
Jiny S. Andrews, MD, MSc for the BENEFIT-ALS Study Group
Cytokinetics Inc, South San Francisco, CA

ABSTRACT

Tirasemtiv is a small molecule activator of the skeletal sarcomere. Tirasemtiv activates the tropomyosin complex of fast skeletal muscle.

Tirasemtiv increases the efficiency of submaximal muscle contraction

- Force-Frequency Relationship
- Specific tension (N/m²)
- Force (mN)
- Frequency (Hz) 

Tirasemtiv increases contractile force in healthy volunteers

- Tirasemtiv affects the tropomyosin complex of fast skeletal muscle
- Encouraging dose/concentration-dependent trends observed in:
  - Respiratory function
  - ALSFRS-R endpoints for secondary analyses
  - ALS Functional Rating Scale-Revised (ALSFRS-R)

Design Considerations in BENEFIT-ALS

Goals of the study:
- Decrease safety and efficacy of tirasemtiv administered for 3 months, at the highest tolerated dose up to 500 mg daily.
- Dosing:
  - First patient enrolled in March 2014
  - Study visits: 8 and 12 weeks
  - Change from baseline in MVV was ≥ 100 mL/min for patients taking tirasemtiv 500 mg daily for 3 months
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BENEFIT-ALS: Outcome Measures

Primary:
- ALSFRS-R (scored by baseline and change from baseline over 3 months)
- Tolerability: AEs, AE-related dose reductions or interruptions, discontinuations, withdrawals, deaths

Secondary:
- QMFS: A measure of daily function
- Tolerability: AEs, AE-related dose reductions or interruptions, discontinuations, withdrawals, deaths

BENEFIT-ALS: Enrollment by Country

Table

<table>
<thead>
<tr>
<th>Country</th>
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<th>Patients Enrolled</th>
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Other Key findings from Phase IIa studies in patients with ALS

- Encouraging dose/concentration-dependent trends observed:
  - Respiratory Measures
  - MVV
  - Quantitative Muscle Testing
  - Handgrip Fatigue

Conclusion:
- Overall, tirasemtiv had a positive safety and tolerability profile, as well as encouraging effect on respiratory and functional outcomes in ALS patients.