Long-term Data from Study APD811-007, an Open-label Extension Study Evaluating Ralinepag for the Treatment of Pulmonary Arterial Hypertension

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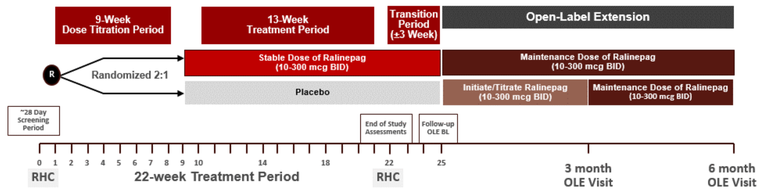
INTRODUCTION

- Ralinepag is a novel, next-generation, oral, selective, potent prostacyclin (IP) receptor agonist in development for pulmonary arterial hypertension (PAH), with optimized pharmacokinetics (PK) and potent activity on vascular smooth muscle cells and platelets.
- APD811-003 was a Phase 2 randomized, double-blind, placebo-controlled clinical study that assessed the effects of ralinepag on hemodynamics and on 6-minute walk distance (6MWD) in 61 subjects with PAH after 22-weeks of treatment.
- Subjects who completed APD811-003 were eligible to enroll in APD811-007, a global, multicenter, open-label extension (OLE) study evaluating the long-term safety and tolerability of ralinepag in patients with PAH who completed APD811-003 or who were assigned to placebo and were discontinued for clinical worsening.
- APD811-007 completed on 29 March 2021. A total of 45 subjects were treated with ralinepag. Efficacy assessments consisted of clinical worsening, 6-Minute Walk Tests, World Health Organization (WHO) Functional Class (FC), hemodynamics, and plasma brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP). Safety assessments included adverse events, clinical laboratory tests, physical examinations, vital signs, and 12-lead electrocardiograms.

METHODS

Figure 1. APD811-003 and APD811-007 Study Design



- Of the 61 subjects in the Phase 2 study, 45 continued into the open-label extension study. Subjects randomly allocated to ralinepag continued on active therapy (n=30), while subjects originally treated with placebo switched to ralinepag (n=15) and titrated drug weekly for 9-weeks until a stable maximum tolerated dose was reached.
- Subjects visited the clinic monthly for the first 3 months, then every 3 months until subject discontinuation or study termination.
- During the study, all subjects transitioned from an immediate release (IR) formulation to an extended-release (XR) formulation that is being used in ralinepag Phase 3 studies. The transition to XR ralinepag occurred at a regularly scheduled visit, with subsequent dose titration occurring, as needed, in 50-mcg weekly increments.

BASELINE DEMOGRAPHICS

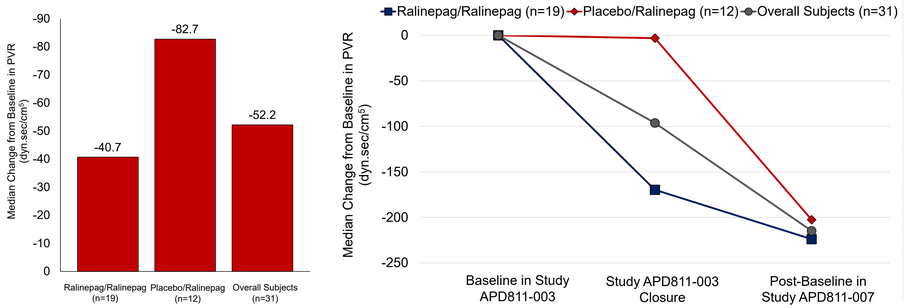
Table 1. Summary of Demographics and PAH History

	Ralinepag/Ralinepag (n=30)	Placebo/Ralinepag (n=15)	All Subjects (n=45)
Age (years), median (range)	47 (20, 68)	60 (34, 71)	51 (20, 71)
Female/Male (%)	80/20	100/0	87/13
PAH Duration (years), median (range)	3.0 (0.8, 16.0)	1.95 (0.8, 11.3)	2.3 (0.8, 16.0)
PAH Concomitant Medication at Randomization in APD811-003, n (%)			
PDE5 Inhibitor Monotherapy	27 (90.0)	11 (73.3)	38 (84.4)
ERA Monotherapy	20 (66.7)	11 (73.3)	31 (68.9)
ERA + PDE5 Inhibitor/sGC	19 (63.3)	7 (46.7)	26 (57.8)
PVR (dyn.sec/cm^5), median (range)	522.65 (126.3, 1165.7)	574.4 (186.6, 971.6)	556.4 (126.3, 1165.7)
6MWD (m), median (range)	446 (158, 696)	383.0 (190, 641)	425 (158, 696)

RESULTS

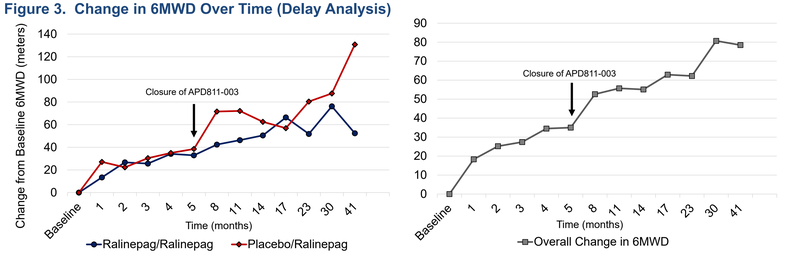
- A total of 31 subjects received a right heart catheterization and participated in the hemodynamic assessments post-Baseline (19 from the ralinepag group and 12 from the placebo group in APD811-003).
- A notable decrease in Pulmonary Vascular Resistance (PVR) was observed post-Baseline in subjects from the placebo group in APD811-003 after initiating ralinepag therapy in Study APD811-007 (decrease of 82.7 dyn.sec/cm^5 in the placebo group from APD811-003 compared with a decrease of 40.7 dyn.sec/cm^5 in the ralinepag group from APD811-003).
- A delayed-start analysis of the placebo and ralinepag groups during APD811-003 and ADP811-007 showed that from Baseline to APD811-003 closure, subjects treated with placebo did not experience a significant change in PVR when compared to the ralinepag group in APD811-003 (-3.1 dyn.sec/cm^5 for the placebo group and -169.7 for the ralinepag group). However, after treatment with ralinepag in the OLE study, the PVR of the placebo group approximated the level of the ralinepag group at post-Baseline (-202.6 dyn.sec/cm^5 for the placebo group and -223.9 dyn.sec/cm^5 for the ralinepag group).

Figure 2. Change in PVR in APD811-003 and APD811-007



RESULTS

Figure 3. Change in 6MWD Over Time (Delay Analysis)



- In the subjects who continued ralinepag in the OLE, mean improvement in 6MWD from Baseline after 41 months was 52.4 meters (n=10; Baseline at APD811-003 = 393 m). In the subjects who switched from placebo to ralinepag in the OLE, mean improvement in 6MWD from Baseline was 130.8 meters after 41 months (n=5; Baseline in APD811-003 = 351 m). Overall, there was a mean increase of 78.5 meters at the 41-month timepoint in APD811-007.
- The most common adverse events (AEs) in subjects originally randomized to ralinepag were lower in the OLE (headache, 53%; nausea, 27%) versus the original study (headache, 77%; nausea, 50%). The most common AEs in subjects originally randomized to placebo were headache (86.7%), diarrhea (46.7%), nausea (40%), myalgia (33%), and flushing (27%).
- Changes from Baseline were also observed for several hemodynamic parameters.

Table 2. Summary of Hemodynamic Parameters

Hemodynamic Parameter Median (min, max)	Ralinepag/Ralinepag (N=19)		Placebo/Ralinepag (N=12)	
	APD811-007 Baseline	Δ from Baseline	APD811-007 Baseline	Δ from Baseline
mPAP, mmHg	38.5 (22, 72)	-1 (-11, 5)	39.0 (23, 62)	-6.0 (-23, 18)
Systolic PAP, mmHg	67.5 (36, 131)	-1.0 (-23, 14)	70.0 (34, 117)	-14.0 (-27, 27)
Diastolic PAP, mmHg	28.0 (15, 61)	-1.0 (-7, 17)	25.0 (17, 39)	-2.5 (-21, 13)
Cardiac Output, l/min	5.1 (2, 9)	0 (-2, 2)	5.0 (3, 8)	-0.1 (-2, 5)
Cardiac Index, l/min/m^2	2.9 (2,6)	0 (-1, 1)	2.7 (2, 4)	0 (-1, 3)
MAP, mmHg	80.5 (58, 118)	-1.0 (-22, 12)	87.0 (79, 106)	-12.5 (-26, 25)
SVR, dyn.sec/cm^5	1156.8 (461, 1941)	-69.4 (-561, 998)	1408.1 (823, 2195)	-91.5 (-1456, 267)

CONCLUSIONS

- Following treatment with ralinepag in the long-term OLE study (APD811-007), improvements were observed in 6MWD and PVR compared with Baseline. A notable improvement in PVR was observed post-Baseline in subjects from the placebo group in APD811-003 following the initiation of ralinepag therapy in Study APD811-007.
- To date, the safety profile of ralinepag in PAH subjects is favorable. The most common events reported in this study were those known to be associated with IP receptor agonist therapy.
- The overall safety profile of ralinepag was similar to that reported in Study APD811-003; therefore, the benefit-risk ratio of ralinepag remains unchanged and positive.

SCAN ME

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