RANDOMIZED, OPEN-LABEL, PHASE 2A COMPARATOR STUDY TO ASSESS THE PHARMACODYNAMICS, SAFETY AND PHARMACOKINETICS OF ORAL ADMINISTRATION OF MNK6106 (L-ORNITHINE PHENYLACETATE) VS. RIFAXIMIN IN SUBJECTS WITH HEPATIC CIRRHOSIS AND A PREVIOUS HISTORY OF HEPATIC ENCEPHALOPATHY

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Introduction

Ammonia plays a central role in the pathogenesis of hepatic encephalopathy (HE). There are no approved treatments targeting ammonia. L-Ornithine Phenylacetate (L-OPA) has a unique mechanism of action involving its permanent excretion as phenylacetylglutamine (PAGN). It lowers ammonia rapidly when administered by iv.

Aim

The aims of this dose response study were to evaluate the efficacy of oral L-OPA on reducing plasma ammonia (AMM). Safety, tolerability, pharmacokinetics and exposure response relationships were also evaluated.

Method

48-decompensated cirrhosis patients with previous history of overt HE (28 male, mean 57.2 years; mean MELD (range): 8.8-12.1; Pugh (range): 7-8) were randomized 1:1:1:1 to receive 1 of the 3 dosing regimens of L-OPA [Group A, 2g TID; Group B, 4g BID, Group C, 4g TID], or rifaximin (Group D, 550 mg bd), for 5-days. Subjects were assessed for clinical functional scoring and liver scores. All biochemical variables were measured in a central laboratory. Adverse events (AEs) were recorded.

Results

AMM levels decreased significantly more in Groups B and C compared with the rifaximin, Group D. The levels between baseline and Day 5 [umol/L; mean (SD)] were; Group A: 68.1 (26.8) to 75.2 (27.3); Group B: 88.9 (34.4) to 59.3 (13.6); Group C: 87.5 (33.8) to 74.1 (11.6); Group D: 81.5 (23.8) to 75.4 (29.7). Percentage change from baseline to Day 5 were +2.04 (35.6); -26.3 (27.0); -11.9 (30.6); and -4.20 (26.8) in Groups A, B, C and D respectively.

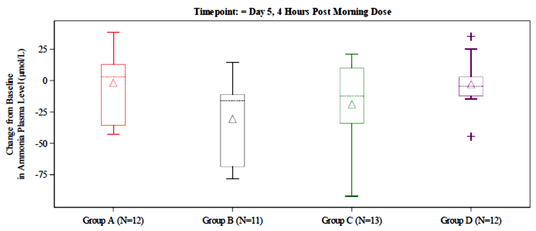

Figure 1. Box Plot for Change from Baseline in Ammonia Plasma Level on Day 5, 4 Hours Post Morning Dose Based on Central and Local Laboratory Results – mITT Population

Change from Baseline in Ammonia Plasma Level (µmol/L) along the y-axis, and treatment groups along the x-axis including: Group A (N=12), Group B (N=11), Group C (N=13), Group D (N=12).
Group A: MNK6106 2 g (2 tablets), TID for 5 days.
Group B: MNK6106 4 g (4 tablets), BID for 5 days.
Group C: MNK6106 4 g (4 tablets), TID for 5 days.
Group D: Rifaximin 550 mg tablet (1 tablet), BID for 5 days.

In general, in the L-OPA groups, mean increases in plasma L-ornithine, phenylacetate and PAGN concentrations were observed with increase in dose and dosing regimen. Cumulative amount of urinary excretion of PAGN in general was similar on all days for each group. Overall, 20 (55.6%) patients who received L-OPA and 5 (41.7%) subjects who received rifaximin had at least 1 treatment-emergent adverse event. No significant differences in adverse events (AEs) were observed between groups. No significant trends were seen in laboratory results, neuropsychiatric tests, vital signs or ECGs (no subject had a QT or QTcF interval > 500 ms or increased by > 60 ms) between groups. Overall, the subjects reported improvement in clinical function during treatments.

Table 1. Potentially CNS-related Adverse Events of Special Interest by System Organ Class, Preferred Term, and Treatment Group – Safety Population

	Treatment				
System Organ Class Preferred Term	Group A (N=12) n (%)	Group B (N=11) n (%)	Group C (N=13) n (%)	Group D (N=12) n (%)	Pooled MNK6106 (N=36) n (%)
Subjects with at least 1 AESI	1 (8.3)	1 (9.1)	4 (30.8)	2 (16.7)	6 (16.7)
Nervous system disorders	1 (8.3)	0	3 (23.1)	2 (16.7)	4 (11.1)
Dizziness	0	0	2 (15.4)	1 (8.3)	2 (5.6)
Headache	1 (8.3)	0	1 (7.7)	1 (8.3)	2 (5.6)
Hepatic encephalopathy	0	0	1 (7.7)	0	1 (2.8)
Tremor	0	0	1 (7.7)	0	1 (2.8)
Tension headache	0	0	0	1 (8.3)	0
General disorders and administration site conditions	0	1 (9.1)	1 (7.7)	0	2 (5.6)
Fatigue	0	1 (9.1)	1 (7.7)	0	2 (5.6)
Eye disorders	1 (8.3)	0	0	0	1 (2.8)
Vision blurred	1 (8.3)	0	0	0	1 (2.8)
Psychiatric disorders	0	0	1 (7.7)	0	1 (2.8)
Confusional state	0	0	1 (7.7)	0	1 (2.8)

Treatment:
Group A: MNK6106 2 g (2 tablets), TID for 5 days.
Group B: MNK6106 4 g (4 tablets), BID for 5 days.
Group C: MNK6106 4 g (4 tablets), TID for 5 days.
Group D: Rifaximin 550 mg tablet (1 tablet), BID for 5 days.
Pooled MNK6106: combined Groups A, B, and C.
Percentages were based on N.

Conclusions

Group B (L-OPA 4 g BID) showed the highest decrease in plasma AMM concentrations which was about 6 times greater than Rifaximin and this dose may be selected for future trials. All doses of L-OPA were safe and well tolerated.

References

1. MNK61062107: A RANDOMIZED, OPEN-LABEL, PHASE 2A COMPARATOR STUDY TO ASSESS THE PHARMACODYNAMICS, SAFETY AND PHARMACOKINETICS OF ORAL ADMINISTRATION OF MNK6106 (L-ORNITHINE PHENYLACETATE) VERSUS RIFAXIMIN IN SUBJECTS WITH HEPATIC CIRRHOSIS AND A HISTORY OF PRIOR EPISODES OF HEPATIC ENCEPHALOPATHY

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