United Therapeutics
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United Therapeutics Corporation
Phase 3 *ADVANCE OUTCOMES* Results Webcast

MARCH 2, 2026

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INTRODUCTION

Today's Speakers

Dr. Martine Rothblatt

Chairperson and Chief Executive Officer

Dr. Derek Solum

Senior Director, Product Development and Lead for the Global *ADVANCE OUTCOMES* Program

Michael Benkowitz

President and Chief Operating Officer

Dr. Daniel Lachant, DO, MSCI, ATSF

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Dr. Leigh Peterson

Executive Vice President, Product Development and Xenotransplantation

Dr. Martine Rothblatt

CHAIRPERSON AND CHIEF EXECUTIVE OFFICER

ADVANCE OUTCOMES RESULTS

ADVANCE OUTCOMES Headline Conclusions

1

Ralinepag reduced the risk of a clinical worsening event versus placebo by 55% (HR: 0.45, [95% CI: 0.33-0.62]; p<0.0001)

2

The study also met several important secondary endpoints, including change in NT-proBNP[1], 6MWD[2], and clinical improvement

3

Treatment with ralinepag was well-tolerated, and the safety profile was consistent with known prostacyclin-related adverse events. No new safety signals were observed.

The use of ralinepag for PAH is an investigational use and has not been approved by the FDA

1. NT-proBNP=N-terminal pro-B-type natriuretic peptide 2. 6MWD=six-minute walk distance

Dr. Derek Solum

SENIOR DIRECTOR, PRODUCT DEVELOPMENT AND LEAD FOR THE GLOBAL ADVANCE OUTCOMES PROGRAM

ADVANCE OUTCOMES Study Design[1]

PRIMARY ENDPOINT

Time from randomization to the first adjudicated protocol-defined clinical worsening event

SECONDARY ENDPOINTS

Change from Baseline to Week 28 in:

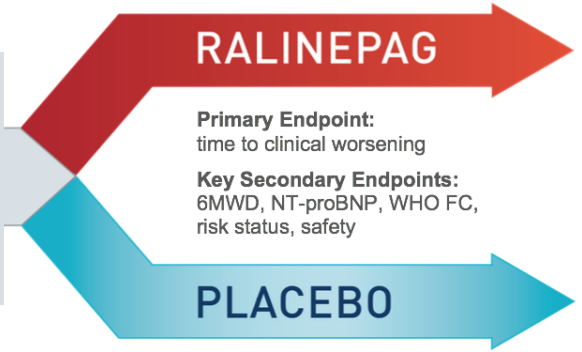
- NT-proBNP
- 6MWD
- WHO[2]/NYHA[3] Functional Class

Clinical improvement[4]
Time to first all-cause nonelective hospitalization
Time to all-cause mortality
Shift and proportion of subjects[5]
REVEAL[6] risk score
HRQoL[7] measures
HRR[8] following completion of 6MWT[9]
Safety and tolerability

STUDY VISIT SCHEDULE

All participants receiving PAH standard of care or PAH-specific background therapy were randomized 1:1.

Treatment Period lasted until the 180th adjudicated clinical worsening event.



OPEN-LABEL EXTENSION: Subjects that experienced a CW event are eligible to enroll

All subjects will receive Ralinepag

1. https://clinicaltrials.gov/study/NCT03626688 2. WHO = World Health Organization. 3. NYHA = New York Heart Association 4. Defined by the absence of clinical worsening and fulfillment of at least 2 of the 3 of the following: increase in 6MWD ≥10% or ≥30 m, improvement to or maintenance of WHO FC I or II, and decrease in NT-proBNP by at least 30%. 5. Subjects who attain all 3 of the following: NT-proBNP <300 pg/mL, 6MWD >440 m, WHO/NYHA FC I or II 6. REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management 7. HRQoL = Health-related quality of life 8. HRR = Heart rate recovery 9. 6MWT = 6-Minute Walk Test

ADVANCE OUTCOMES Study Design[1]

CLINICAL WORSENING DEFINITION

A protocol-defined clinical worsening event is defined as 1 of the following:

- Death (all causes)
- Nonelective hospital admission lasting at least 24 hours and/or right heart failure inclusive of lung transplant, heart/lung transplant, or atrial septostomy
- Initiation of parenteral (intravenous [IV] or subcutaneous [SC] infusion) or inhaled therapy with a prostacyclin pathway agent
- Disease progression, defined as:
  - A decrease in 6-Minute Walk Distance (6MWD) of at least 15% from Baseline:
    - A worsening from Baseline of at least 1 WHO Functional Class (FC)
    - Initiation of additional PAH-specific therapy
- Unsatisfactory long-term clinical response (all criteria required)
  - Has received study drug for at least 28 weeks
  - A decrease from Baseline in 6MWD at or after Week 28
  - Sustained WHO FC III or IV symptoms for at least 28 consecutive weeks

1. https://clinicaltrials.gov/study/NCT03626688

ADVANCE OUTCOMES BASELINE

Baseline Demographics of Enrolled Subjects

	Ralinepag N=350	Placebo N=337	Overall N=687
Age at Study Entry (years), median (range)	54.0 (18, 83)	52.0 (19, 84)	53.0 (18, 84)
Female (%)/Male (%)	256 (73.1)/94 (26.9)	264 (78.3)/73 (21.7)	520 (75.7)/167 (24.3)
Time Since Diagnosis (years), mean (SD)	4.3 (5.6)	4.8 (6.4)	4.5 (6.0)
Ethnicity, n (%)			
Hispanic or Latino	95 (27.1)	100 (29.7)	195 (28.4)
Not Hispanic or Latino	235 (67.1)	222 (65.9)	457 (66.5)
Race, n (%)			
White	283 (80.9)	268 (79.5)	551 (80.2)
Black	10 (2.9)	12 (3.6)	22 (3.2)
Native Hawaiian/Pacific Islander	2 (0.6)	1 (0.3)	3 (0.4)
Asian	21 (6.0)	38 (11.3)	59 (8.6)
Multiple	2 (0.6)	4 (1.2)	6 (0.9)
Other	18 (5.1)	11 (3.3)	29 (4.2)
Not Reported	13 (3.7)	3 (0.9)	16 (2.3)

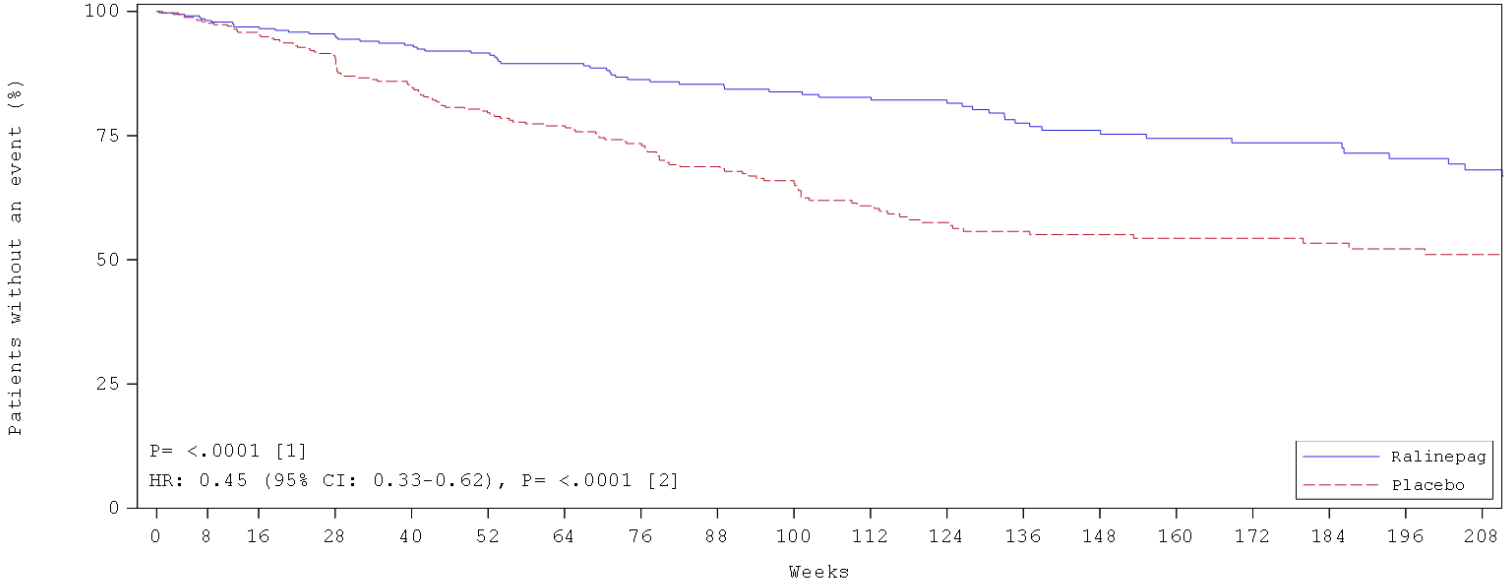
ADVANCE OUTCOMES BASELINE

Baseline Demographics Cont'd

	Ralinepag N=350	Placebo N=337	Overall N=687
Weight (kg), mean (SD)	73.2 (16.3)	73.8 (17.9)	73.5 (17.1)
Background Therapy			
One or No Background Therapy, n (%)	68 (19.4)	71 (21.1)	139 (20.2)
Dual Background Therapy, n (%)	282 (80.6)	266 (78.9)	548 (79.8)
Baseline 6MWD (m), mean (SD)	441.3 (106.9)	436.5 (102.7)	438.9 (104.8)
6MWD <400m, n (%)	118 (33.7)	118 (35.0)	236 (34.4)
≥400m, n (%)	232 (66.3)	219 (65.0)	461 (67.1)
WHO Functional Class, n (%)			
II	261 (74.6)	223 (66.2)	484 (70.5)
III	89 (29.4)	113 (33.5)	202 (29.4)
IV	0	1 (0.3)	1 (0.1)

Primary Endpoint

Time to Adjudication Clinical Worsening (Weeks); Kaplan-Meier Estimates



No. at Risk

Ralinepag	350	311	286	261	238	220	204	185	172	158	144	135	111	98	90	76	72	66	59
Placebo	337	327	313	283	246	217	197	180	150	135	112	99	86	75	69	59	52	45	43

1. P value is calculated with log rank test stratified by background PAH therapy and baseline 6MWD category. 2. Hazard ratio, 95% CI, and P value are calculated with proportional hazard model with treatment and the randomization stratification factors in the model

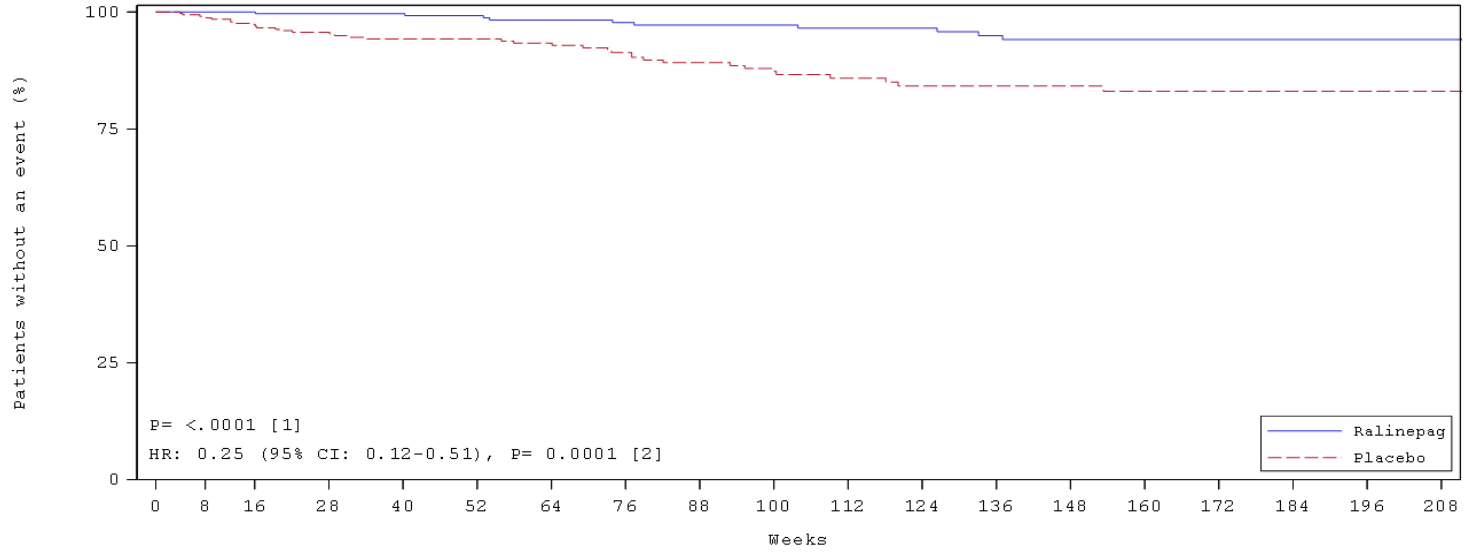
Primary Endpoint
Adjudicated Clinical Worsening Events

		Ralinepag			Placebo	
		N=350	%		N=337	%
Clinical worsening event category as the first event n(%)	**All events**	**64**	**18.3%**		**121**	**35.9%**
	Death (all causes)	11	3.1%		10	3.0%
	Hospitalization due to PAH	19	5.4%		20	5.9%
	Disease Progression	**10**	**2.9%**		**36**	**10.7%**
	Initiation of inhaled or infused prostacyclin	**10**	**2.9%**		**22**	**6.5%**
	Unsatisfactory long-term clinical response	**14**	**4.0%**		**33**	**9.8%**
Hazard Ratio (95% CI) (Ralinepag - Placebo)[1]				**0.45** (0.33, 0.62) ***P<0.0001***		

1. Hazard ratio, 95% CI, and P value are calculated with proportional hazard model with treatment and the randomization stratification factors in the model.

Primary Endpoint

Time to Disease Progression; Kaplan-Meier Estimates



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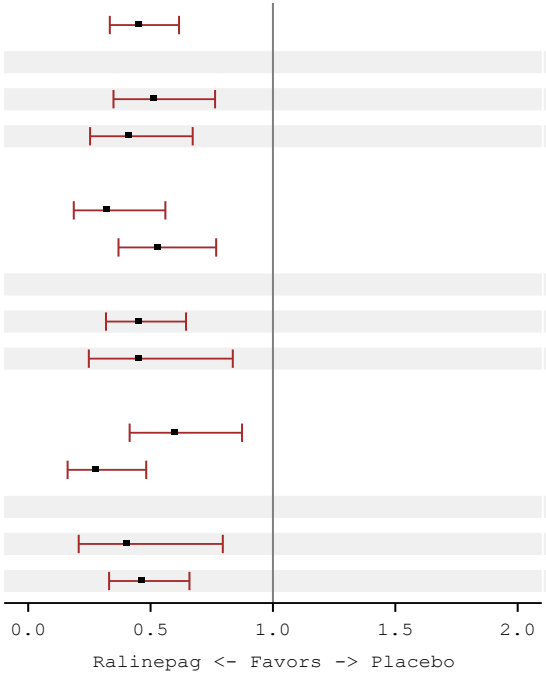
Placebo	337	327	313	283	246	217	197	180	150	135	112	99	86	75	69	59	52	45	43

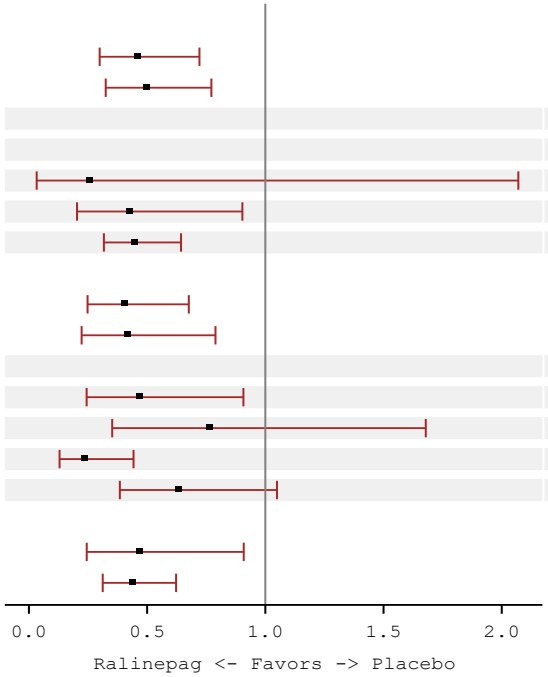
Subgroup Analyses
Time to First Clinical Worsening Event

Subgroup	Ralinepag # of Events / # of Patients	Placebo # of Patients	Hazard Ratio (95% CI)
Overall	64/350	121/337	0.45(0.33, 0.62)
Baseline 6MWD			
<400 m	41/114	67/112	0.52(0.35, 0.76)
>=400 m	23/236	54/225	0.41(0.25, 0.67)
Etiology			
CTD Associated	19/100	40/94	0.32(0.19, 0.56)
Other Etiology	45/250	81/243	0.53(0.37, 0.77)
Background PAH Therapy			
Two	47/283	91/265	0.45(0.32, 0.64)
One or Zero	17/67	30/72	0.46(0.25, 0.84)
Age at Baseline			
<65 yrs	43/260	85/262	0.60(0.41, 0.87)
>=65 yrs	21/90	36/75	0.28(0.16, 0.48)
Sex			
Male	14/94	22/73	0.41(0.21, 0.80)
Female	50/256	99/264	0.47(0.33, 0.66)



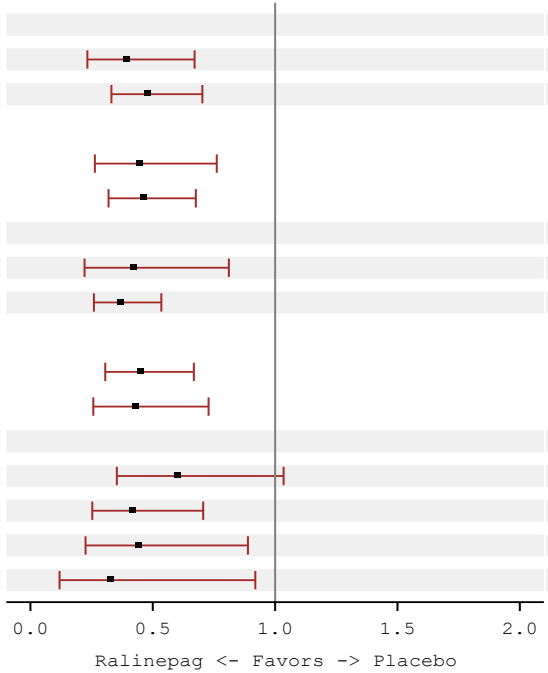
Subgroup Analyses
Time to First Clinical Worsening Event

Subgroup	Ralinepag # of Events / # of Patients	Placebo # of Events / # of Patients	Hazard Ratio (95% CI)
Baseline WHO FC			
WHO FC II	32/261	56/223	0.46(0.30, 0.72)
WHO FC III or IV	32/89	65/114	0.50(0.32, 0.77)
PAH Therapy at Baseline			
None	2/8	5/6	ND
ERA	1/14	9/17	0.26(0.03, 2.07)
PDE5-I/sGC	14/45	16/49	0.43(0.20, 0.90)
ERA + PDE5-I/sGC	47/283	91/265	0.45(0.32, 0.64)
Maximum Dose Achieved			
<600 mcg	53/302	22/66	0.41(0.25, 0.68)
>=600 mcg	11/48	99/271	0.42(0.22, 0.79)
Geographic Region			
North America	14/81	26/96	0.47(0.24, 0.91)
Asia-Pacific	11/46	15/51	0.77(0.35, 1.68)
Europe	14/139	39/106	0.24(0.13, 0.44)
South and Latin America	25/84	41/84	0.64(0.38, 1.05)
Location			
North America	14/81	26/96	0.47(0.24, 0.91)
Rest of World	50/269	95/241	0.44(0.31, 0.62)



Subgroup Analyses
Time to First Clinical Worsening Event

Subgroup	Ralinepag # of Events / # of Patients	Placebo # of Patients	Hazard Ratio (95% CI)
Baseline mean PAP			
<median (44 mmHg)	20/167	45/168	0.40 (0.23, 0.67)
>=median (44 mmHg)	44/182	76/169	0.48 (0.33, 0.70)
Baseline PVR			
<median (577 dyn.sec/cm5)	21/173	40/169	0.45 (0.26, 0.76)
>=median (577 dyn.sec/cm5)	43/176	80/167	0.46 (0.32, 0.68)
Baseline plasma NT-proBNP			
<median (213 pg/mL)	12/163	39/177	0.42 (0.22, 0.81)
>=median (213 pg/mL)	51/183	81/158	0.37 (0.26, 0.53)
Time since PAH diagnosis			
<median (2.285 years)	45/186	62/157	0.45 (0.31, 0.67)
>=median (2.285 years)	19/164	59/179	0.43 (0.26, 0.73)
Baseline Risk Category*			
0	24/42	32/42	0.60 (0.35, 1.03)
1	22/79	48/93	0.42 (0.25, 0.71)
2	12/115	26/97	0.45 (0.23, 0.89)
3	5/110	14/103	0.33 (0.12, 0.92)



ADVANCE OUTCOMES RESULTS

Summary of Most Commonly Reported Adverse Events by Preferred Term

	Ralinepag N=350	Placebo N=337
Preferred Term	**n (%)**	**n (%)**
Any Event	**346 (98.9%)**	**320 (95.0%)**
Headache	284 (81.1%)	140 (41.5%)
Diarrhea	204 (58.3%)	95 (28.2%)
Nausea	158 (45.1%)	86 (25.5%)
Myalgia	126 (36.0%)	36 (10.7%)
Pain in jaw	125 (35.7%)	30 (8.9%)

Note: Table reflects top 5 most reported adverse events.

ADVANCE OUTCOMES RESULTS

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The study also met several important secondary endpoints, including change in NT-proBNP[1], 6MWD[2], and clinical improvement

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Dr. Daniel Lachant, DO, MSCI, ATSF

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Q&A

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ADVANCE™ outcomes

We are incredibly thankful to the participants, investigators, and research teams whose work contributed to the development of ralinepag