Utrophin modulators to treat Duchenne muscular dystrophy (DMD): Clinical trial update for SMT C1100

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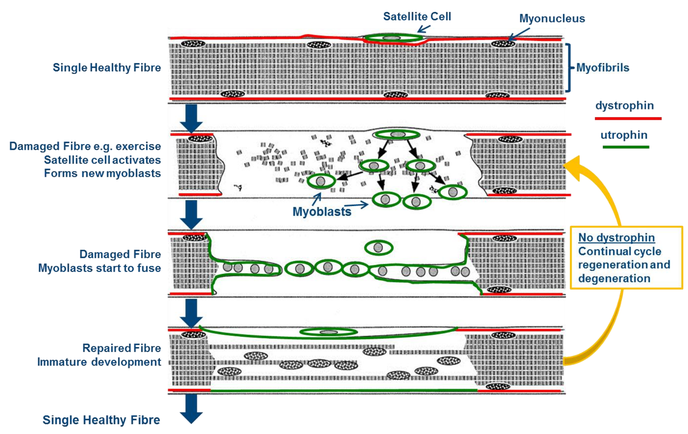
1. Utrophin Modulation: A Disease-modifying Strategy for all DMD

- Duchenne muscular dystrophy (DMD) is a lethal, progressive muscle wasting disease caused by the loss of sarcolemmal bound dystrophin that results in the death of muscle fibres and gradual depletion of skeletal muscle. There is currently no effective treatment for the disease
- Utrophin, is the functionally equivalent protein to dystrophin in developing foetal muscle and adult regenerating muscle
- Utrophin modulation i.e. the re-programming of utrophin transcription such that utrophin RNA and protein is continually expressed in mature fibres is expected to be a disease modifying treatment for all DMD patients, regardless of their underlying dystrophin defect (Tinsley *et al.* 1998: Nat Med; 4, 1441-4)



- *Ex vivo* human studies and *in vivo* mouse studies with SMT C1100 demonstrate that concentrations above 200nM for several hours per day are enough for at least two fold activation of the utrophin promoter
- Summit is developing the oral small molecule utrophin modulator, SMT C1100, for DMD
- Results of the first clinical trials of an oral utrophin modulator are detailed in this poster

2. Successful Phase 1 Healthy Volunteer Trial with SMT C1100

- The Phase 1 double-blind, placebo-controlled study in 48 healthy male subjects evaluated the safety, tolerability and PK of oral ascending single and multiple oral doses of SMT C1100
- The oral aqueous suspension formulation was safe and well tolerated at all doses and appropriate for paediatric use
- Large inter-individual variation was observed
- The levels of SMT C1100 stabilised after 3- 4 days of dosing at levels around 70% of the original dose
- Markedly lower exposure was seen for SMT C1100 under fasted conditions compared with that observed following food, with AUClast and Cmax being AUClast 5.2 (95% CI: 3.3, 8.2) and 4.8 (95% CI: 3.3, 7.0)-fold higher, respectively, in the fed state compared with the fasted state.

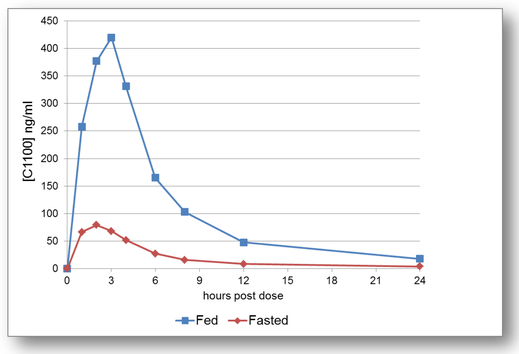
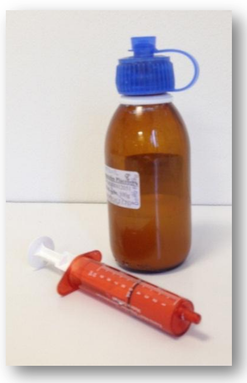


Figure 2: Average PK of 200mg/kg SMT C1100 taken with food vs. SMT C1100 taken after 12h fasting

3. Phase 1b: Study Design

- UK based study 4 sites: London, Liverpool, Birmingham, Manchester
- Enrolled 12 ambulatory DMD patients aged 5 to 11 years old
- 3 escalating dose cohorts, 4 patients per cohort:
  - 50mg/kg BID, 100mg/kg BID, 100mg/kg TID
- 10 days of oral dosing
- Dosing to occur "ideally within 10 minutes of consuming food"



Primary endpoint: Tolerability & Safety

Secondary endpoint: PK levels of SMT C1100 parent and metabolites

4. Phase 1b Results: Safety and PK

- **Safety: Primary endpoint of trial achieved**
  - ✓ SMT C1100 was safe and well-tolerated in all subjects
  - ✓ Patient compliance was 100%
- **PK**
  - High inter-individual variation of drug plasma levels was observed
  - 2/12 boys had good SMT C1100 plasma levels appropriate for over two fold activation of utrophin modulation
  - 10/12 boys plasma levels were lower with levels similar to fasted healthy adult volunteers (Figure 3)

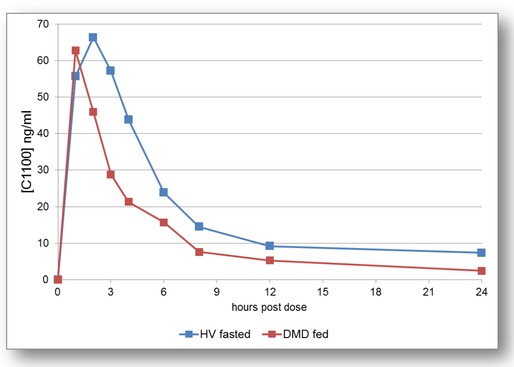


Figure 3: Plasma levels of 5 fasted healthy adults (200mg/kg) and 10 DMD Boys (100mg/kg) who didn't achieve plasma levels appropriate for utrophin activation

5. Phase 1b Results: Observations With Enzymes Associated With Muscle Membrane Damage

- Creatine phosphokinase (CPK) , the aminotransfeases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are significantly elevated in the blood of DMD boys., most likely due to muscle membrane damage due to dystrophin deficiency resulting in accumulation in blood
- Other serum markers of liver function such as gamma-glutamyl transferase (GGT), alkaline phosphatase (ALK) and albumin (alb) should be reasonably stable over time

Phase 1b data observations

- Concomitant reduction in plasma CPK, ALT and AST levels was observed with a statistically significant reduction of all three enzymes compared to baseline levels during the 11 days of dosing (Figure 4). Further assessment of this phenomenon in a randomised blinded study will provide further clarification
- Plasma levels of these enzymes returned towards baseline after cessation of treatment (Figure 4)
- Other liver associated markers, GGT, ALK and ALB showed no significant change over the same dosing period (Figure 4)
- Result is consistent with SMT C1100 treatment of *mdx* which demonstrated a significant fall in plasma CPK levels after 15 days of dosing with a single daily dose of SMT C1100 (Tinsley *et al.* PLoS ONE, 6 (4), 2011)

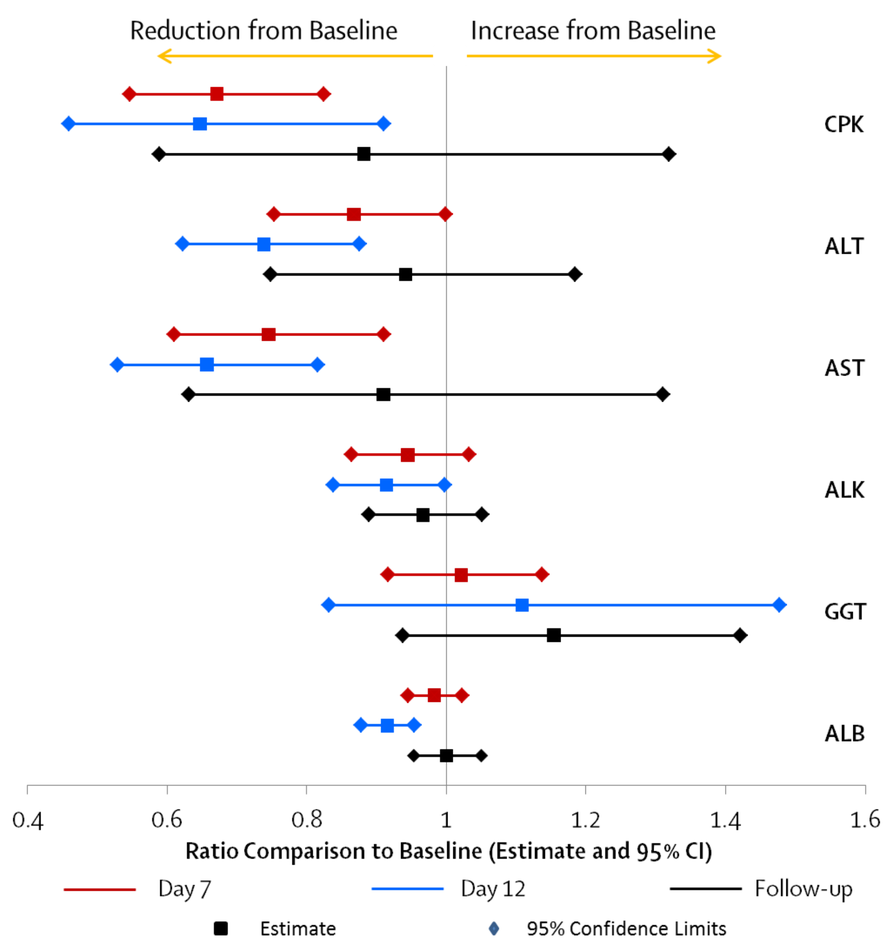


Figure 4: Plot of the average reduction from baseline (Estimate, square) with upper and lower 95% confidence limits (diamond) for each time point after dosing (Day 7, Day 12) and follow-up (Follow-up, 3 days after completion of dosing).

6. Next Steps: Targeting all Patients with DMD

- Future clinical trials of SMT C1100 to be modified to reflect Summit's greater understanding of the importance of diet and other potential disease related factors
- We will seek to determine the optimal way to address drug exposure variability through:
  - Dietary means and/or
  - Drug formulation change
- In parallel Summit has identified modified SMT C1100 formulations that increase exposure in animal PK studies in comparison to the current SMT C1100 aqueous microfluidised formulation
- Next patient study now expected to start in Q4 2014

7. Summary

- Utrophin modulation has the potential to treat all DMD patients regardless of the dystrophin mutations
- SMT C1100 is the first utrophin modulator to enter into DMD clinical trials
- A Phase 1b safety and PK dose finding study in DMD boys demonstrated the drug was safe and well tolerated
- Concomitant reductions in plasma levels of enzyme markers of muscle membrane damage were observed in the majority of the boys which may be related to SMT C1100 action.

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