28th Annual Meeting of the European Charcot Foundation (ECF)
PD Response to Oral DRF
Submission deadline: 20 September 2020; 11:59pm CEST

Title: Orally Administered Diroximel Fumarate Induces Activation of the Nuclear Factor (erythroid-derived 2)-like 2 Transcriptional Pathway

Short Title: Pharmacodynamic Response to Oral DRF

Authors:

Michael J. Palte, Ankur M. Thomas, Davide Gianni, Kristopher King, Jordan Messer, Ellen Cahir-McFarland

Corresponding/submitting author: Michael J. Palte

Presenting author: Michael J. Palte

Affiliations:

Biogen, Cambridge, MA, USA

28th Annual Meeting of the European Charcot Foundation (ECF)
PD Response to Oral DRF
Submission deadline: 20 September 2020; 11:59pm CEST

Abstract (300 words)

Introduction: Diroximel fumarate (DRF) is a novel oral fumarate for relapsing forms of multiple sclerosis (MS). Upon oral administration, DRF is rapidly converted to monomethyl fumarate (MMF), the same active metabolite of dimethyl fumarate (DMF), and is expected to have a similar pharmacodynamic (PD) effect as DMF. Diester fumarates such as DRF and DMF are hypothesized to impact MS pathophysiology via Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) dependent mechanisms of neuroprotection and cytoprotection, in addition to immunomodulatory effects.

Objective: To measure MMF exposure and Nrf2-dependent transcriptional PD responses in C57BL/6 mice after orally administered DRF. Orally administered DMF served as a positive control.

Methods: C57BL/6 mice were administered a single oral dose of DRF 192.5 mg/kg (n=18), DRF vehicle (n=18), DMF 100 mg/kg (n=18), or DMF vehicle (n=18). Mice were euthanized at 15 minutes, 2 hours, or 6 hours postdose (6 per time point in each group); plasma and tissue (brain, spleen, kidney, and jejunum) were analyzed for MMF exposure (by liquid chromatography mass spectroscopy) and Nrf2 activation (via up-regulation of Aldo-keto reductase family 1, member b8 [Akr1b8], heme oxygenase 1 [Hmox1], and oxidative stress induced growth inhibitor 1 [Osgin1] genes as measured by quantitative real-time polymerase chain reaction).

Results: Overall, MMF exposure with DRF and DMF was comparable in plasma and tissues, with slight differences observed in brain and spleen. After DRF administration, Akr1b8, Hmox1, and Osgin1 transcripts were elevated within the brain, jejunum, kidney, and spleen at 2 and 6 hours postdose compared to vehicle-treated animals. At 2 and 6 hours postdose, Akr1b8, Hmox1, and Osgin1 levels were overall similar between DRF- and DMF-treated animals.

Conclusions: The MMF-mediated Nrf2 activation profiles of the diester fumarates DRF and DMF are very similar, suggesting each may confer comparable neuroprotective, cytoprotective, and immunomodulatory effects.

Support: Biogen

28th Annual Meeting of the European Charcot Foundation (ECF)
PD Response to Oral DRF
Submission deadline: 20 September 2020; 11:59pm CEST

Author Disclosures

Michael J. Palte reports being a full-time employee of and holding stock/stock options in Biogen.

Ankur M. Thomas reports being a full-time employee of and holding stock/stock options in Biogen.

Davide Gianni reports being a full-time employee of and holding stock/stock options in Biogen.

Kristopher King reports being a full-time employee of and holding stock/stock options in Biogen.

Jordan Messer reports being a full-time employee of and holding stock/stock options in Biogen.

Ellen Cahir-McFarland reports being a full-time employee of and holding stock/stock options in Biogen.