Duchenne Muscular Dystrophy
SMT C1100 Utrophin Upregulator

Clinic-ready novel oral compound with potential to treat all DMD patients

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Rationale for Utrophin Upregulation as DMD Therapy

• Duchenne Muscular Dystrophy (DMD) is caused by loss of dystrophin
  • Loss of dystrophin breaks the internal actin cytoskeleton and extracellular laminin matrix
  • Membrane damage due to exercise, these damaged fibres degenerate

• Utrophin is an endogenous protein with function similar to dystrophin
  • Normally expressed in foetal and regenerating muscle, localised at the sarcolemma
  • Expression normally switched off in adult, non-regenerating, muscle
  • Switched on then off in DMD muscle

• **Treatment rationale:** Replace missing dystrophin with functionally similar utrophin
• **Approach:** Use pharmacological means to keep utrophin transcription turned on
Can we replace dystrophin with increased utrophin?
- Yes, transgenic expression and viral delivery
  - Viable approach

Can utrophin replacement cure *mdx* mice?
- Yes
  - Disease modifying

Can the utrophin promoter be manipulated to increase utrophin RNA levels?
- Yes, regulatory mechanisms partially dissected
  - Assay design

How much utrophin for muscle recovery?
- Similar levels to *mdx* *i.e.* normal fibre generating levels
  - Relevant to potency criteria

Does increased utrophin throughout the body have any side effects?
- Probably not; ubiquitous transgene overexpression
  - Relevant to mechanism based toxicology
- **No** toxicity observed in animals after 28 days of dosing at 1g/kg
Efficacy Data

SMT C1100 Profile in Human Cells *In Vitro*

Increases Utrophin RNA and Protein levels above the natural levels

- Maximal utrophin protein increase of 100% *above* natural levels was achieved with SMT C1100 in DMD patient myoblasts
- Maximal utrophin protein increase of 45% *above* normal levels was achieved with SMT C1100 in human myotubes
- This observation is important as it confirms SMT C1100 potential to increase utrophin levels above the natural cell levels
Summary of SMT C1100 in *Mdx* Mouse Model

- Increases Utrophin RNA and protein *in vivo* (~2 fold)

As a result of changing this specific regulation

- Reduces membrane damage and consequent rate of muscle fibre degeneration
- Increases fibre survival leading to decrease in pathological symptoms
- Protects against forced exercise changes
  - Calcium influx profile equivalent to wildtype mouse
  - Increases numbers of normal fibers
  - Over 75% decrease in necrotic areas
  - Improved muscle function completely protects against loss of grip strength
  - Improved muscle function reduces muscle fatigue

- **Surrogate for 6 minute distance walk test - primary efficacy endpoint in DMD clinical trials**
SMT C1100 Protects Against Forced Exercise Changes - Increased Muscle Function; Increases Grip Strength

Fore Limb Strength Assessment
• Determined once a week
• Measures ability to maintain grip
• No difference between wt and sedentary mdx

SMT C1100 completely protects against the loss of function otherwise seen with exercise
• This demonstrates that greater force can be maintained during muscle contraction
• This is a result of increased numbers of fibres with intact membranes
SMT C1100 Protects Against Forced Exercise Changes - Increased Muscle Function Reduces Muscle Fatigue

Resistance To Fatigue Assessment

• Calculate distance travelled before exhaustion
• Surrogate for 6 minute walking distance test (6MWD) - primary efficacy endpoint in DMD clinical trials

1. SMT C1100 increases distance travelled before exhaustion by ~50%
   • Halts continued increase in fatigue with forced exercise

2. Impressive combination effect with steroid treatment (current standard of care)
   • SMT C1100 plus Prednisolone, (PDN), increased distance travelled by ~350%
Proposed Development Plan for SMT C1100
Observations From 1st Phase I Trial

• Cell and animal work predicts plasma exposure required for efficacy >0.5µM for several hours per day

Healthy Volunteers (males >18yrs)

• No significant adverse events
  – The compound was safe and well tolerated in all subjects including those which achieved efficacy levels

• Significant inter-subject variability in plasma levels
  – Efficacy levels achieved in some volunteers

• Repeat level dosing fell to 30% after 7 days then remained constant for the further 7 days
  – Repeat dosing still achieved ~50% efficacy level after 14d

• Is low exposure a formulation related absorption issue or is it compound related?

Phase I trial inconclusive and all points to the pressing need to repeat the Phase I with a more appropriate formulation
SMT C1100 Immediate Development Plan

• Preclinical status
  – Complete, New formulation ready

• Next steps
  – Start GMP drug product manufacture of aqueous nanoparticle formulation
  – Write regulatory and file regulatory documents (IMPD, IB) and submit CTA to UK’s MHRA

• Phase I (4 SADs / 2 MADs)
  – Trial design: Phase I plan to identify appropriate oral Single Ascending Dose (SAD) exposure then go to oral Multiple Doses (MAD)
    • Double blind, placebo controlled, safety, tolerability and pharmacokinetic study
    • Multiple daily dosing, food effect, steroid combination also included in study plan
  – Outcome: Confirm formulation works, levels after repeat dosing not an issue resulting in full safety tolerability, and identifying first patient doses ready for Phase IIa CTA

• Time to complete
  – Approximately 12 months from start of C1100 manufacture
SMT C1100 Scientific Summary

- Only disease modifying treatment in clinical development for all DMD patients
  - Mechanism of action via utrophin replacement of missing dystrophin
- Efficacy demonstrated in target cells: myocytes from DMD patients
- Outstanding profile in gold standard preclinical animal model in mdx mouse
  - Addresses all the key defects of DMD muscle pathology
- Orally bioavailable small molecule drug
- Clinic ready
  - Initial Phase I demonstrated safety but limited exposure
  - Plan established to evaluate appropriate formulation in new Phase I

Prof. Francesco Muntoni, Paediatric Neurologist, ICH London
“If this mdx activity profile translated across to DMD patients then undoubtedly this would be a disease modifying therapy for DMD”
THANK YOU

– Remember Sign Up To The Registries

– For more info on SMT C1100; http://www.summitplc.com/DMD-utrophin-upregulation.aspx