Pharmacokinetics and Safety of Pegbelfermin (BMS-986036) Administered in the Abdomen and Upper Arm to Normal, Overweight, and Obese Healthy Participants

SAT-359

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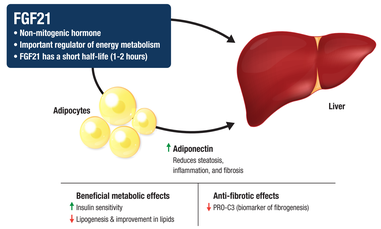
INTRODUCTION

- Fibroblast growth factor 21 (FGF21) is a non-mitogenic hormone that is a key regulator of energy metabolism[1] (**Figure 1**) and may have direct and indirect beneficial effects on nonalcoholic steatohepatitis (NASH) and NASH-related fibrosis[1–5]
- Pegbelfermin (BMS-986036), a PEGylated human FGF21 analogue administered via subcutaneous (SC) abdominal injection, improved steatosis, liver injury, and fibrosis biomarkers in a Phase 2 study of overweight and obese patients (body mass index [BMI]: ≥ 25.0) with NASH[6]
- **Objectives:** Evaluate pharmacokinetics (PK) and safety of a single SC pegbelfermin dose administered in the abdomen and upper arm to obese, overweight, and normal BMI healthy participants

Figure 1. Fibroblast Growth Factor (FGF21)

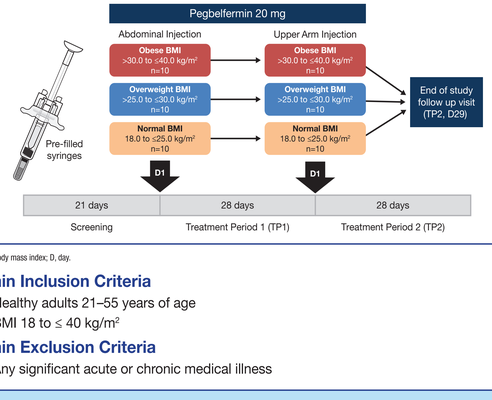


PRO-C3, N-terminal type III collagen propeptide.

METHODS

- MB130-070 was a Phase 1, open-label, fixed-sequence, crossover study in participants grouped into 3 cohorts according to BMI: obese, >30.0 ≤ 40.0 kg/m^2; overweight, >25.0 ≤ 30.0 kg/m^2; normal, 18.0 ≤ 25.0 kg/m^2 (**Figure 2**)
- Participants were admitted to the clinical facility on Day –2 of each treatment period, fasted overnight on Days –2 and –1, and remained at the clinic until Day 5
- While at the clinical facility, participants were served standardised meals consisting of 45%–65% carbohydrates, 20%–35% fat, and 10%–35% protein
- Pre-filled syringes were used to administer pegbelfermin 20 mg via SC injection to the abdomen (Day 1, treatment period 1) followed by an injection in the upper arm (Day 1, treatment period 2)
- Follow-up visits were scheduled for Days 8, 15, 22, and 29 of each treatment period; serum was collected for PK analysis and safety was assessed throughout the study

Figure 2. MB130-070 Study Design



BMI, body mass index; D, day.

Main Inclusion Criteria

- Healthy adults 21–55 years of age
- BMI 18 to ≤ 40 kg/m^2

Main Exclusion Criteria

- Any significant acute or chronic medical illness

METHODS (CONT)

Outcomes (Single-Dose Pegbelfermin 20 mg)

- PK in healthy obese, overweight, and normal BMI participants
- Relative bioavailability when administered to the abdomen vs upper arm
- Safety when administered to the abdomen vs upper arm
- Immunogenicity

Statistical Analysis

- Safety analyses were performed with all participants
- Summary statistics were tabulated for PK

RESULTS

- Baseline demographics and participant characteristics were similar between groups except for weight, waist circumference, and BMI (**Table 1**)

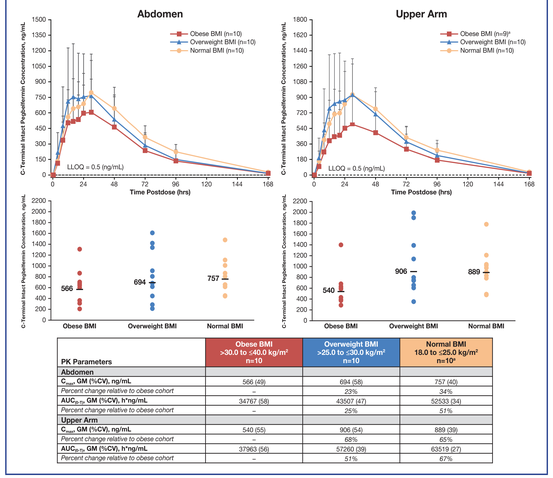
Table 1. Baseline Demographics and Participant Characteristics

Characteristics	Obese BMI >30.0 to ≤40.0 kg/m^2 n=10	Overweight BMI >25.0 to ≤30.0 kg/m^2 n=10	Normal BMI 18.0 to ≤25.0 kg/m^2 n=10	All Ppts N=30
Male, n (%)	8 (80)	9 (90)	10 (100)	27 (90)
Race, White, n (%)	9 (90)	8 (80)	10 (100)	27 (90)
Age, mean (SD), y	34 (11)	30 (9)	34 (8)	33 (9)
Weight, mean (SD), kg	104 (16)	86 (7)	73 (7)	88 (16)
Waist circumference, mean (SD), cm	102 (7)	91 (5)	82 (7)	92 (10)
Height, mean (SD), cm	178 (11)	177 (5)	178 (5)	178 (7)
BMI, mean (SD), kg/m^2	32.8 (1.9)	27.6 (1.6)	23.2 (1.2)	27.8 (4.3)

BMI, body mass index; ppts, participants; SD, standard deviation; y, years.

- Within both administration sites, serum pegbelfermin exposure was up to 51% and 67% higher in overweight and normal BMI participants, respectively, vs obese BMI participants (**Figure 3**)
- There was a trend towards lower peak concentrations with increasing BMI; however, there was considerable overlap in the range of individual estimates across cohorts

Figure 3. Effect of BMI on C-Terminal Intact Pegbelfermin Peak Concentration and Exposure After Abdomen and Upper Arm Administration



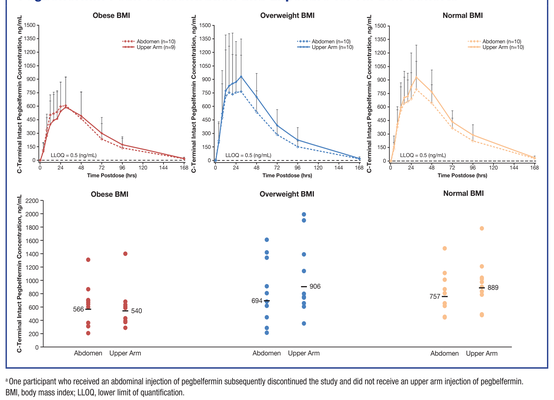
PK Parameters	Obese BMI >30.0 to ≤40.0 kg/m^2 n=10	Overweight BMI >25.0 to ≤30.0 kg/m^2 n=10	Normal BMI 18.0 to ≤25.0 kg/m^2 n=10ª
Abdomen			
C_{max}, GM (%CV), ng/mL	566 (49)	694 (58)	757 (40)
Percent change relative to obese cohort	–	23%	34%
AUC_{0-Tz}, GM (%CV), h*ng/mL	34767 (58)	43507 (47)	52533 (34)
Percent change relative to obese cohort	–	25%	51%
Upper Arm			
C_{max}, GM (%CV), ng/mL	540 (55)	906 (54)	889 (39)
Percent change relative to obese cohort	–	68%	65%
AUC_{0-Tz}, GM (%CV), h*ng/mL	37963 (56)	57260 (39)	63519 (27)
Percent change relative to obese cohort	–	51%	67%

ª One participant who received an abdominal injection of pegbelfermin subsequently discontinued the study and did not receive an upper arm injection of pegbelfermin.
AUC_{0-Tz} exposure; BMI, body mass index; C_{max}, peak concentration; CV, coefficient of variation; GM, geometric mean; LLOQ, lower limit of quantification; PK, pharmacokinetics.

RESULTS (CONT)

- Serum pegbelfermin exposure was similar between administration sites in obese BMI participants, but up to 32% higher in the upper arm vs abdomen in normal and overweight BMI participants (**Figure 4**)

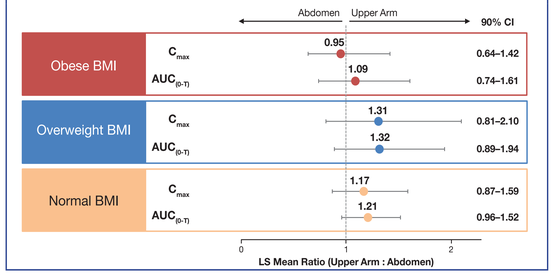
Figure 4. Effect of Upper Arm vs Abdominal Administration on C-Terminal Intact Pegbelfermin Peak Concentration and Exposure for All BMI Cohorts



ª One participant who received an abdominal injection of pegbelfermin subsequently discontinued the study and did not receive an upper arm injection of pegbelfermin.
BMI, body mass index; LLOQ, lower limit of quantification.

- For the normal and overweight BMI cohorts, a modest increase in exposure of up to 32% was observed with upper arm administration (**Figure 5**)

Figure 5. Comparison of C-Terminal Intact Pegbelfermin PK Parameters by Administration Site



AUC_{0-Tz}, exposure; BMI, body mass index; C_{max}, peak concentration; CI, confidence interval; LS, least squares; PK, pharmacokinetics.

- Six adverse events (AEs) were reported in 5 participants following pegbelfermin administration to the abdomen; none were reported in more than 1 participant (**Table 2**)
- Eighteen AEs were reported in 12 participants after pegbelfermin administration to the upper arm
- All AEs were mild or moderate; there were no serious AEs or deaths in any group
- One participant in the obese BMI cohort discontinued due to an AE of ankle pain that was not considered to be related to pegbelfermin
- One participant in the obese BMI cohort had high creatine kinase at Day 29 after the upper arm injection (4132 U/L); a follow-up assessment 8 days later showed normal creatine kinase levels (90 U/L)
- One participant from the overweight BMI cohort was anti-drug antibody positive with respect to baseline in treatment period 2 on Days 15 and 29; titers were the lowest measurable (1) and the participant was lost to follow-up
- Five participants had mild injection site reactions that were characterized as oedema (n=1), erythema (n=1), haemorrhage (n=1), paraesthesia (n=1), and/or pruritus (n=2)

RESULTS (CONT)

Table 2. Safety Summary

	Obese BMI >30.0 to ≤40.0 kg/m^2 n=10	Overweight BMI >25.0 to ≤30.0 kg/m^2 n=10	Normal BMI 18.0 to ≤25.0 kg/m^2 n=10	All Ppts N=30
	Abdomen n, (%)			
Participants with ≥1 AE	2 (20)	3 (30)	0	5 (17)
Discontinuation due to AEs	1 (10)	0	0	1 (3)
AEs in ≥2 participants	0	0	0	0
	Upper Arm n, (%)			
Participants with ≥1 AE	5 (56)ª	2 (20)	5 (50)	12 (41)ᵇ
Discontinuation due to AEs	0	0	0	0
AEs in ≥2 participants				
Increased appetite	0	1 (10)	1 (10)	2 (7)
Headache	0	1 (10)	1 (10)	2 (7)
Injection site pruritus	0	0	2 (20)	2 (7)

ª n=9; ᵇ N=29.
AE, adverse event; BMI, body mass index; ppts, participants.

SUMMARY & CONCLUSIONS

- Pegbelfermin was generally well tolerated when administered SC to the abdomen or upper arm in obese, overweight, and normal BMI healthy participants
- There was a trend towards moderately increased pegbelfermin exposure and peak concentration with decreased BMI
- In obese BMI participants, pegbelfermin exposure and peak concentration were generally similar after either abdominal or upper arm administration
- In normal and overweight BMI participants, pegbelfermin exposure and peak concentration were modestly higher after upper arm administration compared with abdomen administration
- Incidence of immunogenicity was low and not correlated to any AEs
- Study limitations:
  - Small sample size; this study was not powered for comparisons as the intent was to generate representative PK data for participants with overweight and normal BMI, upper arm injection site, and use of the new device (pre-filled pegbelfermin syringe)
  - Lack of randomisation; injection site reaction data must be interpreted with caution since participants received pegbelfermin consecutively in the abdomen followed by the upper arm (vs using separate groups of participants per injection site)
- Phase 2b studies are underway to evaluate histological response to pegbelfermin in patients with NASH and advanced fibrosis

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