Combination therapy of lanifibranor with empagliflozin: metabolic improvement in patients with Metabolic Dysfunction-Associated Steatohepatitis and Type-2 Diabetes

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1-INTRODUCTION

The broad disease biology of Metabolic Dysfunction-Associated Steatohepatitis (MASH), from upstream insulin resistance to progressive liver fibrosis, underlies the concept that many patients may benefit from tailored, complementary combination therapy.

We compared therapeutic effects of lanifibranor alone and the combination of lanifibranor with an SGLT2 inhibitor versus placebo in the prospective proof-of-concept study LEGEND.

2-MATERIAL/METHODS

The LEGEND trial enrolled 39 patients (33 completers) with MASH and type-2 diabetes (T2D), randomized 1:1:1 to lanifibranor (L), lanifibranor with empagliflozin (L+E) and placebo (P) for a treatment duration of 24 weeks.

Trial design

Key inclusion criteria:

1) Adult patients with **MASH/NASH:**
   - historical biopsy with NAS ≥4
   - or cT1 ≥875 ms
   - or cT1 ≥ 25 ms and MRI-PDFF ≥10%
2) **T2D** diagnosed
3) Screening **HbA1c** in 7-10%

Stratification by sex and HbA1c at screening (>7.5% vs. ≥7.5%)

24-week treatment + 4-week follow-up

Double blind for L and P, open label for L+E, randomized (1:1:1), placebo-controlled

- Placebo
- Lanifibranor 800mg
- Lanifibranor 800mg + empagliflozin 10mg

Full analysis set	39 randomized and treated patients, 33 completed the 24-week treatment
Placebo	14 randomized and treated patients, 9 completed the 24-week treatment, 5 prematurely discontinued (2 withdrawal by patient, 2 lost to follow-up, 1 non-compliance with study drug)
Lanifibranor	12 randomized and treated patients, 12 completed the 24-week treatment
L+E	13 randomized and treated patients, 11 completed the 24-week treatment, 1 prematurely discontinued (AE)

MASH was diagnosed per historical liver biopsy or MRI imaging (cT1 or cT1+PDFF).

Change in HbA1c from baseline to treatment week (TW) 24 was the primary efficacy endpoint.

Circulating biomarkers included liver enzymes, inflammation and fibrosis markers, lipid and glucose metabolism; MRI-based imaging included hepatic steatosis (PDFF), MASH composite disease activity and fibrosis (cT1), visceral (VAT) and subcutaneous (SAT) adipose tissue, spleen and liver volume; vital signs and safety were evaluated.

Parameters sensitive to pre-defined intercurrent events (initiation of significant diet change affecting metabolism [1 patient in L+E after TW12] and initiation of a rescue medication [1 patient before TW4 in L and 1 patient after TW12 in P]) were analyzed excluding data after the occurrence of the intercurrent event.

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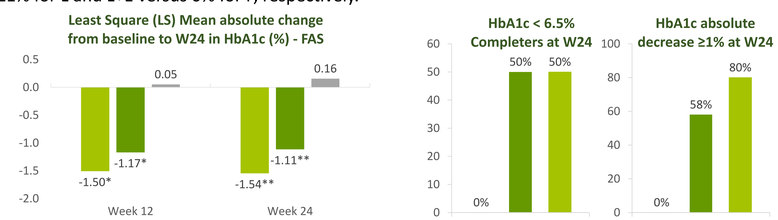
3-RESULTS

Baseline

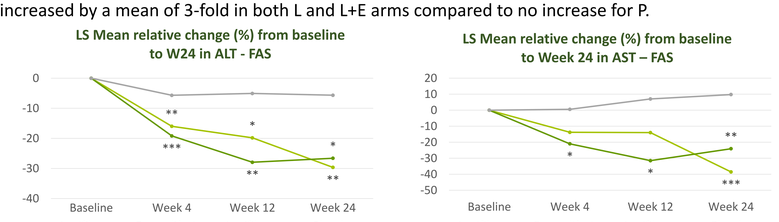
Median or n (%)	Lanifibranor	Lanifibranor + Empagliflozin	Placebo	Total
Age (years)	55.5	54.0	55.5	55.0
Sex (% female)	6 (50)	8 (62)	7 (50)	21 (54)
Country (% USA)	11 (92)	12 (92)	12 (86)	35 (90)
Weight (kg)	93.9	99.9	97.4	97.2
HbA1c (%)	7.7	8.0	7.50	7.7
ALT (U/L)	53.0	52.0	33.0	39.0
AST (U/L)	30.0	37.0	28.0	31.0

Median or n (%)	Lanifibranor	Lanifibranor + Empagliflozin	Placebo	Total
Insulin (pmol/L)	152	238	265	220
HOMA-IR	9.4	10.9	16.3	10.8
hsCRP (mg/L)	3.0	3.4	8.0	4.4
Glucose (mmol/L)	7.61	8.55	7.36	8.05
HDL-C (mmol/L)	1.07	1.11	1.07	1.09
Triglycerides (mmol/L)	2.30	1.77	1.74	1.79
cT1 (ms)	938	926	942	931
MRI-PDFF (%)	18.6	21.1	20.3	19.3

Both L and L+E met the primary endpoint of HbA1c improvement versus P at TW24 (both p<0.001, FAS); 50% in both active arms reached HbA1c < 6.5% at TW24, with 58% and 80% HbA1c decrease ≥1% for L and L+E versus 0% for P, respectively.



Liver tests (ALT, AST, GGT), fibrosis markers (TIMP-1, P3NP, Pro-C3), insulin, HOMA-IR, hs-CRP, ferritin, glycemia, lipid profile (HDL-C, Triglycerides) improved with L and L+E treatment, and adiponectin increased by a mean of 3-fold in both L and L+E arms compared to no increase for P.



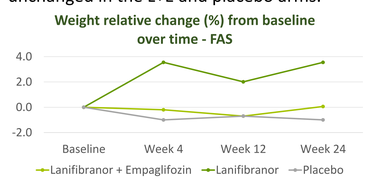
*p<0.05, **p<0.01, ***p<0.001 from MMRM

LS means at Week 24 (pvalue[1])	Lanifibranor	Lanifibranor + Empagliflozin	Placebo
GGT absolute change (IU/L)	-21.9 (0.010)	-17.8 (0.015)	22.8
TIMP-1 absolute change (ng/mL)	-42.8 (0.040)	-40.0 (0.056)	-6.8
ProC3[2] absolute change (ng/mL)	-1.26 (0.120)	-3.54 (0.062)	7.33
Insulin relative change (%)	-38 (0.077)	-33 (0.046)	10
HOMA-IR relative change (%)	-51 (0.010)	-45 (0.015)	35
hs-CRP relative change (%)[3]	-32 (0.024)	-48 (0.008)	34
Ferritin absolute change (µg/L)	-78 (0.002)	-59 (0.022)	-8

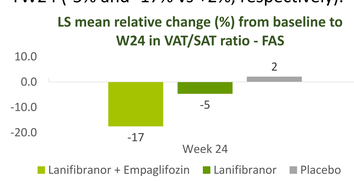
LS means at Week 24 (pvalue[1])	Lanifibranor	Lanifibranor + Empagliflozin	Placebo
Glucose absolute change (mmol/L)	-2.36 (0.005)	-1.98 (0.022)	-0.23
HDL-C relative change (%)	16 (0.098)	15 (0.143)	3
Triglycerides relative change (%)[3]	-26 (0.006)	-27 (0.005)	-2
Adiponectin fold	2.9 (0.009)	3.0 (0.004)	1.2

1 pvalue from MMRM, if more than one post-baseline timepoint or Analysis of Covariance (ANCOVA), vs. placebo; 2 ProC3 method: ROCHE Cobas e801; 3 Results excluding outliers

Patients had a mean weight increase of 3.6% with L at TW24, while mean weight remained unchanged in the L+E and placebo arms.



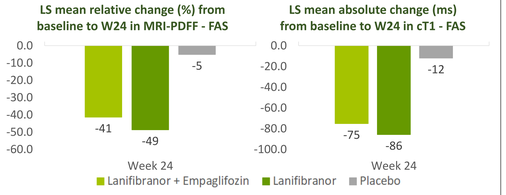
The ratio VAT/SAT shifted favorably toward SAT for both L and L+E compared to placebo at TW24 (-5% and -17% vs +2%, respectively).



Spleen volume decreased with L and L+E compared to placebo at TW24.

Significant improvements of hepatic steatosis and composite MASH activity + fibrosis were observed for both L and L+E with mean relative MRI-PDFF changes of -49% (p=0.005) and -41% (p=0.02) and mean absolute cT1 changes of -86 and -75 ms respectively.

L and L+E were safe and well tolerated.



4-CONCLUSION

The combination of lanifibranor with an SGLT2 inhibitor has comparable beneficial effects to lanifibranor alone on noninvasive hepatic and cardiometabolic markers of MASH, including a shift toward SAT, without observed weight gain. The combination is well tolerated.