Utrophin Modulation: A Universal Treatment Approach to DMD

PPMD End Duchenne Tour - NJ
February 3, 2018

Karen McClendon, PhD
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Summit Overview

Publicly traded company located in the UK (Abingdon) and US (Cambridge, MA)

Technology pioneered by Prof. Kay Davies, University of Oxford, who identified utrophin and utrophin modulation as a universal treatment approach for DMD

Utrophin modulation:

> Potential to slow or stabilize disease progression in all patients with DMD
> Independent of dystrophin gene mutation
> Could be complementary to other approaches to DMD

> Exclusive license and collaboration agreement granting Sarepta Therapeutics Inc. European rights to Summit’s utrophin modulator pipeline
Dystrophin and Utrophin Look and Act Similarly in Muscles

Dystrophin or utrophin protein

Muscle cell membrane

Dystrophin or utrophin protein
But They do so at Different Times in Muscle Development

- Utrophin is present in early developing fibers and repairing muscle fibers; dystrophin is present in mature muscle fibers

![Diagram showing the timeline of muscle fiber development with markers for Utrophin and Dystrophin](image)
Muscles Affected by Duchenne Naturally Make Utrophin in Early Development and Fiber Repair

> Without dystrophin, muscle fibers are easily damaged and when the muscle fiber begins the natural repair process, utrophin is turned on again.
Utrophin Modulation Aims to Keep Natural Production of Utrophin Turned on in All Muscle Fibers

> Modulation of utrophin protein has potential to compensate for lack of dystrophin
Ezutromid: Oral Utrophin Modulator in a Phase 2 Clinical Trial
Ezutromid Clinical Program Aimed to Answer Key Questions

**Phase 1**
- Is ezutromid well-tolerated and suitable for future testing? (Well tolerated in ~100 healthy volunteers and 22 individual patients with DMD)

**Phase 2 (PhaseOut DMD)**
- Can ezutromid modulate utrophin in patients with DMD?
- Can ezutromid have a positive effect on biomarkers of muscle structure and health?

**Future trials**
- Over the long term, does ezutromid have positive effects on muscle function?
- Does ezutromid have positive effects on Quality of Life measures?
PhaseOut DMD:
A Phase 2 Proof of Concept Trial of Ezutromid

- Open-label, 48-week Phase 2 clinical trial
- 40 patients enrolled at sites in US and UK
- Additional extension phase and safety arm
- Aim to see changes in endpoints over time
- Scientific rigor in place to assure quality data and analyses

- Muscle health: fiber damage (biopsy)
- Muscle health: fat fraction (MRI/MRS)
- Utrophin engagement (biopsy)

Start of Dosing
Focus on Biopsy Measures for Interim 24-Week Assessments

<table>
<thead>
<tr>
<th>Biopsy Assessment</th>
<th>Result</th>
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<tbody>
<tr>
<td>Utrophin expression</td>
<td>Increase in mean intensity</td>
</tr>
<tr>
<td>Developmental myosin (muscle damage/repair)</td>
<td>Significant decrease in mean percentage of developmental myosin positive fibers</td>
</tr>
<tr>
<td>Muscle fiber diameter (muscle maturity)</td>
<td>Small decrease in mean fiber diameter</td>
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</tbody>
</table>

> 24-week biopsy samples were compared to baseline samples  
> Rigorous collection and analytical methods for biopsies:  
>  Automated muscle biopsy imaging removes human bias, ensures data quality  
>  Following strict handling and processing, all biopsies contributed to the overall dataset  
>  Evaluated on average several thousand individual fibers
24 Weeks of Ezutromid Treatment
Increased Utrophin Intensity

> Demonstrated 7% increase overall in mean utrophin intensity
Developmental Myosin is Expressed in Muscle Development and During Damage/Repair Cycle

Significant Reduction in Muscle Damage after 24 Weeks of Ezutromid Treatment

Example biopsies taken from a single patient and evaluated for amount of damage/repair via developmental myosin at baseline and week 24.

Significant reduction in muscle damage observed.
Significant Reduction in Muscle Damage after 24 Weeks of Ezutromid Treatment

Reduction in Mean Developmental Myosin after 24 Weeks of Ezutromid Dosing

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 24</th>
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<tr>
<td>11.37%</td>
<td>8.76%</td>
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</table>

95% CI, -4.33, -0.90

23% decrease in mean developmental myosin (MHCd) after 24 weeks
Reduction in Muscle Damage in PhaseOut DMD is Meaningful; Supported by Validation Studies

> A reduction in the percentage of developmental myosin positive fibers correlates with a reduction in disease severity as determined by validation work assessing DMD, BMD and control biobank muscle biopsy samples

*From Summit’s validation work using biobank samples*
## PhaseOut DMD: Additional Interim 24-Week Measures

<table>
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<tr>
<th>Measure</th>
<th>Result</th>
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<tbody>
<tr>
<td>Magnetic resonance spectroscopy (MRS): Fat fraction in thigh muscle</td>
<td>• Mean fat fraction in the vastus lateralis was 14.7% at baseline and 18.5% at 24 weeks</td>
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<td>Functional assessments: Six-minute walk distance</td>
<td>• Mean six-minute walk distance was 404m at baseline and 395m at 24 weeks</td>
</tr>
<tr>
<td>North Star Ambulatory Assessment</td>
<td>• Mean North Star Ambulatory Assessment score was 25.0 at baseline and 24.4 at 24 weeks</td>
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<td></td>
<td>• All patients retained ambulation after 24-weeks of treatment</td>
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> Longer term dosing is expected to be required to detect changes in MRI/MRS parameters
> Ezutromid has been well tolerated to date
> No apparent difference in safety or muscle parameters between the formulations
> Regardless of formulation, all patients achieved plasma levels of ezutromid sufficient to modulate utrophin.
Positive Interim 24-Week Data Show Ezutromid Activity in PhaseOut DMD; Other Changes Expected Over Time

- Ezutromid activity evidenced by a maintenance and even increase in utrophin expression + concurrent decrease in developmental myosin
- Interim data encouraging for detecting changes in MRI/MRS parameters at 48 weeks
- Established natural history control population for 48-week comparison of MRI/MRS parameters & functional endpoints

Muscle health: fiber damage (biopsy)
Muscle health: fat fraction (MRI/MRS)
Utrophin engagement (biopsy)
Functional endpoints

Start of Dosing
What’s Next?

PhaseOut DMD
- Ongoing trial
- Positive interim 24-week data reported
- Top-line 48-week data expected to be reported Q3 2018
- Extension phase could provide valuable long term safety and efficacy data

Pivotal Trial
- Data could support an accelerated or conditional approval pathway
- Design will be influenced by PhaseOut DMD
Keep in Touch

> Sign up for utrophin modulator clinical trial news at www.utrophintrials.com

Utrophin Modulation in DMD

Utrophin modulation is being evaluated for its potential to slow or stop the disease progression in all boys and men with Duchenne muscular dystrophy (DMD).

Summit Therapeutics is currently conducting clinical trials in patients using this approach. This site is intended for patients and families to find out more information about utrophin modulation and associated clinical trials.

View our clinical trials
Contact Details

michelle.avery@summitplc.com
P: +1 617-225-4455
Twitter: @summitplc
www.utrophintrials.com

One Broadway
Cambridge
Massachusetts US

136a Eastern Ave
Milton Park
Oxfordshire UK