First-In-Human Study Results for BMF-650 a Small Molecule Oral GLP-1 Receptor Agonist

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Background and Aim

- GLP-1 receptor agonists are positively impacting the management of obesity and diabetes. Most current GLP-1 based therapy is based on the subcutaneous drug injection. [1]
- Clinical results with optimized small molecule GLP-1 receptor agonists have shown good weight loss efficacy. GI side effects are observed and principally addressed with lengthy titration schemes. [2]

- **The BMF-650 program aims to achieve better tolerability by combining consistent systemic exposure and a differentiated agonist potency profile avoiding local absorption-site over-stimulation to alleviate GI effects.**

Table 1: Key nonclinical data comparison of BMF-650 and orforglipron

Compound	GLP-1 hu EC_{50}	β-arrestin EC_{50}	%F in rat	%F in monkey
BMF-650	2.6 nM	>10 μM	33	54
orforglipron	0.1 nM	>10 μM	11	29

GLP-1RA induced cAMP release was measured by HTRF at 37 °C using human HEK293 cells overexpressing the human GLP-1 receptor. The potential for GLP-1 RAs to induce β-arrestin recruitment was measured via a NanoBiT assay using HEK293T cells. Oral bioavailability of BMF-650 and orforglipron after single oral dose of 5 mg/kg (rat, male) and 0.36 mg/kg (monkey, male) using the same set-up. Compounds were dosed as solutions. The results from IV studies using 1 mg/kg and 0.12 mg/kg in rat and monkey, respectively were used to calculate the %F.

Figure 1: Weight loss study in obese cynomolgus monkeys

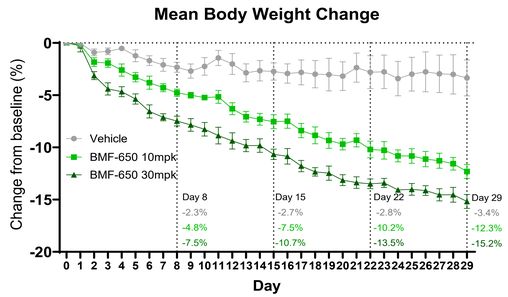
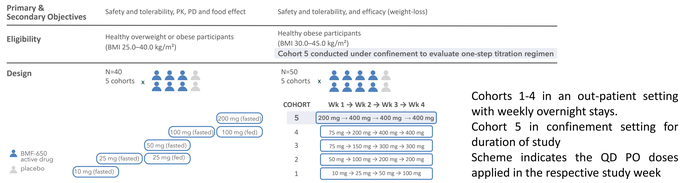


Figure 1. 15 Obese cynomolgus monkeys were distributed among 3 groups of 5. Monkeys were dosed QD with BMF-650: 10 or 30 mg/kg, or vehicle as a solution via oral gavage for 28 days. Significant and dose-dependent weight loss was observed.

Figure 2: Design, demographics, and weight Loss

A Design



Cohorts 1-4 in an out-patient setting with weekly overnight stays.
Cohort 5 in confinement setting for duration of study
Scheme indicates the QD PO doses applied in the respective study week

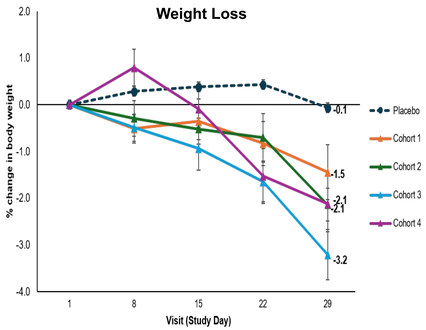
B Demographics

	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)	MAD active (N=40)	Pooled Placebo (N=10)
Sex*, female	6 (75)	6 (75)	3 (38)	4 (50)	5 (63)	24 (60)	5 (50)
Age, years	49.5	45.6	49.9	42.3	41.6	45.8	37.4
Weight, kg	97.0	109.1	96.1	97.6	102.1	100.4	107.2
BMI, kg/m2	34.8	36.2	31.9	34.4	34.0	34.3	35.3

*Reported as number of participants (%); Age, weight, and BMI as mean

C Weight loss versus baseline (Cohorts 1-4)

	Mean percentage change in BW from base line at Day 29
Pooled Placebo (n=8) Cohort 1-4 only	-0.1%
Cohort 1 (n=8) 10/25/50/100 mg QD	-1.5%
Cohort 2 (n=8) 50/100/200/200 mg QD	-2.1%
Cohort 3 (n=8) 75/150/300/300 mg QD	**-3.2%**
Cohort 4 (n=8) 75/200/400/400 mg QD	-2.1%



- **PK analysis suggested less than full dosing compliance; a 5th fully confined cohort was added.**
- **Cohort 5 was added with 1 step titration, full dosing compliance, and daily PI oversight for adverse event monitoring. Daily food presentation of ~ 2200 kcal as three meals and one evening snack.**
- **For the confined cohort 5, a mean weight loss of 6.1% (6.2 kg) on day 29 versus baseline was recorded. Due to extensive food avoidance from the 2 placebo participants no meaningful difference between BMF-650 and placebo dosed participants was observed.**

Table 2: Total and key GI related treatment emergent adverse events (TEAE)

	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)	Cohort 4 (N=8)	Cohort 5 (N=8)	MAD active (N=40)	Pooled Placebo (N=10)
Any TEAE Grade 1 Grade 2	6 (75) 3 (37.5) 3 (37.5)	4 (50) 3 (37.5) 1 (12.5)	5 (62.5) 4 (50) 1 (12.5)	6 (75) 5 (62.5) 1 (12.5)	7 (87.5) 5 (62.5) 2 (25)	28 (70) 20 (50) 8 (20)	4 (40) 4 (40) 0
Nausea	0	3	1	2	1	7	0
Constipation	0	1	1	0	2	4	1
Vomiting	1	0	1	0	1	3*	0
Diarrhea	0	1	1	0	0	2	1

Reported as number of participants (%)

* 3 participants for a total of 4 emesis events.

- **All treatment emergent adverse events were mild to moderate. No severe adverse events.**
- **No treatment emergent adverse events leading to study discontinuation.**
- **No treatment emergent adverse events leading to dose / dosing schedule modifications.**
- **No dose dependency among the mild GI adverse events.**

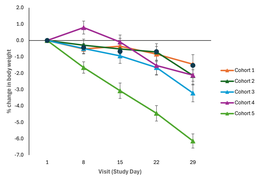
Table 3: BMF-650 exposure analysis

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
C_{max} [ng/mL]	1370 (17%)	2440 (22%)	3670 (28%)	4460 (30%)	4400 (26%)
AUC_{0-24} [h*ng/mL]	19600 (26%)	36700 (32%)	55900 (26%)	76500 (27%)	79000 (32%)

Table 3: Preliminary PK analysis derived from the 24 hours post day 28 dose. Format: value (CV%)

- **Dose dependent exposure increases over the dosing range.**
- **Exposures in cohort 2 and cohort 4 / 5 align with the exposures seen in the low and high dose groups in the monkey study.**
- **Low interindividual exposure variability.**

Conclusions



Weight loss (%) vs baseline of BMF-650 dosed participants, active only. No placebo included.

- BMF-650 in an outpatient setting shows up to 3.2% weight loss vs baseline at the 300 mg QD target dose (PBO -0.1%)
- BMF-650 in a confinement setting shows 6.1% weight loss vs baseline at the 400 mg QD target dose, with similar weight loss for placebo
- Single titration step to 400 mg QD target dose successfully achieved in cohort 5
- The GI tolerability profile for BMF-650 shows very low incident rate and severity grade with potential to be class leading

References

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