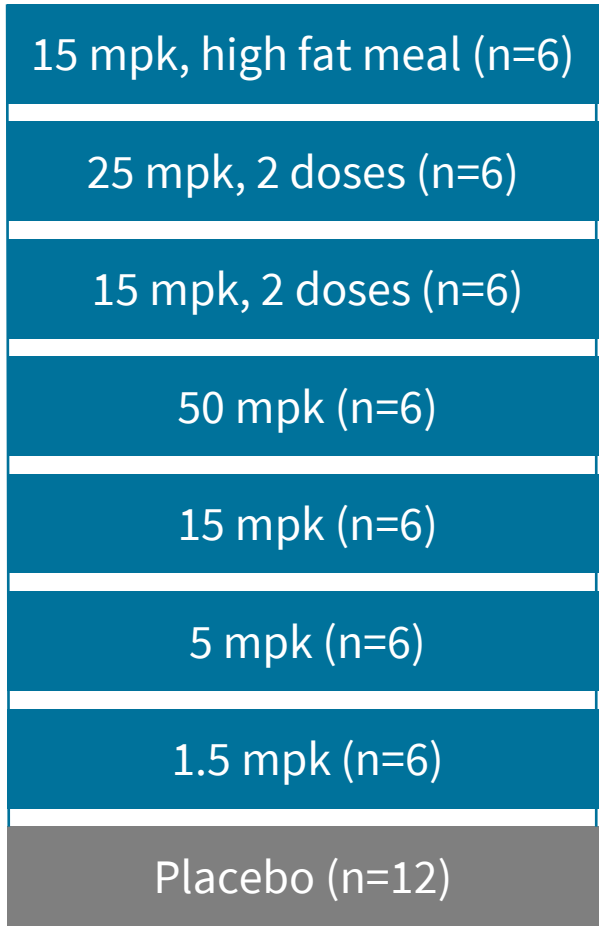
In addition to increasing functional A1AT levels, ZF874 improved liver pathology in the PiZ mouse

- 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

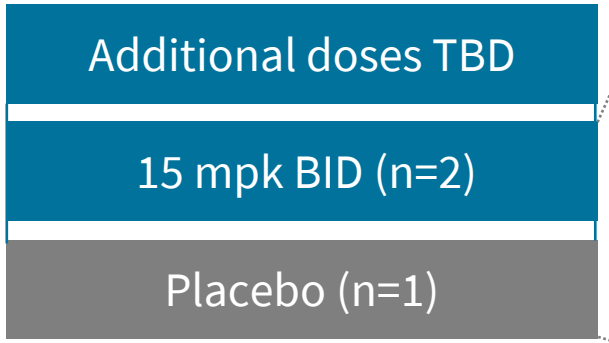
Abbreviations: mpk = milligrams per kilogram; PAS-D = Periodic Acid-Schiff staining with diastase; HED = human equivalent dose

Schematic of Phase 1 clinical trial for ZF874

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



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



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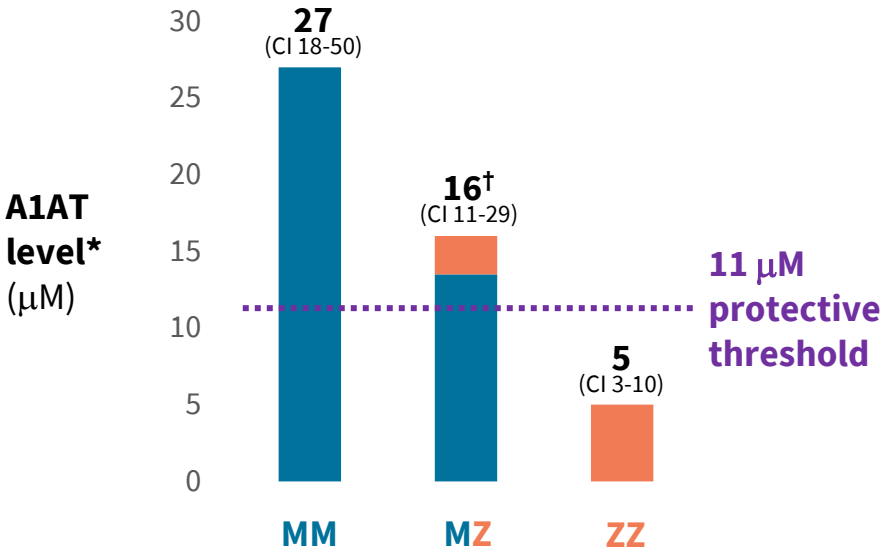
A1AT levels for different genotypes and conceptual target for an effective folding corrector

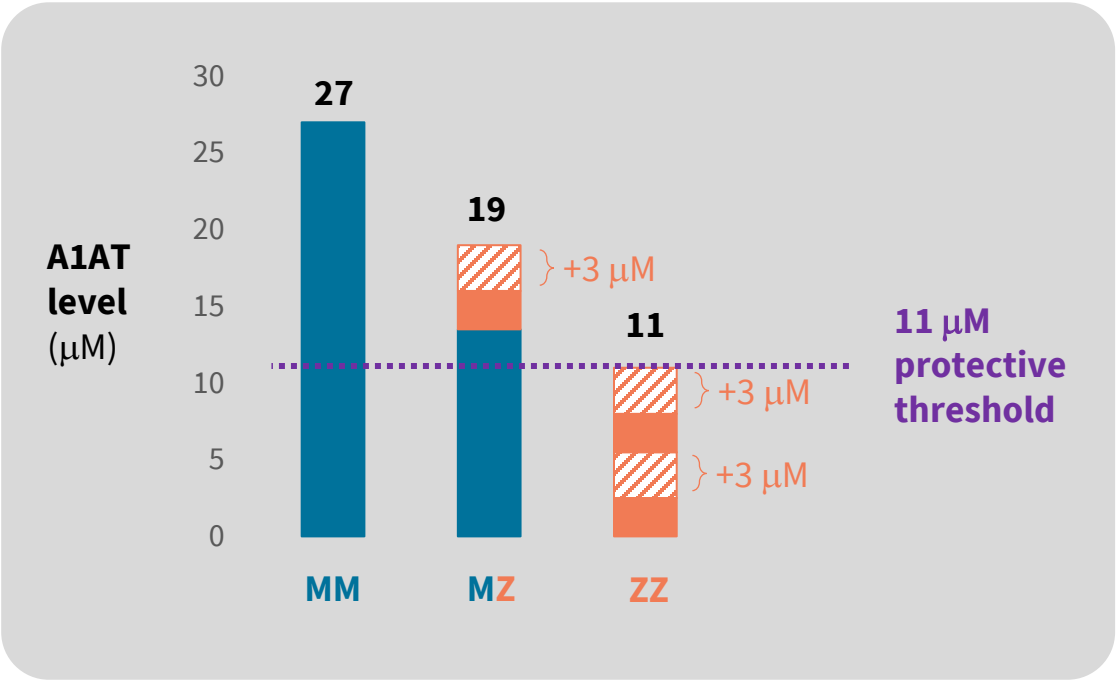
Expected level produced by M allele
Expected level produced by Z allele
Conceptual increase from treatment

Published median A1AT level by genotype

Historical based on 21,444 samples



Conceptual target: increase of 3 μM *per gene copy* to achieve 11 μM protective threshold



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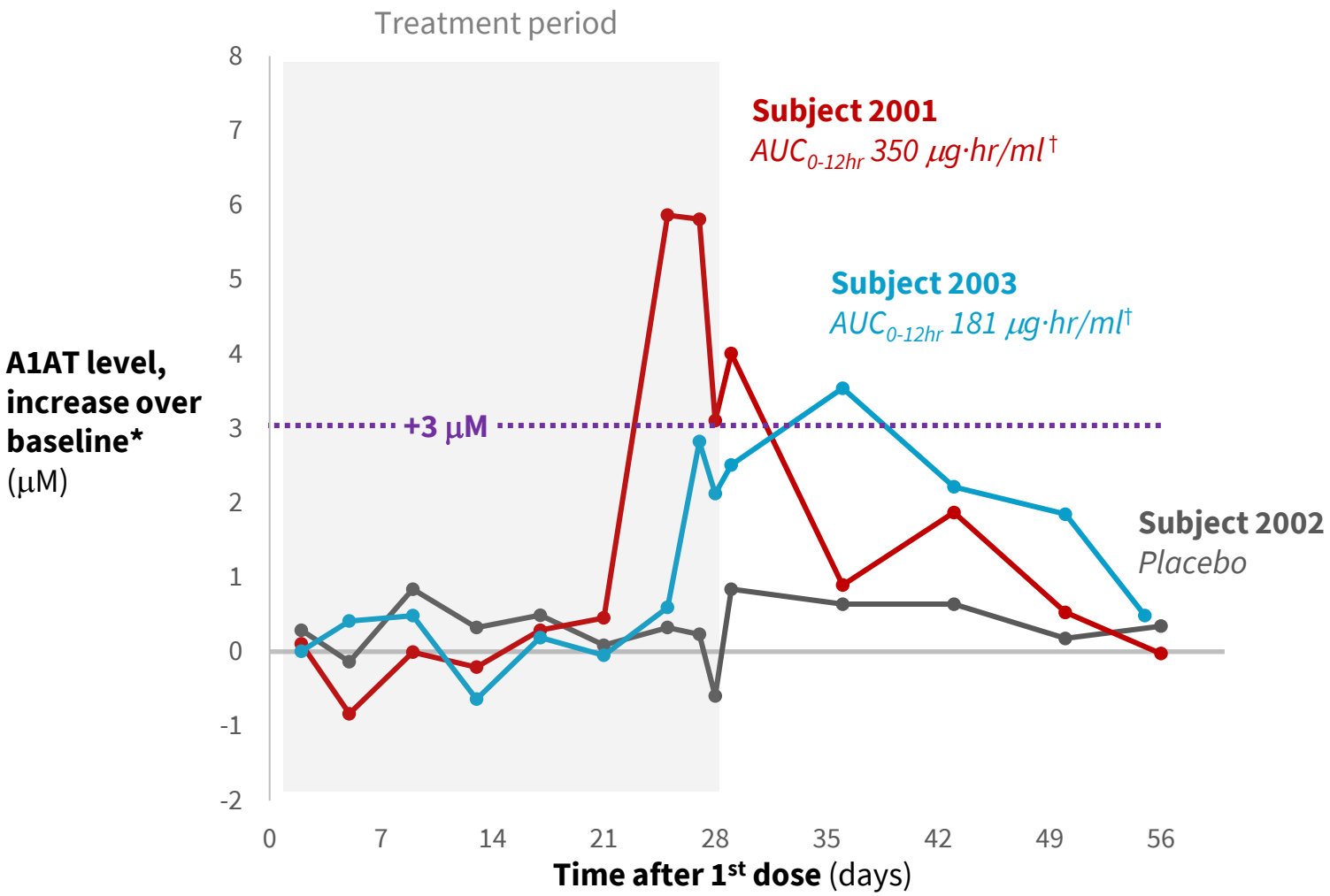
Change in A1AT functional activity for three PiMZ subjects dosed with placebo or ZF874 15 mpk BID



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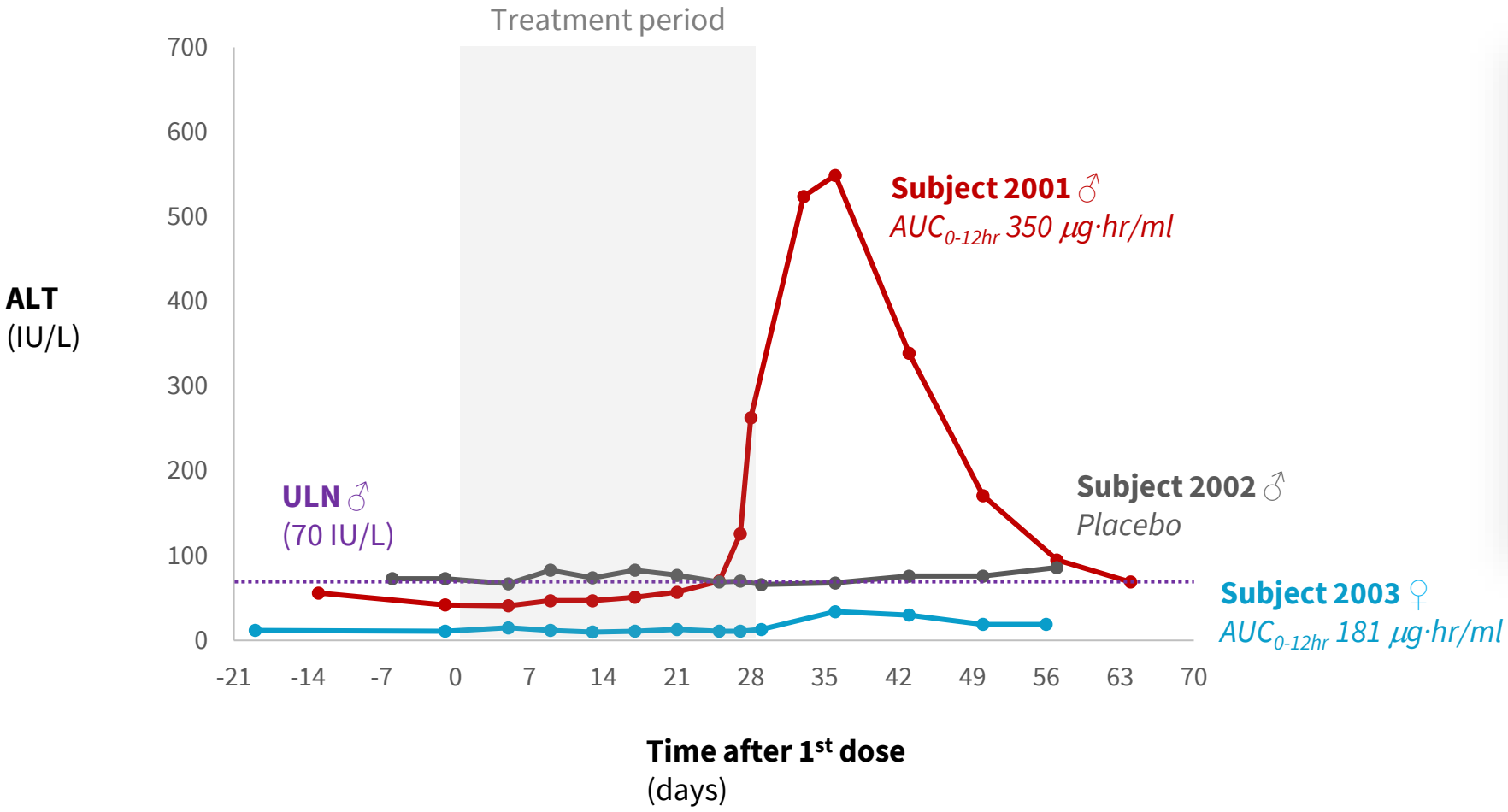
Liver signal in one PiMZ subject with highest exposure in Part B



- 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

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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