Relevant Financial Relationship Disclosure Statement

Ralinepag Plasma Levels Correlate With Improvements in Functional and Hemodynamic Parameters in Patients With Pulmonary Arterial Hypertension

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I will discuss investigational use of the following drug: ralinepag

The following relevant financial relationships exist related to this presentation:

HW Farber: Consultant, United Therapeutics

N Sood: Principal Investigator, United Therapeutics

IR Preston: Principal Investigator, United Therapeutics

J Adams, J Grundy, C King, P Klassen: Employees, Arena Pharmaceuticals

VF Tapson: Consultant, United Therapeutics

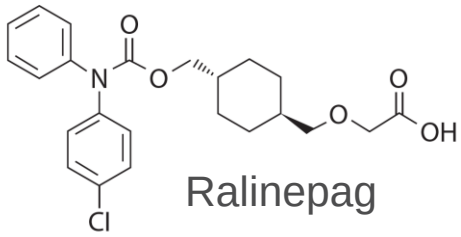
VV McLaughlin: Principal Investigator, United Therapeutics

RJ Oudiz: Principal Investigator, United Therapeutics

Introduction and Ralinepag Phase 2 Study Design

Background

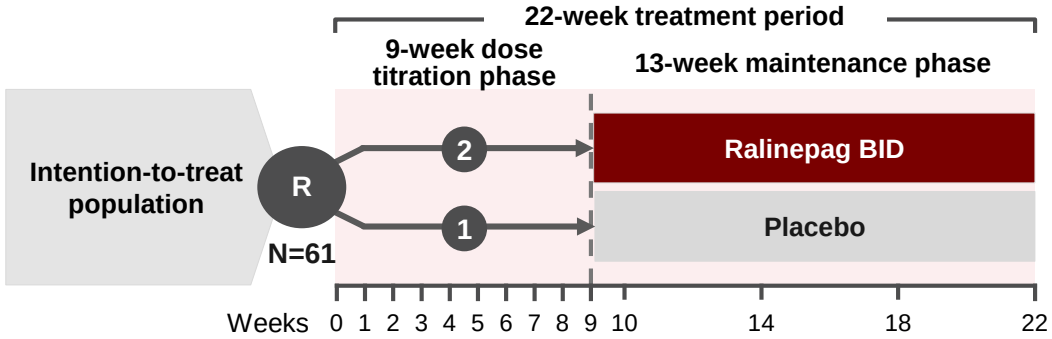
- Ralinepag is a next-generation, oral, selective, and potent prostacyclin receptor agonist in development for PAH[1,2]
- In a Phase 2 study of patients with stable FC II–IV Group 1 PAH and a 6MWD of 100–500 m, ralinepag significantly improved PVR compared with placebo in patients on monotherapy or dual background therapy
- The dose–response relationship on hemodynamic parameters for oral prostacyclin receptor agonists is unclear[3]



Ralinepag

Objective

- This *post hoc* analysis of the Phase 2 study evaluated whether ralinepag dose and plasma levels correlated with improvements in functional and/or hemodynamic parameters and/or serum biomarkers, including PVR and 6MWD



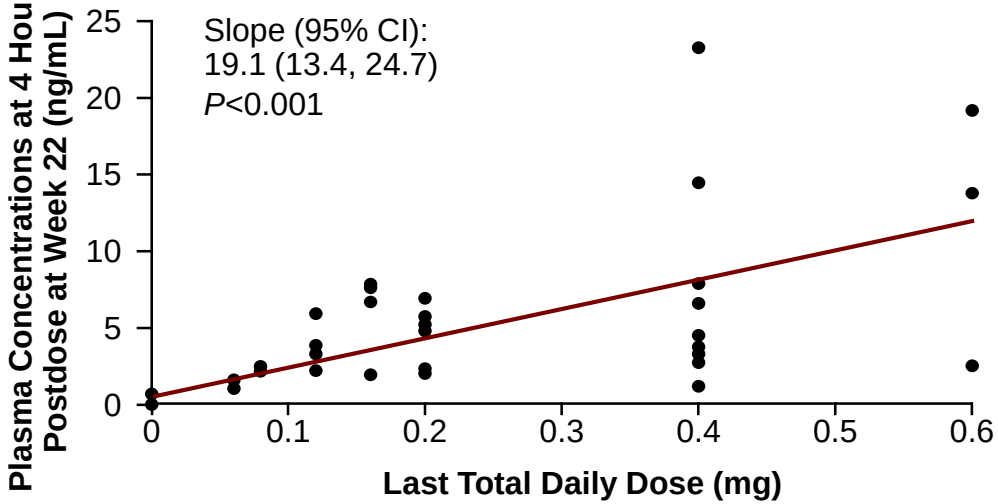
Primary Efficacy Endpoint

- Absolute change in PVR from baseline to Week 22

Secondary Endpoints

- Δ6MWD and hemodynamics
- ΔPVR from baseline
- Safety and tolerability

Relationship Between Ralinepag Dose and Plasma Levels



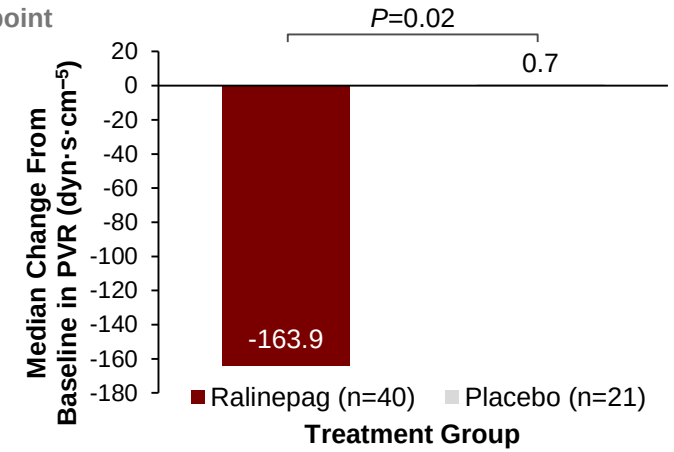
6MWD, 6-minute walk distance; BID, twice daily; CI, confidence interval; FC, functional class; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; R, randomization.

1. Tran TA *et al*. *J Med Chem* 2017;60(3):913–927. 2. Preston IR *et al.* Presented at: American Thoracic Society 2016 International Conference; May 13–18, 2016; San Francisco, CA, USA. 3. Sitbon O *et al*. *N Engl J Med* 2015;373(26):2522–2533.

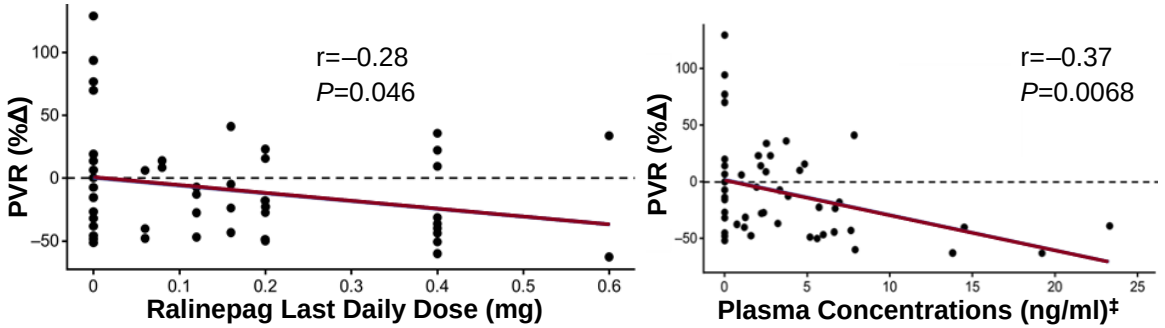
Results: Ralinepag Effects on PVR and 6MWD

Change in PVR and Relation to Ralinepag Treatment and Exposure Measures

Primary Endpoint



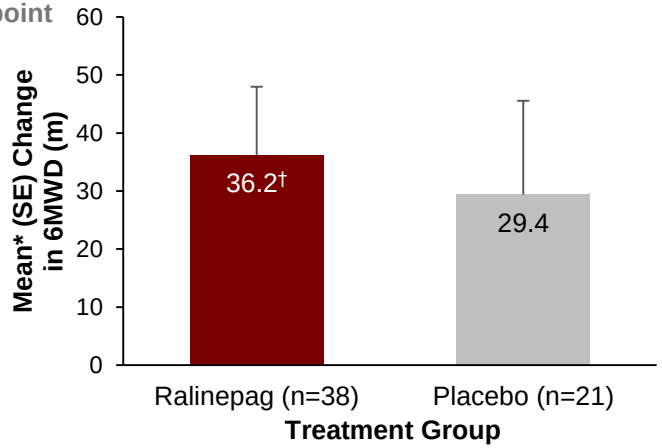
- PVR significantly decreased from baseline to Week 22 in patients receiving ralinepag compared with patients receiving placebo



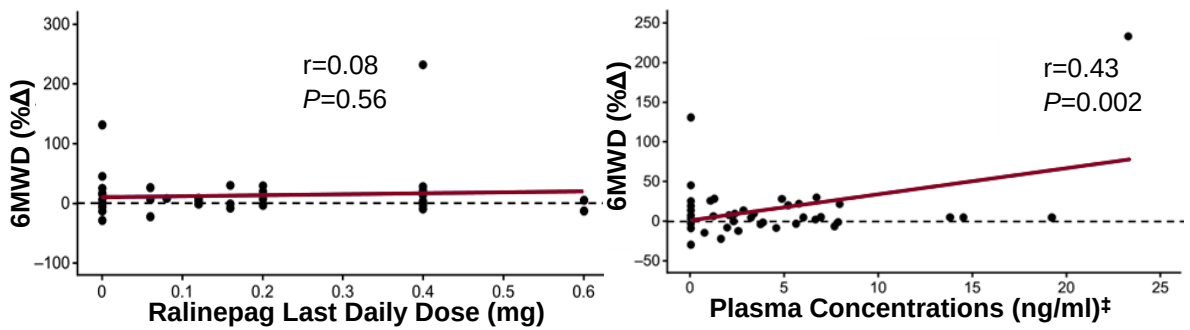
- Significant linear relationships seen between ralinepag dose and plasma levels versus improvements in PVR

Change in 6MWD and Relation to Ralinepag Treatment and Exposure Measures

Secondary Endpoint



- The magnitude of improvement in 6MWD for the ralinepag arm was higher than that for placebo but not statistically different



- Significant linear relationship seen between ralinepag plasma levels, but not dose, versus improvements in 6MWD

*Least-squares mean. †Significant change from baseline within ralinepag group (*P*=0.003). ‡Placebo doses are represented at 0, and plasma concentrations are measured 4 hours postdose on Week 22.
6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; SE, standard error.

Summary and Conclusion

- Ralinepag is a next-generation, oral, selective, and potent prostacyclin receptor agonist in development for PAH
- Ralinepag significantly reduced PVR compared with placebo in patients with FC II–IV Group 1 PAH on single or dual background therapy
- This *post hoc* analysis of the Phase 2 study revealed that efficacy (change in PVR and 6MWD) better related to ralinepag plasma levels than to ralinepag dosing
- This is the first study demonstrating a linear relationship between plasma levels of an oral drug targeting the prostacyclin receptor and hemodynamic parameters, potentially improving the clinical management of optimal dosing
- Dose–exposure–response relationships will be further explored in Phase 3 studies

6MWD, 6-minute walk distance; FC, functional class; PAH, pulmonary arterial hypertension; PVR pulmonary vascular resistance.