Phase 1, Randomized, Controlled Trial of GFB-024, a Once-Monthly CB1 Inverse Agonist, in Healthy Overweight and Obese Participants and in Participants with Type 2 Diabetes Mellitus

Edwin Tucker[1], Gregory Gaich[1], Sanela Bilic[2], John Lawler[1], Yossi Dagon[1], Thomas A. Gustafson[1], Leslie Johnson[1], Lori Rudolph-Owen[1]
[1]Goldfinch Bio Inc, Cambridge, MA, United States; [2]Vanadro, West Des Moines, IA, United States

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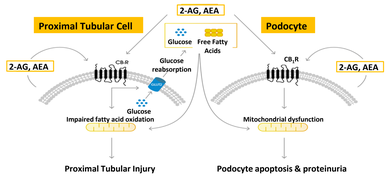
BACKGROUND

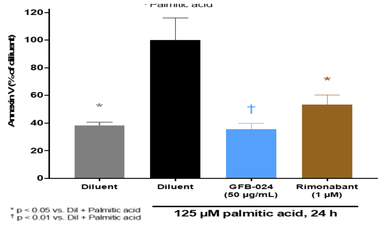
Elevated circulating endocannabinoids and autocrine CB1 activation results in podocyte and tubular cellular injury. Evidence from nonclinical studies suggests a role of cannabinoid-1 receptor (CB1) in the development of diabetic nephropathy (DN). Kidney CB1 expression is upregulated in podocytes and tubular cells in murine models of obesity and diabetes mellitus (DM).



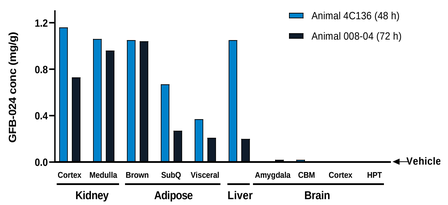
Inhibition by CB1 inverse agonists has been shown to ameliorate diabetes-induced albuminuria, inhibit kidney fibrosis and inflammation, and prevent podocyte dysfunction. Murine models of DM have shown that genetic deletion of CB1 in podocytes or proximal tubular cells protects against glomerular and tubular dysfunction.

GFB-024 is a recombinant humanized monoclonal antibody functioning as a CB1-specific inverse agonist. It is peripherally-restricted, a feature expected to reduce the risk for CNS-associated side effects observed with centrally-active CB1 antagonists. Targeting the CB1 pathway with GFB-024 is a potentially novel approach to protecting podocytes from injury in patients with CB1-associated DN.

GFB-024 attenuates podocyte cell death induced by palmitic acid, a mediator of diabetic lipotoxicity



GFB-024 is found in peripheral tissues with minimal brain exposure



SubQ = subcutaneous
CBM = cerebellum
HPT = hypothalamus

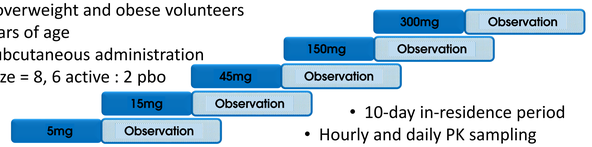
GFB-024 CLINICAL STUDY SYNOPSIS

The safety, tolerability, and pharmacokinetic profile of GFB-024 was evaluated in a Phase 1 study. GFB-024-102 is a randomized, double-blind, placebo-controlled trial with a single ascending dose (SAD) component to evaluate the safety, tolerability, pharmacokinetics (PK), and immunogenicity of GFB-024 in healthy overweight and obese (BMI 25 – 40 kg/m^2) participants.

Objectives	Endpoints
Primary	
To assess the safety and tolerability after 4 weeks of exposure following single ascending doses of GFB-024	Number of participants with serious and other nonserious AEs
Secondary	
To characterize PK of GFB-024 following single ascending doses	C_{max} and AUC_{last}
To characterize the incidence and persistence of immunogenicity of GFB-024 following single ascending doses	Number of participants with confirmed ADA
Exploratory	
To explore additional PK characteristics of GFB-024 following single ascending doses	T_{max}, C_{last}, Tlast, AUC_{inf}, CL, V, and $t_{1/2}$
To explore effects of GFB-024 on clinical laboratory assessments, 12-lead ECG, and vital signs following single ascending doses	Incidence of clinically significant changes in laboratory parameters, 12-lead ECG parameters, and vital signs measurements
To explore the impact of ADA on the PK profile of GFB-024 following single ascending doses	Impact of ADA on AUC or impact on overall exposure of GFB-024

GFB-024 CLINICAL STUDY DESIGN

- Healthy overweight and obese volunteers
- 18-75 years of age
- Single, subcutaneous administration
- Cohort size = 8, 6 active : 2 pbo



- 10-day in-residence period
- Hourly and daily PK sampling
- Hourly and daily safety and tolerability assessments
- Non-residence follow up though study week 10 post-dose

GFB-024 was safe and well-tolerated in the Phase 1 study

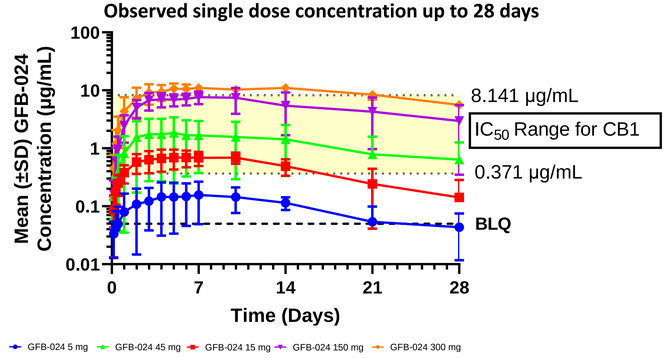
Adverse Event Summary: Category, n	Placebo (n=10)	GFB-024 5 mg (n=6)	GFB-024 15 mg (n=6)	GFB-024 45 mg (n=4)	GFB-024 150 mg (n=6)	GFB-024 300 mg (n=6)	Overall (n=38)
Any AEs	5	2	3	2	3	1	16
SAEs	0	0	0	0	0	0	0
Non-Serious AEs	5	2	3	2	3	1	16
TEAEs	4	2	3	2	3	1	15

Adverse Events ≥10%: Preferred Term, n (%)	Placebo (n=10)	GFB-024 Pooled Doses (n=28)
Incision Site Pain	1 (10%)	1 (3.6%)
Skin Laceration	1 (10%)	1 (3.6%)
Injection Site Pain	1 (10%)	1 (3.6%)
Vessel Puncture Site	1 (10%)	0
Ecchymosis	1 (10%)	2 (7.1%)
Back Pain	1 (10%)	0
Haematuria	1 (10%)	0

GFB-024 CLINICAL STUDY PHARMACOKINETICS

Increasing concentrations of GFB-024 were observed with at increasing single dose levels. Doses of ≥ 45 mg resulted in concentrations in the target range for CB1 inhibition based on preclinical models that were sustained for 28 days.

Observed single dose concentration up to 28 days

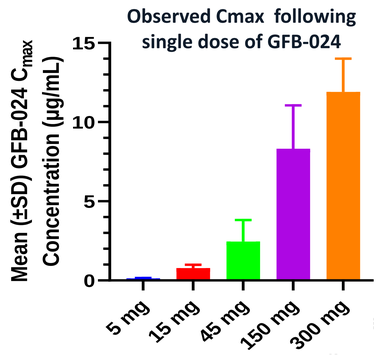


GFB-024 CLINICAL STUDY PHARMACOKINETICS

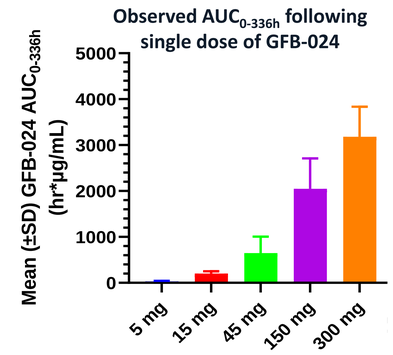
Tmax was reached between 10-21 days following 5 mg dose, 3-14 days following 15 and 45 mg, and between 6-14 days following doses of 150 and 300 mg. The half-life ranged between 14.8 – 31.3 days at 5 mg dose and 11.3 – 18.2 days for 300 mg dose. Single doses of GFB-024 resulted in dose-dependent increases in C_{max} and AUC_{0-336}, though less than dose proportional increases were observed between 150 and 300 mg.

All participants evaluated were ADA positive, although ADA does not appear to impact the PK profile except at lower doses.

Observed Cmax following single dose of GFB-024



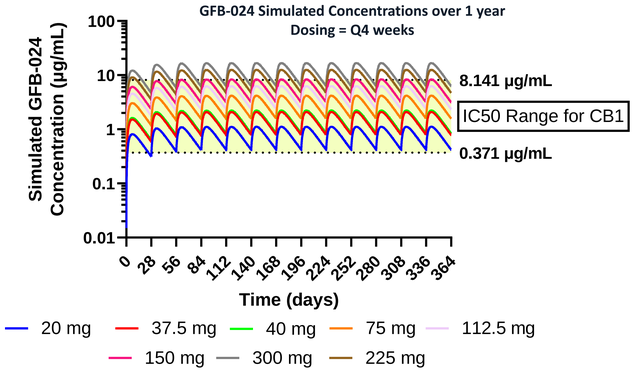
Observed AUC_{0-336h} following single dose of GFB-024



PREDICTED GFB-024 CONCENTRATIONS

GFB-024 concentrations were simulated following dosing every 1, 2, 4, 6, and 8 weeks for several doses. Results suggested that all doses tested would achieve concentrations in the target range with at least monthly (below). Doses of at least 37.5 mg and 75 mg are expected to achieve target GFB-024 concentrations when dosed every 6 or 8 weeks, respectively.

GFB-024 Simulated Concentrations over 1 year
Dosing = Q4 weeks



GFB-024 CLINICAL STUDY CONCLUSIONS

- PK and safety profile support continued clinical development
- Exposures exceeding the predicted efficacious dose range will allow for dose flexibility for efficacy study designs
- GFB-024, a CB1 inverse agonist, should continue to be evaluated as a novel therapy for diabetic nephropathy and other CB1-mediated diseases

Contact: ggaich@goldfinchbio.com