Population Pharmacokinetics and Pharmacodynamics (PK/PD) Modeling of Mirdametinib in Patients With Neurofibromatosis Type 1-Related Plexiform Neurofibromas

Tomoyuki Mizuno, Todd Shearer, Alexander A. Vinks, Thuy Hoang, Abraham J. Langseth, Brian D. Weiss

Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; Department of Pediatrics, University of Cincinnati, College of Medicine, Cincinnati, OH, USA; SpringWorks Therapeutics, Stamford, CT, USA

Introduction

- Plexiform neurofibromas (PNs) are nerve sheath tumors that develop in ~40% of patients with neurofibromatosis type 1 (NF1).
- Substantial morbidities and complications are associated with PNs, such as severe pain, disfigurement, reduced quality of life, and malignant transformation.

Methods

- Mirdametinib is an investigational, oral MEK inhibitor that was evaluated in the Neurofibromatosis Clinical Trials Consortium Phase 2 NF106 clinical trial (NCT02096471) in adults and adolescents ≥16 years of age (n=19).
  - Mirdametinib was dosed at 2 mg/m² twice per day on an intermittent dosing schedule (3 weeks on followed by 1 week off).
  - Mirdametinib treatment was associated with a 42% partial response (P) rate.

Results

- The observed tumor volume data in the NF106 study were well captured by the clinical trial simulations using the final model.

Conclusions

- A mirdametinib PK-TGI model was developed in adolescent and young adult patients with NF1-related PNs.
- The observed tumor volume data in the NF106 study were well captured by the clinical trial simulations using the final model.
- At the mirdametinib dose level evaluated in clinical trials (2 mg/m² for 3 weeks-on/1 week-off), approximately 80% of patients in the simulation analysis reached a clinical response (35% tumor reduction) after 96 weeks (24 cycles) of treatment.
- Mirdametinib safety, tolerability, and maximization of time on treatment should be considered when determining the optimal dose and regimen.

Acknowledgements

Funding for this analysis was provided by SpringWorks Therapeutics, Inc. The NF106 study, an NF Clinical Trials Consortium study, was supported by DOD award W81XWH-12-1-0555.

References