Preclinical Efficacy of BMF-650, an Oral Small-Molecule GLP-1 Receptor Agonist

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Background

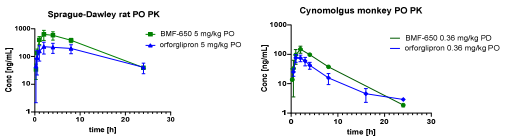
- GLP-1 receptor agonists (GLP-1 RA) positively impact the management of obesity and diabetes[1]
- Most current GLP-1 RA-based therapies rely on subcutaneous drug injection and feature compounds with long half-lives [2]
- Recently, small-molecule, orally available receptor agonists have been discovered. For these, key primate-specific interactions with the GLP-1 receptor have been identified[3]
- Clinical results with optimized candidates have shown good weight loss efficacy; however, GI side effects are still observed. Improved PK and a differentiated potency profile could help alleviate these[4]

Table 1: Activity of BMF-650 and Comparison with orforglipron

Compound	GLP-1 hu EC_{50}		β-arrestin1 EC_{50}	β-arrestin2 EC_{50}
	25 °C	37 °C		
BMF-650	8.6 nM	2.6 nM	>10 µM	>10 µM
orforglipron	2.6 nM	0.1 nM	>10 µM	>10 µM

Table 1: GLP-1RA induced cAMP release was measured by HTRF at 25 °C and 37 °C using human HEK293 cells overexpressing the human GLP-1 receptor. The potential for GLP-1RAs to induce b-arrestin recruitment was measured via a NanoBiT assay using HEK293T cells overexpressing human GLP-1receptor and either b-arrestin 1 or b-arrestin 2 fused to separate subunits for the NanoLuc luciferase protein.

Figure 1: Preclinical PK of BMF-650 and Comparison with orforglipron



Compound	%F	
	Rat	Monkey
BMF-650	33	54
orforglipron	11	29

Figure 1. PK comparison of BMF-650 and orforglipron after single oral dose in males using the same formulation and set-up. Compounds were dosed as solutions. The results from IV studies using 1 mg/kg and 0.12 mg/kg in rats and cynomolgus monkeys, respectively were used to calculate the %F shown in the table.

Figure 2: IVGTT Results in Male Cynomolgus Monkeys

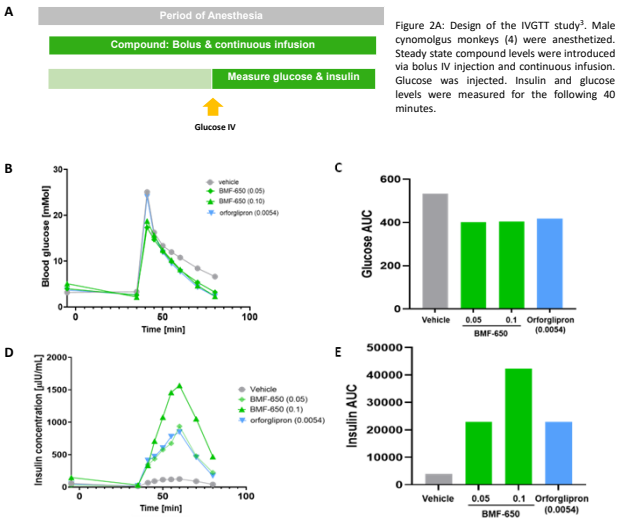


Figure 2A: Design of the IVGTT study[3]. Male cynomolgus monkeys (4) were anesthetized. Steady state compound levels were introduced via bolus IV injection and continuous infusion. Glucose was injected. Insulin and glucose levels were measured for the following 40 minutes.

Parameter	Vehicle	BMF-650 0.05 mg/kg	BMF-650 0.1 mg/kg	orforglipron 0.0054 mg/kg
Glucose AUC*	533	401	404	418
Glucose lowering	Baseline	-25%	-24%	-22%
Insulin AUC*	3871	24544	42207	28920
Insulin increase	Baseline	634%	1090%	747%

* Glucose AUC: min*mmol/L Insulin AUC: min*mIU/mL

Figure 2B-E. Results from a cross-over IVGTT study in male cynomolgus monkeys (n = 4). Panel B and C show the glucose time vs concentration profile (B) and the calculated area under the concentration curve value (C). Panel D and E show the insulin time vs concentration profile (D) and the calculated area under the concentration curve (E). The table summarizes AUC and drug induced differential.

Design of the 28 Days Weight Loss Study in Obese Cynomolgus Monkeys and Baseline Measures

Pre-study 14 days	28 days of once-daily PO dosing

	Group 1	Group 2	Group 3
Weight average [kg]	12.0	12.2	12.0
Daily food intake [g]	154	156	147

- 15 obese cynomolgus monkeys were placed into the study and evaluated for 14 days prior to dosing start to create balanced groups
- Monkeys were distributed among 3 groups of 5 individuals at day -2
- Monkeys were dosed QD with BMF-650 (10 or 30 mg/kg), or vehicle, administered as a solution via oral gavage for 28 days
- No dose titration was performed at any point
- Food rations were presented as breakfast, fruit snack, and dinner
- Body weight and food consumption was recorded daily
- Clinical observations were recorded daily
- Clinical chemistry was measured on days -5, 13, 20, and 29 per protocol

Figure 3: Results of the 4 Weeks Weight Loss Study in Obese Cynomolgus Monkeys

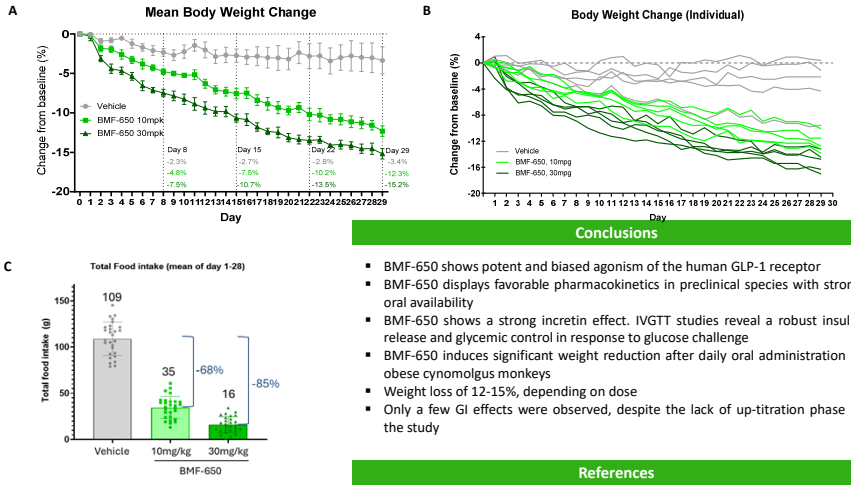


Figure 3. (A) Results of the weight loss study by dosing group as the average of 5 monkeys tracked daily and annotated weekly vs baseline. (B) Results for the individual monkeys. (C) Mean food consumption by dosing group; individual daily averages as single data points within the respective bar.

Conclusions

- BMF-650 shows potent and biased agonism of the human GLP-1 receptor
- BMF-650 displays favorable pharmacokinetics in preclinical species with strong oral availability
- BMF-650 shows a strong incretin effect. IVGTT studies reveal a robust insulin release and glycemic control in response to glucose challenge
- BMF-650 induces significant weight reduction after daily oral administration in obese cynomolgus monkeys
- Weight loss of 12-15%, depending on dose
- Only a few GI effects were observed, despite the lack of up-titration phase in the study

References

1. Mueller, T. D., et al. Glucagon-like peptide 1 (GLP-1). Molecular Metabolism 2019; 30, 72-130.
2. Wilding, J. P. H., et al. Once Weekly Semaglutide in Adults with Overweight or Obesity. New Engl. J. Med., 2021; 384, 989–1002.
3. Kawai, T., et al. Structural basis for GLP-1 receptor activity by LY3502970, an orally active nonpeptide agonist. Proc Nat Aca Science 2020, 117, 29959-29967.
4. Wharton, S., et al. Daily oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. New Engl. J. Med., 2023, 389, 877-888.