MONDAY-524

A Single-Centre, Double-Blind, Placebo-Controlled Study in Healthy Men to Assess the Safety and Tolerability of Single and Repeated Ascending Doses of MGB-BP-3, a New Class of Antibacterial Agent

M. Ravic[1], D. Firmin[1] O. Sahgal[2], F. van den Berg[2], C. Suckling[3], I.S. Hunter[3]

[1]MGB Biopharma, Glasgow, UK, [2]Hammersmith Medicines Research, London, UK. [3]University of Strathclyde, Glasgow, UK.

mravic@mgb-biopharma.com

ABSTRACT

Background: MGB-BP-3 (MGB) binds selectively to the bacterial DNA minor groove and has strong bactericidal *in vitro* and *in vivo* activity against *Clostridium difficile*. Completion of a full non-clinical package, including formal GLP toxicology and safety pharmacology, allowed progression to a Phase I human study, to assess the safety, tolerability and PK profile of single (Part A) and multiple (Part B) ascending oral doses of MGB.

Methods: Part A was a randomised, double-blind, placebo-controlled, cross-over, single ascending-dose trial in 16 healthy men. Subjects were enrolled in 2 groups of 8 (Groups 1-2). Each subject received a single oral dose of MGB in each of 3 study sessions; Group 1 – 250mg, 500mg, 750mg; Group 2 – 1000mg, 1500mg, 2000mg; 6 volunteers received matching placebo in 1 study session. Part B was a randomised, double-blind, placebo-controlled, sequential-group, repeated ascending-dose trial in 24 healthy men. Subjects were enrolled in 3 groups of 8 (Groups 3–5). Each subject had 1 study session, receiving twice-daily oral doses of MGB, or matching placebo, for 9 days (Days 1–9) and a single dose on the morning of Day 10. Doses were 2X250mg, 2X500mg and 2X1000mg. Primary safety and tolerability variables, and secondary variables were assessed throughout.

Results: No serious adverse events were reported during Parts A or B at any dose level tested. Adverse events were mild to moderate and primary safety variables (including vital signs, cardiac monitoring, lab safety tests, medical examinations and FOB) were all within acceptable limits. Plasma PK assessment showed no absorption after oral administration. Details of intestinal permeability, urine and faecal PK and faecal flora analysis will be presented.

Conclusion: Orally-administered MGB was tolerated well in healthy volunteers at all dose levels tested in Phase I clinical trial, with no dose limiting toxicity or serious adverse events. The safe dose was 2000mg MGB, administered orally at 1000mg twice a day over 10 days. MGB is suitable for progression into Phase II clinical trials to assess efficacy in patients with *C. difficile* infection.

INTRODUCTION

MGB is a new class of antibiotic, belonging to the DNA Minor Groove Binder group, that has very strong antibacterial activity against all susceptible and multi-resistant Gram-positive pathogens tested, including methicillin-resistant and susceptible *Staphylococcus* species, pathogenic *Streptococcus* species, Vancomycin-Resistant and susceptible *Enterococcus* and *Clostridium difficile.*

MGB was originally developed by scientists at the University of Strathclyde [1]. It has the architecture of a typical minor groove binder and is based upon the structure of naturally occurring product, Distamycin (Figure 1).

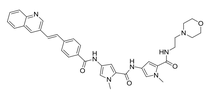


Figure 1. Molecular structure of MGB-BP-3

MGB binds selectively to the bacterial DNA minor groove and has strong bactericidal *in vitro* and *in vivo* activity against *Clostridium difficile*. Time to kill experiments, and assessment of efficacy in a CDAD hamster model, showed very strong bactericidal activity, superior to vancomycin. Completion of a full non-clinical package, allowed progression to a Phase I human study where the safety, tolerability and PK profile of single (Part A) and multiple (Part B) ascending oral doses of MGB were assessed.

METHODS

This was a two-part, randomized, double-blind, placebo-controlled trial to assess the safety, tolerability and pharmacokinetics of MGB. Part A was a single ascending-dose, crossover study in 18 healthy men. Part B was a repeated ascending-dose, sequential group study in 24 healthy men.

MGB was formulated as liquid filled, enterically coated capsules.

Part A (Single Dose Escalation)

Subjects were enrolled in 2 groups of 8 (Groups 1 and 2). Each subject received a single dose of MGB in up to 3 study sessions. 6 subjects per group received placebo in 1 of their study sessions. At each dose level, 6 subjects were randomized to receive MGB and 2 subjects received placebo. The treatment sequence and dose levels for Part A are shown in Table 1 and Table 2, respectively.

There was a washout period of at least 4 days between doses for each subject, and an interval of at least 6 days between the last dose in Group 1 and the first dose in Group 2.

The first dose level was staggered: 2 leading subjects were dosed no later than the day before the remaining subjects in the group were dosed. The leading subjects were dosed at intervals of at least 10 min, as were the remaining subjects. MGB was given under fasting conditions.

METHODS

Table 1: Treatment sequence in Part A

Group	Study session	n=2	n=2	n=2	n=2
1	1	DL 1	DL 1	DL 1	Placebo
	2	DL 2	DL 2	Placebo	DL 2
	3	DL 3	Placebo	DL 3	DL 3
2	1	DL 4	DL 4	DL 4	Placebo
	2	DL 5	DL 5	Placebo	DL 5
	3	DL 6	Placebo	DL 6	DL 6

Table 2: Dose levels in Part A

Group	Dose level	Dose (mg)
1	1	250
	2	500
	3	750
2	4	1000
	5	1500
	6	2000

Part B (Multiple Dose Escalation)

Subjects were enrolled in 3 groups of 8 (Groups 3–5). Each subject underwent 1 study session in which they received twice-daily oral doses of MGB or placebo for 9 days (Days 1–9), and a single dose on the morning of Day 10. The doses for each group are shown in Table 3.

The highest total daily dose tested in Part B was 2000 mg MGB, the highest dose in Part A that was acceptably tolerated and for which there were no safety concerns.

Table 3: Dose levels in Part B

Group	Total daily dose (mg)	Number of 250 mg capsules
3	500	2
4	1000	4
5	2000	8

In each group, 6 subjects were randomized to receive MGB and 2 subjects were randomized to receive placebo. The dose was escalated as the safety and tolerability of the previous dose level was acceptable.

Study assessments in Part A and B

Safety: Laboratory assessments (routine hematology, biochemistry and urinalysis), physical examination, 12-lead electrocardiogram (ECG), telemetry (Part A only), fecal occult blood, intestinal permeability (the ratio of lactulose to rhamnose excreted in urine, Part B only), fecal flora (Part B only), vital signs and adverse events (AEs).

Tolerability: AEs.

Pharmacokinetic: Blood samples for assay of MGB, and possible metabolites, were taken before, and frequently up to 48 h after dosing in Part A, and up to 12 h after the subjects' morning dose on Day 1, and up to 48 h after dosing on Day 10 in Part B. In addition, in Part B, a blood sample was taken before the morning dose on each of Days 2 to 9. Urine was collected for 24 h after each dose for assay of MGB in Part A, and for 12 h after the morning dose on Day 1 and 10 (Part B only). Fecal samples were collected daily until 72 h after the subjects' (final) dose for assay of MGB BP 3 in each session, and in Part B for 24 h after dosing on Days 1 and 5.

RESULTS

Part A (Single Dose Escalation)

18 men entered Part A of the trial and 16 completed it. There were 2 subject withdrawals; both subjects were replaced. One subject withdrew consent after 7 days after receiving a single dose of 250mg. The other subject was withdrawn 4 days after receiving a single dose of 1500 mg MGB due to an increase in AST and ALT. This subject had abnormal LFT at screening and after placebo in the first study section.

Safety and tolerability: There were no SAEs. No TEAEs were reported by subjects who received the highest dose of MGB (2000 mg). TEAEs were reported by 16.7 %–33.3% of subjects at all other dose levels of MGB (1–2 subjects per dose level) and 33.3% of subjects who received placebo (4 subjects) (Table 4). All TEAEs were mild or moderate in severity. TEAEs that were considered by the investigator to be drug related were reported by 16.7% of subjects who received placebo (2 subjects). No subjects reported drug-related TEAEs following doses of 250 or 2000 mg MGB.

Table 4: Treatment emergent adverse events

System Organ Class	Preferred Term	Placebo (N=12) n (%)	MGB-BP-3 250 mg (N=6) n (%)	500 mg (N=6) n (%)	750 mg (N=6) n (%)	1000 mg (N=6) n (%)	1500 mg (N=6) n (%)	2000 mg (N=6) n (%)
Any AE		4 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	0
Nervous system disorders	Total	1 (8.3)	1 (16.7)	1 (16.7)	0	1 (16.7)	0	0
	Headache	1 (8.3)	1 (16.7)	1 (16.7)	0	1 (16.7)	0	0
	Dizziness	0	1 (16.7)	0	0	0	0	0
General disorders and administration site conditions	Total	1 (8.3)	2 (33.3)	0	0	0	0	0
	Catheter site related reaction	1 (8.3)	1 (16.7)	0	0	0	0	0
	Chest discomfort	0	1 (16.7)	0	0	0	0	0
Gastrointestinal disorders	Total	1 (8.3)	1 (16.7)	0	0	0	0	0
	Nausea	1 (8.3)	1 (16.7)	0	0	0	0	0
	Abdominal discomfort	0	1 (16.7)	0	0	0	0	0
Investigations	Total	0	0	0	1 (16.7)	0	1 (16.7)	0
	LFT abnormal	0	0	0	0	0	1 (16.7)	0
	Occult blood positive	0	0	0	1 (16.7)	0	0	0
Eye disorders	Total	0	0	0	0	0	1 (16.7)	0
	Ocular discomfort	0	0	0	0	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders	Total	1 (8.3)	0	0	0	0	0	0
	Musculoskeletal pain	1 (8.3)	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	Total	0	1 (16.7)	0	0	0	0	0
	Hyperhidrosis	0	1 (16.7)	0	0	0	0	0

There were no changes in mean laboratory variables that could be attributed to the trial medication.

Fecal occult blood tests in Part A were negative in all except one subject. This subject had positive tests on Day 1 and Day 3, but negative on Days 2 and 8.

RESULTS

Pharmacokinetic: MGB was not detected in any plasma or urine PK samples at all doses tested in Part A. However, MGB was detected in all fecal samples collected at 48–72 h after doses of 1000, 1500 and 2000 mg; and in 33 %, 40% and 67 % of all 48–72 h samples after doses of 250, 500 and 750 mg, respectively.

Part B (Multiple Dose Escalation)

Safety and tolerability: There were no SAEs. The number of subjects who reported TEAEs was highest in the 1000 mg MGB bid dose group, followed by the placebo group. TEAEs were reported by 16.7% of subjects (1 subject) who received 250 mg MGB bid; 33% of subjects (2 subjects) who received 500 mg MGB bid; 66.7% of subjects (4 subjects) who received 1000 mg MGB bid; and 50.0% of subjects (3 subjects) who received placebo (Table 5). All TEAEs were mild or moderate in severity. There were no changes in mean laboratory variables that could be attributed to the trial medication, with the exception of two subjects. One subject had an isolated increased AST on Day 11, and the other subject had an increase in AST and ALT levels at follow-up assessments. The results of all physical examinations and ECG's were of no clinical significance.

There were no clinically significant fecal occult blood test results in Part B.

There were no changes in intestinal permeability attributed to MGB.

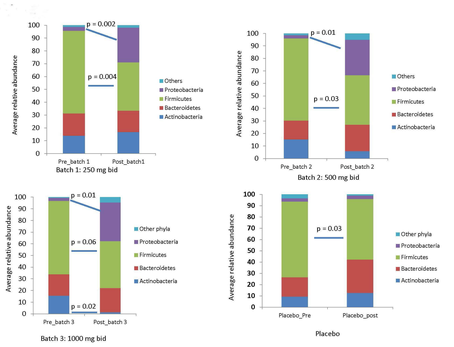
Table 5: Treatment emergent adverse events

System Organ Class	Preferred Term	Placebo (N=6) n (%)	MGB-BP-3 250 mg bid (N=6) n (%)	500 mg bid (N=6) n (%)	1000 mg bid (N=6) n (%)
Any AE		3 (50.0)	1 (16.7)	2 (33.3)	4 (66.7)
Gastrointestinal disorders	Total number of subjects	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)
	Flatulence	2 (33.3)	0	0	0
	Nausea	0	0	0	2 (33.3)
	Abdominal distension	0	0	0	1 (16.7)
	Abdominal pain lower	0	0	0	1 (16.7)
	Diarrhoea	1 (16.7)	0	0	0
	Faeces soft	0	1 (16.7)	0	0
	Frequent bowel movements	0	0	1 (16.7)	0
Nervous system disorders	Total number of subjects	2 (33.3)	0	0	2 (33.3)
	Headache	2 (33.3)	0	0	2 (33.3)
Skin and subcutaneous tissue disorders	Total number of subjects	1 (16.7)	0	0	1 (16.7)
	Dermatitis contact	0	0	0	1 (16.7)
	Rash erythematous	1 (16.7)	0	0	0
Infections and infestations	Total number of subjects	0	0	1 (16.7)	0
	Oral herpes	0	0	1 (16.7)	0

Pharmacokinetic: MGB was not detected in any plasma and urine PK samples at all doses tested in Part B. However, MGB was detected in all samples collected at 24–48 h after the last dose and in 59 % of samples collected at 48–72 h after the last dose.

Fecal flora: Overall, a relative decrease of bacteria belonging to the Gram-positive bacterial phylum Firmicutes, and relative increase in Gram-negative bacterial phyla Proteobacteria in post treated samples, was observed (Figure 2). All *Clostridium* categories, Eubacteria and *Faecalibacterium prausnitzii* were absent from subjects after 10 days on active treatment. No significant differences with regard to dosing were observed. All samples were described as healthy gut flora.

Figure 2. Effect of MGB on fecal flora



CONCLUSION

- Single and repeated daily doses of up to 2000 mg MGB were well tolerated and had a good safety profile.
- MGB remained in the gastrointestinal system with no systemic absorption.
- MGB was excreted in feces and was present in samples collected up to 72 h post-dose.
- The data from this Phase I study warrants further clinical development of MGB.

REFERENCES

1. Antimicrobial lexitropsins containing amide, amidine, and alkene linking groups. C.J. Suckling, D. Breen, A.I. Khalaf, E. Ellis, I.S. Hunter, G. Ford, C.G. Gemmell, N. Anthony, J.-J. Helsebeux, S.P. Mackay, and R.D. Waigh. J. Med. Chem. 2007, 50, 6116-6125