SMT C1100 Utrophin Upregulator

Novel oral compound with potential to treat all DMD patients

Jon Tinsley PhD
jon.tinsley@summitplc.com
FORWARD LOOKING STATEMENTS

This Document contains forward-looking statements. These statements relate to, among other things, analysis and other information that are based on forecasts of future results and estimates of amounts not yet determinable. These statements also relate to the Company’s future prospects, developments and business strategies. Forward-looking statements are identified by their use of terms and phrases such as “believe”, “could”, “envisage”, “estimate”, “expect”, “intend”, “may”, “plan”, “will” or the negative of those, variations or comparable expressions, including references to assumptions. The forward-looking statements in this Document are based on current expectations and are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by those statements. Given the risks and uncertainties associated with a company of this nature, potential investors should not place reliance on forward-looking statements. These forward-looking statements speak only as at the date of this Document.

The Company does not undertake any obligation to update forward-looking statements or risk factors other than as required by any relevant regulations, whether as a result of new information, future events or otherwise.
Dystrophin Function in Muscle

• Dystrophin stabilizes the membrane of mature muscle fibers and links the actin cytoskeleton to an extracellular matrix via the dystrophin protein complex – “a molecular shock absorber”

• Loss of dystrophin results in membrane damage during contraction and relaxation of the fiber

• Membrane damage causes calcium influx preventing contraction and activating natural degenerative response and fiber destruction

• In the regeneration phase, only utrophin is expressed, enabling the link between actin and extracellular matrix
Muscle Fiber Repair

- Single Healthy Fiber
- Damaged Fiber e.g. exercise
  - Satellite cell activates
  - Forms new myoblasts
- Damaged Fiber
  - Myoblasts start to fuse
- Repaired Fiber
  - Immature development

- Single Healthy Fiber

Satellite Cell
Myonucleus
Myofibrils

- dystrophin
- utrophin

No dystrophin
Continual cycle regeneration and degeneration
Utrophin is the Functional Replacement for Dystrophin

- Utrophin functional equivalent to dystrophin in both fetal and regenerating muscle
- Utrophin is continually expressed at specialized sites in normal mature muscle fibers
- Dystrophin can be replaced by increased utrophin
- Utrophin replacement can “cure” dystrophin deficient (mdx) mice
- Only normal utrophin levels required for DMD muscle recovery
- Utrophin muscle-specific promoter can be manipulated to increase utrophin RNA levels
- SMT C1100 designed to increase and maintain utrophin transcription
Efficacy Data

Data published in PLoS ONE Journal:
“Daily Treatment with SMT C1100, a Novel Small Molecule Utrophin Upregulator, Dramatically Reduces the Dystrophic Symptoms in the mdx Mouse”
SMT C1100 Scientific Summary

• Only disease modifying treatment in clinical development for all DMD patients
  – Designed to increase and maintain utrophin transcription
  – Capable of doubling utrophin levels

• Efficacy demonstrated in target cells: myocytes from DMD patients

• Established proof-of-concept in animal models
  – Addresses all the key defects of DMD muscle pathology
  – Most importantly continued exposure to SMT C1100 significantly increases whole body muscle function

• Orally bioavailable small molecule drug

• Phase 1 safety trial underway (healthy volunteers)
  – Safety, tolerability and PK data end 2012
  – Formulation appropriate for the pediatric population
SMT C1100 Increases Utrophin in Human Muscle Cells

- SMT C1100 doubled utrophin levels in myoblasts from DMD patients
- SMT C1100 increased utrophin by 45% in normal human myotubes

This observation confirms the potential for utrophin upregulation activity in patients
Summary of SMT C1100 in *Mdx* Mouse Model

- Maintains utrophin expression *in vivo*
- Leads to increased survival of mature fibres
- Significant improvement in the disease
- Reduces membrane damage and rate of muscle fibre degeneration
- Increases fibre survival leading to decrease in pathological symptoms
- Protects against forced exercise changes – “more DMD like”
  - 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

Increased utrophin staining – white circles
Whole Animal Assessment After Forced Exercise

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

**Resistance To Fatigue Assessment**
- **Analogous to the 6 minute walking distance test (6MWD) - primary efficacy endpoint in DMD clinical trials**
- 5 meters/min for 5 minutes, speed then increased 1 meter/min each minute until exhaustion
- Calculate total distance travelled before exhaustion
SMT C1100 Normalizes Grip Strength

• Completely protects against the loss of grip strength otherwise seen with exercise
  – This demonstrates that greater force can be maintained during muscle contraction
  – This is a result of increased numbers of fibers with intact membranes
  – Reducing calcium imbalance allowing contraction to be maintained
SMT C1100 Reduces Muscle Fatigue

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

- SMT C1100 plus Prednisolone, (PDN), increased distance travelled by ~350%
  - Striking combination effect with corticosteroid treatment (current Standard of Care)
Clinical Development Plan for SMT C1100
Foundations Sponsoring SMT C1100 Phase 1 Trial

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
SMT C1100 Immediate Development Plan

Phase 1, Double-Blind, Placebo-Controlled, Ascending Single and Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Healthy Male Subjects

• Primary Objective
  – To determine the safety and tolerability of single oral ascending doses and multiple oral doses of SMT C1100 in healthy male subjects

• Secondary Objectives
  – To determine the levels of SMT C1100 in the plasma after single and multiple doses in healthy male subjects

• Outcome
  • Confirm formulation works, levels after repeat dosing remain above efficacy levels
  • Complete safety tolerability package
  • Identifying first patient doses ready for Phase 2 CTA
SMT C1100 Current Status

- Clinical trial application authorised by UK regulators - April 2012
- Orphan drug status in US and EU
- Phase 1 trial initiated - May 2012
- Aqueous suspension formulation, suitable for all age groups
- Trial progressing to testing SMT C1100 in repeat dosing phase
- Full data to be reported by end of 2012
- Planning Phase 2 scenarios – Pharma partner / community support
THANK YOU

- Remember Sign Up To The Patient Registries

For more info on SMT C1100;
- Visit: www.summitplc.com
- Email: DMD@summitplc.com