

Managing HBV Infection



HBV Treatment Guidelines: Starting Treatment

When to Start

Guideline	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Disease	HBV DNA, IU/mL	ALT	Liver Disease
AASLD ^[1]	> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis
EASL ^[2]	> 2000	> ULN*	Moderate inflammation or fibrosis*	> 2000	> ULN*	Moderate inflammation or fibrosis*
	> 20,000	> 2 x ULN	N/A	> 20,000	> 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis

*In pts with HBV DNA > 2000 IU/mL, treatment indicated if ALT > ULN and/or at least moderate fibrosis.

What to Start

Preferred: entecavir, tenofovir alafenamide,[†] tenofovir disoproxil fumarate, peginterferon[‡][1,2]

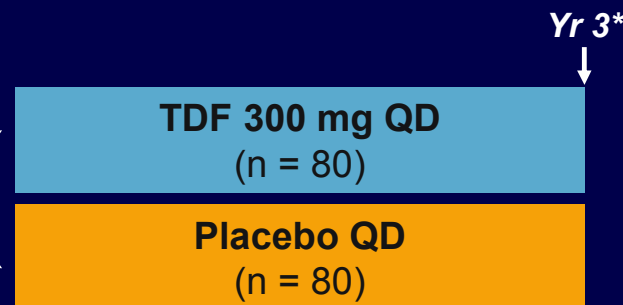
[†]AASLD guidelines not yet updated since approval of tenofovir alafenamide. [‡]May be considered for select pts (eg, pts with mild/moderate CHB)



TDF vs Placebo for HBsAg-Positive CHB With Mild ALT Elevation

§ Multicenter, triple-blind phase IV trial

Pts with HBeAg-positive or HBeAg-negative chronic hepatitis B, ALT 1-2 x ULN, HBV DNA > 2000 IU/mL, no cirrhosis (N = 160*)



*Preliminary results for 114 pts completing treatment with paired biopsy.

Baseline Fibrosis Stage, %	TDF (n = 57)	Placebo (n = 57)
0/1	51	42
2	39	32
3	7	12
4	4	14

Selected Baseline Characteristic	TDF (n = 57)	Placebo (n = 57)
HBeAg positive, %	16	26
Median HBsAg, log IU/mL (IQR)	3.07 (2.39-3.63)	3.12 (2.61-3.84)

TDF vs Placebo for HBsAg-Positive CHB With Mild ALT Elevation: Key Findings

3-Yr Outcome, n (%)	TDF (n = 57)	PBO (n = 57)
Progression		
§ In fibrosis stage	14 (24.6)*	25 (43.9)*
§ To cirrhosis	2 (3.5)	8 (14.0)
Inflammation score		
§ Median (IQR)	2 (1-3)†	3 (2-4)†
§ Decrease	31 (54.4)	24 (42.1)

*P = .03 for any progression in fibrosis stage. †P = .002.

§ OR for fibrosis progression with TDF vs PBO: 0.42 (95% CI: 0.19-0.93)

§ Significantly higher 3-yr rates with TDF vs PBO for:

- Undetectable HBV DNA: 85.5% vs 10.9%
- ALT normalization: 76.8% vs 51.8%

§ Entecavir only needed for clinical flare in PBO-treated pts (n = 8)

Selected Studies on Emerging Investigational Agents for Treating HBV

§ Study 002*: randomized, single-blind phase IIa study of 8 wks of ARB-1467 IV Q4W (2 doses) vs PBO or open-label ARB-1467 IV Q2W in HBeAg-negative, noncirrhotic pts with chronic HBV on ETV or TDF (N = 30)^[1]

- ARB-1467: siRNAs targeting HBV RNA

	ARB-1467		
	0.2 mg/kg Q4W	0.4 mg/kg Q4W	0.4 mg/kg Q2W
Mean change in HBsAg (log IU/mL), Wk 12 [‡]	-0.6	-0.9	-1.1

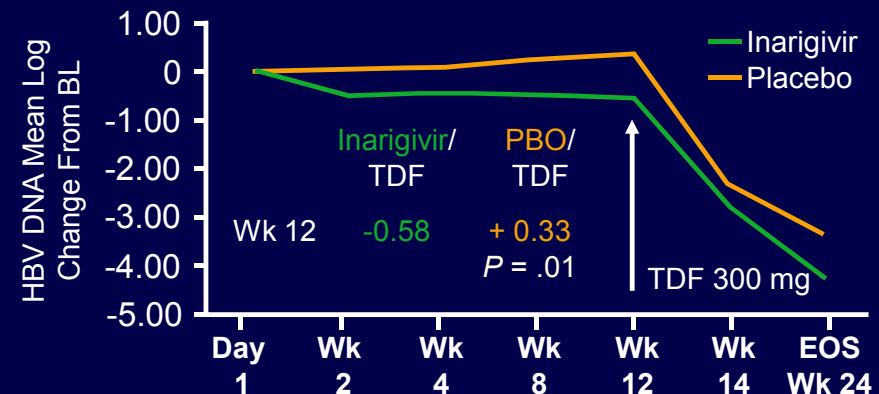
*Cohorts 1, 2, 4. †Part A, Cohort 1. ‡Estimated from graph.

1. Agarwal K, et al. AASLD 2017. Abstract 40. 2. Yuen M, et al. AASLD 2017. Abstract 39. Reproduced with permission.

§ ACHIEVE[†]: randomized, double-blind phase II study of 4 doses of inarigivir PO QD or PBO for 12 wks for tx-naive, noncirrhotic pts with HBV (N = 20)^[2]

- Inarigivir (formerly SB 9200): activates RIG-I, NOD-2, subsequent IFN responses

HBV DNA Mean Log Change From BL

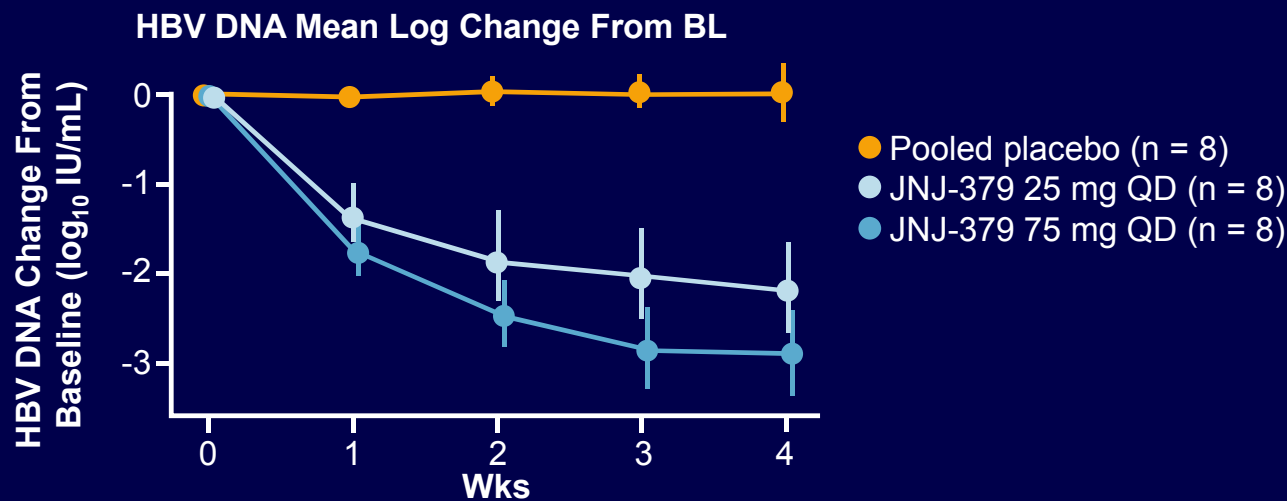


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Selected Studies on Emerging Investigational Agents for Treating HBV

§ HPB1001, Part 2: randomized, double-blind, phase I study of 2 doses of JNJ-379 QD for 28 days or placebo for pts with chronic HBV infection (N = 24)^[1]

– JNJ-379: capsid assembly modulator



Emerging Therapeutics for HDV Infection



Selected Studies on Emerging Investigational Agents for Treating HDV

§ Open-label, randomized phase IIb study of 3 doses of Myrcludex B SC QD + TDF or TDF for 24 wks in pts with chronic HBV/HDV (N = 120)^[1]

- Myrcludex B: HBV/HDV entry inhibitor

Outcome*	MyrB + TDF			TDF
	2 mg	5 mg	10 mg	
HDV RNA reduction at Wk 24, log ₁₀ IU/mL	NR	-1.63 (n = 7)	-2.42 (n = 10)	-0.015 (n = 9)
Complete ALT normalization at Wk 12, n/N (%)	7/21 (33)	5/21 (24)	9/22 (41)	NR

*Interim results.

1. Wedemeyer H, et al. AASLD 2017. Abstract 37. Data from abstract.

2. Hamid S, et al. AASLD 2017. Abstract 927. 3. Chan HLY, et al. J Hepatol. 2016;64:1011-1019.

§ LIMT: open-label, randomized phase II study of 2 doses of pegIFN lambda for 48 wks in pts with chronic HDV infection (N = 33)^[2]

- pegIFN λ: type III IFN with unique receptor binding; reduced cytopenias and other AEs vs IFN alfa^[3]

§ At Wk 24*:

- 5/10 (50%) analyzable pts achieved ≥ 2 log HDV RNA decline
- 4/10 (40%) analyzable pts HDV PCR negative



NAFLD/NASH: Disease Outcomes and Novel Therapeutics



NAFLD Prevalence and Outcomes Among Racial and Ethnic Subgroups in the United States

§ Meta-analysis of 34 studies of NAFLD prevalence, severity, or prognosis (N = 368,569)

Parameter	Finding
NAFLD prevalence, %*	11.2
NAFLD relative risk (95% CI)*	
§ Hispanic vs white pts	1.36 (1.08-1.73)
§ Black vs white pts	0.68 (0.54-0.84)
NASH prevalence in NAFLD pts, %†	31.4
NASH relative risk in NAFLD pts (95% CI)†	
§ Hispanic vs white pts	1.24 (1.02-1.52)
§ Black vs white pts	0.72 (0.60-0.87)

Parameter	Finding
F3-F4 fibrosis prevalence in NAFLD pts, %‡	19.5
F3-F4 fibrosis relative risk in NAFLD pts (95% CI)‡	
§ White vs Hispanic pts	1.02 (0.94-1.11)
§ White vs black pts	1.10 (1.00-1.22)

*Based on 9 studies, n = 343,393.

†Based on 10 studies, n = NR (subset of 16,083).

‡Based on 11 studies, n = NR (subset of 16,083).

Rich NE, et al. AASLD 2017. Abstract 57.

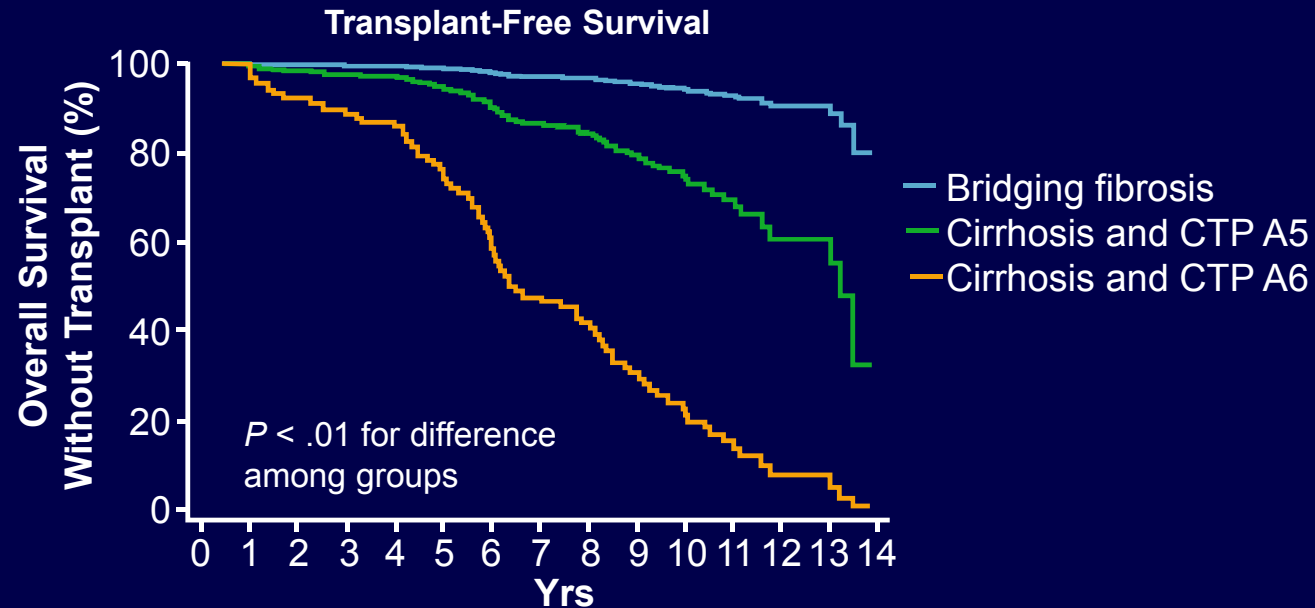
Rich NE, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print].



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Association Between Fibrosis Severity and Clinical Outcomes in Advanced NAFLD

§ International, prospective cohort study of clinical outcomes in NAFLD pts with compensated cirrhosis or biopsy-proven bridging fibrosis from 1995-2013 (N = 458)



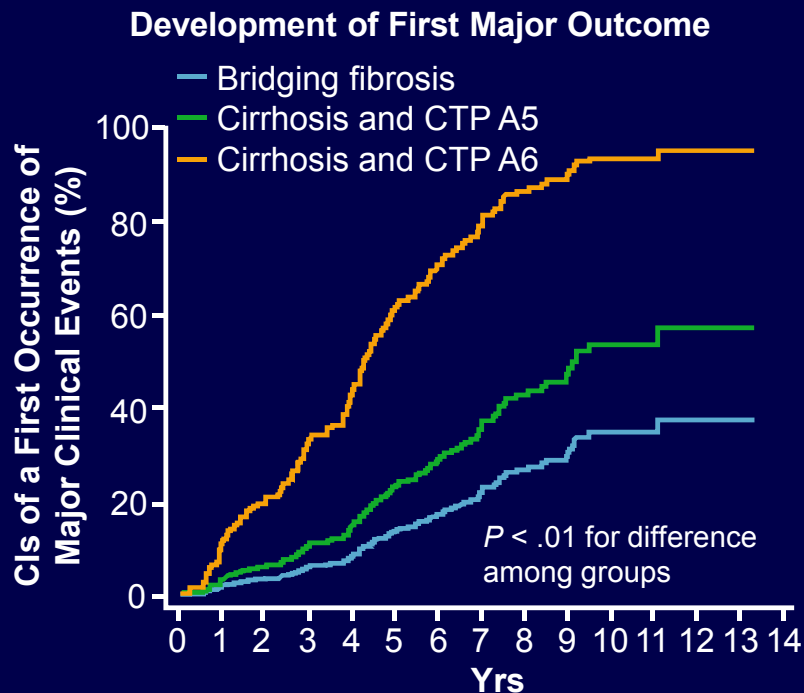
*Adjusted by age, center, sex, and race/ethnicity.

Vilar-Gomez E, et al. AASLD 2017. Abstract 60. Reproduced with permission.



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Association Between Fibrosis Severity and Clinical Outcomes in Advanced NAFLD



Clinical Outcome	F3 Fibrosis (n = 159)	Cirrhosis CTP-A5 (n = 222)	Cirrhosis CTP-A6 (n = 77)
1st event occurrence, n (%)	26 (16)	63 (28)	52 (66)
§ Hepatic decompensation, n/N (%)	5/26 (19)	37/63 (59)	44/52 (85)
§ HCC, n/N (%)	2/26 (8)	12/63 (19)	8/52 (15)
§ Major vascular event, n/N (%)	9/26 (35)	4/63 (6)	0
§ Nonhepatic malignancy, n/N (%)	10/26 (38)	10/63 (16)	0

Cardiovascular Risk in Pts With NAFLD

§ Retrospective analysis of sex-related incidence of CV events in pts diagnosed with NAFLD (n = 3869) and matched controls (n = 15,209) in Rochester County, Minnesota, from 1997-2014

– 122,758 PYFU; 1375 CV events, 1551 deaths

§ Risk of CV event:

– General population: **23% lower** in women vs men

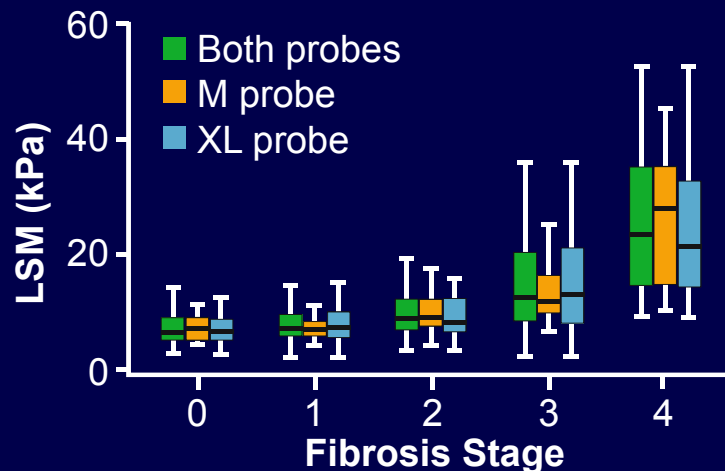
– NAFLD population: **not different** between women vs men, suggesting NAFLD may attenuate the sex-based CVD risk “advantage” for women

Female:Male HR (95% CI)	NAFLD	Control
Any incident CV event	0.94 (0.80-1.11)	0.77 (0.69-0.85)

Diagnostic Performance of *FibroScan* for Assessing Liver Stiffness in NAFLD

- § Multicenter, prospective study evaluating diagnostic performance of *FibroScan* for liver stiffness measurement in pts undergoing biopsy for suspected NAFLD (N = 374 analyzed)
- § Fibrosis (biopsy): F0, 17%; F1, 23%; F2, 23%; F3, 29%; F4, 9%

FibroScan LSM Correlation With Fibrosis Stage

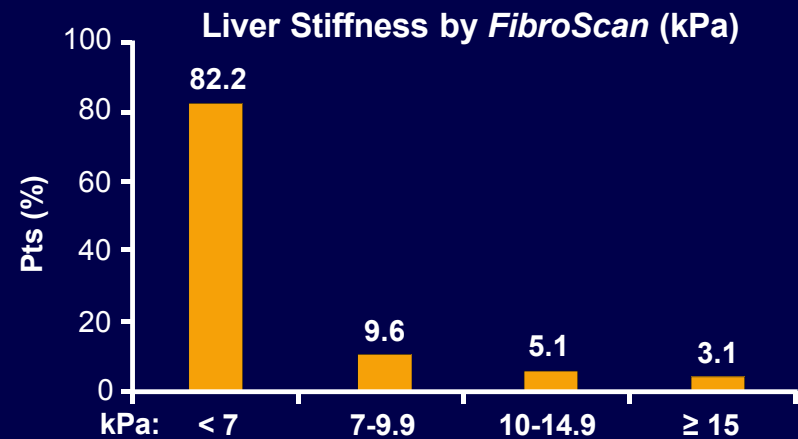
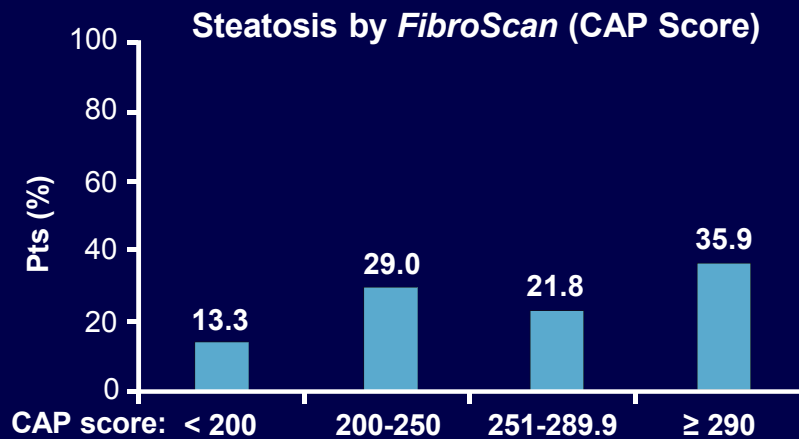


AUROC (95% CI)		
≥ F2	≥ F3	≥ F4
0.77 (0.72-0.82)	0.80 (0.75-0.84)	0.89 (0.84-0.93)

- § By multivariate analysis, only factor significantly influencing LSM was fibrosis stage

Assessment of Fatty Liver and Fibrosis Among Pts Attending Primary Care Clinic

- § Single-center, *FibroScan*-based assessment of fatty liver and liver fibrosis in pts without liver disease history (N = 958)
- Pts offered free *FibroScan*; most evaluated pts were female (64%), Hispanic ethnicity (85%), and above normal BMI (overweight, 36%; obese, 24%; morbidly obese, 19%)

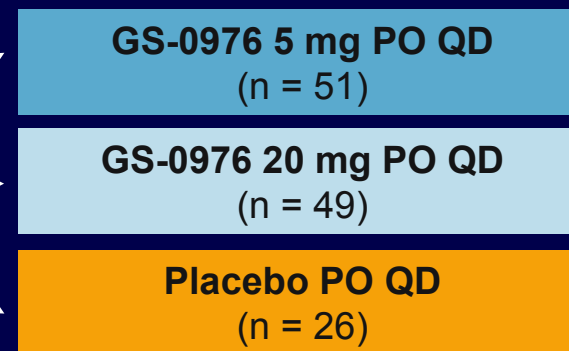


- § In pts with CAP ≥ 290 and complete NAFLD/NASH workup, diagnostic performance of *FibroScan* CAP and LSM will be compared with biopsy results

GS-0976: Acetyl-CoA Carboxylase Inhibitor in Pts With NASH

- § No agents currently approved for treating NASH; numerous agents in phase II/III studies
- § GS-0976: randomized, double-blind, placebo-controlled phase II study
 - GS-0976: liver-targeted inhibitor of acetyl-CoA carboxylase, which catalyzes rate-limiting step of de novo lipogenesis
 - Primary endpoint: safety; additional endpoints: MRI-PDFF, MRE, *FibroScan*, and serum fibrosis markers

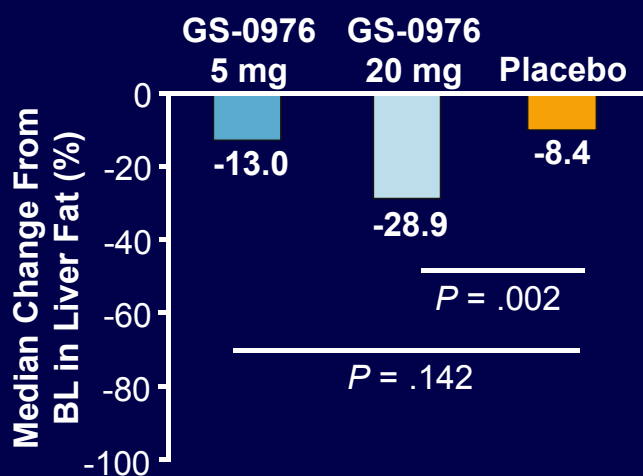
Pts with either NAFLD, MRI-PDFF $\geq 8\%$, and MRE ≥ 2.5 kPa or a historical liver biopsy consistent with NASH and F1-3 fibrosis (N = 126)



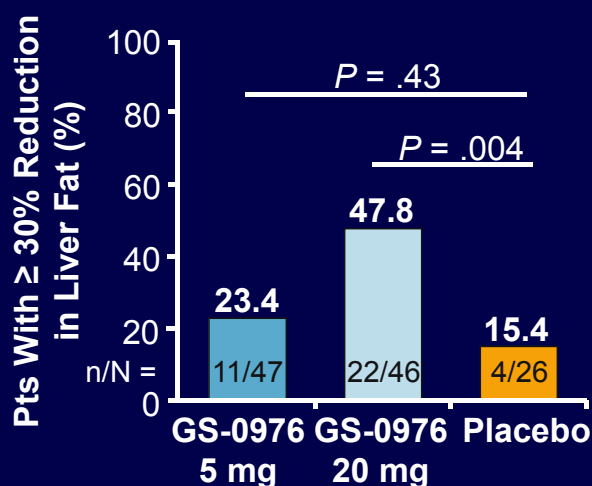
GS-0976: Key Efficacy Findings at Wk 12

§ Statistically significant decrease in liver fat content with 20 mg, but not 5 mg, vs placebo by MRI-PDFF; no statistically significant decrease in ALT vs placebo

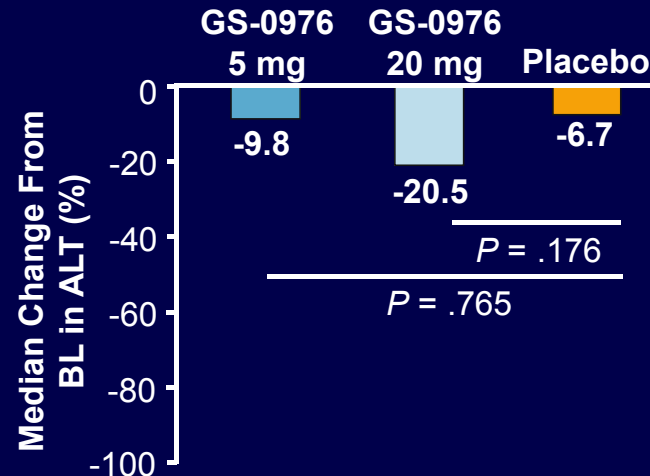
Relative Change in Liver Fat



Categorical Change in Liver Fat



ALT Change

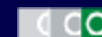


GS-0976: Safety

Safety Event	GS-0976 5 mg (n = 51)	GS-0976 20 mg (n = 49)	Placebo (n = 26)
AE, n (%)	36 (71)	35 (71)	16 (62)
Serious AE, n (%)	2 (4)	2 (4)	0
Discontinuation for AE, n (%)	2 (4)	0	0
Median relative change in TG, %	13	11	-4
Asymptomatic grade 3/4 TG elevation, n (%)	9 (18)	7 (14)	0
§ Grade 3 (> 500-1000 mg/dL)	5 (10)	5 (10)	0
§ Grade 4 (> 1000 mg/dL)	4 (8)	2 (4)	0

§ Grade 3/4 TG elevation predicted by BL TG > 250 mg/dL ($P < .001$)

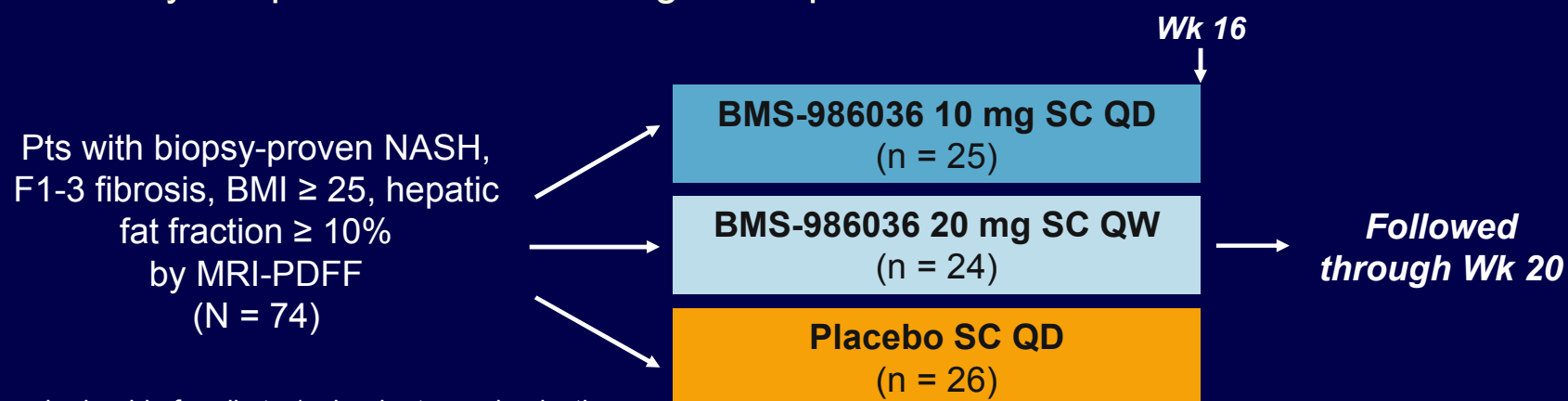
§ Of 16 pts with grade 3/4 TGs, n = 11 lowered TGs to < 500 mg/dL at Wk 12 (response to fibrate or fish oil, n = 4; resolution without treatment or study drug cessation, n = 7)



BMS-986036 in Pts With NASH, F1-3 Fibrosis

§ Multicenter, randomized, double-blind, placebo-controlled phase II study

- BMS-986036: pegylated analogue of metabolism regulator FGF21
- Primary endpoint: absolute change in hepatic fat fraction



Placebo lead-in for all pts 1 wk prior to randomization.

Planned N = 90; enrollment ended early due to significant effect of BMS-986036 on primary endpoint in preplanned interim analysis at Wk 8.

BMS-986036 for Pts With NASH: Key Efficacy Findings

§ Significant reduction in liver fat content vs placebo by MRI-PDFF at Wk 16

Endpoint, n (%)	BMS-986036		Placebo (n = 25)
	10 mg QD (n = 23)	20 mg QW (n = 22)	
Absolute change in hepatic fat fraction from baseline, % (<i>P</i> value vs placebo)	-6.8 (< .001)	-5.2 (< .01)	-1.3
Pts with ≥ 30% reduction in hepatic fat fraction, % (<i>P</i> value vs placebo)	56 (.02)	54 (.03)	24

§ Improvements in ALT and AST with BMS-986036 vs placebo through Wk 16

BMS-986036 for Pts With NASH: Key Safety Data

§ HDL levels improved from BL with BMS-986036 QD and QW vs no meaningful changes from BL with placebo; BMS-986036 QD only arm to show mean reduction in LDL from BL

§ No deaths, treatment-related serious AEs, or AE-related discontinuations

Event, n (%)	BMS-986036		Placebo (n = 26)
	10 mg QD (n = 25)	20 mg QW (n = 24)	
Serious AEs	1 (4)	1 (4)*	1 (4)
AEs in > 10% of pts			
§ Diarrhea	3 (13)	5 (22)	2 (8)
§ Nausea	4 (16)	3 (13)	2 (8)
§ Frequent bowel movements	5 (20)	0	0
Grade 3 lab abnormalities [†]	1 (4)	2 (8)	2 (8)

*Pt randomized in error; received small amount of 20 mg BMS-986036 on Day 1, should have received placebo.

[†]ALT elevation, n = 4; glucose elevation, n = 1 (in 20 mg QW arm).

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