AZD2693, a potent PNPLA3 antisense oligonucleotide, decreases hepatic PNPLA3 mRNA and liver fat content in participants with presumed MASH and homozygous for the PNPLA3 148M risk allele

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Introduction

- A common genetic variant (rs738409) encoding isoleucine (I) to methionine (M) at position 148 in the PNPLA3 protein is a key genetic determinant of hepatic steatosis, inflammation, fibrosis, cirrhosis and liver-related mortality.[1,2]
- PNPLA3 148M expression in the liver is hypothesized to impair hepatic processing of polyunsaturated fatty acids (PUFA) enriched triglycerides, and induce inflammatory pathways (hsCRP/STAT3/IL6).[3]
- AZD2693, a potent GalNAc-conjugated PNPLA3-targeted antisense oligonucleotide (ASO) is designed to specifically silence liver PNPLA3 mRNA and subsequent protein expression, potentially treating metabolic dysfunction-associated steatohepatitis (MASH).

Aim

- To evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic effects of AZD2693 in a phase 1 program.

Methods

- The potency of AZD2693 was first assessed in 3D cultures of 148MM primary human hepatocytes. AZD2693 was clinically evaluated in a Phase 1 programme comprising a single ascending dose (SAD) study and a multiple ascending dose (MAD) study. The SAD study was a single-blind, placebo-controlled study to evaluate one subcutaneous dose ranging from 2mg to 110mg. The MAD study was double-blind, placebo-controlled study to evaluate three monthly doses of 25 mg, 50 mg, and 80 mg in participants with MRI-PDFF >7%. The MAD study included MRI-PDFF assessments of liver fat content (LFC) at baseline and at 8 and 12 weeks. The 80 mg MAD cohort included liver biopsy at baseline and one week after third dose for target engagement of PNPLA3 mRNA knock-down.

MAD Study Design

Study population

- Adults, 18–70 years
- Presumed NASH (F0-F3)
- Evidence of liver steatosis (MRI-PDFF > 7%)
- Normal renal function

Randomization 3:1

Design overview per cohort

Cohort demographics and clinical characteristics

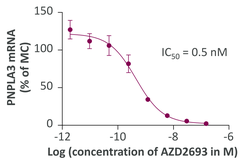
	AZD2693 25 mg (n=15)	AZD2693 50 mg (n=16)	AZD2693 80 mg (n=6)	Placebo (n=14)
Age, years	57.1 ± 10.65	54.3 ± 9.25	62.5 ± 5.39	60.3 ± 9.51
Female	2 (13.3%)	10 (62.5%)	3 (50.0%)	9 (64.3%)
Ethnicity – Hispanic/Latino	15 (100%)	14 (87.5%)	5 (83.3%)	14 (100%)
Body weight, kg	94.2 ± 21.76	87.5 ± 16.54	83.8 ± 17.53	88.6 ± 16.88
Body mass index, kg/m^2	32.7 ± 4.88	33.0 ± 4.80	30.7 ± 4.59	33 ± 4.40
Type 2 diabetes, n (%)	8 (53.3%)	7 (43.8%)	4 (66.7%)	7 (50.0%)
Haemoglobin A1c, %	6.9 ± 2.21	7.0 ± 1.40	7.0 ± 1.13	6.7 ± 1.41
eGFR, mL/min/1.73 m^2	93 ± 15.6	97 ± 10.1	84 ± 11.1	83 ± 17.5
Aspartate aminotransferase, U/L	35.8 ± 20.53	39.3 ± 26.08	40.2 ± 20.36	31.3 ± 21.92
Alanine aminotransferase, U/L	26.9 ± 16.04	29.9 ± 17.49	29.2 ± 15.05	24.9 ± 13.65
Gamma-glutamyl transferase, U/L	41.7 ± 28.98	35.8 ± 17.22	32.3 ± 21.86	28.2 ± 17.37
Liver Fat Content, %	16.5 ± 7.14	15.5 ± 6.65	17.6 ± 5.36	17.7 ± 9.23
Total cholesterol, mmol/L	4.6 ± 0.84	5.1 ± 0.88	5.4 ± 1.21	5.2 ± 1.24
High-density lipoprotein, mmol/L	1.1 ± 0.36	1.2 ± 0.17	1.1 ± 0.18	1.3 ± 0.24
Low-density lipoprotein, mmol/L	2.7 ± 0.70	3.0 ± 0.81	3.5 ± 1.01	3.2 ± 1.00
Triglyceride, mmol/L	1.9 ± 1.11	1.7 ± 0.52	2.1 ± 0.76	1.6 ± 0.51
Concomitant medications				
Lipid modifying	1 (6.7%)	3 (18.8%)	2 (33.3%)	5 (35.7%)
Antidiabetics	6 (40.0%)	9 (56.2%)	4 (66.7%)	7 (50.0%)

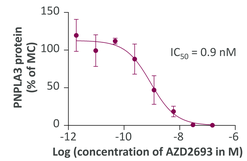
Date reported as mean ± SD for continuous and n (%) for categorical variables. eGFR, estimated glomerular filtration rate

Results

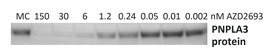
AZD2693 is a potent GalNac-ASO in 3D-cultures of 148MM primary human hepatocytes

Primary human hepatocytes from a 148MM donor were exposed to indicated concentrations of AZD2693 for 24 hours after seeding in ultra-low attachment plates. Spheroids were collected for RNA and protein measurements after 7 days in culture.





MC, medium control



AZD2693 is well-tolerated, with no treatment-related discontinuations

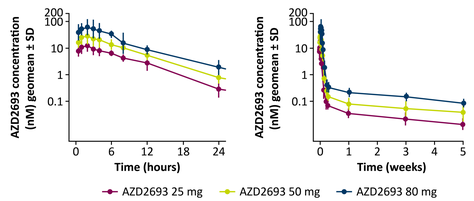
No safety or tolerability concerns were identified in the SAD study with the single subcutaneous doses of up to 110 mg AZD2693 in the healthy volunteer population (n=49) and single subcutaneous doses up to 90 mg AZD2693 in the healthy Japanese (n=16) and healthy Chinese populations (n=8). One serious AE of appendicitis was reported in a participant in the 6 mg dose.

Adverse events (AE) category (MAD study)	AZD2693 25 mg (n=15)	AZD2693 50 mg (n=16)	AZD2693 80 mg (n=6)	Placebo (n=14)
Any AE*	7 (46.7)	12 (75.0)	5 (83.3)	5 (35.7)
Any AE including events leading to death	0	0	0	0
Any serious AE including events leading to death	0	0	1 (16.7)**	0
Any AE leading to discontinuation of IP	0	0	0	0
Any AE leading to withdrawal from the study	0	0	0	0

IP, investigational product
*Number of participants with AEs in any category
**Non-cardiac chest pain; not considered related to AZD2693 by the investigator

AZD2693 displays multiple doses PK profile in presumed MASH participants suitable for once monthly dosing

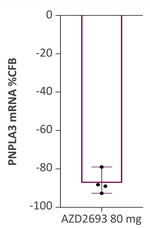
AZD2693 maximum plasma concentrations reached at approximately 2 hours post-dose. A rapid distribution phase was followed by a slow terminal elimination phase with half-life of 17 to 33 days across the doses.



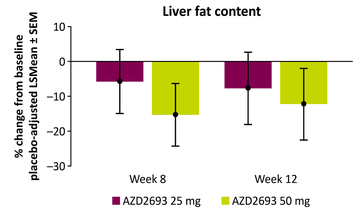
AZD2693 significantly reduces PNPLA3 mRNA levels in the liver

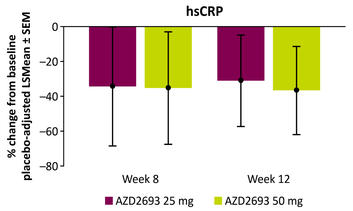
Treatment*	Baseline (2^-ΔCT)	Week 10 (2^-ΔCT)	%CFB
80mg AZD2693	0.877	0.104	**-88.2**
80mg AZD2693	0.415	0.045	**-89.0**
80mg AZD2693	0.901	0.189	**-79.0**
80mg AZD2693	0.824	0.060	**-92.7**
Placebo	0.603	1.815	**201.0**
Placebo	1.173	0.555	**-52.7**

CFB, change from baseline; CT, cycle threshold
*Only four participants receiving AZ2693 80 mg and two receiving placebo had evaluable samples for mRNA

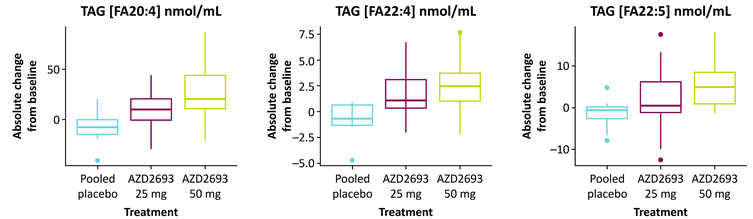


AZD2693 reduces liver fat content and the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) in a dose-dependent manner





AZD2693 treatment significantly increases polyunsaturated fatty acids (PUFA) in circulating triglycerides (TG)



25 mg vs placebo: p=0.027
50 mg vs placebo: p=0.00076

25 mg vs placebo: p=0.012
50 mg vs placebo: p=0.002

25 mg vs placebo: p=0.22
50 mg vs placebo: p=0.00065

Conclusions

- AZD2693 treatment potently reduced liver *PNPLA3* mRNA levels.
- AZD2693 was well-tolerated, with a PK profile supporting monthly dosing and no AEs leading to withdrawal from the study or discontinuation of the investigational medicinal product.
- Therapeutic knock-down of PNPLA3 in homozygous PNPLA3 148MM risk allele participants demonstrates improvement in proposed pathogenic drivers. Short-term treatment resulted in a dose-dependent increase in PUFAs in circulating triglycerides, decreases in inflammatory markers, and mild reduction of liver fat content.
- These data support the continued development of AZD2693 in the FORTUNA Ph2b study (NCT05809934).

References

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Disclosures

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