# BMS-986036 (PEGylated FGF21) in Patients with Non-Alcoholic Steatohepatitis: A Phase 2 Study

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# Disclosures

- Arun Sanyal received research support from Bristol-Myers Squibb which was provided to his institution
- He has stock ownership in Sanyal Bio, Genfit, Hemoshear, Tiziana, Natural Shield, Indalo and Durect
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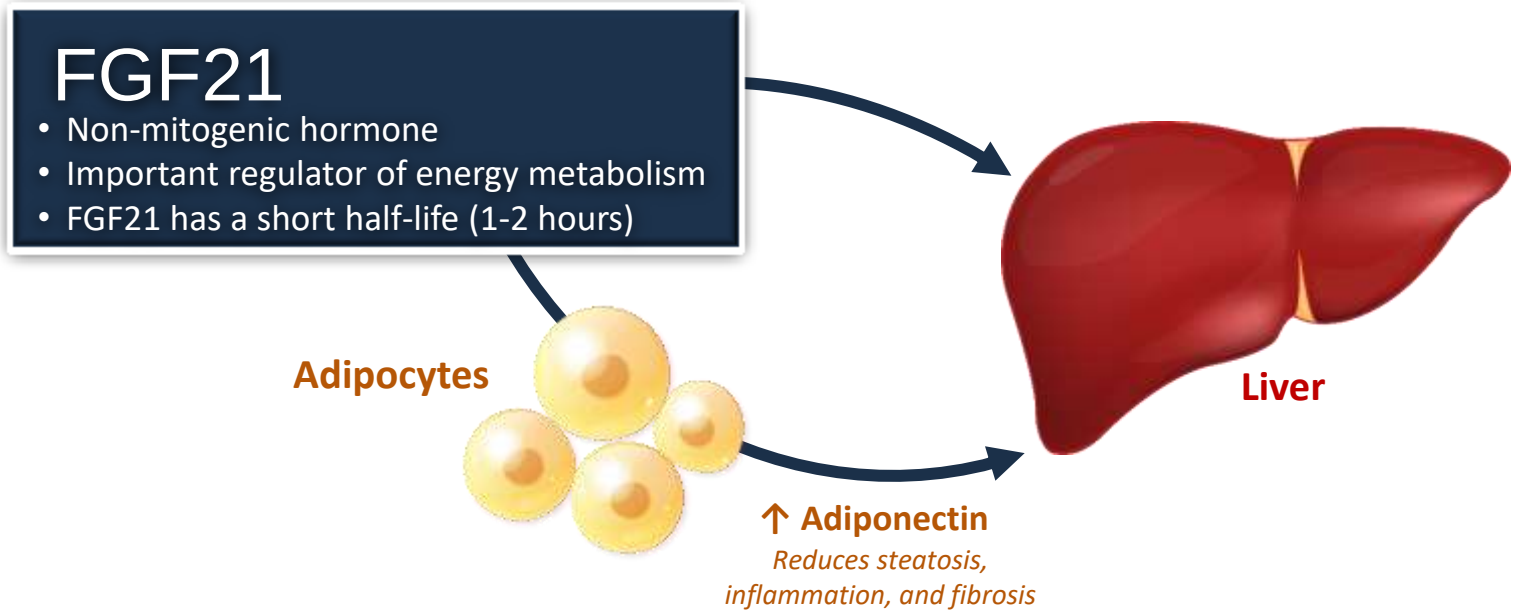
# Non-Alcoholic Steatohepatitis (NASH)

- NASH, the most advanced form of non-alcoholic fatty liver disease (NAFLD), is characterized by steatosis, with inflammation and liver cell injury[1]
- The overall prevalence of NASH in the general population is 1.5% to 6.5%[2]
- Individuals with NASH have an increased mortality rate due to cardiovascular events, cirrhosis, hepatocellular carcinoma, and liver transplant-related complications[1]
- There is currently no approved drug therapy for NASH
- New and effective treatments for NASH are needed

1. Chalasani N, et al. *Hepatology* 2012;**55**:2005-23; 2. Younossi ZM, et al. *Hepatology* 2016;**64**:73-84

# Fibroblast Growth Factor 21 (FGF21)




| Beneficial metabolic effects | Anti-fibrotic effects |
|---|---|
| ↑ Insulin sensitivity | ↓ Pro-C3 (biomarker of fibrosis) |
| ↓ Lipogenesis & improvement in lipids | |

***FGF21 may have direct and indirect beneficial effects on non-alcoholic steatohepatitis (NASH) and NASH-related fibrosis***

1. Owen BM, *et al. Trends Endocrinol Metab.* 2015; **26**(1):22-29; 2. Gimeno RE, Moller DE. *Trends Endocrinol Metab.* 2014; **25**(6):303-11;
3. Polyzos SA. Et al. *Diabetes Obes Metab*. 2010**;12**(5): 365-83; 4. Kharitonenkov A and Larsen P, *Trends Endocrinol Metab.* 2011;**22**(3):81-86;
5. Charles E. et al. *Hepatology* 2016;**64**(Suppl):17A.

# BMS-986036 (PEGylated FGF21)

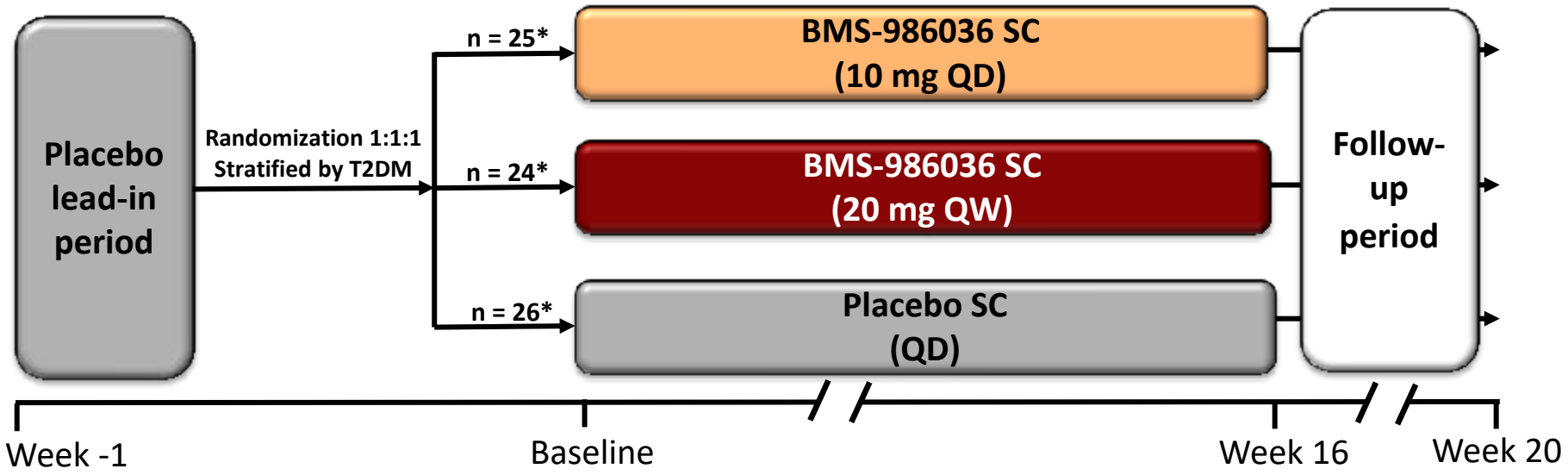
**BMS-986036 is a PEGylated, recombinant human FGF21 analog with a prolonged half-life, supporting weekly dosing**

- Improves NAFLD activity score (NAS) and fibrosis in animal models[1]
- Increases adiponectin, a key adipokine with insulin-sensitizing, anti-inflammatory, and anti-fibrotic properties[1,2]
- Decreases Pro-C3, an emerging biomarker of fibrosis[3-6]
- Improved insulin sensitivity and lipids in a phase 2 study in obese patients with type-2 diabetes[6]

1. Krupinski J, et al. *Hepatol* 2016;**64**(Suppl):749A; 2. Polyzos SA, et al. *Diabetes Obes Metab*. 2010;**12**(5): 365-83;
3. Nielsen MJ, et al, *PLOS One* 2015;**10**(9):e0137302; 4. Nielsen MJ, et al. *Liver Int* 2015;**35**:429-437;
5. Karsdal MA, et al. *Am J Physiol Gastrointest Liver Physiol* 2016;**311**(6):G1009-1017;
6. Charles E, et al. *Hepatol* 2016;**64**(Suppl):17A.

NAFLD, non-alcoholic fatty liver disease.

# Study Design
# Phase 2 Double-Blind, Placebo-Controlled Study




- **Key Eligibility Criteria:** biopsy-proven NASH with fibrosis stage 1-3 (within 1 year of screening), BMI ≥25 kg/m$^2$, hepatic fat fraction ≥ 10% (MRI-PDFF)
- **Primary Efficacy Endpoint:** change in hepatic fat fraction (%) from baseline to Week 16
- **Key Exploratory Endpoints**: adiponectin, lipids, ALT, AST, MRE, and serum Pro-C3
- **Safety Assessments:** AEs, laboratory parameters, and vital signs

*Planned sample size was 30 per group; enrollment ended early due to the significant effect of BMS-986036 on the primary endpoint seen during preplanned interim analysis at treatment Week 8.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, non-alcoholic steatohepatitis; QD, once daily; QW, once weekly; SC, subcutaneous; T2DM; type-2 diabetes mellitus.

# Baseline Demographics and Disease Characteristics

| Characteristics | BMS-986036 | | Placebo |
|---|---|---|---|
| | 10 mg QD (n=25) | 20 mg QW (n=24) | (n=26) |
| **Demographics** | | | |
| Age, years, mean (SD) | 52 (10) | 51 (12) | 47 (12) |
| Men, n (%) | 10 (40) | 7 (29) | 10 (38) |
| Race, White, n (%) | 24 (96) | 23 (96) | 25 (96) |
| BMI, kg/m$^2$, mean (SD) | 34 (4) | 35 (6) | 37 (7) |
| **Disease Characteristics** | | | |
| T2DM, n (%) | 9 (36) | 8 (33) | 11 (42) |
| **NASH CRN Fibrosis, n (%)** | | | |
| Stage 1 | 10 (40) | 13 (54) | 17 (65) |
| Stage 2 | 6 (24) | 6 (25) | 8 (31) |
| Stage 3 | 9 (36) | 5 (21) | 1 (4) |
| **NAFLD activity score, mean (SD)[a]** | 4.4 (1) | 4.4 (1) | 4.0 (1) |

Baseline demographics and disease characteristics were generally comparable between treatment groups

[a]One patient in the 20 mg QW group was missing data for NAFLD activity score.

BMI, body mass index; NASH CRN, non-alcoholic steatohepatitis clinical research network; NAFLD, non-alcoholic fatty liver disease; T2DM, type-2 diabetes mellitus; QD, once daily; QW, once weekly; SD, standard deviation.

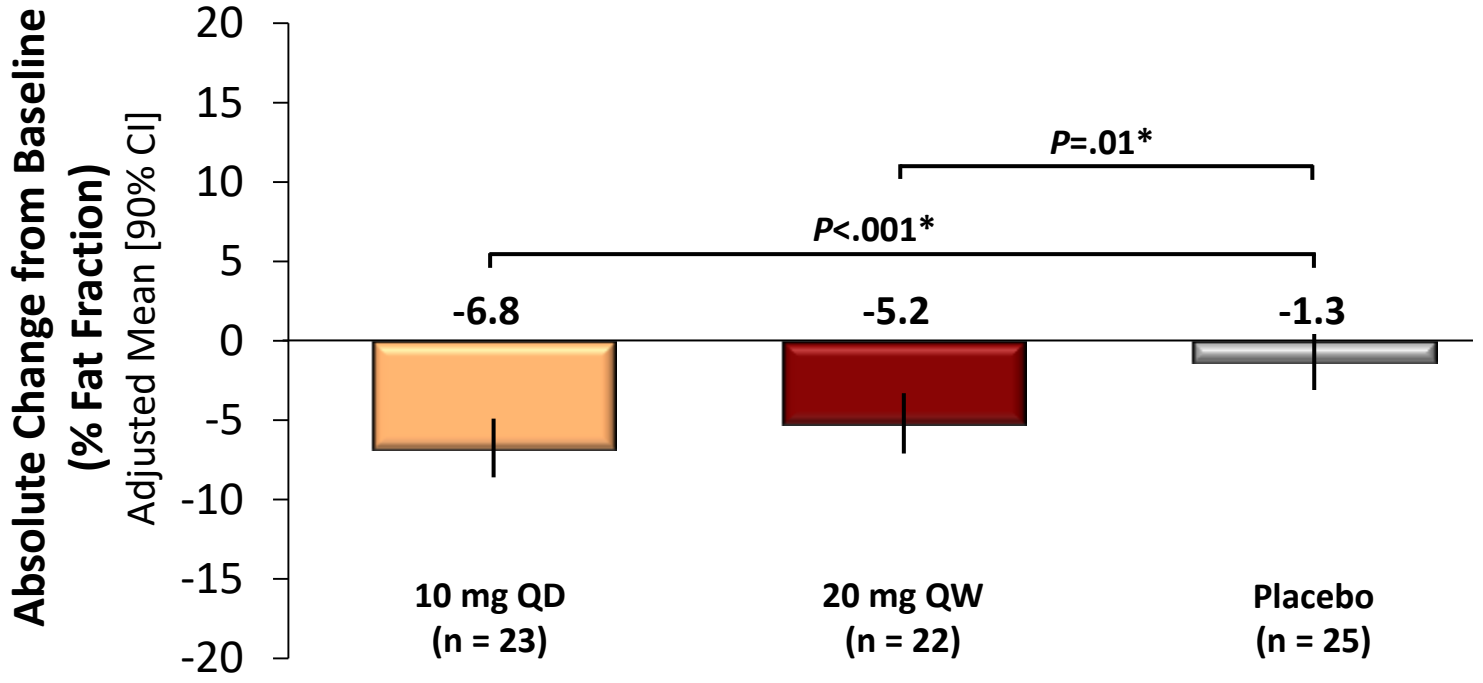
# Baseline Liver and Metabolic Parameters

| Parameters | BMS-986036 | | Placebo |
|---|---|---|---|
| | 10 mg QD (n=25) | 20 mg QW (n=24) | (n=26) |
| **Liver, mean (SD)** | | | |
| Hepatic fat fraction (by MRI-PDFF), % | 18 (7) | 20 (6) | 21 (7) |
| ALT, U/L | 66 (37) | 70 (33) | 80 (51) |
| AST, U/L | 48 (23) | 51 (22) | 58 (49) |
| Pro-C3, ng/mL | 19 (15) | 22 (15) | 19 (13) |
| **Metabolic, mean (SD)** | | | |
| Triglycerides, mg/dL | 207 (110) | 186 (55) | 171 (75) |
| LDL cholesterol, mg/dL | 129 (38) | 120 (36) | 128 (55) |
| HDL cholesterol, mg/dL | 47 (10) | 45 (12) | 50 (11) |
| $HbA_{1c}$, % | 6.1 (0.9) | 6.2 (1.1) | 6.0 (0.9) |

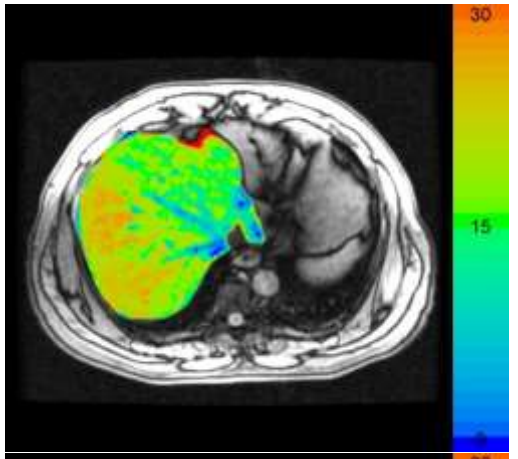
Liver and metabolic parameters were comparable between treatment groups

ALT, alanine aminotransferase; AST, aspartate aminotransferase; $HbA_{1c}$, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; MRI-PDFF, magnetic resonance imaging-proton density fat-fraction; QD, once daily; QW, once weekly; SD, standard deviation.

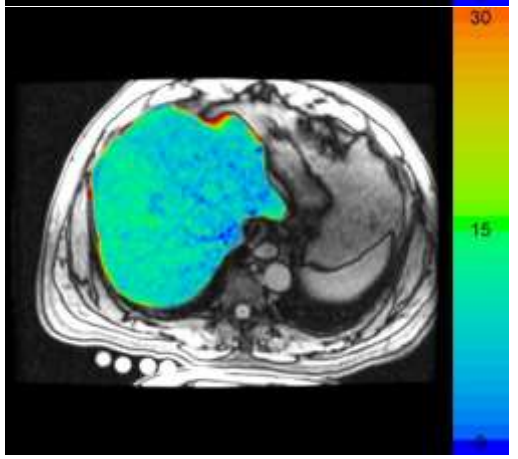
# Absolute Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16




Baseline fat fraction **18.8%**



Week 16 fat fraction **8.3%**

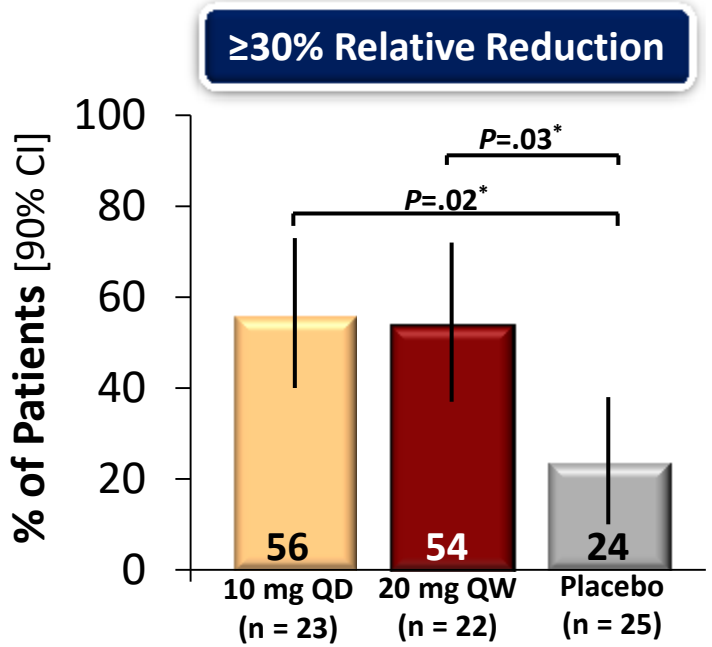


BMS-986036 QD and QW treatment compared with placebo significantly reduced hepatic fat fraction

*Inferential statistical analyses were conducted using a MMRM and not adjusted for multiple comparisons.

CI, confidence interval; MRI-PDFF, magnetic resonance imaging-proton density fat-fraction; MMRM, mixed effects model for repeated measures; QD, once daily; QW, once weekly.

# Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16



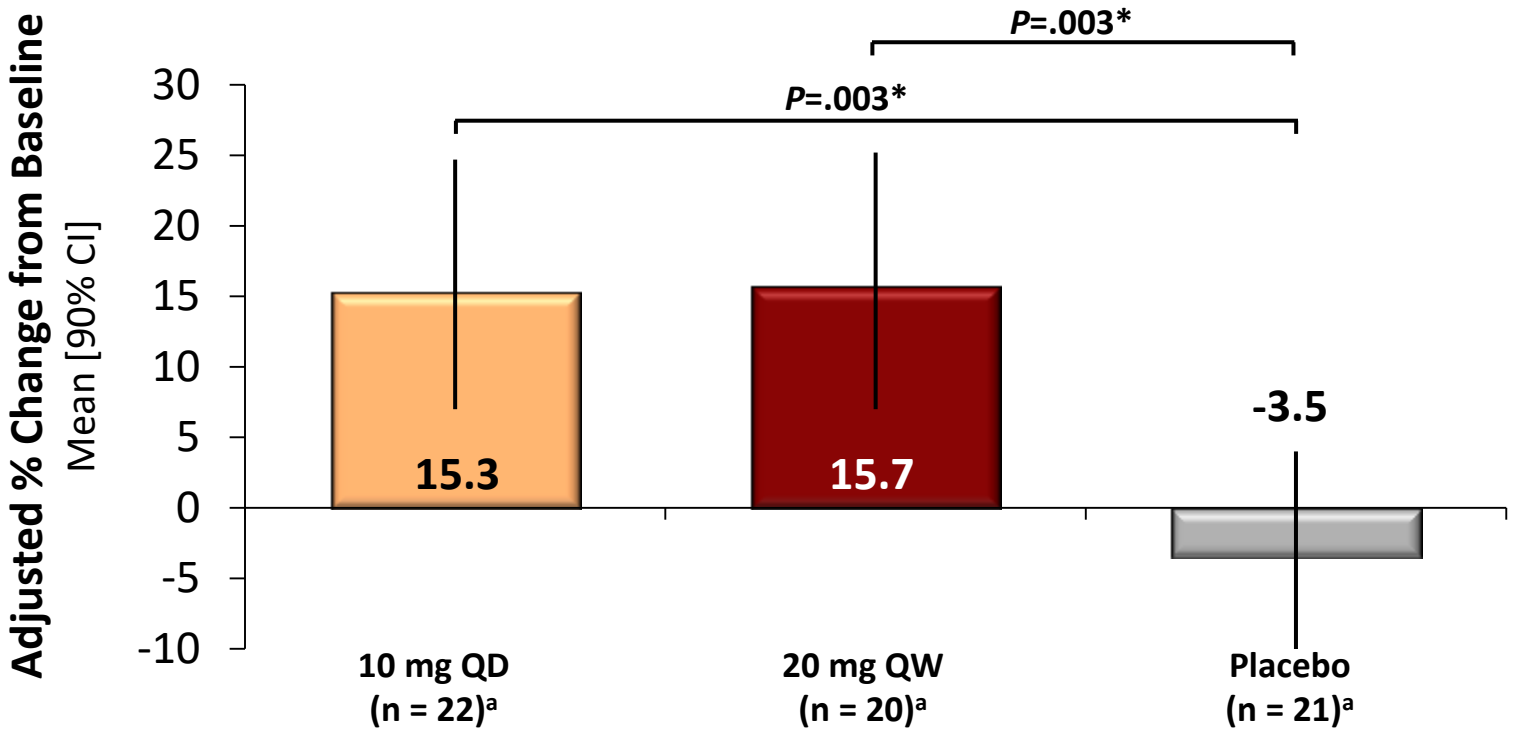

- Relative reduction of ≥29% in MRI-PDFF is associated with histologic response in NASH patients[1]
- Significantly more BMS-986036 QD patients compared with placebo patients had ≥30% reduction in MRI-PDFF
  - More QW patients versus placebo patients had ≥30% reduction in MRI-PDFF

*Inferential statistical analyses were conducted post hoc using Fisher's Exact test and not adjusted for multiple comparisons.

1. Patel J, et al. *Therap Adv Gastroenterol* 2016;**9**:692-701.

CI, confidence interval; MRI-PDFF, magnetic resonance imaging - proton density fat-fraction; QD, once daily; QW, once weekly.

# Improvement in Adiponectin at Week 16




- Previous studies have suggested that higher adiponectin levels are associated with reductions in steatosis, inflammation, and fibrosis[1]
- BMS-986036 QD and QW compared with placebo significantly increased adiponectin levels

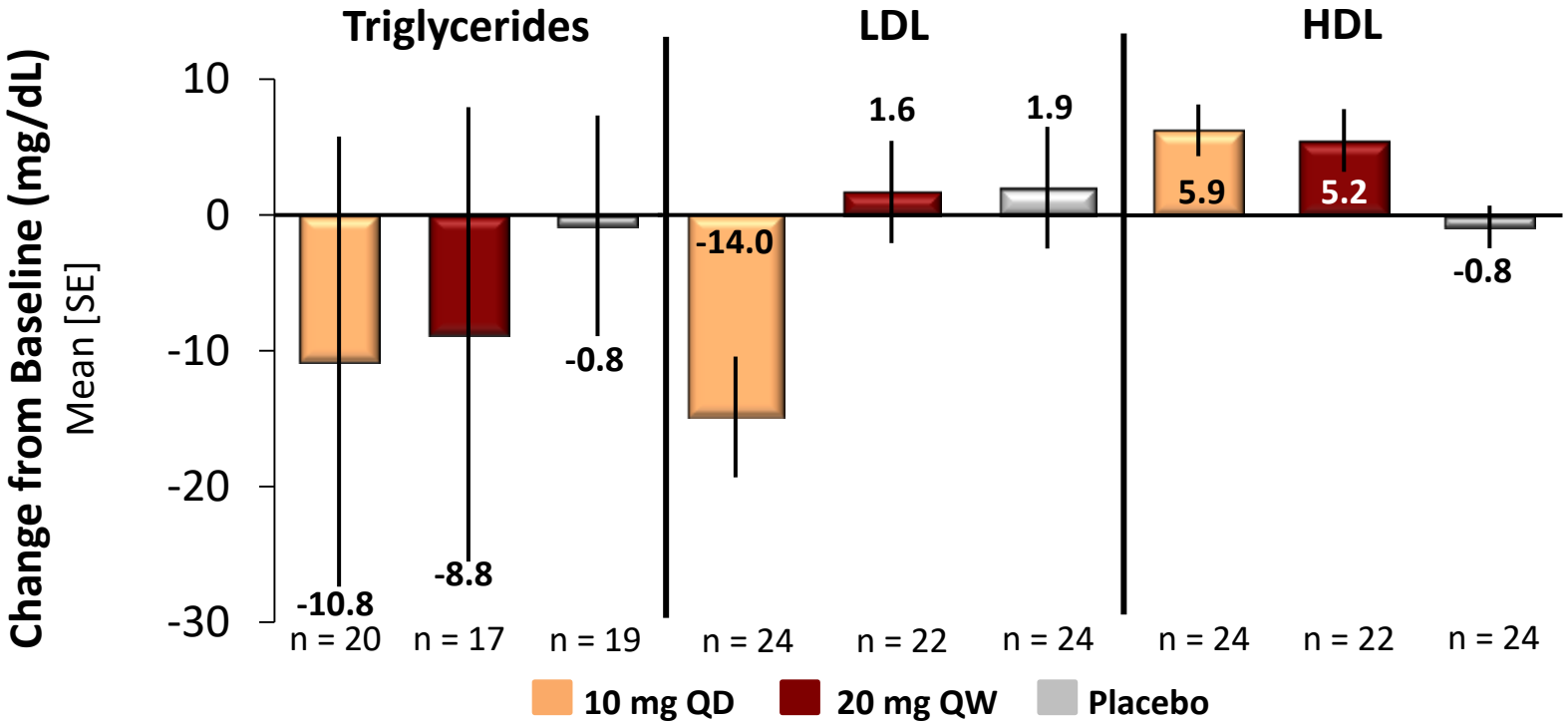
*Inferential statistical analyses were conducted post hoc using a MMRM and not adjusted for multiple comparisons

[a]Sample size for adiponectin was smaller than MRI-PDFF due to some non-evaluable samples at baseline.

1. Polyzos SA, et al. *Diabetes Obes Metab* 2010;12(5):365-83.

CI, confidence interval; MMRM, mixed effects model repeated measures; QD, once daily; QW, once weekly.

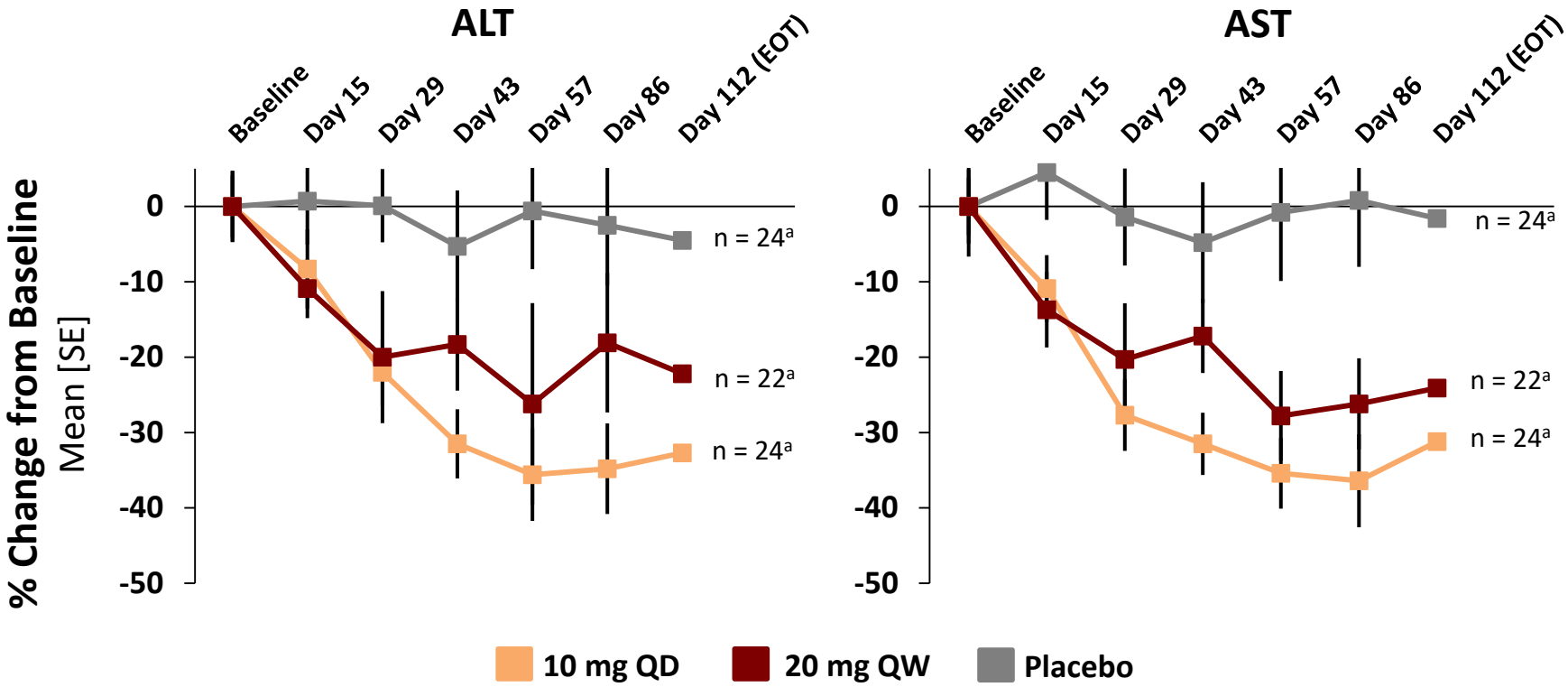
# Improvement in Triglycerides, LDL, and HDL Cholesterol at Week 16




- Fasting triglycerides were highly variable across treatment groups
- BMS-986036 QD and QW groups showed improved HDL levels from baseline
- BMS-986036 10 mg QD reduced LDL levels relative to baseline
- No meaningful changes in triglycerides, LDL or HDL levels were observed with placebo

HDL, high density lipoprotein; LDL, low density lipoprotein;
QD, once-daily; QW, once weekly; SE, standard error of the mean.

# Improvements in ALT and AST Over Time

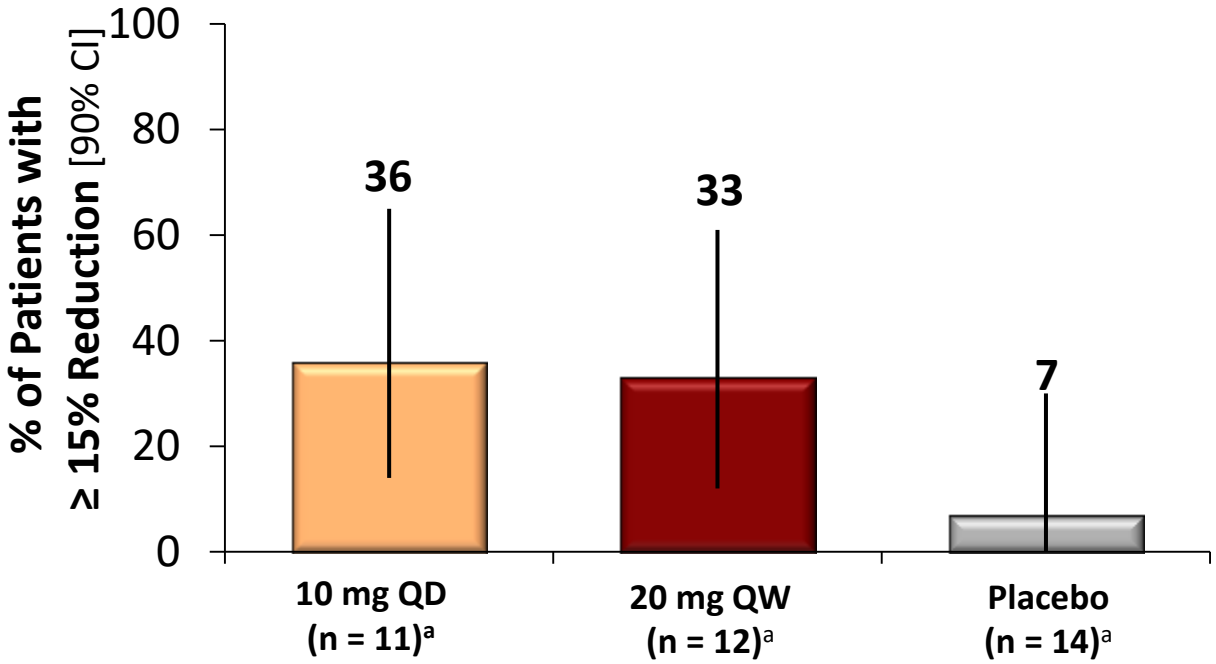


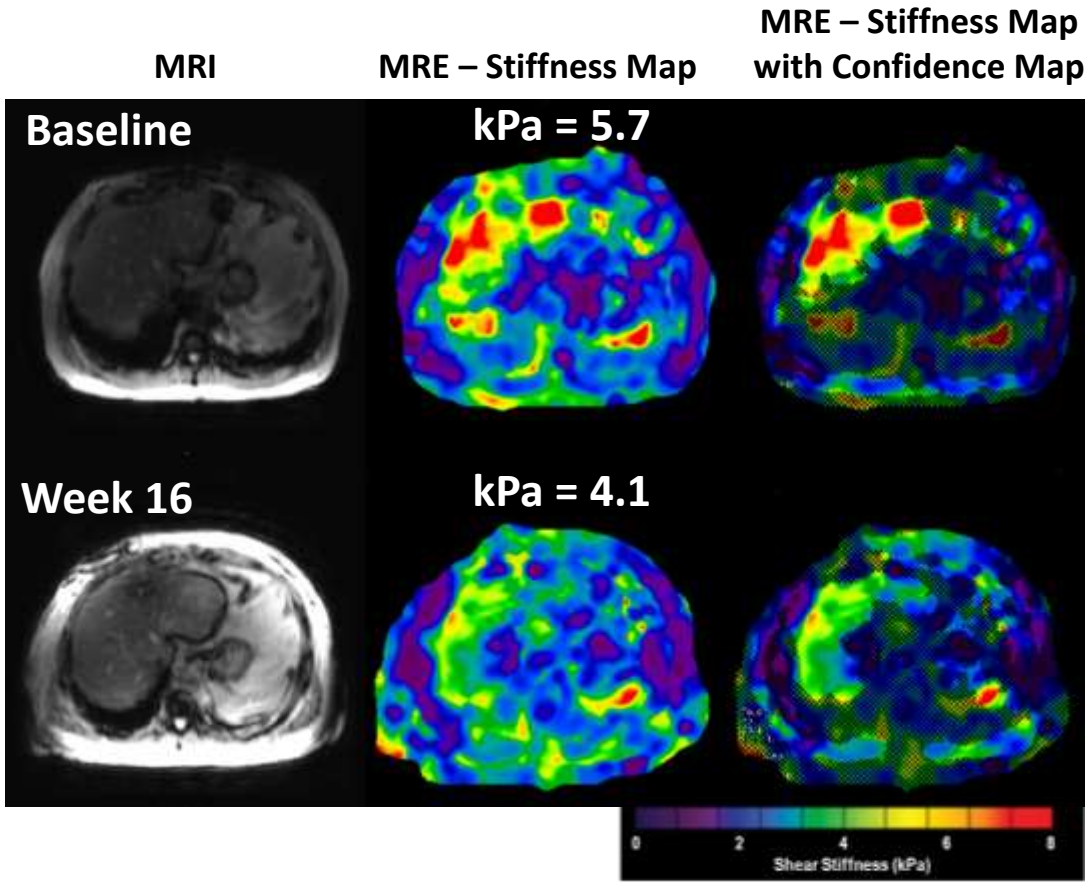

- BMS-986036 QD and QW treatment were associated with improvements from baseline in biomarkers of liver injury
- Changes from baseline were minimal in the placebo group

[a]n indicates number of patients with ALT/AST data at EOT.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; QD, once daily; QW once weekly; SE, standard error of the mean.

# Improvement in Liver Stiffness (MRE) at Week 16




- BMS-986036 QD and QW groups relative to placebo had a numerically greater percentage of patients with ≥15% reduction in liver stiffness[a]

[a]Sample size for the liver stiffness (MRE) analysis was smaller than other endpoints because MRE was only conducted at a subset of imaging facilities with the appropriate hardware and software.

CI, confidence interval; kPa, kilopascal; MRE, magnetic resonance elastography; QD, once daily; QW, once weekly.

# Safety Summary

| Event, n (%) | BMS-986036 10 mg QD (n=25) | BMS-986036 20 mg QW (n=24) | Placebo (n=26) |
|---|---|---|---|
| **Deaths** | 0 | 0 | 0 |
| **Discontinuation due to AEs** | 0 | 0 | 0 |
| **Serious AEs**[a] | 1 (4) | 1 (4)[b] | 1 (4) |
| Treatment-related SAEs | 0 | 0 | 0 |
| **Overall AEs** | 18 (72) | 13 (54) | 15 (58) |
| **AEs in > 10% of participants** | | | |
| Diarrhea | 3 (13) | 5 (22) | 2 (8) |
| Nausea | 4 (16) | 3 (13) | 2 (8) |
| Fatigue | 1 (4) | 0 | 3 (11) |
| Headache | 1 (4) | 2 (8) | 1 (4) |
| Urinary tract infection | 1 (4) | 3 (12) | 2 (8) |
| Frequent bowel movements | 5 (20) | 0 | 0 |
| **Grade 3 laboratory abnormalities**[c] | 1 (4) | 2 (8) | 2 (8) |

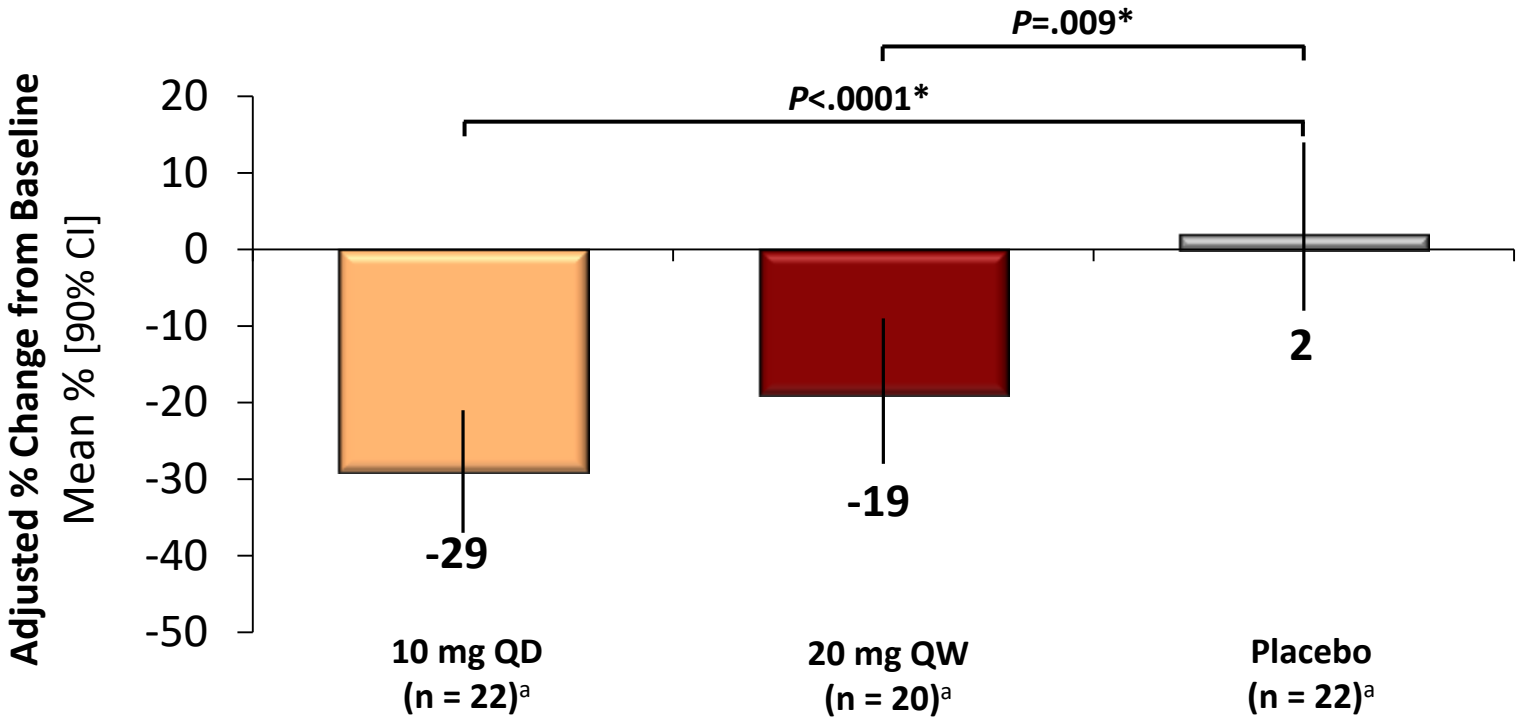
- BMS-986036 was generally well tolerated; most AEs were mild, none were considered severe

- There were no grade 4 laboratory abnormalities

[a]2 SAEs occurred during the screening period so no treatment group was assigned and those patients do not appear on this table; [b]This patient was given a small amount of BMS-986036 20 mg on Day 1 incorrectly. This patient was randomized twice in error and should have received placebo; [c]4 events of increased ALT, 1 event of high glucose (20 mg QW).

AE, adverse event; ALT, alanine aminotransferase; QD; daily dosing; QW, once weekly; SAE, serious adverse event.

# Reduction in Serum Pro-C3 at Week 16




- Elevated serum Pro-C3 levels are associated with fibrosis, progression of fibrosis, and may identify patients who are likely to benefit from anti-fibrotic therapy[1-3]
- All patients had comparable serum Pro-C3 levels at baseline
- BMS-986036 QD and QW compared with placebo significantly reduced serum Pro-C3 levels

*Inferential statistical analyses were conducted post hoc using a longitudinal repeated measurements model analysis.

[a]Sample size for serum Pro-C3 was smaller than MRI-PDFF due to some non-evaluable samples at baseline.

1. Nielsen MJ, et al. *PLOS One* 2015;**10**(9):e0137302; 2. Nielsen MJ, et al. *Liver Int* 2015;**35**:429-437;
3. Karsdal MA, et al. *Am J Physiol Gastrointest Liver Physiol* 2016;**311**(6):G1009-1017.

CI, confidence interval; QD, once daily; QW, once weekly.

# Summary and Conclusions

- BMS-986036 10 mg QD and 20 mg QW for 16 weeks, compared with placebo, significantly decreased hepatic fat fraction in patients with NASH (F1–F3)
- BMS-986036 QD and QW relative to placebo was associated with improvements in biomarkers of fibrosis (MRE and Pro-C3), metabolic parameters (adiponectin and lipids), and markers of hepatic injury (ALT and AST)
- BMS-986036 QD and QW were generally well tolerated with no deaths, SAEs related to treatment, or discontinuations due to AEs
- These results suggest that BMS-986036 has beneficial effects on steatosis, liver injury, and fibrosis in NASH
- Future clinical studies of weekly administration of BMS-986036 for NASH are warranted

# BMS-986036 Posters at AASLD

| Number/Title | Session | Date | Presentation Time | Room |
|---|---|---|---|---|
| **612:** Multi-Biomarker Validation of MRI-PDFF- and MRE-Derived Treatment Response with BMS-986036 (PEG-FGF21): A Secondary Analysis of a Multi-Center Clinical Trial in Non-Alcoholic Steatohepatitis (NASH) | Imaging and Noninvasive Fibrosis Assessment | October 20 | 12:00 – 1:30 pm | Washington Convention Center, Hall D |
| **2112**: Baseline Serum Pro-C3 Predicts Response to BMS-986036 (PEG-FGF21): A Secondary Analysis of a Multi-Center Clinical Trial in Non-Alcoholic Steatohepatitis (NASH) | Steatosis and Steatohepatitis | October 23 | 12:30 – 2:00 pm | Washington Convention Center, Hall D |

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- ClinicalTrials.gov, registration number study NCT02413372 (MB130045)