Next Generation Prodrug Troriluzole: Increased Bioavailability of Riluzole with No Food Effect in Healthy Subjects

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Background: Troriluzole and Neurological Disorders

- Troriluzole, a third-generation tripeptide prodrug, was designed to improve the bioavailability, delivery and safety of the glutamate modulator riluzole
  - Riluzole is approved by the FDA for the treatment of amyotrophic lateral sclerosis (ALS)

- Riluzole use has been limited due to factors including:
  - High pharmacokinetic (PK) variability
  - Elevated liver function tests
  - Negative food effect
  - Relatively low bioavailability
  - Requirement for twice-daily dosing

- Troriluzole, which metabolizes in the body into the active metabolite riluzole, was developed to improve the PK and therefore the treatment potential, efficacy and safety of riluzole for use in neurological and neuropsychiatric disorders

Background: Troriluzole and Phase 1 Studies

- The troriluzole prodrug was designed to overcome limitations present with oral riluzole treatment including the following:

- Food effect and bioavailability of troriluzole were evaluated in three Phase 1 clinical studies
- Studies BHV4157-101 and BHV4157-105 included assessments of food effect on riluzole after oral administration of troriluzole
- BHV4157-105 was the definitive food effect study, while BHV4157-101 was exploratory
- Study BHV4157-107 evaluated bioavailability of riluzole from the prodrug troriluzole compared to oral riluzole

Methods: BHV4157-101, BHV4157-105 and BHV4157-107

- All three single-center, randomized studies assessed single dose troriluzole in healthy subjects
- Liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to determine plasma concentrations of riluzole
- Riluzole PK parameters were calculated by noncompartmental analysis

BHV4157-101

- N=6, food effect assessment arm within larger study
- Assessed food effect on riluzole administered as troriluzole (200 mg) under fasting conditions and with a high fat meal

BHV4157-105

- N=20, definitive food effect study
- Assessed food effect on riluzole administered as troriluzole (280 mg) under fasting conditions and with a high fat meal

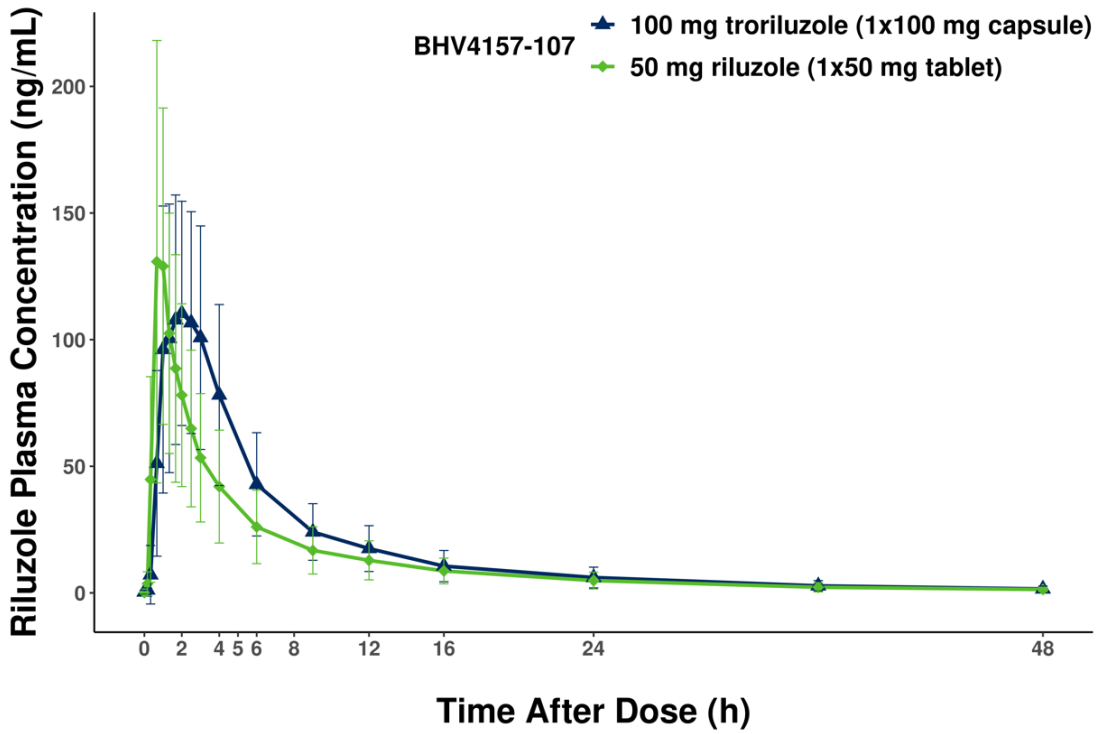
BHV4157-107

- N=24, bioavailability study which assessed relative bioavailability of riluzole from troriluzole (equimolar dose of 100 mg [Treatment A] and therapeutic dose of 280 mg [Treatment B]) versus oral riluzole 50 mg (Treatment C)

Results: Bioavailability

- In BHV4157-107, following administration of troriluzole, riluzole $AUC_{0\text{-inf}}$ values were 40% to 50% higher than for oral riluzole 50 mg, even when adjusting for molar dose
- After troriluzole, riluzole C_{max} was similar and T_{max} was delayed by 1 hour versus oral riluzole (median T_{max} 1.99 versus 0.824 hours)
- Riluzole variability was consistently lower after troriluzole (AUC CV% ~40% for troriluzole versus 54% for oral riluzole)

Riluzole Plasma Concentrations (Mean ± SD) After Administration of 100 mg Troriluzole vs 50 mg Riluzole (Study BHV4157-107)



Plasma concentrations were plotted as arithmetic mean and error bars represent standard deviation.
All values below the limit of quantitation are assumed to be 0.
Note: 100 mg troriluzole is the molar equivalent of 50 mg riluzole.

Results: Bioavailability

Troriluzole 100 mg vs Oral Riluzole 50 mg

Riluzole PK Parameter	N	Troriluzole 100 mg Geometric Mean (CV%)	Oral Riluzole 50 mg Geometric Mean (CV%)	Ratio[b] (%)	90% Geometric CI[c] Lower (%)	90% Geometric CI[c] Upper (%)
$AUC_{0\text{-inf}}$ (h•ng/mL)	23	791 (43.3)	571 (53.8)	140	131	150
C_{max} (ng/mL)	23	131 (35.6)	129 (55.1)	101	86.3	118

Troriluzole 280 mg (dose normalized to 50 mg) vs Oral Riluzole 50 mg

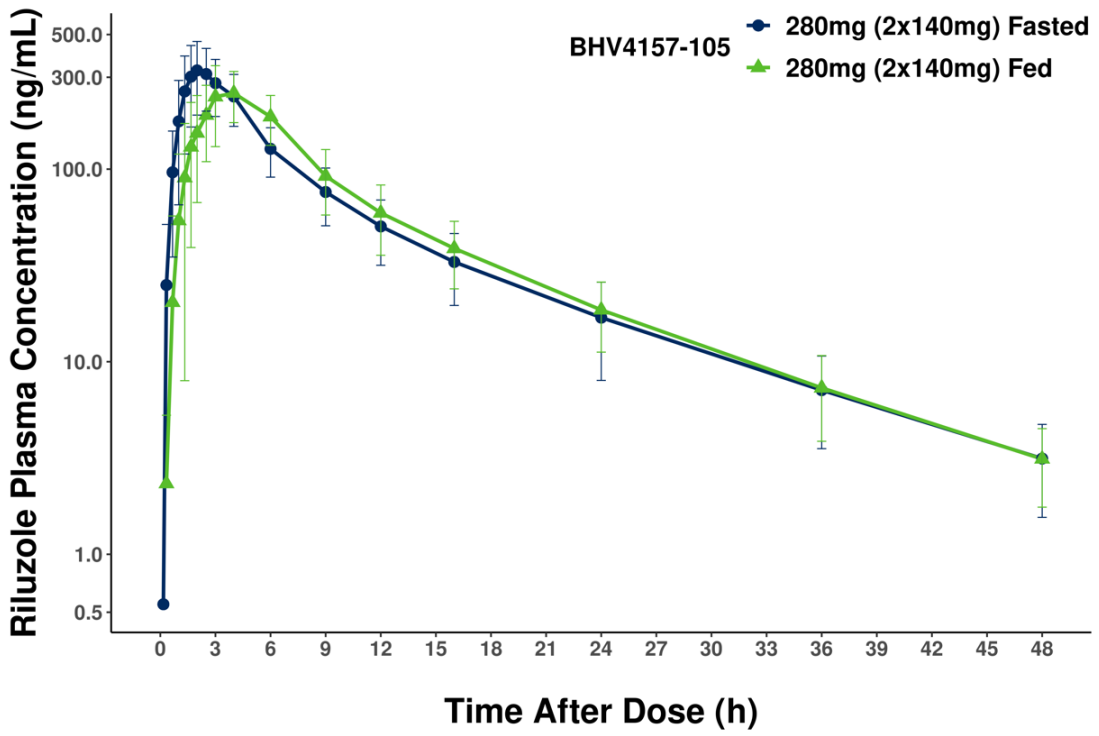
Riluzole PK Parameter	N	Troriluzole 280 mg[a] Geometric Mean (CV%)	Oral Riluzole 50 mg Geometric Mean (CV%)	Ratio[b] (%)	90% Geometric CI[c] Lower (%)	90% Geometric CI[c] Upper (%)
$AUC_{0\text{-inf}}$ (h•ng/mL)	24	857 (39.8)	571 (53.8)	150	140	160
C_{max} (ng/mL)	24	131 (41.7)	129 (55.1)	102	87.1	119

a. To dose-normalize AUC0-inf and Cmax for Treatment B (280 mg troriluzole) to a 50 mg riluzole dose, AUC0-inf and Cmax were multiplied by a correction factor of 50/125.
b. Calculated using least squares means on ln-transformed data according to the formula: exp(DIFFERENCE) * 100.
c. 90% Geometric CI calculated according to the formula: exp(DIFFERENCE ± t(dfResidual)* SEDIFFERENCE) * 100

Results: Food Effect

- BHV4157-105 (definitive food effect study) demonstrated the following:
  - After troriluzole administration with food, riluzole median T_{max} was delayed (4 hours under fed conditions versus 2.23 hours under fasting conditions) and C_{max} was reduced by 22%
  - However, overall riluzole absorption (AUC) was unaffected by food
- The results of BHV4157-101 (exploratory, smaller sample size) were consistent with the results of BHV4157-105

Riluzole Semi-log Plasma Concentrations (Mean ± SD) Under Fasted and Fed Conditions After Administration of Troriluzole 280 mg (Study BHV4157-105)



Plasma concentrations were plotted as arithmetic mean and error bars represent standard deviation. All values below the limit of quantitation are assumed to be 0.

Results: Food Effect

Riluzole PK following Troriluzole 280 mg with a High Fat Meal versus Fasted Conditions (Study BHV4157-105)

Parameter	N	Geometric Mean (CV%) Fasted	Geometric Mean (CV%) Fed	Ratio Fed/Fasting[a] (%)	90% Geometric CI[b] Lower (%)	90% Geometric CI[b] Upper (%)
$AUC_{0\text{-inf}}$ (h•ng/mL)	20	2330 (27.7)	2290 (24.7)	98.4	91.6	106
C_{max} (ng/mL)	20	354 (28.1)	274 (31.4)	77.6	68.8	87.4

a. Calculated using least squares means on ln-transformed data according to the formula: $\exp^{(DIFFERENCE)} * 100$.
b. 90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$

Conclusions

- Troriluzole, a novel prodrug, was rationally designed to overcome the shortcomings of oral riluzole and confers important PK enhancements versus oral riluzole
- The results from Studies BHV4157-101, BHV4157-105 and BHV4157-107 confirm higher bioavailability of riluzole administered as troriluzole as compared to oral riluzole and demonstrate troriluzole may be taken without regard to food
- Additionally, results show lower variability of riluzole, representing an optimized profile allowing once daily administration
- These studies support the continued clinical development of troriluzole in neurological and neuropsychiatric conditions involving abnormal glutamate levels

Thank you!