Single doses of gatuzosiran (GSK4532990) produce sustained HSD17B13 suppression and liver biochemical improvement in patients with metabolic dysfunction-associated steatohepatitis

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A single dose of gatuzosiran resulted in durable knockdown of HSD17B13 mRNA and protein that outlasted its short plasma half-life, leading to improvements in biomarkers of liver health and a favourable safety profile in participants with MASH

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Background

- MASH is characterised by hepatocyte inflammation and injury over background steatosis and carries a risk for progressive fibrosis, cirrhosis and end-stage liver disease[1]
- LOF gene mutations in *HSD17B13* are associated with reduced risk of MASH and ALD[2,3]
- Gatuzosiran (GSK4532990), an *N*-acetylgalactosamine conjugated siRNA, selectively targets *HSD17B13* in hepatocytes to mimic naturally occurring LOF gene mutations[4]
- PoC studies in MASH and ALD are ongoing to inform gatuzosiran dose selection for further development

Aim

- A Phase 2a, open-label, multicentre study (NCT06104319) was designed to assess hepatic target engagement, PK, safety and tolerability of single doses of gatuzosiran in participants with MASH or suspected MASH

Methods

- **Key inclusion criteria:** Adult participants with MASH (biopsy proven) or suspected MASH (phenotypic criteria)
- **Key exclusion criteria:** Cirrhosis or history of liver decompensation, other causes of liver disease, homozygosity for the *HSD17B13* rs72613567:TA variant and LSM ≥20 kPa
- **Primary objective:** To assess the effect of a single SC dose of gatuzosiran on PK-PD target engagement (pre- and post-dose liver biopsy-derived HSD17B13 protein and mRNA expression levels)
- **Secondary objectives:** Evaluation of gatuzosiran plasma exposure parameters after a single dose
- **Exploratory objectives:** Evaluation of the effect of gatuzosiran on liver biochemistry tests and non-invasive tests (LSM and MRI-PDFF)
- **Study procedures:** Paired liver biopsies were collected pre- and post-dose (8, 12 or 28 weeks) after a single dose of 25, 200, 400 or 800mg
- **Safety assessments:** Laboratory tests, TEAEs and SAEs

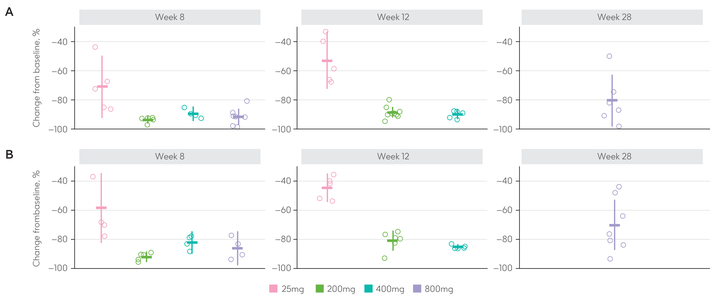
Results

Table 1: **Baseline demographics and clinical characteristics (enrolled population, N=61)**

Gatuzosiran dose:	25mg N=17	200mg N=15	400mg N=15	800mg N=14
Age, years, mean (SD)	50.8 (10.11)	51.9 (9.68)	50.7 (11.04)	55.4 (11.13)
Race, White, n (%)	16 (94)	13 (87)	15 (100)	13 (93)
Body mass index, kg/m², mean (SD)	37.0 (5.38)	33.9 (3.86)	37.3 (6.87)	32.8 (6.22)
Hepatic fat fraction by MRI-PDFF, %, mean (SD)	12.2 (9.36)	14.9 (9.55)	11.7 (7.36)	15.6 (6.49)
LSM by VCTE, kPa, mean (SD)	10.49 (3.34)	10.53 (3.73)	11.06 (3.04)	8.94 (1.85)
ALT, IU/L, mean (SD)	57.5 (28.78)	58.8 (37.14)	85.8 (47.4)	53.0 (21.53)
AST, IU/L, mean (SD)	47.8 (24.52)	40.1 (19.01)	57.9 (35.07)	39.0 (14.37)
GGT, IU/L, mean (SD)	79.50 (63.46)	63.40 (50.06)	111.70 (147.66)	56.30 (65.11)

- Single doses of gatuzosiran resulted in dose-dependent reductions in hepatic HSD17B13 mRNA and protein expression (**Figure 1**)
  - At Week 12, mean reductions in mRNA ranged from ~50% (25mg dose) to >85% (200–400mg), with similar reductions in protein (~45% [25mg] to >80% [200–400mg])
  - Sustained suppression of both mRNA and protein was observed with the 800mg dose at Week 28

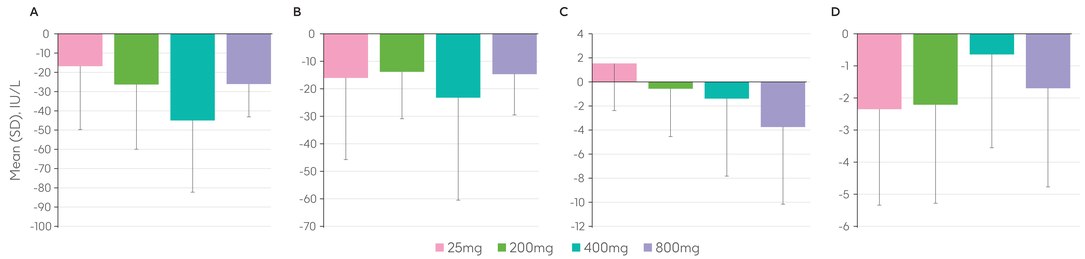
Figure 1: **Change from baseline in hepatic HSD17B13 mRNA (A) and protein (B)**



Mean values are plotted, with whiskers depicting the SD of observed data.

- At Week 12, similar trends of reduction from baseline in ALT, AST and GGT (data not shown) were seen; this was also observed for MRI-PDFF and LSM at Week 16 (**Figure 2**)

Figure 2: **Change from baseline to Week 12 in ALT (A) and AST (B), and change from baseline to Week 16 in MRI-PDFF (C) and LSM (D) (safety population, N=61)**



- Gatuzosiran exhibited short plasma elimination $t_{1/2}$ with plasma concentrations rapidly declining by 48 hours, suggesting efficient ASGPR-mediated hepatocyte uptake
- Plasma exposure (C_{max} and $AUC_{(0-t)}$) increased more than in proportion to dose over the 25 to 800mg range, indicative of transient ASGPR saturation
- Low renal excretion was observed over the first 24 hours (**Table 2**)
- TEAEs were reported in 25 participants (41%) and were mainly mild–moderate, including three non-drug-related SAEs (chest pain, scrotal cellulitis and increased hepatic enzymes) in two participants; no liver AEs were considered gatuzosiran-related (**Table 3**)

Table 2: **Gatuzosiran PK parameters (PK population, N=61)**

	Gatuzosiran dose:			
	25mg N=17	200mg N=15	400mg N=15	800mg N=14
Plasma, geometric mean (%CV)	n=15	n=15	n=15	n=14
C_{max}, ng/mL	43.6 (46.3)	412 (51.0)	914 (61.3)	2890 (60.2)
$AUC_{(0-inf)}$, hours per ng/mL	601 (27.8)*	7230 (31.1)†	14,700 (46.3)‡	48,300 (40.5)§
$t_{1/2}$, hours	8.17 (42.6)*	5.48 (44.7)†	5.28 (41.7)‡	5.15 (33.4)§
t_{max}, hours, median (min–max)	3.0 (1.0–12.0)	6.0 (1.1–12.0)	6.0 (2.0–12.0)	8.0 (3.0–12.0)
Urine, mean (SD)	n=15	n=15	n=15	n=14
$Fe_{(0-24)}$, %	11.3 (7.0)	12.0 (5.5)	14.5 (8.4)	25.9 (13.6)

n=4; †n=12; ‡n=13; §n=11. Intensive PK sampling was conducted up to 48 hours post-dose to estimate PK parameters.

Table 3: **TEAEs (safety population, N=61)**

	Gatuzosiran dose:			
	25mg N=17	200mg N=15	400mg N=15	800mg N=14
Any event, by SOC, n (%)	8 (47.1)	4 (26.7)	5 (33.3)	8 (57.1)
Infections and infestations	4 (23.5)	2 (13.3)	2 (13.3)	5 (35.7)
General disorders and administration site conditions*	2 (11.8)	0	2 (13.3)	3 (21.4)
Injury, poisoning, procedural complications	0	0	2 (13.3)	1 (7.1)
Investigations	2 (11.8)	0	1 (6.7)	0
Nervous system disorders	0	0	0	2 (14.3)
TEAEs related to study treatment, by SOC, n (%)	0	1 (6.7)	2 (13.3)	3 (21.4)
General disorders and administration site conditions*	0	0	1 (6.7)	3 (21.4)

TEAEs are only shown where there is >10% incidence in at least one treatment arm.
**Injection site reactions were reported in one patient (6.7%) in the 400mg arm and two patients (14.3%) in the 800mg arm, all of which were considered related to study drug.*

Conclusions

A single dose of gatuzosiran, an siRNA targeting *HSD17B13*, demonstrated profound and durable target knockdown lasting through 28 weeks for the highest tested dose

This sustained target engagement led to meaningful improvements in liver enzymes and non-invasive markers of fibrosis and steatosis, validating HSD17B13 as a therapeutic target in MASH

Gatuzosiran was well tolerated, with a mild–moderate AE profile, consistent with Phase 1/2a study results

These data provide confidence in doses tested in ongoing PoC studies in MASH

Abbreviations

AE, adverse event; ALD, alcohol-related liver disease; ALT, alanine aminotransferase; ASGPR, asialoglycoprotein receptor; AST, aspartate aminotransferase; $AUC_{(0-inf)}$, area under the plasma concentration-time curve from zero to infinity; C_{max}, maximum observed concentration; $Fe_{(0-24)}$, fraction of dose excreted unchanged into urine from time zero to 24 hours; GGT, gamma glutamyl transferase; HSD17B13, hydroxysteroid 17-beta-dehydrogenase-13; kPa, kilopascals; LOF, loss of function; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; max, maximum; min, minimum; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; mRNA, messenger ribonucleic acid; n/N, number of participants; PD, pharmacodynamic; PK, pharmacokinetic; PoC, proof of concept; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; siRNA, small interfering ribonucleic acid; $t_{1/2}$, half-life; TEAE, treatment-emergent adverse event; t_{max}, time to reach C_{max}; VCTE, vibration-controlled transient elastography; SOC, system organ class.

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Acknowledgements

The authors would like to thank Yvonne Bookelmann-Janssen, Troy Richard, Sonu Dixon and our safety colleagues for their contributions to this study. Medical writing support for the development of this poster, under the direction of the authors, was provided by Jennifer Lawton, PhD, of Ashfield MedComms, an Inizio company, and funded by GSK.

Disclosures

This study was funded by GSK (study 218675, clinicaltrials.gov: NCT06104319). Trademarks are the property of their respective owners (FIROSCAN, Echosens).

EL has consulted for 89Bio Inc, AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly and Company, Inventiva, Merck & Co, Novo Nordisk Inc, Organovo, Regeneron and Sagimet Biosciences; has received lectures sponsorship from Gilead Sciences, Novo Nordisk and Madrigal; has acted as a researcher for 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cour Pharmaceuticals, Corcept Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GSK, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics and Zydus Pharmaceuticals. NA and NK declare no conflicts of interest. RV has consulted for Medpace, Thermo Fisher, Madrigal Pharmaceuticals, Intercept, Akero Therapeutics, Regeneron, 89 Bio, GSK, Cogent Biosciences, Agios and Takeda in various roles, including on steering committees, data safety monitoring committees and adjudication committees related to hepatic safety and clinical outcomes and has received grants from Eli Lilly, Galectin Therapeutics, GSK, Takeda and Zydus Therapeutics Inc. K-AC and HC are former GSK employees. II-A, MG, AR, BS and MJK are GSK employees.

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