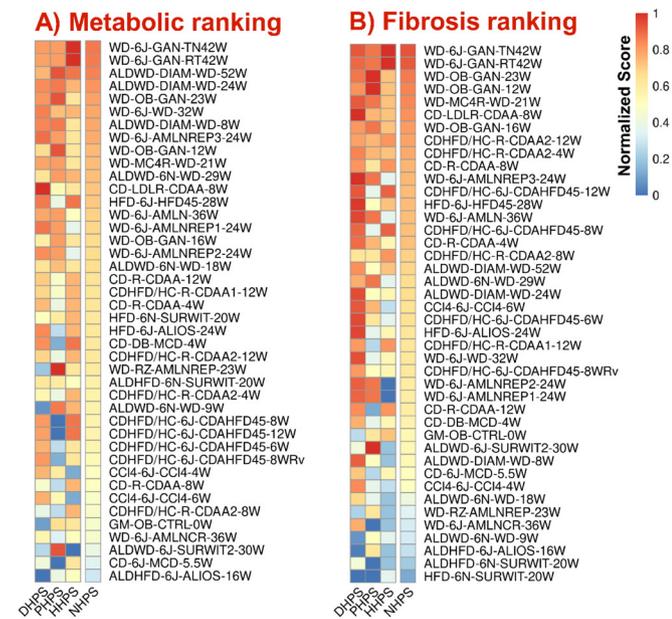


# ORAL PRESENTATIONS

without sugars in the drinking water, were the most similar to human NASH in terms of metabolic significance (induction of obesity and dyslipidaemia; Fig. A), and ability to induce histologically significant fibrosis (without compromising metabolic relevance; Fig. B). A plethora of choline-deficient (CD) models with varying nutrient (fat, cholesterol, methionine) compositions quickly induced NASH-fibrosis; however, body weight, metabolic profiling and transcriptomic data suggest relatively poor translatability to human NASH (especially in WT mice); these models should be used with caution only for specific purposes (e.g. to test anti-inflammatory or anti-fibrotic compounds). Across the diets investigated, WT rats and genetically altered (GA) models of obesity (e.g. ob/ob, MC4r KO) or hypercholesterolemia (e.g. LDLR KO) had the added benefit of aggravating liver damage and accelerating fibrosis progression while preserving metabolic traits.

**Conclusion:** Our findings give us a clear picture of how well the phenotype, liver histology, and liver transcriptome of common NAFLD models mimic human illness, and rank the proximity of their phenotype to human NASH. Overall, WD models rank best from a metabolic/transcriptomic standpoint; however, only a few models show substantial fibrosis (F2+), necessitating extended induction durations unless combined with GA backgrounds. The reverse translational value of human biomarkers of NASH progression is being investigated in prospective studies.

Funded by EU Horizon 2020 IMI2 and EFPIA, Grant Agreement 777377 (LITMUS).



**NHPS: Weighted sum (1/3 each) of DHPS (DSEA Human Proximity Score – Sequencing data), PHPS (Phenotype Human Proximity Score), HHPS (Histology Human Proximity Score).**

**Abbreviations:** ALDHFD, American Lifestyle Diets (High Fat Diet supplemented with refined sugars in the drinking water); ALDWD, American Lifestyle Diets (WD supplemented with refined sugars in the drinking water); ALIOS, American Lifestyle-Induced Obesity Syndrome diet (high in trans-fats and sugar); AMLN, (Trans-fat containing) Amylin Liver NASH diet; AMLNCR, AMLN diet with caloric restriction; AMLNREP, Replacement diets for AMLN (without trans-fat); CCL4, Carbon tetrachloride (Positive controls for fibrosis); CD, Choline Deficient diets; CDAA, Choline Deficient amino acid defined diet; CDAA1, CDAA supplemented with 1% cholesterol; CDAA2, CDAA supplemented with 2% cholesterol; CDAHFD45, CD-HFD 45% Fat; CDHFD/HC, Choline Deficient diets, supplemented with Fat and/or Cholesterol; CTRL, Control/chow diet; DB, db/db mice; DIAM, DIAMOND mice; GAN, Gubra Amylin NASH diet; GM, Genetically Manipulated animals; HFD, High Fat Diets; LDLR, LDLR-KO mice; MCD, Methionine-Choline Deficient Diet; MC4R, MC4rKO mice; OB, ob/ob mice; R, Rat (Janvier RjHan:Wj); RT42W, Room Temperature (42 weeks); RZ, Rat (ZSF1); SURWIT, Surwit diet; SURWIT2, Surwit Diet (2% Cholesterol); TN42W, Thermo-neutral conditions (42 weeks); WD, Western Diets (high in cholesterol, refined carbohydrates, and fat); 6J, C57BL/6J mice; 6N, C57BL/6N mice; 8WRv, 8-week diet followed by a 4-week reversal to chow.

Figure: NASH Human Proximity Score (NHPS).

## GS10

### Efficacy and safety of finite 48-week treatment with the siRNA JNJ-3989 and the capsid assembly modulator (CAM-N) JNJ-6379 in HBeAg negative virologically suppressed (VS) chronic hepatitis B (CHB) patients: results from REEF-2 study

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**Background and aims:** JNJ-3989 is an siRNA designed to target all hepatitis B virus (HBV) RNAs, thus reducing synthesis of all HBV proteins. JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of empty viral particles. The REEF-2 study assessed the efficacy and safety of JNJ-3989 200 mg SC Q4W, JNJ-6379 250 mg PO QD, and nucleos(t)ide analog (NA) PO QD in patients with HBeAg negative CHB.

**Method:** In this Phase 2b, double-blind, multicenter (EU only), placebo (PBO)-controlled study, non-cirrhotic HBeAg negative CHB patients with HBsAg >100 IU/ml and NA treatment for ≥2 years were randomized (2:1) to receive add-on JNJ-3989 + JNJ-6379 or PBO. All treatment including NA was discontinued after 48 weeks. The primary end point was the proportion of patients achieving HBsAg <0.05 IU/ml at follow-up week 24 without restarting NA treatment. Here, we report interim data at week 48 (end of treatment; EOT).

**Results:** 130 patients (67% male, 20% Asian, mean age 46 [23–65] years) were analyzed (85 active, 45 control). In the active and control arm at baseline (BL), 80% and 76% of patients had HBsAg levels ≥1,000 IU/ml (mean 3.4 [2.0–4.6] and 3.5 [2.0–4.8] log<sub>10</sub> IU/ml) and mean duration of prior NA use was 8.4 (2.2–20.7) and 8.1 (2.2–17.4) years. At EOT, mean (SE) reductions in HBsAg from BL were –1.89 (0.060) log<sub>10</sub> IU/ml in the active arm and –0.06 (0.012) log<sub>10</sub> IU/ml in the control arm. In Asian (n = 15) and non-Asian patients (n = 61) in the active arm, HBsAg reductions were –2.05 (0.52) log<sub>10</sub> IU/ml and –1.85 (0.52) log<sub>10</sub> IU/ml, respectively. At EOT, the proportion of patients achieving HBsAg <100, <10, <1 IU/ml was 71.1%, 19.7%, and 2.6% in the active arm; and 2.4%, 0%, and 0% in the control arm; no patient in either arm achieved HBsAg seroclearance. Adverse events (AEs) were reported in 81.2% and 71.1% of patients in the active and control arms (grade 3/4 AEs were 15.3% and 4.4%). 7.1% of patients in the active arm had grade 3 eGFR events. After treatment initiation, eGFR reductions were seen in the active arm without further progression on continued treatment. Serious AEs were reported in 2 patients in the active arm and 1 patient in the control arm; none were considered related to study drug. Treatment discontinuation rates were 3.5% and 2.2% in the active and control arms; no AEs led to death.

**Conclusion:** JNJ-3989 + JNJ-6379 + NA showed greater reduction in HBsAg levels over 48 weeks compared to PBO + NA and was generally well tolerated and safe.