Increased Exposure of Aramchol by Using a Split Dose – Potential For Greater Efficacy in NASH

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INTRODUCTION

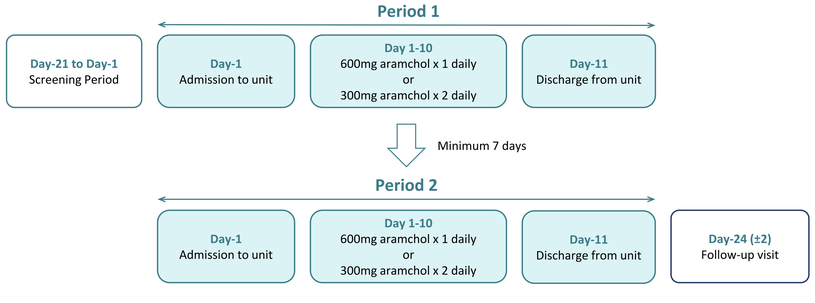
Nonalcoholic steatohepatitis (NASH) is the advanced form of nonalcoholic fatty liver disease (NAFLD) that sets the stage for further liver damage. The mechanism for the progression of NASH involves oxidative stress, mitochondrial dysfunction and inflammation. Aramchol is a novel, fatty acid bile acid conjugate of MW 702 g/mol that reduces hepatic triglyceride and fibrosis by down-regulation of steroyl-CoA desaturase-1 (SCD-1).

In a Phase 2 study in patients with NASH treated for 52 weeks with Aramchol 600 mg/day, 400mg/day or placebo, efficacy with the 600mg dose was superior to that of 400mg in all key end points including NASH resolution without worsening of fibrosis with response rates of 16.7% (n=78), 7.5% (n=80) and 5.0% (n=40) respectively. The data suggest that exposure greater than that achievable with a dose higher than 600mg might further increase efficacy but Aramchol is a BCS class IV agent with exposure sub-proportional to dose. Absorption is slow with median t_{max} of 12h. Its effective $t_{1/2}$ is *ca.*30h with steady state reached within 7 days.

To overcome this class IV common problem and be able to increase exposure and potentially efficacy, PK data from phase 1 and 2 studies were modelled and a simulation performed. A 300mg dose of Aramchol administered 12 hourly was predicted to produce a C_{min} 1.4-fold and an AUC 1.3-fold higher than that of a single dose of 600mg daily. A phase 1 study in healthy volunteers was then performed to compare plasma concentrations at steady state after oral dosing with Aramchol 300 mg twice daily with those after dosing with 600mg once daily.

METHODS

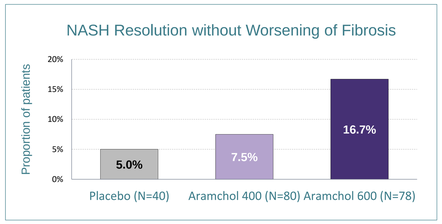
- Study design: 2 period, open label, randomised, crossover
- Subjects: 16 young, healthy volunteers
- Period 1: 8 subjects randomised to 300mg 12 hrly (BID) for 9.5 days
- 8 subjects randomised to 600mg 24 hrly (QD) for 10 days
- PK sampled over dosing interval on Day 10
- Washout - > 3 weeks
- Period 2: Alternate treatment



RESULTS

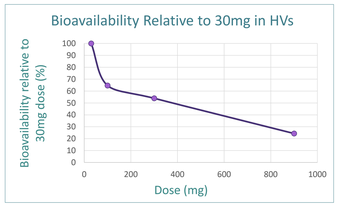
A. Aramchol Efficacy Demonstrate Dose Response Pattern

In ARREST trial increasing the Aramchol exposure by 22%, changed the response rate significantly between 400mg and 600mg. The efficacy of 600mg was more pronounced vs placebo.



B. Prediction of Relative Bioavailability, AUC and C_{min} at 300mg BID to 600mg QD

Relative bioavailability (F) across the dose range 30-900mg was calculated from dose normalised AUC relative to 30mg reflecting sub-proportional exposure at higher dose levels of Aramchol.

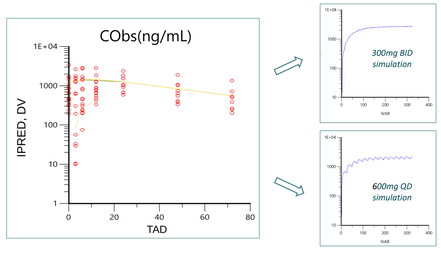


Relative F@Dose2 = (AUC@Dose2/Dose2)/(AUC@Dose1/Dose1)

Dose 1 = 30mg: Relative F @ 300mg = 0.53, Relative F @ 600mg = *ca.* 0.4

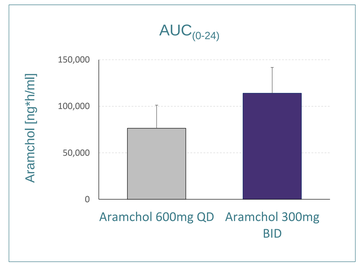
300mg BID will, at steady state, achieve twice the AUC over 24h as 300mg QD. Using this relationship, the predicted ***relative* AUC** at 300mg BID versus 600mg QD = 2x300x0.53/(600*0.4) = **1.3 fold higher**

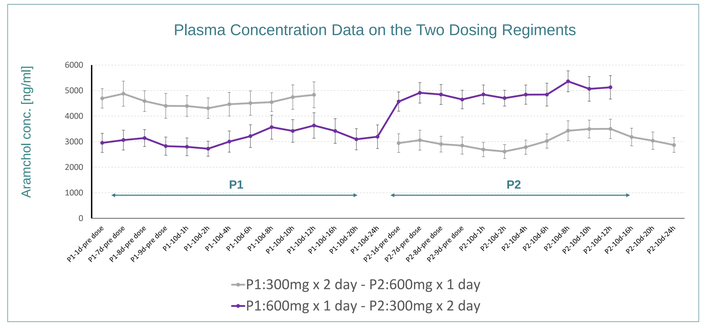
A compartmental model of clinical exposure at 300mg QD was combined with the prediction of relative bioavailability and predicts a **relative C_{min}** increase of **1.4 fold** from 300mg BID versus 600mg QD



C. "Dose Split" Method Leads to Significant Increase in Exposure

The administration of Aramchol in a divided dose of 300 mg BID resulted in 24-hour plasma concentrations significantly greater than those observed with the administration of Aramchol 600 mg QD (P<0.0001).





Treatment	N	C_{avg}	SE	AUC (0-24)	SD
300mg BID	16	4,619	379	114,031	27,728
600 mg QD	16	3,022	404	76,356	24,857

Twice daily dosing with Aramchol 300mg resulted in significantly higher exposures than once daily dosing of Aramchol 600 mg. The ratio of geometric mean values of AUC_{tau} was 1.53 (90%CIs 1.38, 1.69). Notably, all subjects showed higher values on the twice-daily regimen.

CONCLUSIONS

The prediction from the PK model was born out in practice with substantially higher concentrations of Aramchol obtained in human plasma, with the twice daily regimen compared with the same total dose taken once daily. Based on the Phase 2 apparent dose-response pattern, this increase in exposure offers the possibility for greater efficacy in the treatment of NASH with Aramchol than was observed with 600 mg once daily in the Phase 2b study. The ARMOR, Phase 3 study, is dose NASH patients with Aramchol 300 mg BID.