Utrophin Modulation: A Universal Treatment Approach to DMD

End Duchenne Tour
April 2018
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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

- Actin Binding
- H1
- H2
- Rod domain
- H3
- H4
- CRD
- CTD

Utrophin

- Actin Binding
- H1
- H2
- Rod domain
- H3
- H4
- CRD
- CTD

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.
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

![Diagram showing the modulation of utrophin in different muscle fibers](image)

- **Normal Fiber**: Fully functional, with natural production of utrophin.
- **DMD (Duchenne Muscular Dystrophy) Fiber**: Degeneration due to lack of dystrophin.
- **DMD Fiber + Utrophin modulator**: Functional fiber, with utrophin modulation compensating for lack of dystrophin.
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 in Phase 1 clinical trials)

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

<table>
<thead>
<tr>
<th><strong>Design:</strong></th>
<th>Open label, 48-week trial with extension phase</th>
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<tbody>
<tr>
<td><strong>Subjects:</strong></td>
<td>40 ambulatory DMD boys, fully enrolled 5-10 years old</td>
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<td><strong>Trial Sites:</strong></td>
<td>9 US 7 UK</td>
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| **Endpoints:** | *Primary:* leg magnetic resonance parameters  
*Secondary:* biopsy parameters  
*Exploratory:* range of functional endpoints  
*Other:* safety and pharmacokinetics |
| **Data:** | 24-week data reported Q1 2018  
48-week data expected Q3 2018 |
Endpoints in PhaseOut DMD Track Impact of Ezutromid Over Time

Membrane instability → Damage → Repair → Replacement of muscle with fat → Loss of function

Immediate disease impact → Longer-term disease impact

Inflammation → MRS-T2

Developmental myosin → MRS Fat Fraction

6 Minute walk / North Star
PhaseOut DMD Interim Data: Key Findings after 24-Weeks of Ezutromid Treatment

1. Stabilization of muscle membranes
   - Background utrophin levels high in DMD patients due to muscle damage
   - Ezutromid maintained utrophin expression with a mean increase of 7% observed in muscle biopsies

2. Significant decrease in muscle damage
   - Developmental myosin is a muscle damage biomarker with higher levels shown to correlate with disease severity
   - Ezutromid statistically, meaningfully decreased developmental myosin (23%)

3. Significant decrease in muscle inflammation
   - MR-T2 is a precise technique for measuring muscle damage and inflammation
   - Ezutromid significantly decreased inflammation as measured by MRS-T2
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
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.
Significant Reduction in Muscle Inflammation After 24 Weeks of Ezutromid Treatment

Mean Decrease from Baseline in MRS-T2

Soleus (n=38)

Vastus Lateralis (n=37)

Evidence of early impact of ezutromid on downstream muscle health

* (95% CI, -1.440, -0.281)
PhaseOut DMD: Additional Interim 24-Week Measures

> All patients retained ambulation after 24 weeks of treatment
> Ezutromid has been well tolerated to date
> Regardless of formulation, all patients achieved plasma levels of ezutromid sufficient to modulate utrophin with no apparent difference in safety or muscle parameters between the formulations
Positive Interim 24-Week Data Show Ezutromid Activity in PhaseOut DMD; Other Changes Expected Over Time

- Immediate disease impact
- Longer-term disease impact

- Membrane instability
- Utrophin
- Developmental myosin
- Inflammation
- Damage
- Repair
- MRS-T2
- Replacement of muscle with fat
- Loss of function

- MRS Fat Fraction
- 6 Minute walk / North Star
What's Next?

If 48-week results from PhaseOut DMD are positive:

- **Accelerated path**
  - Confirmatory clinical trial
  - Full approval
  - Market

- **Traditional path**
  - Pivotal clinical trial
  - Full approval
  - Market
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]
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