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Duchenne Muscular Dystrophy SMT C1100 Utrophin Upregulator

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

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**9th International Annual
Duchenne Conference**

Forward-Looking Statements

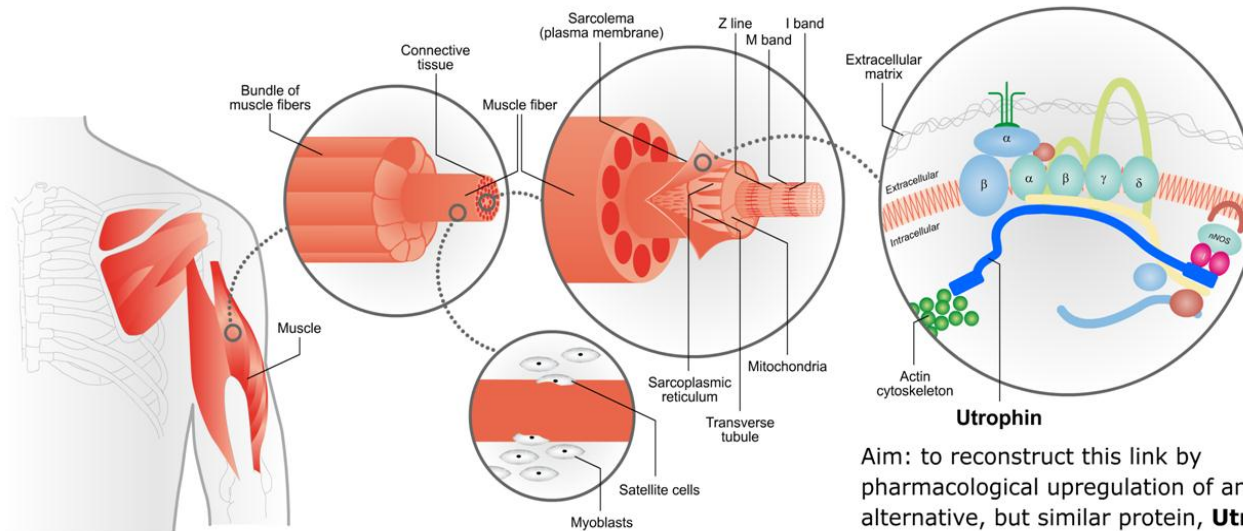
This Document contains forward-looking statements.

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.

Rationale for Utrophin Upregulation as DMD Therapy

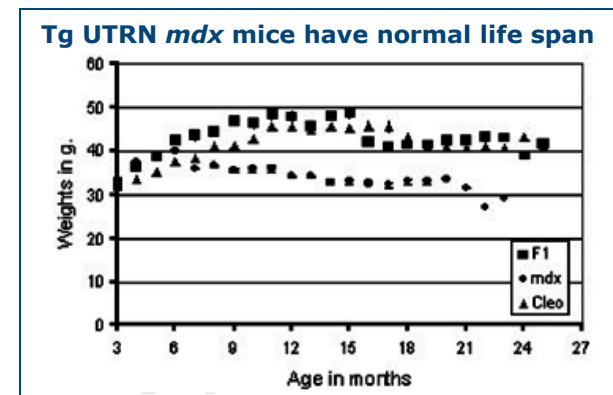
- Duchenne Muscular Dystrophy (DMD) is caused by loss of dystrophin
 - Loss of dystrophin breaks the internal actin cytoskeleton and extracellular laminin matrix
 - Membrane damage due to exercise, these damaged fibres degenerate
- Utrophin is an endogenous protein with function similar to dystrophin
 - Normally expressed in foetal and regenerating muscle, localised at the sarcolemma
 - Expression (RNA production) normally switched off in adult, non-regenerating, muscle
 - Switched “on” then “off” in DMD muscle. Gradual loss of utrophin protein at muscle membrane
- **Treatment rationale: Replace missing dystrophin with functionally similar utrophin**
- **Approach: Use pharmacological means to keep utrophin transcription turned on**





Utrophin Upregulation: Questions Already Addressed

- Dystrophin can be replaced by increased utrophin
 - Transgenic expression and viral delivery
- Utrophin replacement can “cure” *mdx* mice
 - Disease modifying
- Utrophin promoter can be manipulated to increase utrophin RNA levels
 - Regulatory mechanisms partially dissected
- Only normal utrophin levels required for muscle recovery
 - Similar levels to *mdx* *i.e.* normal fibre generating levels
- Increased utrophin throughout the body does not have any side effects
 - Ubiquitous transgene overexpression
 - Relevant to mechanism based toxicology
 - No toxicity observed in animals after 28 days of dosing at utrophin upregulator, SMT C1100



Heregulin ameliorates the dystrophic phenotype in *mdx* mice

Thomas O. B. Krag^{1*}, Sasha Bogdanovich¹, Claus J. Jensen², M. Dominik Fischer³, Jacob Hansen-Schwartz¹, Elisabeth H. Javazon¹, Alan W. Flake⁴, Lars Edvinsson², and Tejvir S. Khurana^{1*}

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Communicated by Louis M. Kunkel, Harvard Medical School, Boston, MA, August 13, 2004 (received for review June 7, 2004)



Efficacy Data

Data recently 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”

Jonathon M. Tinsley et al. Volume 6, Issue 4, May 2011

Overview

1. SMT C1100 increases the level of utrophin above the natural levels
 - Mechanism increases utrophin RNA levels which leads to increased protein
2. The continual expression of utrophin allows fibres to mature and survive in the absence of dystrophin
 - Mechanism overrides the normal cellular switch-off
 - Leads to significant improvement in disease pathology
3. Most importantly continued exposure to SMT C1100 significantly increases whole body muscle function
 - Increases the ability of animal to run and grip

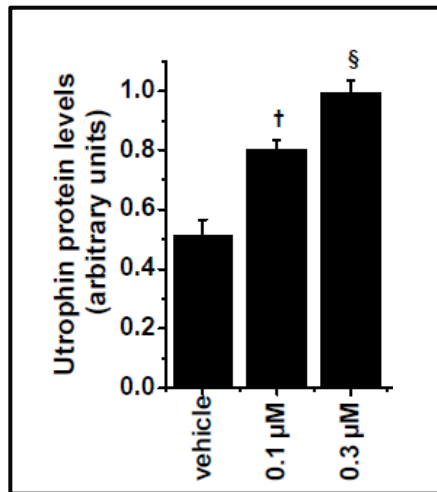
“If this mdx activity profile translated across to DMD patients then undoubtedly this would be a disease modifying therapy for DMD”

Prof. Francesco Muntoni, Paediatric Neurologist, ICH London

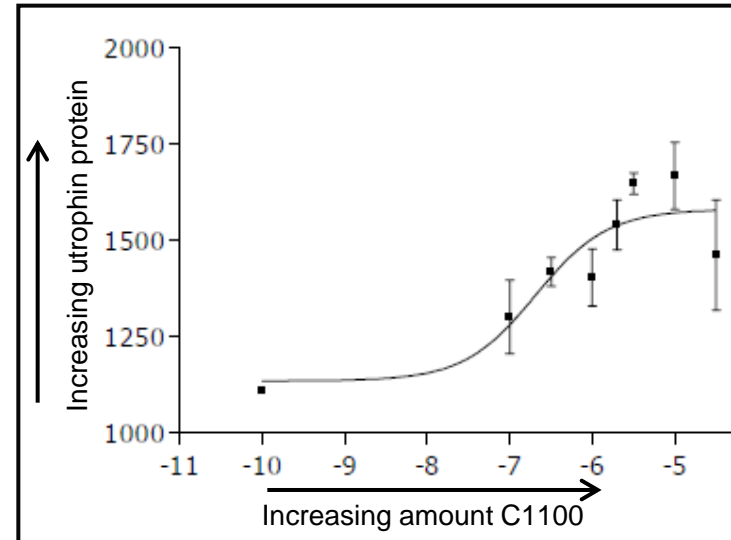


SMT C1100 Profile in Human Cells *In Vitro*

Increases Utrophin RNA and Protein levels above the natural cell levels



DMD myoblasts



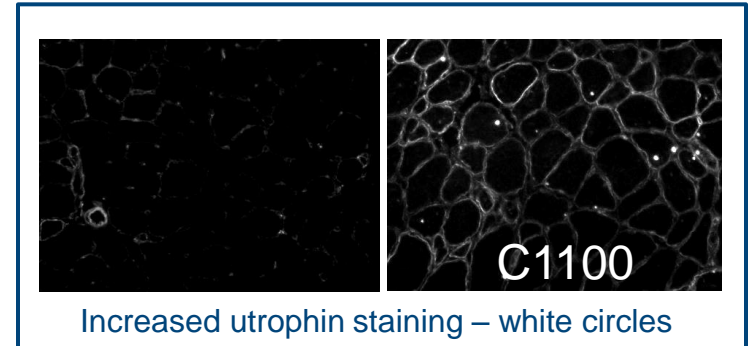
Human cultured myotubes

- 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 (“opens the tap further”)

Summary of SMT C1100 in *Mdx* Mouse Model

- Maintains utrophin expression *in vivo*
- Leads to increased survival of mature fibres
 - “stops the tap from being turned off”
- Results in a significant improvement in the disease
- 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. Controlled calcium levels fundamental to function
 - 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



A surrogate for 6 minute distance walk test: Primary efficacy endpoint in DMD clinical trials



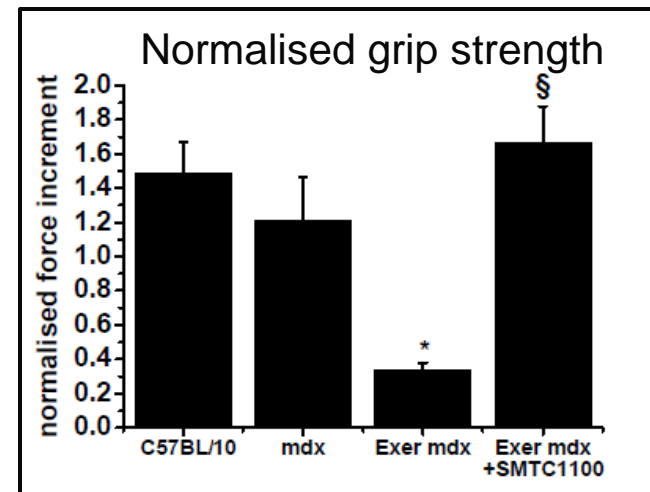
SMT C1100 Protects Against Forced Exercise Changes - Increased Muscle Function; Increases Grip Strength

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

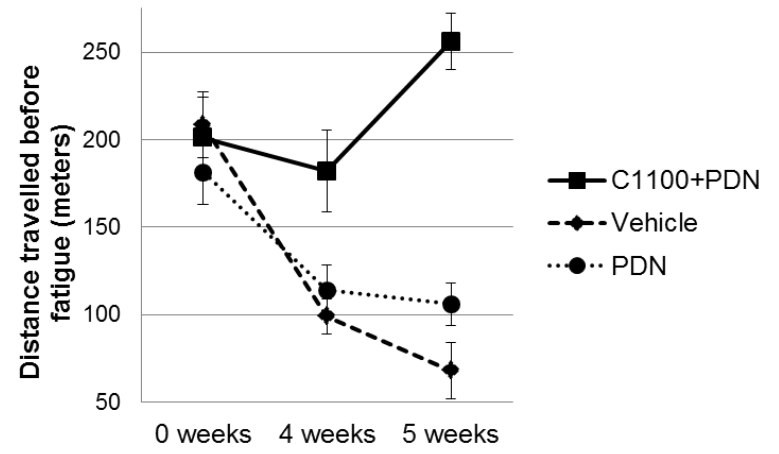
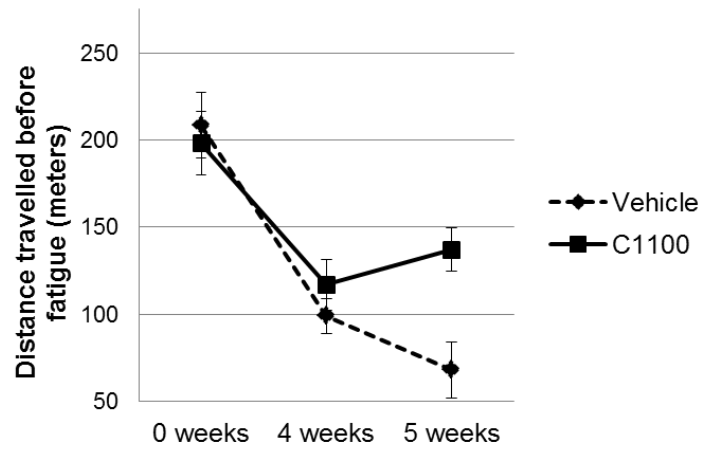
- Calculate distance travelled before exhaustion
- Surrogate for 6 minute walking distance test (6MWD) - primary efficacy endpoint in DMD clinical trials

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

- Only low plasma quantities of SMT C1100 required for efficacy effect
 - Cell and animal work predicts plasma exposure required for low μM for several hours per day

Healthy Volunteers (males >18yrs)

- No significant adverse events
 - The compound was safe and well tolerated in all subjects
- Efficacy levels achieved in some volunteers
 - Significant inter-subject variability in plasma levels

A Reformulation Challenge

- First Phase I trial showed inconsistent levels of SMT C1100 in the blood stream
- Two major factors that influence the levels of drug in the blood stream
 1. **Metabolism:** Drug broken down by enzymes as it passes across the gut wall and then as it continually circulates back through the liver
 2. **Wrong formulation:** Unable to assist in transporting drug across gut wall

1. No evidence indicating SMT C1100 is metabolised too quickly

- Either by human enzymes from extracts of liver and gut cells or
- During preclinical development where animals were treated daily with high doses for several weeks

2. Summit believes use of an appropriate formulation can produce consistent elevated levels of SMT C1100 in the blood stream

- Summit has chosen a new formulation appropriate for the physical properties of SMT C1100 using an approach, nanosizing, which has been used in many marketed drugs
- New formulation is suitable for all patient clinical trials *i.e.* aqueous flavoured suspension

Points to the pressing need to conduct a new Phase I with this appropriate formulation

SMT C1100 Immediate Development Plan

- Preclinical status
 - Complete, New aqueous suspension formulation ready
- Next steps
 - 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
 - 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 remain high (above efficacy levels) resulting in full safety tolerability, and identifying first patient doses ready for Phase IIa CTA**
- Time to complete
 - Approximately 12 months from initiating SMT 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
 - Mechanism capable of increasing and sustaining utrophin expression
 - Complementary to all other approaches
- Efficacy demonstrated in target cells: myocytes from DMD patients
- Outstanding profile in gold standard preclinical *in vivo* model
 - Addresses all the key defects of DMD muscle pathology from protecting dystrophin deficient muscle fibres to demonstrating increase muscle function in whole animals
- Orally bioavailable small molecule drug
- Clinic ready
 - Initial Phase I demonstrated safety but limited exposure
 - Plan established to evaluate more appropriate formulation in new Phase I

THANK YOU

- Remember Sign Up To The Registries
- For more info on SMT C1100:
 - Visit: www.summitplc.com
 - Email: DMD@summitplc.com