Near-Term Launches + High-Value Pipeline Day: Scientific Posters

December 12, 2022

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Efficacy and Safety of Zavegepant Nasal Spray for the Acute Treatment of Migraine: Results of a Phase 3 Double-Blind, Randomized, Placebo-Controlled Trial

Kathleen Mullin, MD[1]; Robert Croop, MD[2]; Jelena M. Pavlovic, MD, PhD[3]; Linda Mosher, MA[2]; Timothy R. Smith, MD, RPh[4]; Jennifer Madonia, MS, PA-C[2]; Meghan Lovegren, BS[2]; Vladimir Coric, MD[2]; Richard B. Lipton, MD[3]

1 New England Institute for Neurology and Headache, Stamford, CT, USA; 2 Biohaven Pharmaceuticals, New Haven, CT, USA; 3 Albert Einstein College of Medicine, Bronx, NY, USA; 4 StudyMetrix Research, St. Louis, MO, USA

Introduction

- In the acute treatment of migraine, nonoral therapies are recommended for:
  - Attacks that include severe nausea or vomiting or rapidly escalating headache pain
  - Patients in whom oral forms are associated with inadequate response, slow onset of action, or poor tolerability[1]
- Although people with migraine commonly cite rapid relief as a high-priority treatment goal, lack of efficacy, adverse events (AEs), and cardiovascular complications limit the clinical utility of existing nonoral alternatives (triptans, ergot alkaloids)[2]
- Zavegepant is the only small molecule CGRP receptor antagonist delivered by nasal spray in late-stage development for the acute treatment of migraine
- A Phase 1 study found that the 10 mg nasal spray was rapidly absorbed (T_{max}~30 minutes)[3]; a dose-ranging study (NCT03872453) found that zavegepant 10 mg was the optimal dose[4]

Objective

- The objective of this study was to compare the efficacy and safety of zavegepant nasal spray with placebo in the acute treatment of migraine

Results

Subjects

- In total, 1978 subjects were recruited and screened for eligibility between 27 October 2020 and 20 August 2021; of these, 1405 were randomized, and 1269 were evaluable for efficacy (zavegepant n=623, placebo n=646)
- Demographics and other baseline characteristics are described in **Table 1**

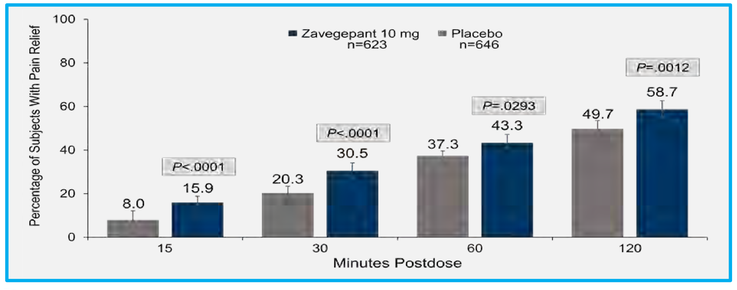
Table 1. Demographics and baseline characteristics

	Zavegepant Nasal Spray 10 mg (n=623)	Placebo (n=646)	Overall N=1269
Age, years, mean (SD)	40.9 (13.22)	40.8 (13.46)	40.8 (13.34)
Female, n (%)	506 (81.2)	546 (84.5)	1052 (82.9)
Race, n (%)			
White	511 (82.0)	540 (83.6)	1051 (82.8)
Black or African American	85 (13.6)	83 (12.8)	168 (13.2)
Other	27 (4.3)	23 (3.6)	50 (3.9)
Moderate-severe attacks per month, n, mean (SD)	4.6 (1.81)	4.7 (1.81)	4.7 (1.81)
Using preventive migraine medication, n (%)	88 (14.1)	82 (12.7)	170 (13.4)

Efficacy

- Zavegepant was superior to placebo for the coprimary endpoints of freedom from pain (23.6% vs 14.9%, *P*<0.0001) and freedom from the MBS (39.6% vs 31.1%, *P*=0.0012) at 2 hours postdose
- Zavegepant was also superior to placebo on multiple secondary endpoints (**Table 2**), including pain relief at 15 minutes, return to normal function at 30 minutes, and sustained pain relief from 2 to 48 hours postdose
- Zavegepant was more effective than placebo for pain relief from 15 minutes through 2 hours postdose (**Figure 1**)

Figure 1. Pain relief at 15, 30, 60 and 120 minutes postdose.



Methods

Design

- This was a phase 3, double-blind, randomized, placebo-controlled multicenter trial (NCT04571060)
- Subjects self-administered 1 dose of zavegepant 10 mg nasal spray or placebo to treat 1 migraine attack of moderate or severe pain intensity; they used an eDiary to record data from predose through 48 hours postdose
- Subjects were permitted to use only the following rescue medications: aspirin, ibuprofen, acetaminophen [up to 1000 mg/d]-(including Excedrin Migraine), naproxen [or any other nonsteroidal anti-inflammatory], antiemetics, or baclofen) 2 hours after study medication dose

Subjects

- Adults aged ≥18 years with ≥ 1-year history of migraine and, in the 3 months prior to screening, 2-8 moderate to severe monthly migraine attacks and >15 monthly headache days (migraine or nonmigraine)
- If using preventive medication, the dose had to be stable for ≥3 months

Assessments

- The coprimary efficacy endpoints were freedom from pain at 2 hours postdose and freedom from the most bothersome symptom (MBS) at 2 hours postdose; safety assessments included adverse events (AEs), ECGs, vital signs, physical measurements, clinical laboratory tests, Sheehan Suicidality Tracking Scale
- Randomization (1:1) was stratified by use of preventive migraine medication (yes or no)
- A hierarchical gatekeeper approach was used to control for multiple comparisons

Table 2. Summary of results on coprimary and secondary efficacy endpoints.[a]

	Zavegepant Nasal Spray 10 mg	Placebo	P-value[b]
Pain freedom at 2 hours postdose	**147/623 (23.6)**	**96/646 (14.9)**	**<0.0001**
Freedom from the MBS at 2 hours postdose	**247/623 (39.6)**	**201/646 (31.1)**	**0.0012**
Pain relief at 2 hours postdose	366/623 (58.7)	321/646 (49.7)	0.0012
Return to normal function at 2 hours postdose[c]	204/570 (35.8)	152/593 (25.6)	0.0001
Sustained pain relief from 2 to 24 hours postdose	253/623 (40.6)	213/646 (33.0)	0.0048
Sustained pain relief from 2 to 48 hours postdose	225/623 (36.1)	191/646 (29.6)	0.0130
Sustained pain freedom from 2 to 24 hours postdose	91/623 (14.6)	63/646 (9.8)	0.0076
Sustained pain freedom from 2 to 48 hours postdose	77/623 (12.4)	56/646 (8.7)	0.0308
Phonophobia freedom at 2 hours postdose[d]	167/407 (41.0)	139/425 (32.7)	0.0123
Photophobia freedom at 2 hours postdose[d]	207/558 (37.1)	167/585 (28.5)	0.0018
Pain relief at 60 minutes postdose	270/623 (43.3)	241/646 (37.3)	0.0293
Return to normal function at 60 minutes postdose[c]	115/570 (20.2)	92/593 (15.5)	0.0362
Pain relief at 30 minutes postdose	190/623 (30.5)	131/646 (20.3)	<0.0001
Return to normal function at 30 minutes postdose[c]	60/570 (10.5)	36/593 (6.1)	0.0059
Pain relief at 15 minutes postdose	99/623 (15.9)	52/646 (8.0)	<0.0001
Return to normal function at 15 minutes postdose[c]	19/570 (3.3)	12/593 (2.0)	0.1826
Rescue medication use within 24 hours postdose[e]	184/620 (29.7)	230/643 (35.8)	0.0194
Nausea freedom at 2 hours postdose[d]	199/380 (52.4)	206/405 (50.9)	0.6753
Pain relapse from 2 to 48 hours postdose[f]	60/147 (40.8)	34/96 (35.4)	0.3944

[a]Subjects taking rescue medication at or before the time point were imputed as failures for all endpoints except rescue medication use within 24 hours postdose; [b]Cochran-Mantel-Haenszel test stratified by preventive migraine medication use at randomization; [c]Among subjects with functional disability at time of dosing; [d]Among subjects with the symptom present at time of dosing; [e]Subjects with rescue medication start date on or before the study drug start date + 1 day and missing rescue medication start time were excluded; [f]Among subjects with pain freedom at 2 hours postdose.

Safety and Tolerability

- Table 3 presents a summary of safety for treated subjects
- There were no serious AEs, and most AEs were mild or moderate in intensity; no signal of hepatotoxicity was observed
- The most common (≥2% of subjects) AEs were dysgeusia (20.5% vs 4.7%), nasal discomfort (3.7% vs 0.8%), and nausea (3.2% vs 1.1%)

Table 3. Treatment-emergent adverse events (≥2% of subjects)

	Zavegepant Nasal Spray 10 mg[a] (n=629)	Placebo[a] (n=653)
Subjects with ≥1 AE, n (%)	186 (29.6)	102 (15.6)
AEs reported by ≥2% of subjects, n (%)		
Dysgeusia	129 (20.5)	31 (4.7)
Nasal discomfort	23 (3.7)	5 (0.8)
Nausea	20 (3.2)	7 (1.1)

[a]Safety was analyzed in subjects who took any dose of study medication (zavegepant or placebo).

Conclusions

1. A 10 mg dose of zavegepant nasal spray was more effective than placebo in the acute treatment of migraine
2. Zavegepant nasal spray achieved its coprimary endpoints and provided a rapid onset of pain relief as early as 15 minutes postdose, sustained benefits to 48 hours postdose, and favorable safety and tolerability

Author Disclosures: RC, JM, JH, LM, ML, and VC are employed by and own stock/stock options in Biohaven Pharmaceuticals. RBL has received honoraria and research support from Biohaven Pharmaceuticals; he is also a stockholder.

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A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for the Preventive Treatment of Migraine

Robert Croop, MD[1]; Richard B. Lipton, MD[2]; David Kudrow, MD[3]; David A. Stock, PhD[1]; Lisa Kamen, MHA[1]; Charles M. Conway, PhD[1]; Elyse G. Stock, MD[1]; Vladimir Coric, MD[1]; Peter J. Goadsby, MD, PhD[4]

1 Biohaven Pharmaceuticals, Inc., New Haven CT, USA; 2 Albert Einstein College of Medicine, Bronx, NY; 3 California Medical Clinic for Headache, Santa Monica, CA; 4 NIHR-Wellcome Trust King's Clinical Research Facility, King's College Hospital/SLaM Biomedical Research Centre, King's College London, UK and University of California, Los Angeles, Los Angeles, CA, USA

Introduction

- Rimegepant is an FDA-approved, orally-administered calcitonin gene-related peptide receptor antagonist that has demonstrated efficacy and safety in the acute treatment of migraine across multiple randomized, placebo-controlled clinical trials[1-4]
- In a long-term, open-label safety study, a reduction in monthly migraine days (MMDs) was observed with rimegepant 75 mg dosed every other day for 12 weeks, with no signs of medication-overuse headache[5]
- The reduction in MMDs generated the hypothesis that an every-other-day dosing regimen of rimegepant might be safe and effective for preventive treatment of migraine
- This was the first randomized, placebo-controlled clinical trial designed to evaluate rimegepant for the preventive treatment of migraine[6]

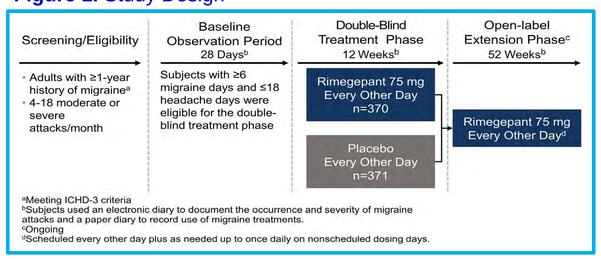
Objective

- Compare the efficacy, safety, and tolerability of rimegepant with placebo for the preventive treatment of migraine

Methods

- This randomized, double-blind, placebo-controlled trial (NCT03732638) was conducted at 92 study centers in the United States

Figure 1. Study Design



Assessments

- Primary efficacy endpoint: mean change from the 4-week observation period in the number of migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12)
- Safety assessments: adverse events (AEs), including hepatic-related, and laboratory tests, including liver function tests

Statistical Analysis

- Efficacy population: randomized subjects who received ≥1 dose of rimegepant or placebo and had ≥14 days of electronic diary efficacy data from the 4-week observation period and for ≥1 of the 4-week intervals during double-blind treatment
- The primary efficacy endpoint was tested for superiority versus placebo using a generalized linear mixed-effect model; secondary endpoints were tested hierarchically to control Type I error
- A post-hoc analysis assessed mean percentage changes from the observation period in weekly migraine days at each week during the first 4 weeks of double-blind treatment; weekly migraine frequency in the observation period was computed using the number of migraine days over the 4-week period prorated to 7 days
- Safety population: subjects who received ≥1 dose of rimegepant or placebo

Results

Subjects

- In total, 747 subjects were randomized (rimegepant n=373, placebo n=374); 741 were treated (rimegepant n=370, placebo n=371); and 695 were evaluated for efficacy (rimegepant n=348, placebo n=347)
- Most subjects (82.7%) were female, with a mean (SD) age of 41.2 (13.1) years
- The treated population had a mean (SD) history of 7.8 (2.7) moderate or severe attacks per month; 23.3% had a history of chronic migraine (rimegepant n=78 [21.1%], placebo n=95 [25.6%])
- During the observation period, efficacy-evaluable subjects in the rimegepant (n=348) and placebo (n=347) groups had a mean (SD) of 10.3 (3.2) and 9.9 (3.0) MMDs, respectively

Efficacy

- Rimegepant 75 mg was superior to placebo for the primary endpoint of mean change in MMDs during Weeks 9 through 12 (−4.3 vs −3.5, *p*=0.0099), as shown in Table 1

Table 1. Efficacy of Rimegepant in the Modified Intention-To-Treat Population[a]

	Rimegepant 75 mg n=348	Placebo n=347	Difference (95% CI)	P value
PRIMARY EFFICACY ENDPOINT				
Mean change in number of MMDs during Weeks 9-12[b]	−4.3	−3.5	−0.8 (−1.5 to −0.2)	0.0099
SECONDARY EFFICACY ENDPOINTS				
≥50% reduction in mean number of moderate or severe MMDs during Weeks 9-12, %	49	41	8 (0 to 15)	0.0438
Mean change in number of total MMDs during Weeks 1-12[b]	−3.6	−2.7	−0.8 (−1.3 to −0.3)	0.0017
Rescue medication days per month during Weeks 9-12[b]	3.7	4.0	−0.2 (−0.8 to 0.3)	0.3868[c]
Change in number of total MMDs during Weeks 1-4[b]	−2.9	−1.7	−1.2 (−1.7 to −0.6)	<0.0001[c]
Change in MSQ restrictive role function at Week 12[b,d]	18.0	14.6	3.5 (0.2 to 6.7)	0.0358[c]
Change in MIDAS total score at Week 12[b,d]	−11.8	−11.7	−0.1 (−4.7 to 4.5)	0.9616[c]

CI, confidence interval; MMD, monthly migraine day; MSQ, migraine-specific quality of life questionnaire; MIDAS, Migraine Disability Assessment
[a]Evaluable subjects had ≥14 days of electronic diary efficacy data (not necessarily consecutive) in the observation period and ≥1 month (4-week interval) in the double-blind treatment phase. To control the type I statistical error rate at 0.05, a pre-planned hierarchical testing procedure was applied; endpoints are presented in the sequence in which they were evaluated; [b]Reported as least squares mean and analyzed using a generalized linear mixed-effects model with treatment group, preventive migraine medication use at randomization, study month, and month-by-treatment group interaction as fixed effects and subject as random effect.; [c]Nominal p-value in hierarchical testing; [d]Reported as least squares mean; analysis only included subjects who completed the MIDAS or MSQ questionnaire within the prespecified on-treatment efficacy analysis window (Weeks 10-13; rimegepant n=269, placebo n=266).

Results *cont.*

Efficacy

- Rimegepant was also superior to placebo on the secondary endpoints of ≥50% reduction in the number of moderate or severe MMDs during Weeks 9-12 (Figure 2) and mean change in the number of total MMDs during Weeks 1-12 (Table 1)
- A post-hoc analysis assessed mean percentage changes from the observation period in weekly migraine days over the first 4 weeks of double-blind treatment (Figure 3); preventive effects of rimegepant were observed within the first week

Figure 2. Subjects With ≥50% Reduction in the Number of Moderate to Severe Migraine Days Per Month During Weeks 9–12

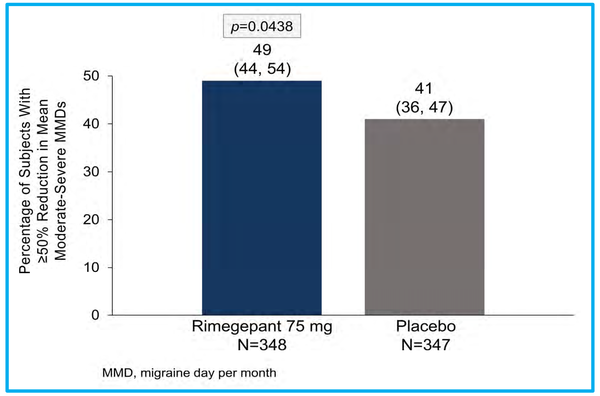
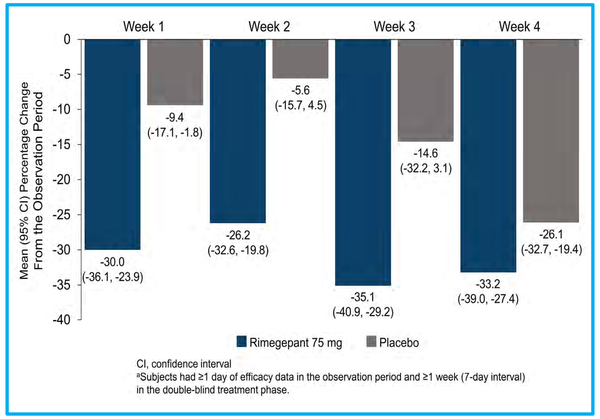


Figure 3. Percentage Change from the Observation Period in Migraine Days per Week During the First 4 Weeks of Double-Blind Treatment[a]



Results *cont.*

Safety

- Subjects in the rimegepant and placebo treatment groups were equally likely to experience an AE, as shown in Table 2
- Nearly all AEs were mild or moderate in intensity
- No treatment-related serious AEs were reported in the rimegepant group
- The rate of discontinuations due to an AE was low in both treatment groups
- Four (1.1%) subjects who were treated with rimegepant and 2 (0.5%) subjects who were treated with placebo had aspartate aminotransferase or alanine aminotransferase elevations >3x ULN
- One (0.3%) subject in the rimegepant group had asymptomatic elevation of transaminases with ALT greater than 10x ULN, and alkaline phosphatase and bilirubin levels were always within normal limits; the site principal investigator deemed the increases not related to study drug, and an independent panel of liver experts concluded that the relation to study medication was not probable
- One (0.3%) subject in the rimegepant group had bilirubin levels greater than 2x ULN and was diagnosed with Gilbert's syndrome after genotyping

Table 2. Adverse Events With Rimegepant 75 mg and Placebo

	Rimegepant 75 mg n=370 n (%)	Placebo n=371 n (%)
Subjects with any AE	133 (35.9)	133 (35.8)
AEs (≥2% of subjects)		
Nasopharyngitis	13 (3.5)	9 (2.4)
Nausea	10 (2.7)	3 (0.8)
Urinary tract infection	9 (2.4)	8 (2.2)
Upper respiratory tract infection	8 (2.2)	10 (2.7)
Subjects with mild AE	92 (24.9)	91 (24.5)
Subjects with moderate AE	64 (17.3)	62 (16.7)
Subjects with AEs related to treatment	40 (10.8)	32 (8.6)
Serious AEs	3 (0.8)	4 (1.1)
Serious AEs related to treatment	0	1 (0.3)
AEs leading to discontinuation	7 (1.9)	4 (1.1)

AE, adverse event

Conclusions

- Oral rimegepant 75 mg taken every other day was effective for the preventive treatment of migraine
- Preventive efficacy was observed within the first week of rimegepant treatment
- Tolerability was similar to placebo, and there were no unexpected or serious safety issues
- These preventive effects, along with previously established acute treatment efficacy, suggest that rimegepant may provide a new approach to treat migraine in an adaptive way depending on an individual's treatment needs from acute to prevention

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Efficacy, Safety, and Tolerability of Rimegepant 75 mg Orally DissolvingTablet for the Acute Treatment of Migraine: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial (Study 303)

Richard B. Lipton, MD[1]; Vladimir Coric, MD[2]; Elyse G. Stock, MD[2]; David A. Stock, PhD[2]; Charles M. Conway, PhD[2]; Christopher M. Jensen, PharmD[2]; Ralph Gosden, MSc[3]; Micaela Forshaw, MPH[2]; Robert Croop, MD[2]
[1]Albert Einstein College of Medicine, Bronx, NY, USA; [2]Biohaven Pharmaceuticals, Inc., New Haven, CT, USA; [3]Catalent UK Swindon Zydis Limited, Swindon, UK

Introduction

- Rimegepant is an orally administered small molecule calcitonin gene-related peptide receptor antagonist
- Currently available acute treatments for migraine may be ineffective, poorly tolerated, or contraindicated in many patients[1]
- People with migraine prefer orally dissolving tablets (ODTs) to oral tablets, mainly for their convenience, onset of action, and ability to be taken without drinking liquids[2-4]
- Two Phase 3 clinical trials demonstrated efficacy and safety of rimegepant 75 mg oral tablet for the acute treatment of migraine (Study 301 and Study 302)
- A novel ODT formulation of rimegepant was developed utilizing the Zydis® fast-dissolve technology to optimize its speed of onset and ease of use
- Unlike other ODTs, rimegepant 75 mg ODT has a shorter T_{max} (1.5 h) than the tablet (1.99 h; *P*=.0028), suggesting that the ODT may have a faster onset of action

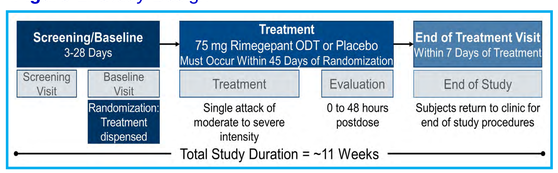
Objective

- Assess rimegepant 75 mg ODT versus placebo on efficacy, safety, and tolerability in the acute treatment of migraine

Methods

- This was a double-blind, randomized, placebo-controlled, multicenter trial (Study 303, NCT03461757)

Figure 1. Study Design



- Subjects used an eDiary to record data from predose through 48 hours postdose

Subjects

- Aged ≥18 years, with ≥1-year history of ICHD-3 beta migraine
- Two to 8 moderate or severe monthly migraine attacks; <15 monthly headache days (migraine or nonmigraine) over the last 3 months
- Preventive migraine medication dose stable for ≥3 months (if using)

Assessments

- Coprimary efficacy endpoints: pain freedom at 2 hours postdose and freedom from the most bothersome symptom (MBS [ie, photophobia, phonophobia, or nausea]) at 2 hours postdose
- Safety assessments: AEs, ECGs, vital signs, physical measurements, routine laboratory tests, including liver function tests

Statistical Analysis

- Efficacy analyses were performed on the modified intent-to-treat population: randomized subjects who had a qualifying migraine attack, took study medication, and provided ≥1 evaluable postbaseline efficacy data point
- Safety analyses were conducted on enrolled subjects who took any dose of study medication (rimegepant or placebo)
- A hierarchical gatekeeper approach was used to control for multiple comparisons

Results

Subjects

- In total, 1375 subjects were randomized and treated (rimegepant n=682, placebo n=693), and 1351 were evaluated for efficacy (rimegepant n=669, placebo n=682)
- Most subjects (84.9%) were female, with a mean (SD) age of 40.2 (12.0) years
- Mean (SD) history of attacks per month was 4.6 (1.8), and mean (SD) duration of untreated attacks was 29.5 (21.6) hours
- Historically, the most common MBS was photophobia (57.0%), followed by nausea (23.5%) and phonophobia (19.3%)
- Approximately 14% were using preventive treatment

Efficacy

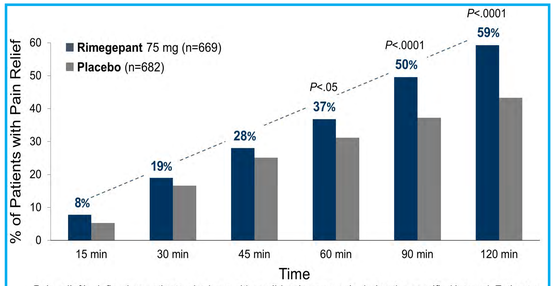
- A single dose of rimegepant 75 mg ODT was superior to placebo for pain freedom (21.2% vs 10.9%, *P*<.0001) and freedom from the MBS (35.1% vs 26.8%, *P*=.0009) at 2 hours potdose, as well as on 19 prespecified, hierarchically-tested secondary endpoints (Figures 2 and 3), including:
  - Pain relief and functional disability freedom at 60 minutes postdose
  - Pain freedom and MBS freedom at 90 minutes postdose
  - Sustained efficacy endpoints from 2 through 48 hours postdose

Results *cont.*

Efficacy

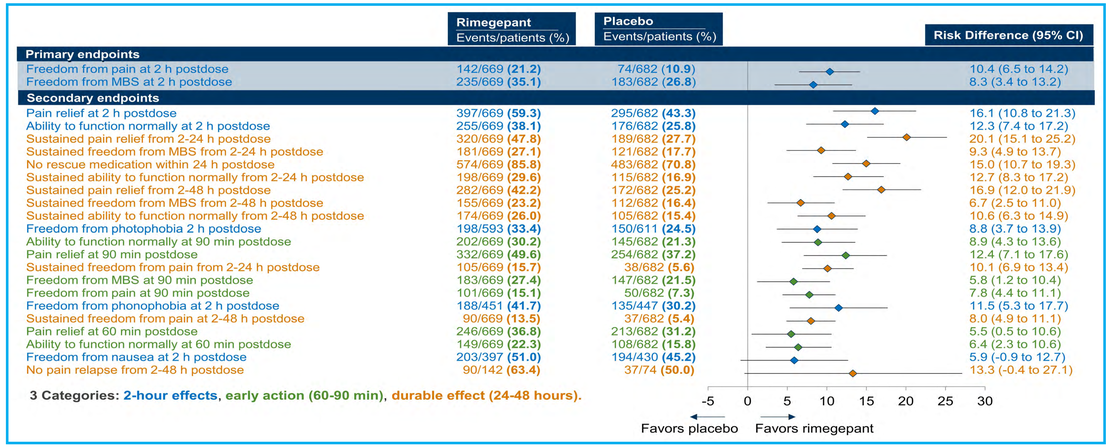
- Rimegepant ODT was numerically separated from placebo on pain relief beginning at 15 minutes postdose; statistically significant at 60 minutes (Figure 4)

Figure 4. Pain Relief Through 2 Hours Postdose



Pain relief is defined as patients who have either mild-pain or no-pain during the specified interval. Estimates computed using the mITT population and CMH methods. Subjects using rescue medications at or before the assessment, and subjects not providing data, are classified as failures.

Figure 2. Efficacy on Coprimary and Secondary Endpoints



	Rimegepant Events/patients (%)	Placebo Events/patients (%)	Risk Difference (95% CI)
Primary endpoints			
Freedom from pain at 2 h postdose	142/669 (**21.2**)	74/682 (**10.9**)	10.4 (6.5 to 14.2)
Freedom from MBS at 2 h postdose	235/669 (**35.1**)	183/682 (**26.8**)	8.3 (3.4 to 13.2)
Secondary endpoints			
Pain relief at 2 h postdose	397/669 (**59.3**)	295/682 (**43.3**)	16.1 (10.8 to 21.3)
Ability to function normally at 2 h postdose	255/669 (**38.1**)	176/682 (**25.8**)	12.3 (7.4 to 17.2)
Sustained pain relief from 2-24 h postdose	320/669 (**47.8**)	189/682 (**27.7**)	20.1 (15.1 to 25.2)
Sustained freedom from MBS from 2-24 h postdose	181/669 (**27.1**)	121/682 (**17.7**)	9.3 (4.9 to 13.7)
No rescue medication within 24 h postdose	574/669 (**85.8**)	483/682 (**70.8**)	15.0 (10.7 to 19.3)
Sustained ability to function normally from 2-24 h postdose	198/669 (**29.6**)	115/682 (**16.9**)	12.7 (8.3 to 17.2)
Sustained pain relief from 2-48 h postdose	282/669 (**42.2**)	172/682 (**25.2**)	16.9 (12.0 to 21.9)
Sustained freedom from MBS from 2-48 h postdose	155/669 (**23.2**)	112/682 (**16.4**)	6.7 (2.5 to 11.0)
Sustained ability to function normally from 2-48 h postdose	174/669 (**26.0**)	105/682 (**15.4**)	10.6 (6.3 to 14.9)
Freedom from photophobia 2 h postdose	198/593 (**33.4**)	150/611 (**24.5**)	8.8 (3.7 to 13.9)
Ability to function normally at 90 min postdose	202/669 (**30.2**)	145/682 (**21.3**)	8.9 (4.3 to 13.6)
Pain relief at 90 min postdose	332/669 (**49.6**)	254/682 (**37.2**)	12.4 (7.1 to 17.6)
Sustained freedom from pain from 2-24 h postdose	105/669 (**15.7**)	38/682 (**5.6**)	10.1 (6.9 to 13.4)
Freedom from MBS at 90 min postdose	183/669 (**27.4**)	147/682 (**21.5**)	5.8 (1.2 to 10.4)
Freedom from pain at 90 min postdose	101/669 (**15.1**)	50/682 (**7.3**)	7.8 (4.4 to 11.1)
Freedom from phonophobia at 2 h postdose	188/451 (**41.7**)	135/447 (**30.2**)	11.5 (5.3 to 17.7)
Sustained freedom from pain at 2-48 h postdose	90/669 (**13.5**)	37/682 (**5.4**)	8.0 (4.9 to 11.1)
Pain relief at 60 min postdose	246/669 (**36.8**)	213/682 (**31.2**)	5.5 (0.5 to 10.6)
Ability to function normally at 60 min postdose	149/669 (**22.3**)	108/682 (**15.8**)	6.4 (2.3 to 10.6)
Freedom from nausea at 2 h postdose	203/397 (**51.0**)	194/430 (**45.2**)	5.9 (-0.9 to 12.7)
No pain relapse from 2-48 h postdose	90/142 (**63.4**)	37/74 (**50.0**)	13.3 (-0.4 to 27.1)

3 Categories: **2-hour effects**, **early action (60-90 min)**, **durable effect (24-48 hours)**.

Figure 3. Efficacy Summary: Pain and Return to Normal Function

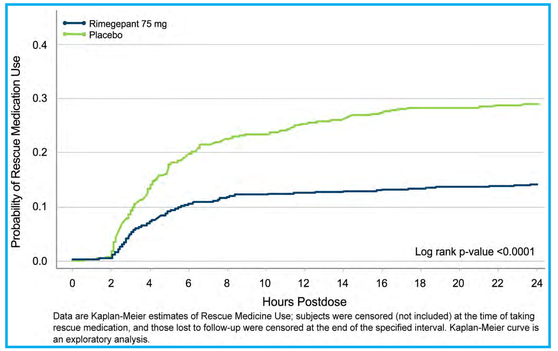


*p < 0.05 vs. placebo

Results *cont.*

- Rimegepant ODT was superior to placebo on rescue medication use (Figure 5); only 14.2% of rimegepant-treated subjects took rescue medication within 24 hours

Figure 5. Rescue Medication Use Up to 24 Hours Postdose[a]



Data are Kaplan-Meier estimates of Rescue Medicine Use; subjects were censored (not included) at the time of taking rescue medication, and those lost to follow-up were censored at the end of the specified interval. Kaplan-Meier curve is an exploratory analysis.

Safety

- The most common AEs were nausea and urinary tract infection (≤1.6%)
- One rimegepant-treated and 1 placebo-treated subject had a transaminase level >3x ULN, but neither was assessed by the principal investigator as related to treatment
- No subjects had elevations in bilirubin >2 times the ULN
- Safety results are shown in Table 2

Table 2. Adverse Events

	Rimegepant 75 mg ODT N=682 n (%)	Placebo N=693 n (%)
Participants with AEs	90 (13.2)	73 (10.5)
AEs reported by ≥1% of subjects		
Nausea	11 (1.6)	3 (.4)
Urinary tract infection	10 (1.5)	4 (.6)
AEs related to treatment	47 (6.9)	36 (5.2)
Serious AEs	0 (.0)	0 (.0)

Conclusions

- In the acute treatment of migraine, a single dose of rimegepant 75 mg ODT was more effective than placebo
- Statistically significant and clinically meaningful effects on pain relief and functional disability freedom were observed at 60 minutes and sustained from 2 through 48 hours postdose
- Safety and tolerability were similar to placebo
- A single dose of rimegepant ODT has potential for early and sustained therapeutic action in the acute treatment of migraine

References: 1. Ferrari MD et al. Lancet. 2001;358:1668-1675; 2. Loder E et al. Headache. 2001;41:745-753; 3. Dowson AJ et al. Curr Med Res Opin. 2005;21 Suppl 3:S13-17; 4. Dowson AJ et al. Int J Clin Pract. 2003;57:573-576. Disclosures This study was sponsored by Biohaven Pharmaceuticals. RBL has received honoraria and research support from Biohaven Pharmaceuticals; he is also a stockholder. VC, EGS, DAS, CMC, CMJ, MF, and RC are employed by and own stock/stock options in Biohaven Pharmaceuticals.; RG is employed by Catalent Pharma Solutions. Zydis is a registered trademark of R.P. Scherer Technologies, Inc.

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Results from "Renoir"
The First Pfizer RSV Vaccine Efficacy Study for Older Adult Immunization

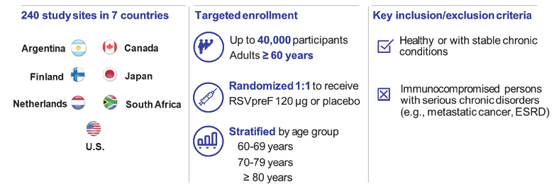
Beate Schmoele -Thoma, Agnieszka Zareba, Kumar Ilangovan, Michael Patton, Elliot DeHaan, Giselle Castillo, Marinela Ingilizova, Daniel Eiras, Tarek Mikati, Yanqing Kan, Qin Jiang for the C3671013 Team; Kathy Schneider, Elena Kalinina, Alejandra Gurtman, Kena Swanson, David Cooper, William Gruber, Kathrin Jansen, and Annaliesa Anderson

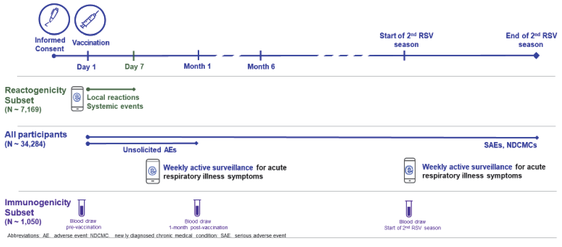
Introduction

Respiratory syncytial virus (RSV) infection is a common cause of lower respiratory tract illness (LRTI) worldwide, with risk of severe presentations in infants, young children, and older adults.[1] Severe RSV disease risk increases among older adults who are frail or with coexisting conditions.[2] Among healthy older adults in the US and Europe, ~3%−7% develop RSV illness annually, with estimates of 177,000 hospitalizations and 14,000 deaths yearly in the US.[3,4] A vaccine to protect this population from RSV-associated LRTI (RSV-LRTI) is a substantial unmet medical need.

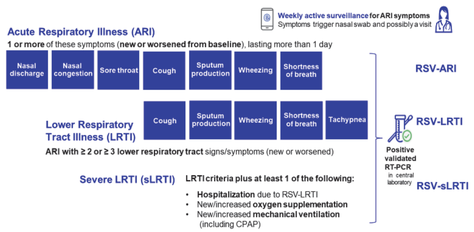
Methods

A Phase 3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of RSVpreF in Older Adults.





Case Definitions



Study Objectives

Safety		• Describe the safety profile of RSVpreF Local reactions and systemic events within 7 days post-vaccination AEs through 1-month post-vaccination SAEs and NDCMCs throughout study
Efficacy	Primary	• Prevention of RSV-LRTI in the 1st RSV season VE of 1st episode RSV-LRTI involving ≥ 2 signs/symptoms in 1st RSV season VE of 1st episode RSV-LRTI involving ≥ 3 signs/symptoms in 1st RSV season
	Secondary	• Prevention of RSV-ARI in 1st season VE of 1st episode RSV-ARI in 1st season • Prevention of RSV-sLRTI in the 1st RSV season • Prevention of RSV-LRTI[1], RSV-ARI, RSV-sLRTI in 2nd RSV season • Prevention of RSV-LRTI[1], RSV-ARI, RSV-sLRTI across 2 RSV seasons

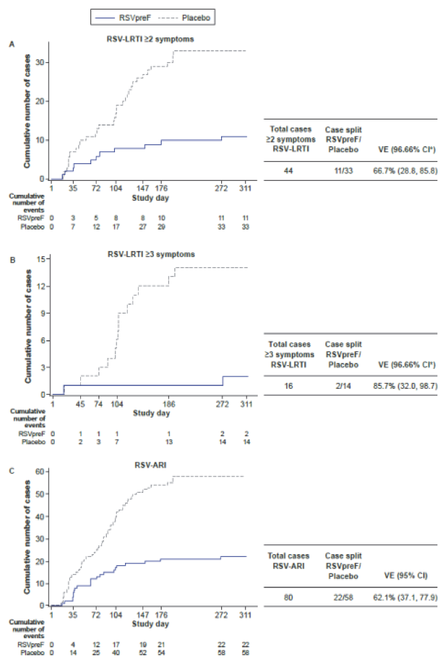
Demographics & Baseline Characteristics

	RSVpreF (N=17,215)	Placebo (N=17,069)
Male, n (%)	8800 (51.1)	8601 (50.4)
Race, n (%)		
White	13,475 (78.3)	13,360 (78.3)
Black or African American	2206 (12.8)	2207 (12.9)
Asian	1352 (7.9)	1333 (7.8)
Hispanic/Latino ethnicity, n (%)	6384 (37.1)	6260 (36.7)
Age at vaccination, n (%)		
60−69 years	10,756 (62.5)	10,680 (62.6)
70−79 years	5488 (31.9)	5431 (31.8)
≥80 years	970 (5.6)	958 (5.6)
Mean (SD) years	68.3 (6.14)	68.3 (6.18)
Prespecified high-risk condition, n (%)		
≥1 Chronic cardiopulmonary condition	2595 (15.1)	2640 (15.5)
Asthma	1541 (9.0)	1508 (8.8)
Chronic obstructive pulmonary disease	1012 (5.9)	1080 (6.3)
Congestive heart failure	293 (1.7)	307 (1.8)
Diabetes	3224 (18.7)	3284 (19.2)
Heart disease	2221 (12.9)	2233 (13.1)
Without any high-risk condition, n (%)	8348 (48.5)	8238 (48.3)

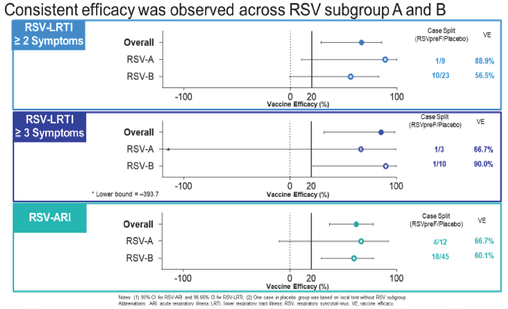
At the time of IA we enrolled 34,284 participants and they all are included in the safety database.

Results

Efficacy



Consistent efficacy was observed across RSV subgroup A and B

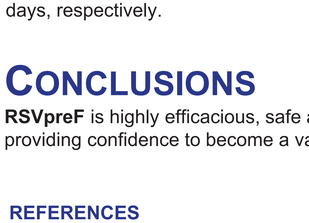


Notes: (1) 95% CI for RSV-ARI and 96.66% CI for RSV-LRTI. (2) One case in placebo group was based on local test without RSV subgroup.
Abbreviations: ARI, acute respiratory illness; LRTI, lower respiratory tract illness; RSV, respiratory syncytial virus; VE, vaccine efficacy.

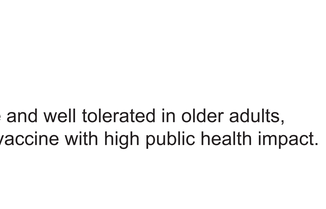
VE values calculated by RSV subgroup A or B were generally similar to those of the primary endpoint, although wide CIs reflecting the small subgroup sizes.

Safety

Local Reactions, by Maximum Severity, within 7 Days After Vaccination



Systemic Events, by Maximum Severity, Within 7 Days After Vaccination



- At this pre-planned interim analysis 44 RSV-LRTI cases with ≥2 symptoms were accrued with 11 in the RSVpreF group and 33 in the placebo group corresponding to VE of 66.7% (96.66%CI 28.8−85.8). The lower bound of the VE CI against RSV-LRTI with ≥2 symptoms was >20%, therefore meeting the primary efficacy objective.
- For the second definition of the primary objective of RSV-LRTI with ≥3 symptoms, 16 cases were accrued with 2 in the RSVpreF group and 14 in the placebo group, corresponding to VE of 85.7% (96.66% CI 32.0−98.7).
- VE values calculated by RSV subgroup A or B were generally similar to those of the primary endpoint, although wide CIs reflecting the small subgroup sizes
- For the secondary endpoint of RSV-ARI, 22 cases accrued in the RSVpreF group and 58 in the placebo group corresponding to VE of 62.1%.
- Among 7169 participants in the e-diary subset, RSVpreF recipients reported slightly more local reactions than placebo recipients (12% vs 7%); systemic event rates were similar between RSVpreF and placebo recipients (27% vs 26%). These were generally self-limiting, and mild-to-moderate; severe events occurred in ≤0.7% of participants in either group. For both RSVpreF and placebo recipients, median onset and duration of reactogenicity events post-vaccination was 2−4 and 1−2 days, respectively.

Conclusions

RSVpreF is highly efficacious, safe and well tolerated in older adults, providing confidence to become a vaccine with high public health impact.

References

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3.Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749-59.

4.Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. Eur Respir J 2021;57.

Breakthroughs that change patients' lives

Results from the First Pfizer RSV Vaccine Efficacy Study for Maternal Immunization

Matisse

Iona Munjal, Alejandra Gurtman, Barbara Pahud, Emma Shittu, Julia Glanternik, Hasra Snaggs, James Baber, Philip Zachariah, Kena Swanson, David Radley, Kenneth Koury, Kathy Schneider, Elena Kalinina, David Cooper, William Gruber, Kathrin Jansen, and Annaliesa Anderson

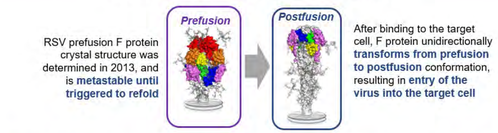
INTRODUCTION

RSV is an important cause of morbidity and mortality worldwide, with a substantial burden of disease borne to young infants, particularly those in lower- and middle-income countries. Rates of severe RSV illness are highest in infants less than 6 months of age, with a peak in hospitalization between 1 and 2 months of life. Maternal immunization to protect infants early in life offers an attractive strategy for infant disease prevention in this population. RSV disease can also affect older adults, particularly those with underlying health conditions.

Structure and Function of RSV F Glycoprotein

RSV F protein, which mediates fusion of the virus to the host cell during viral entry, exists as two conformations: prefusion and postfusion

Overview of RSV F Glycoprotein Conformations



Pfizer Protein Design and Engineering Capabilities Optimized Prefusion F Conformational Stability

RSVpreF is a bivalent vaccine composed of stable RSV prefusion F antigens representing RSV subgroup A (RSV A) and RSV subgroup B (RSV B) to ensure the broadest coverage against RSV illness. The RSVpreF vaccine is a prophylactic vaccine that is being investigated for the prevention of medically-attended (MA) RSV-associated lower respiratory tract illness (LRTI) and/or severe MA-LRTI in infants by active immunization of pregnant women in an ongoing Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial.

METHODS

Study C3671008 is an ongoing Phase 3, multicenter, randomized, double-blinded, placebo-controlled study executed in 18 countries.

Approximately 7500 pairs randomized 1:1 RSVpreF 120 µg or placebo

- Pregnant women ≤ 49 years of age between ≥24 and ≤36 weeks gestation
  - Follow-up 6 months postpartum
- Infants born to vaccinated mothers
  - **Vaccine efficacy against RSV-positive medically attended LRTI and/or severe LRTI**
  - Safety follow-up from birth to the end of the study

Primary Endpoint Criteria

Medically attended LRTI
Medically attended visit and ≥1:
- tachypnea (RR ≥60 (<2 m [60 days]) or ≥50 (≥2 to 12 m);
- peripheral capillary oxygen saturation (SpO2) measured in room air <95%;
- chest wall indrawing

Medically attended severe LRTI
Medically attended visit and ≥1:
- tachypnea (RR ≥70 (<2 m [60 days]) or ≥60 (≥2 to 12 m);
- SpO2 measured in room air <93%;
- high-flow nasal cannula or mechanical ventilation;
- ICU admission for >4 hours; unresponsive/unconscious

Primary Endpoints in Infant Participants

RSV positive MA-LRTI or severe MA-LRTI confirmed by the endpoint adjudication committee occurring within 90, 120, 150, and 180 days after birth

AEs from birth to 1 month of age, Specified birth outcomes, SAEs and newly diagnosed chronic medical conditions (NDCMCs) from birth to the end of the study.

Secondary and Exploratory Endpoints:

- Hospitalization to 2 years
- All-cause MA-LRTI to 2 years
- MA-RTIs to 2 years
- Efficacy against RSV A and B
- Efficacy in pre-term infants < 37 weeks of age

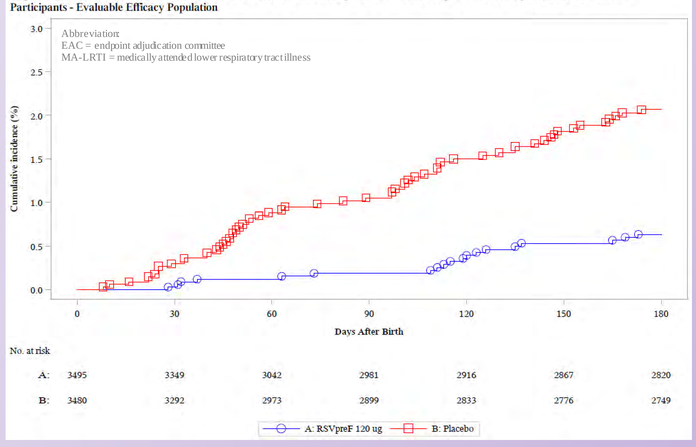
RESULTS:

RSVpreF Highly Efficacious Against Severe Infant MA-LRTI

Potential first maternal vaccine for common, potentially life-threatening, respiratory illness in infants

- Results met study protocol's pre-specified regulatory success criteria for severe MA-LRTI
- Success criterion was not met for MA-LRTI endpoint, however clinically meaningful efficacy was observed
- BLA submission to U.S. FDA planned by end of 2022, additional regulatory authorities in coming months

Kaplan-Meier Curves for Severe MA-LRTIs Due to RSV, Confirmed by the EAC, Occurring Within 180 Days After Birth - Infant Participants - Evaluable Efficacy Population



Primary Endpoint: Severe MA-LRTI

	Vaccine Efficacy
First 90 days of life	**81.8%** (CI: 40.6%, 96.3%)
Six-month follow-up	**69.4%** (CI: 44.3%, 84.1%)

Primary Endpoint: MA-LRTI

	Vaccine Efficacy
First 90 days of life	**57.1%** (CI: 14.7%, 79.8%)
Six-month follow-up	**51.3%** (CI: 29.4%, 66.8%)

Interim analysis of Phase 3 MATISSE clinical trial demonstrated high efficacy against severe MA-LRTI due to RSV from birth through first six months of life

DMC indicated RSVpreF investigational vaccine was well-tolerated with no safety concerns for either vaccinated individuals or their newborns

CONCLUSIONS:

- Pediatric RSV burden high, a substantial unmet medical need
- Single dose, bivalent, unadjuvanted RSVpreF subunit vaccine has a good tolerability and safety profile
- High RSVpreF vaccine immunogenicity with effective transplacental transfer in a trial for maternal immunization
- Early signs of efficacy success in the maternal trial phase 2b study
- Phase 3 efficacy study met one of two primary efficacy endpoints: MA-severe LRTI (81.8%) with persistence of efficacy over a period of 6 months (69.4%)

Future efforts:
- MDV preparation with support from BMGF
- Considerations:
  - Follow-up infants for asthma and wheezing
  - Efficacy in high-risk pregnancy including premature infants

ACKNOWLEDGMENTS

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Pfizer

Etrasimod 2 mg Once Daily as Treatment for Biologic/Janus Kinase Inhibitor-Naïve and -Experienced Patients With Moderately to Severely Active Ulcerative Colitis: Subgroup Analysis From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

MP289

Brian G. Feagan,[1*] Laurent Peyrin-Biroulet,[2*] William J. Sandborn,[3] Geert D'Haens,[4] Julian Panes,[5] Andres Yarur,[6] Douglas C. Wolf,[7] Timothy Ritter,[8] Stefan Schreiber,[9] Sheldon Sloan,[10] Fabio Cataldi,[10] Kevin Shan,[10] Christopher J. Rabbat,[10] Michael Chiorean,[11] Filip Baert,[12] Bruce E. Sands,[13] Marla C. Dubinsky,[14] Séverine Vermeire,[15] Martina Goetsch,[16] Silvio Danese[17]

*Dual first authors; [1]University of Western Ontario, London, ON, Canada; [2]Université de Lorraine, CHRU-Nancy, Department of Gastroenterology, F-54000 Nancy, France, and University of Lorraine, Inserm, NGERE, F-54000 Nancy, France; [3]University of California San Diego School of Medicine, La Jolla, CA, USA; [4]University of Amsterdam, Amsterdam, the Netherlands; [5]Hospital Clínic de Barcelona, IDIBAPS. CIBERehd, Barcelona, Spain; [6]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [7]Atlanta Gastroenterology Associates, Atlanta, GA, USA; [8]GI Alliance Research, Southlake, TX, USA; [9]University Hospital Schleswig-Holstein, Department Internal Medicine I, Kiel University, Kiel, Germany; [10]Arena Pharmaceuticals, San Diego, CA, USA, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA; [11]IBD Center, Swedish Medical Center, Seattle, WA, USA; [12]AZ Delta, Roeselare, Belgium; [13]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [14]Feinstein IBD Center, Mount Sinai, New York, NY, USA; [15]University Hospitals Leuven, Leuven, Flanders, Belgium; [16]Arena Pharmaceuticals Development GmbH, Zug, Switzerland, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA; [17]IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele Milan, Italy

BACKGROUND

- Etrasimod (APD334) is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor 1,4,5 modulator
- In patients with moderately to severely active ulcerative colitis (UC), the phase 2 OASIS (NCT02447302) and phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials demonstrated etrasimod to be safe and efficacious[1,2]
- ELEVATE UC 52 and ELEVATE UC 12 included patients with and without prior exposure to advanced targeted therapy, which includes both biologic and Janus kinase inhibitors (JAKis)
- This efficacy subgroup analysis, predefined in the study statistical analysis plans, evaluated the efficacy of etrasimod 2 mg vs placebo in adults with UC stratified by prior exposure to advanced targeted therapy (biologic/JAKis), including 1 or >1 prior biologic/JAKi

LIMITATIONS

- The studies were not powered to assess efficacy vs placebo in these subgroups
- Further studies with >52 weeks of follow-up are needed to better characterize the long-term safety of etrasimod and long-term durability of efficacy

CONCLUSIONS

- In ELEVATE UC 52, patients naïve to or with prior exposure to 1 biologic/JAKi and treated with etrasimod showed statistically significant and clinically meaningful improvements in induction and maintenance, whereas patients exposed to >1 biologic/JAKi demonstrated less consistent benefits
- In ELEVATE UC 12, patients naïve to prior biologic/JAKi therapy demonstrated consistent benefit with etrasimod in induction, whereas biologic/JAKi–experienced patients showed less consistent benefits
- The results from this subgroup analysis are consistent with findings from the overall ELEVATE trials

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1. Sandborn WJ, et al. *Gastroenterology*. 2020;158(3):550-561.
2. Sandborn WJ, et al. Presented at: Digestive Disease Week 2022; May 24, 2022; San Diego, CA. Abstract 968a.

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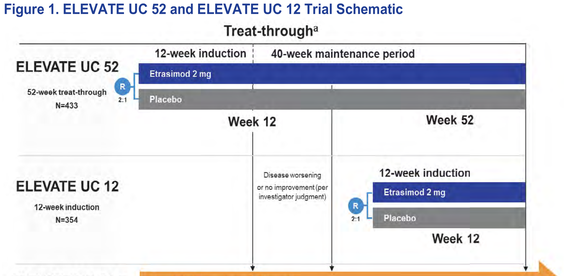
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METHODS

- ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were 2 randomized, multicenter, double-blind, placebo-controlled, phase 3 trials (**Figure 1**)
- This subgroup analysis analyzed outcomes in patients naïve to, or with prior experience with, biologics/JAKis, including 1 or >1 biologic/JAKi
  - Prior biologic and JAKi treatments included tumor necrosis factor antagonists (adalimumab, golimumab, infliximab, or biosimilars), anti-integrin antibodies (vedolizumab), anti–interleukin 12/23 antibodies (ustekinumab), and JAKis (tofacitinib)
  - Efficacy endpoints were the proportions of patients achieving clinical remission (using the modified Mayo Score [MMS]) at week 12 and week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12
  - Key secondary endpoints for both trials included endoscopic improvement, symptomatic remission, and endoscopic-histologic mucosal improvement

Figure 1. ELEVATE UC 52 and ELEVATE UC 12 Trial Schematic



OLE, open-label extension; R, randomization; UC, ulcerative colitis

[a]Beginning at week 12, all patients could continue their randomized treatment into a 40-week maintenance period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue and, if eligible, enroll in an OLE study (NCT03950232).

RESULTS

Patient Demographics

- Of the 144 patients randomized to placebo and the 289 randomized to etrasimod in ELEVATE UC 52, 304 (70.2%) were biologic/JAKi naïve (placebo, 99 [68.8%]; etrasimod, 205 [70.9%]) and 129 (29.8%) were biologic/JAKi experienced (placebo, 45 [31.3%]; etrasimod, 84 [29.1%]) (**Table 1**)
  - The breakdown of prior biologic/JAKi-experienced patients in ELEVATE UC 52 (placebo vs etrasimod) is as follows: 31 (21.5%) and 60 (20.8%) had prior TNFis; 19 (13.2%) and 28 (9.7%) had prior anti-integrin antibodies; 1 (0.7%) and 6 (2.1%) had prior anti–interleukin 12/23 antibodies; and 9 (6.3%) and 20 (6.9%) had prior JAKis
- Among the 116 patients randomized to placebo and the 238 randomized to etrasimod in ELEVATE UC 12, 236 (66.7%) were biologic/JAKi naïve (placebo, 77 [66.4%]; etrasimod, 159 [66.8%]) and 118 (33.3%) were biologic/JAKi experienced (placebo, 39 [33.6%]; etrasimod, 79 [33.2%])
  - The breakdown of prior biologic/JAKi-experienced patients in ELEVATE UC 12 (placebo vs etrasimod) is as follows: 29 (25.0%) and 57 (23.9%) had prior TNFis; 10 (8.6%) and 33 (13.9%) had prior anti-integrin antibodies; 4 (3.4%) and 5 (2.1%) had prior anti–interleukin 12/23 antibodies; and 9 (7.8%) and 15 (6.3%) had prior JAKis
- At baseline, biologic/JAKi-experienced patients had longer disease duration than patients naïve to biologic/JAKis

Table 1. Baseline Demographic and Clinical Characteristics by Prior Biologic/JAKi Exposure

Characteristic, n (%)	Biologic/JAKi exposure status	ELEVATE UC 52		ELEVATE UC 12	
		Placebo	Etrasimod	Placebo	Etrasimod
		Naïve, n=99 1, n=25 >1, n=20	Naïve, n=205 1, n=44 >1, n=40	Naïve, n=77 1, n=20 >1, n=19	Naïve, n=159 1, n=36 >1, n=43
Age, mean (SD), years	Naïve	38.6 (14.6)	39.7 (13.7)	42.0 (14.1)	40.9 (13.9)
	1	38.3 (12.9)	45.6 (14.9)	39.7 (12.3)	41.0 (14.0)
	>1	41.6 (12.8)	43.8 (13.3)	34.8 (9.3)	37.8 (11.2)
Female, n (%)	Naïve	43 (43.4)	102 (49.8)	32 (41.6)	69 (43.4)
	1	5 (20.0)	18 (40.9)	4 (20.0)	16 (44.4)
	>1	8 (40.0)	17 (42.5)	7 (36.8)	18 (41.9)
Extent of UC (left-sided colitis/ proctosigmoiditis), n (%)	Naïve	68 (68.7)	128 (62.4)	43 (55.8)	105 (66.0)
	1	13 (52.0)	27 (61.4)	12 (60.0)	16 (44.4)
	>1	9 (45.0)	17 (42.5)	8 (42.1)	25 (58.1)
Duration of UC, mean (SD), years	Naïve	4.7 (4.6)	5.5 (6.3)	6.6 (6.7)	6.5 (6.6)
	1	8.3 (7.3)	12.9 (10.3)	8.2 (6.3)	8.2 (6.5)
	>1	8.8 (5.3)	11.5 (8.9)	11.4 (9.6)	9.3 (6.4)
MMS, mean (SD)[a]	Naïve	6.6 (1.2)	6.7 (1.2)	6.5 (1.2)	6.5 (1.2)
	1	6.8 (1.0)	6.8 (1.1)	7.2 (1.1)	6.7 (1.2)
	>1	6.8 (1.3)	6.8 (1.3)	6.6 (1.2)	6.6 (1.2)

JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

[a]The modified Mayo Score is defined as the sum of the rectal bleeding subscore, the stool frequency subscore, and endoscopy subscore (each subscore on a scale of 0-3). Overall scores range from 0 to 9, with higher scores indicating greater activity.

Subgroup Analyses of Patients Achieving Primary and Secondary Efficacy Endpoints, Stratified by Prior Biologic/JAKi Exposure

- All efficacy endpoints in ELEVATE UC 52 were achieved at both weeks 12 and 52 in biologic/JAKi-naïve patients treated with etrasimod vs placebo (**Figure 2**)
  - Responses were generally higher in patients naïve to biologic/JAKis than in those with prior biologic/JAKi experience
  - Patients who had prior experience to only 1 biologic/JAKi generally had higher responses rates with etrasimod than patients with >1 prior experience with biologic/JAKis

Figure 2. Efficacy Outcomes in (A) Clinical Remission, (B) Endoscopic Improvement, (C) Symptomatic Remission, and (D) Endoscopic-Histologic Mucosal Improvement in ELEVATE UC 52 Stratified by Prior Biologic/JAKi Exposure[a]

ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.

[a]A prior-data analyses based on Cochran-Mantel-Haenszel analysis of the Full Analysis Set (all randomized patients with a baseline MMS of 4-9 who received ≥1 dose of study drug) and nonresponder imputation method. Significance is represented using nominal 2-sided *P* values.

[b]SF subscore = 0 (or = 1 with ≥1-point decrease from baseline), RB subscore = 0, and ES ≤1.

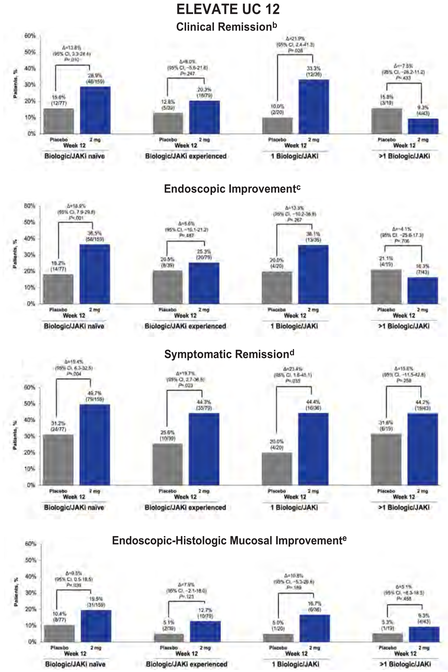
[c]ES ≤1.

[d]SF subscore = 0 (or = 1 with ≥1-point decrease from baseline) and RB subscore = 0.

[e]ES ≤1 with histologic remission measured by Geboes index score <2.0.

- All efficacy endpoints in ELEVATE UC 12 were achieved at week 12 in biologic/JAKi-naïve patients treated with etrasimod vs placebo (**Figure 3**)
  - Etrasimod-treated patients with 1 prior biologic/JAKi achieved significantly higher rates of clinical remission and symptomatic remission than placebo-treated patients at week 12; numerical improvements vs placebo were reported in endoscopic improvement and endoscopic-histologic mucosal improvement

Figure 3. Efficacy Outcomes in (A) Clinical Remission, (B) Endoscopic Improvement, (C) Symptomatic Remission, and (D) Endoscopic-Histologic Mucosal Improvement in ELEVATE UC 12 Stratified by Prior Biologic/JAKi Exposure[a]



ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.

[a]A prior-data analyses based on Cochran-Mantel-Haenszel analysis of the Full Analysis Set (all randomized patients with a baseline MMS of 4-9 who received ≥1 dose of study drug) and nonresponder imputation method. Significance is represented using nominal 2-sided *P* values.

[b]SF subscore = 0 (or = 1 with ≥1-point decrease from baseline) and RB subscore = 0.

[c]ES ≤1.

[d]SF subscore = 0 (or = 1 with ≥1-point decrease from baseline) and RB subscore = 0.

[e]ES ≤1 with histologic remission measured by Geboes index score <2.0.

Etrasimod Safety and Tolerability

- All infections and serious infections were balanced across treatment groups, including herpes zoster and opportunistic infections
- The majority of AEs were considered mild or moderate (**Table 2**)
  - No deaths occurred in either trial
  - No serious/severe AEs of bradycardia or atrioventricular block were reported
  - In both studies, no malignancies or serious/severe hepatic injuries were reported in either treatment group

Table 2. Overall Safety Profile in ELEVATE UC 52 and ELEVATE UC 12

Subjects, n (%)[a]	ELEVATE UC 52 Safety Set (N=433)		ELEVATE UC 12 Safety Set (N=354)	
	Placebo (n=144)	Etrasimod 2 mg (n=289)	Placebo (n=116)	Etrasimod 2 mg (n=238)
Participants with any AEs	81 (56.3)	206 (71.3)	54 (46.6)	112 (47.1)
Participants with any serious AEs	9 (6.3)	20 (6.9)	2 (1.7)	6 (2.5)
AEs leading to death	0	0	0	0
Most common AEs				
Headache	7 (4.9)	24 (8.3)	2 (1.7)	11 (4.6)
Worsening of UC	13 (19.0)	22 (7.6)	1 (0.9)	9 (3.8)
COVID-19 infection	9 (6.3)	20 (6.9)	3 (2.6)	3 (1.3)
AEs of special interest				
Serious Infections	5 (3.5)	3 (1.0)	0	0
Herpes zoster	0	2 (0.7)	2 (1.7)	0
Opportunistic infections	1 (0.7)	0	0	1 (0.4)
Bradycardia[c]	0	4 (1.4)	0	1 (0.4)
Sinus bradycardia[c]	–	–	0	4 (1.7)
AV block, 1st degree[c]	0	1 (0.3)	0	1 (0.4)
AV block, 2nd degree (Mobitz I)[c]	0	1 (0.3)	0	0

AE, adverse event; AV, atrioventricular; UC, ulcerative colitis.

[a]Data is not exposure adjusted.

[b]Of the 9 cases of bradycardia/sinus bradycardia, 2 patients were symptomatic and discontinued treatment, 2 others were asymptomatic and discontinued treatment, and the remaining 5 were asymptomatic and continued treatment.

[c]All 3 patients who experienced an AE of AV block discontinued study treatment without administration of interventional treatment.

Effect of Etrasimod on Circulating Lymphocytes in Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

A0377

Silvio Danese,[1] H. Kiyomi Komori,[2] Rathi D. Ryan,[2] Fabio Cataldi,[2] Caroline A. Lee,[2] Martina Goetsch,[3] Britta Siegmund[4]

[1]IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy; [2]Arena Pharmaceuticals, San Diego, CA, USA, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA; [3]Arena Pharmaceuticals Development GmbH, Zug, Switzerland, a wholly-owned subsidiary of Pfizer Inc, New York, NY, USA; [4]Medizinische Klinik für Gastroenterologie, Infektiologie und Rheumatologie, Charité – Universitätsmedizin Berlin, Berlin, Germany

BACKGROUND

- Etrasimod (APD334) is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor (S1P) 1,4,5 modulator
- Etrasimod demonstrated efficacy in adults with moderately to severely active ulcerative colitis (UC) in the phase 2 OASIS trial (NCT02447302) and the phase 3 ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) trials[1,2]
- Etrasimod reversibly sequesters specific lymphocyte subsets in lymph nodes, reducing circulating lymphocytes and resulting in fewer immune cells available to traffic to the gastrointestinal tract[3,4]
- Previous reports in healthy volunteers demonstrated selective effects of etrasimod on adaptive immune cell subsets and negligible effects on innate cells, such as natural killer cells[5]; however, the impact is unknown in patients with UC
- In this per-protocol exploratory analysis of data from the ELEVATE UC 52 and ELEVATE UC 12 studies, we report the effect of etrasimod on circulating immune cells (T cells, B cells, natural killer cells, and monocytes) in adults with moderately to severely active UC

LIMITATIONS

- There is inherent variability in the assessment of circulating lymphocyte subsets due to the changing course of disease
- Additionally, variations in the time of day at which samples were collected and in site-specific processing of samples may impact measurements

CONCLUSIONS

- This per-protocol exploratory analysis demonstrated that etrasimod had a rapid and differential effect on the frequency of circulating immune cell subsets in peripheral blood in patients with moderately to severely active UC through sequestration of lymphocytes in lymph nodes
- Consistent with the proposed mechanism of action of S1P receptor modulators, as well as previous reports in healthy subjects and those with atopic dermatitis,[5,6] etrasimod reduced adaptive immune cells (T and B cells) in the periphery, with a greater impact on $CD4^+$ T cells than on $CD8^+$ T cells
- Reductions in T and B cell subsets paralleled reductions in absolute lymphocyte counts
- Conversely, etrasimod had no notable impact on innate immune cells (natural killer cells and monocytes) that are important components of immune surveillance

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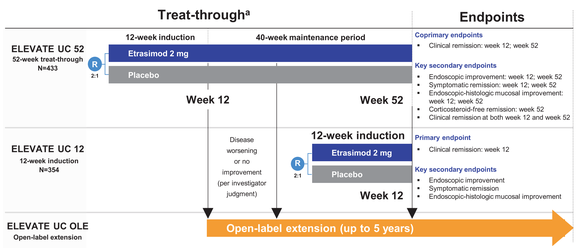
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METHODS

Patient Population and Trial Design

- ELEVATE UC 52 and ELEVATE UC 12 were phase 3, global, randomized, double-blind, placebo-controlled trials (**Figure 1**)
  - In both trials, adults (aged 16-80 years) with moderately to severely active UC (based on a modified Mayo Score [MMS] of 4-9 with a centrally read endoscopic subscore of ≥2 and a rectal bleeding subscore of ≥1) and a documented history of inadequate response, loss of response, or intolerance of ≥1 treatment for UC were randomized 2:1 to once-daily treatment with etrasimod 2 mg or placebo
  - Patients were stratified by prior exposure to biologic/Janus kinase inhibitor (JAKi) therapy, concomitant corticosteroid use, and baseline disease activity (MMS 4-6 or 7-9)
- The biomarker analysis set comprised all randomized subjects who received ≥1 dose of study treatment and had a baseline MMS of 5 to 9

Figure 1. ELEVATE UC 52 and ELEVATE UC 12 Trial Schematic



OLE, open-label extension; R, randomization; UC, ulcerative colitis.
[a] Beginning at week 12, all patients could continue their randomized treatment into a 40-week maintenance period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue, and if eligible, enroll in an OLE study (NCT03950232).

Assessments and Data Analysis

- In this per-protocol exploratory analysis, whole blood was collected at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52 in ELEVATE UC 52 and weeks 2, 4, 8, and 12 in ELEVATE UC 12 for assessment of absolute lymphocyte counts and immunophenotyping
- Absolute lymphocyte counts were determined through complete blood count with differential
- Flow cytometry of fresh samples was used to characterize the following immune cell subsets:
  - Total T cells ($CD3^+$)
  - T helper cells ($CD3^+CD4^+$)
  - Cytotoxic T cells ($CD3^+CD8^+$)
  - B cells ($CD3^-CD19^+$)
  - Natural killer cells ($CD3^-CD56^+CD16^+$)
  - Monocytes ($CD14^+$)
- Mean (SE) percent change from baseline (in cells/μL) at each time point was compared between etrasimod 2 mg and placebo using 2-sided *t* tests
  - Patients with missing baseline samples were not included in the immunophenotyping analysis; such missing sample collections were noted as minor protocol deviations

RESULTS

Patient Demographics

- Immunophenotyping analysis was performed on whole blood from 419 patients in ELEVATE UC 52 (etrasimod 2 mg, n=274; placebo, n=135) and 333 patients in ELEVATE UC 12 (etrasimod 2 mg, n=221; placebo, n=112) who had a baseline sample collection
- Baseline characteristics were similar between treatment arms and across both trial populations[2] (**Table 1**)

Table 1. Summary of Subject Baseline Demographic Characteristics[a]

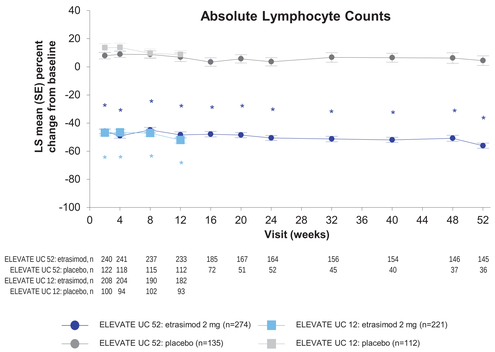
Characteristic	ELEVATE UC 52 Etrasimod 2 mg (n=274)	ELEVATE UC 52 Placebo (n=135)	ELEVATE UC 12 Etrasimod 2 mg (n=221)	ELEVATE UC 12 Placebo (n=112)
Age, mean (SD), years	41.6 (14.0)	38.6 (14.0)	40.4 (13.7)	40.7 (13.2)
Male, n (%)	144 (52.6)	80 (59.3)	124 (56.1)	70 (62.5)
Ethnicity, n (%)				
Hispanic or Latino	12 (4.4)	7 (5.2)	9 (4.1)	9 (8.0)
Non–Hispanic or Latino	260 (94.9)	127 (94.1)	210 (95.0)	103 (92.0)
Extent of disease, n (%)				
Left-sided colitis/ proctosigmoiditis	161 (58.8)	81 (60.0)	134 (60.6)	61 (54.5)
Pancolitis	92 (33.6)	47 (34.8)	75 (33.9)	40 (35.7)
Proctitis	19 (6.9)	6 (4.4)	12 (5.4)	11 (9.8)
Prior biologic/JAKi naive, n (%)	194 (70.8)	93 (68.9)	148 (67.0)	74 (66.1)
Concomitant CS use, n (%)	93 (33.9)	43 (31.9)	63 (28.5)	34 (30.4)
Concomitant 5-ASA use, n (%)	213 (77.7)	102 (75.6)	187 (84.6)	91 (81.3)
Baseline MMS, mean (SD)	6.88 (1.04)	6.84 (0.95)	6.74 (1.06)	6.71 (1.13)
Duration of UC, mean (SD), years	7.6 (8.1)	6.0 (5.6)	7.2 (6.5)	7.9 (7.4)

5-ASA, 5-aminosalicylic acid; CS, corticosteroid; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; UC, ulcerative colitis.
[a] Data are derived from the safety analysis set and include all subjects who received ≥1 dose of study treatment and had a baseline MMS of 5 to 9.

Etrasimod Effect on Absolute Lymphocyte Counts

- Subjects treated with etrasimod demonstrated nearly nadir absolute lymphocyte counts by week 2; counts were maintained during the treatment period through week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 2**)

Figure 2. LS Mean (SE) Percent Change From Baseline in Absolute Lymphocyte Counts Over Time (MMS 5-9)[a]

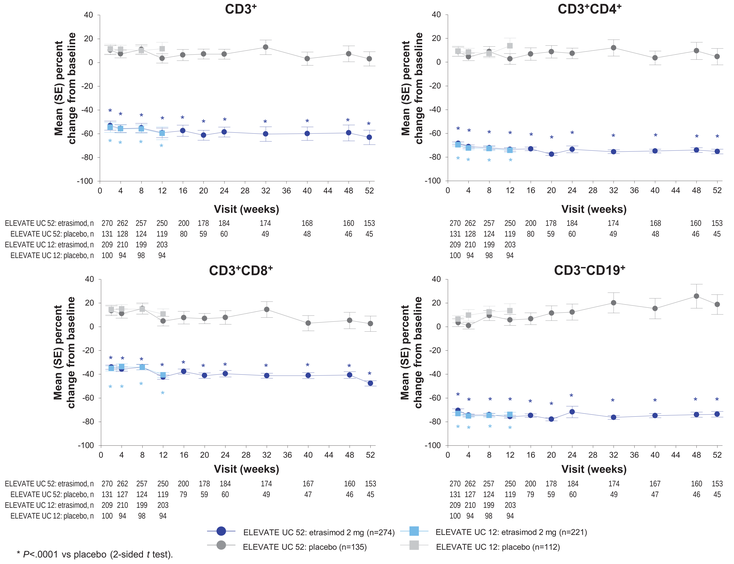


JAKi, Janus kinase inhibitor; LS, least squares; MMRM, mixed model of repeated measures; MMS, modified Mayo Score.
[a] Only subjects with a baseline MMS between 5 and 9 are included. Estimates are from an MMRM model of percent change from baseline, with a covariate for baseline score and factors for naivety to biologic/JAKi therapy at study entry, baseline corticosteroid use, baseline disease activity (MMS, 4-6 or 7-9), treatment, visit, and treatment-by-visit interaction.
* $P<.001$ vs placebo (2-sided *t* test).

Etrasimod Effect on Circulating Lymphocyte Subsets

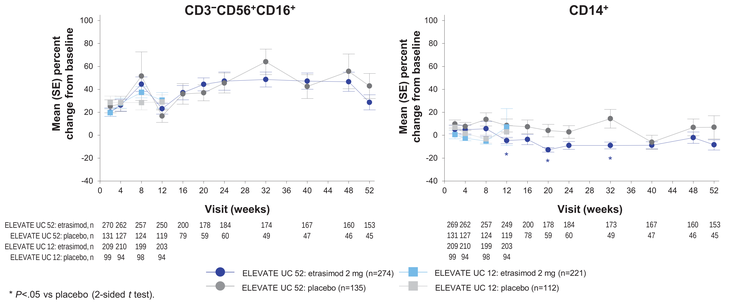
- Treatment with etrasimod 2 mg resulted in rapid mean percent reductions from baseline to week 2, with nadir and near nadir changes from baseline reached by week 4 in ELEVATE UC 52 and ELEVATE UC 12, respectively, for total T cells ($CD3^+$: −55.6% [1.50] and −55.9% [1.65]), T helper cells ($CD3^+CD4^+$: −71.1% [1.33] and −72.5% [1.30]), cytotoxic T cells ($CD3^+CD8^+$: −35.7% [1.94] and −33.8% [2.60]), and B cells ($CD3^-CD19^+$: −74.5% [1.05] and −75.2% [1.18])
- Reductions were maintained through week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 3**)
- No clinically significant changes in natural killer cell ($CD3^-CD56^+CD16^+$) or monocyte ($CD14^+$) levels were found during the treatment period of either study (**Figure 4**)

Figure 3. Mean (SE) Percent Change From Baseline in Circulating Adaptive Immune Cell Subsets (cells/μL) Over Time (MMS 5-9; safety set)



* $P<.0001$ vs placebo (2-sided *t* test).

Figure 4. Mean (SE) Percent Change From Baseline in Circulating Innate Immune Cell Subsets (cells/μL) Over Time (MMS 5-9; safety set)



* $P<.05$ vs placebo (2-sided *t* test).

Etrasimod 2 mg Once Daily as Treatment for Patients With Moderately to Severely Active Ulcerative Colitis: Topline and Subgroup Analysis From ELEVATE UC 52 and ELEVATE UC 12

D0381

Brian G. Feagan,[1]* **Laurent Peyrin-Biroulet**,[2]* **William J. Sandborn**,[3] **Geert D'Haens**,[4] **Julian Panes**,[5] **Andres Yarur**,[6] **Douglas C. Wolf**,[7] **Timothy Ritter**,[8] **Stefan Schreiber**,[9] **Sheldon Sloan**,[10] **Fabio Cataldi**,[10] **Kevin Shan**,[10] **Christopher J. Rabbat**,[10] **Michael Chiorean**,[11] **Filip Baert**,[12] **Bruce E. Sands**,[13] **Marla C. Dubinsky**,[14] **Séverine Vermeire**,[15] **Martina Goetsch**,[16] **Silvio Danese**[17]

*Dual first authors; [1]University of Western Ontario, London, ON, Canada; [2]Université de Lorraine, CHRU-Nancy, Department of Gastroenterology, F-54000 Nancy, France, and University of Lorraine, Inserm, NGERE, F-54000 Nancy, France; [3]University of California San Diego School of Medicine, La Jolla, CA; [4]University of Amsterdam, Amsterdam, the Netherlands; [5]Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; [6]Cedars-Sinai Medical Center, Los Angeles, CA; [7]Atlanta Gastroenterology Associates, Atlanta, GA; [8]GI Alliance Research, Southlake, TX; [9] Department Internal Medicine I, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany; [10]Arena Pharmaceuticals, San Diego, CA, a wholly-owned subsidiary of Pfizer Inc, New York, NY; [11]IBD Center, Swedish Medical Center, Seattle, WA; [12]AZ Delta, Roeselare, Belgium; [13]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY; [14]Feinstein IBD Center, Mount Sinai, New York, NY; [15]University Hospitals Leuven, Leuven, Flanders, Belgium; [16]Arena Pharmaceuticals Development GmbH, Zug, Switzerland, a wholly-owned subsidiary of Pfizer Inc, New York, NY; [17]IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele Milan, Italy

BACKGROUND

- Etrasimod (APD334) is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor 1,4,5 modulator
- Here, we report data from ELEVATE UC 52 and ELEVATE UC 12, 2 randomized, double-blind, placebo-controlled, phase 3 trials that evaluated the efficacy and safety of etrasimod 2 mg/day in adults with ulcerative colitis (UC) as well as data from a predefined subgroup analyses which stratified patients by prior exposure to advanced therapy (biologic/Janus kinase inhibitors [JAKis])

LIMITATIONS

- The studies were not powered to assess efficacy vs placebo in the biologic/JAKi subgroups
- The long-term safety and efficacy data are limited to 52-weeks of follow up

CONCLUSIONS

- In both studies, treatment with etrasimod 2 mg/day resulted in clinically meaningful and statistically significant improvements in primary and key secondary outcomes measures
- Patients who were naïve to or received 1 prior biologic/JAKi therapy experienced similar benefit with etrasimod in both ELEVATE UC 52 and ELEVATE UC 12, whereas patients who had experience with multiple advanced therapies showed less consistent benefit
- The safety profile of etrasimod was favorable with that in previous studies

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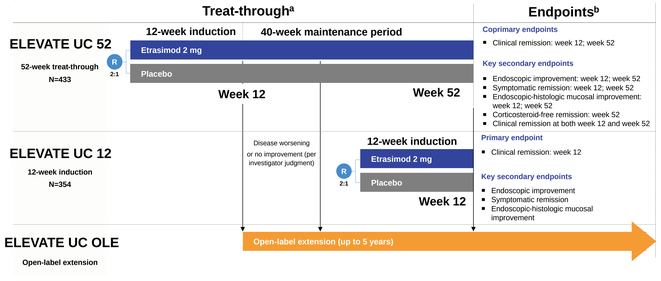
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METHODS

- ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were 2 global, randomized, multicenter, double-blind, placebo-controlled, phase 3 trials with pre-established primary and key secondary endpoints; the primary analysis included patients with a modified Mayo Score (MMS) of 5-9 (**Figure 1**)
  - ELEVATE UC 52 used a treat-through design comprising a 12-week induction period followed by a 40-week maintenance period
  - ELEVATE UC 12 comprised a 12-week induction period only
- This subgroup analysis examined outcomes in patients naïve to, or with prior experience with 1 or >1 biologics/JAKi; the subgroup analysis included patients with an MMS of 4-9

Figure 1. ELEVATE UC 52 and ELEVATE UC 12 Trial Schematic



JAKi, Janus kinase inhibitor; OLE, open-label extension; R, randomization; UC, ulcerative colitis.
[a] Beginning at week 12, all patients could continue their randomized treatment into a 40-week maintenance period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue treatment and, if eligible, enroll in an OLE study (NCT03950232).
[b] Subgroup analyses included patients who had received prior biologic and JAKi treatments which included tumor necrosis factor antagonists (adalimumab, golimumab, infliximab, or biosimilars), anti-integrin antibodies (vedolizumab), anti–interleukin 12/23 antibodies (ustekinumab), and JAKis (tofacitinib).

RESULTS

Patient Demographics

- Among the prior biologic/JAKi-experienced patients, drug histories were similar across both treatment arms and included patients with exposure to tumor necrosis factor inhibitor (TNFi), anti-integrin, anti–interleukin (IL)-12/23, and JAKi therapy (**Table 1**)
- At baseline, prior biologic/JAKi–experienced patients had longer disease duration than patients naïve to biologic/JAKis

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Population	ELEVATE UC 52 Placebo Overall, N=144 Bio/JAKi naïve, n=99 1 bio/JAKi, n=25 >1 bio/JAKi, n=20	ELEVATE UC 52 Etrasimod Overall, N=289 Bio/JAKi naïve, n=205 1 bio/JAKi, n=44 >1 bio/JAKi, n=40	ELEVATE UC Placebo Overall, N=116 Bio/JAKi naïve, n=77 1 bio/JAKi, n=20 >1 bio/JAKi, n=19	ELEVATE UC Etrasimod Overall, N=238 Bio/JAKi naïve, n=159 1 bio/JAKi, n=36 >1 bio/JAKi, n=43
Extent of UC (left-sided colitis/ proctosigmoiditis), n (%)	Overall	90 (62.5)	172 (59.5)	63 (54.3)	146 (61.3)
	Bio/JAKi naïve	68 (68.7)	128 (62.4)	43 (55.8)	105 (66.0)
	1 bio/JAKi	13 (52.0)	27 (61.4)	12 (60.0)	16 (44.4)
	>1 bio/JAKi	9 (45.0)	17 (42.5)	8 (42.1)	25 (58.1)
Duration of UC, mean (SD), years	Overall	5.9 (5.5)	7.5 (8.0)	7.7 (7.3)	7.3 (6.6)
	Bio/JAKi naïve	4.7 (4.6)	5.5 (6.3)	6.6 (6.7)	6.5 (6.6)
	1 bio/JAKi	8.3 (7.3)	12.9 (10.3)	8.2 (6.3)	8.2 (6.5)
	>1 bio/JAKi	8.8 (5.3)	11.5 (8.9)	11.4 (9.6)	9.3 (6.4)
MMS, mean (SD)[a]	Overall	6.7 (1.2)	6.7 (1.2)	6.6 (1.2)	6.6 (1.2)
	Bio/JAKi naïve	6.6 (1.2)	6.7 (1.2)	6.5 (1.2)	6.5 (1.2)
	1 bio/JAKi	6.8 (1.0)	6.8 (1.1)	7.2 (1.1)	6.7 (1.2)
	>1 bio/JAKi	6.8 (1.3)	6.8 (1.3)	6.6 (1.2)	6.6 (1.2)

Bio, biologic; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; UC, ulcerative colitis.
[a] The MMS is defined as the sum of the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore (each subscore on a scale of 0-3). Overall scores range from 0 to 9, with higher scores indicating greater disease activity.

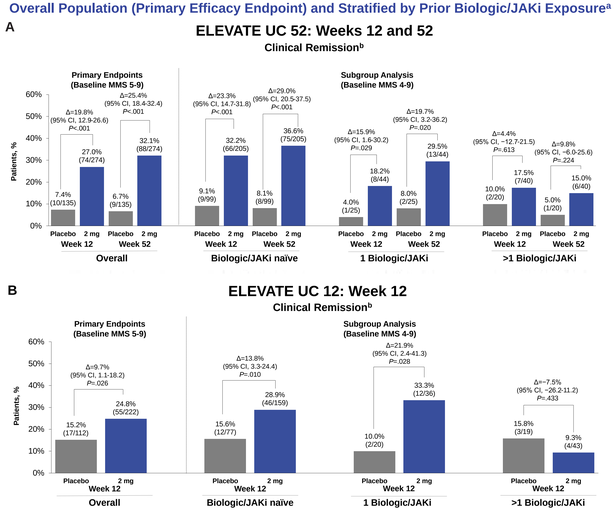
Clinical Remission in Overall Population (Primary Efficacy Endpoint) and Stratified by Prior Biologic/JAKi Exposure

- The primary efficacy endpoint of clinical remission was achieved with etrasimod vs placebo at both weeks 12 and 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 2**)
- Clinical remission in ELEVATE UC 52 was achieved at both weeks 12 and 52 in biologic/JAKi-naïve patients treated with etrasimod vs placebo and responses were generally greater than in those with prior biologic/JAKi experience (**Figure 2A**)
  - Etrasimod-treated patients with 1 prior biologic/JAKi achieved significantly higher rates of clinical remission than placebo-treated patients at weeks 12 and 52
  - Patients who had prior experience with only 1 biologic/JAKi generally had higher responses rates with etrasimod than patients with prior experience with >1 biologic/JAKi
- Clinical remission in ELEVATE UC 12 was achieved at week 12 in biologic/JAKi-naïve patients treated with etrasimod vs placebo (**Figure 2B**)
  - Etrasimod-treated patients who had received 1 prior biologic/JAKi achieved significantly higher rates of clinical remission than placebo-treated patients at week 12

Achievement of Key Secondary Efficacy Endpoints (Overall Population)

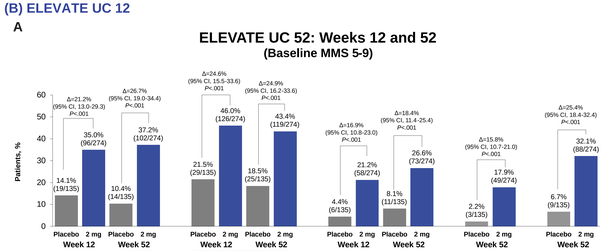
- In ELEVATE UC 52, significant improvements with etrasimod were observed in all key secondary endpoints at week 12 and week 52 (**Figure 3A**); similar findings were observed at week 12 in ELEVATE UC 12 (**Figure 3B**)

Figure 2. Achievement of Clinical Remission in (A) ELEVATE UC 52 and (B) ELEVATE UC 12 Overall Population (Primary Efficacy Endpoint) and Stratified by Prior Biologic/JAKi Exposure[a]



ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
[a] The a priori defined analyses were based on Cochran-Mantel-Haenszel analysis of the full analysis set (all randomized patients who received ≥1 dose of study drug) and used the nonresponder imputation method with a baseline MMS of 5-9 in the primary analysis and a baseline MMS of 4-9 in the subgroup analysis. Significance for the subgroup analysis is represented using nominal 2-sided P values.
[b] SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1.

Figure 3. Achievement of Key Secondary Efficacy Outcomes in (A) ELEVATE UC 52 and (B) ELEVATE UC 12



ES, endoscopic subscore; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
[a] ES ≤1.
[b] SF subscore =0 (or =1 with a ≥1-point decrease from baseline) and RB subscore =0.
[c] ES ≤1 with histologic remission as measured by a Geboes Index score <2.0.
[d] Clinical remission at both weeks 12 and 52.
[e] Patients in remission at week 52 with no use of corticosteroids for at least the last 12 study weeks immediately before week 52.

Secondary Efficacy Endpoints (Subgroup Analysis)

- In both trials, significant improvements in endoscopic improvement, symptomatic remission, and endoscopic-histologic mucosal improvement were observed in biologic/JAKi–naïve patients treated with etrasimod vs placebo
- In ELEVATE UC 52, significant improvements in endoscopic improvement, symptomatic remission, and endoscopic-histologic mucosal improvement were observed in the subgroups with exposure to 1 prior biologic/JAKi; numerically greater improvements in ELEVATE UC 12 were observed in endoscopic improvement and endoscopic-histologic mucosal improvement with significant improvements experienced in symptomatic remission
- In patients with exposure to >1 prior biologic/JAKi, significant improvements were demonstrated at both weeks 12 and 52 in endoscopic-histologic mucosal improvement and at week 52 in endoscopic improvement in ELEVATE UC 52
- Overall, results from the subgroup analysis are consistent with data observed in the key secondary endpoints of the overall population

Etrasimod Safety and Tolerability

- Infections and serious infections were similar across treatment groups, including herpes zoster and opportunistic infections
- The majority of adverse events (AEs) were considered mild or moderate (**Table 2**)
  - No deaths occurred in either trial
  - 9 patients experienced bradycardia/sinus bradycardia with 8/9 occurring on day 1; 2/9 were symptomatic (dizziness) and 5/9 discontinued treatment
  - No serious/severe AEs of bradycardia or atrioventricular block were reported
  - 3 patients experienced AEs of atrioventricular block, all were asymptomatic and 2 of which discontinued treatment
  - In both studies, no malignancies or serious/severe hepatic injuries were reported in either treatment group

Table 2. Overall Safety Profile in ELEVATE UC 52 and ELEVATE UC 12

Participants, n (%)[a]	ELEVATE UC 52 Safety Set (N=433) Placebo (n=144)	ELEVATE UC 52 Safety Set (N=433) Etrasimod 2 mg (n=289)	ELEVATE UC 12 Safety Set (N=354) Placebo (n=116)	ELEVATE UC 12 Safety Set (N=354) Etrasimod 2 mg (n=238)
Any AEs	81 (56.3)	206 (71.3)	54 (46.6)	112 (47.1)
Any serious AEs	9 (6.3)	20 (6.9)	2 (1.7)	6 (2.5)
AEs leading to death	0	0	0	0
Overall infections and infestations	32 (22.2)	72 (24.9)	14 (12.1)	27 (11.3)
Most common AEs in etrasimod group				
Headache	7 (4.9)	24 (8.3)	2 (1.7)	11 (4.6)
Worsening of UC	13 (19.0)	22 (7.6)	1 (0.9)	9 (3.8)
COVID-19 infection	9 (6.3)	20 (6.9)	3 (2.6)	3 (1.3)

AE, adverse event; UC, ulcerative colitis.
[a] Safety set included all randomized patients who received ≥1 dose of study treatment. Data are not exposure adjusted.

Efficacy and Safety of Ritlecitinib, an Oral JAK3/TEC Inhibitor, in Adolescents With Alopecia Areata: Results From the ALLEGRO Phase 2b/3 Randomized, Double-Blind, Placebo-Controlled Trial up to Week 48

Maria Hordinsky,[1] Adelaide Hebert,[2] Melinda Gooderham,[3] Ohsang Kwon,[4] Nikolay Murashkin[5], Hong Fang,[6] Kazutoshi Harada,[7] Fan Zhang,[8] Maureen P. Neary,[9] Liza Takiya,[9] Samuel H. Zwillich,[8] Robert Wolk,[8] Helen Tran[10]

[1]Department of Dermatology, University of Minnesota, Minneapolis, MN, USA; [2]UTHealth McGovern Medical School, Houston, TX, USA; [3]Skin Centre for Dermatology, Canada Probity Medical Research, Waterloo, ON, Canada; [4]Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea; [5]Dermatology Department, Scientific Center of Children's Health of the Ministry of Health of the Russian Federation, Moscow, Russia; [6]Department of Dermatology, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou City, China; [7]Department of Dermatology, Tokyo Medical University, Tokyo, Japan; [8]Pfizer Inc, Groton, CT, USA; [9]Pfizer Inc, Collegeville, PA, USA; [10]Pfizer Inc, New York, NY, USA

BACKGROUND

- Alopecia areata (AA) is an autoimmune disease with underlying immuno-inflammatory pathogenesis characterized by non-scarring hair loss ranging from small bald patches to complete loss of scalp, face, and/or body hair[1]
- Majority of patients (60%) are diagnosed with AA between the ages of 10 and 25 years; 21-24% are younger than 16 years of age[2]
- Ritlecitinib, an oral JAK3/TEC inhibitor, demonstrated efficacy and safety in patients aged ≥12 years with AA in the ALLEGRO phase 2b/3 trial (NCT03732807)[3,4]

OBJECTIVE

- To evaluate the efficacy and safety of ritlecitinib use up to 48 weeks in adolescent patients aged 12-17 years from the ALLEGRO phase 2b/3 study

METHODS

Study design

- ALLEGRO was an international, randomized, double-blind, placebo-controlled, combined dose-ranging and pivotal phase 2b/3 study (**Figure 1**)
- Patients received daily ritlecitinib (± a 4-week 200-mg daily loading dose): 200/50, 200/30, 50, 30, or 10 mg (10 mg assessed for dose ranging only) or placebo for 24 weeks
- During the 24-week extension, ritlecitinib groups continued on their 50-, 30-, or 10-mg maintenance doses, and patients initially assigned to placebo switched to 200/50 or 50 mg ritlecitinib daily
- Randomization was stratified to achieve ~15% of adolescents in each group

Key eligibility criteria

- Patients aged ≥12 years with a diagnosis of AA and ≥50% scalp hair loss (including patients with alopecia totalis and alopecia universalis) and a current AA episode duration of 6 months to 10 years
  - This post hoc analysis included adolescent patients aged 12-17 years

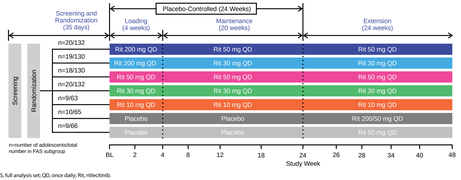
Outcomes

- Proportion of patients achieving Severity of Alopecia Tool (SALT) score ≤20 (≤20% scalp without hair); proportion of patients achieving SALT score ≤10 (≤10% scalp without hair); change from baseline in SALT score; proportion of patients with Patients' Global Impression of Change (PGI-C) response of "moderately improved" or "greatly improved" through Week 48
  - **SALT** assesses the amount of scalp hair loss with scores ranging from 0 (no scalp hair loss) to 100 (complete scalp hair loss)
  - **PGI-C** is a self-reported single-item scale where patients rate the improvement or worsening of AA compared with the start of the study, using a scale of 7 responses ranging from "greatly improved" to "greatly worsened"

Statistical analysis

- Descriptive analyses were used to evaluate proportions of patients achieving SALT score ≤20, SALT score ≤10, change from baseline in SALT score, and proportions of patients achieving PGI-C response
- 95% CIs were calculated based on normal approximation

Figure 1. Study design



BL, Baseline; FAS, full analysis set; QD, once daily; Rit, ritlecitinib.

RESULTS

Table 1. Baseline characteristics in adolescent patients

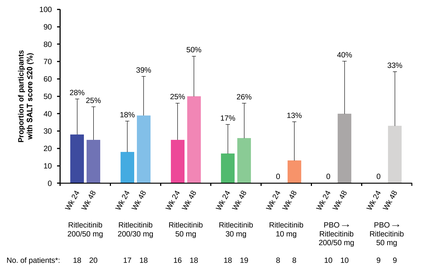
n (%)	Ritlecitinib 200/50 mg (n=20)	Ritlecitinib 200/30 mg (n=19)	Ritlecitinib 50 mg (n=18)	Ritlecitinib 30 mg (n=20)	Ritlecitinib 10 mg (n=9)	PBO → Ritlecitinib 200/50 mg (n=10)	PBO → Ritlecitinib 50 mg (n=9)
Age, mean (SD), years	15.0 (1.76)	14.7 (1.85)	15.3 (1.41)	15.1 (1.61)	15.4 (1.33)	14.6 (1.07)	13.8 (1.56)
Female, n (%)	7 (35.0)	14 (73.7)	6 (33.3)	9 (45.0)	6 (66.7)	6 (60.0)	6 (66.7)
White race, n (%)	14 (70.0)	9 (47.4)	12 (66.7)	15 (75.0)	5 (55.6)	9 (90.0)	8 (88.9)
AT/AU*, n (%)	8 (40.0)	9 (47.4)	8 (44.4)	8 (40.0)	3 (33.3)	5 (50.0)	4 (44.4)
Baseline SALT score in non-AT/AU patients, mean (SD)	88.6 (12.21)	79.2 (18.52)	86.2 (16.33)	83.2 (14.48)	79.1 (17.99)	85.7 (16.16)	83.0 (11.91)
Duration since AA onset, mean (SD), years	6.8 (4.37)	7.7 (4.73)	5.8 (5.53)	6.4 (3.95)	5.9 (4.01)	5.6 (4.87)	6.7 (5.15)
Duration of current AA episode, mean (SD), years	3.3 (3.02)	3.7 (3.17)	2.3 (2.04)	3.1 (2.18)	1.8 (1.57)	2.5 (1.56)	2.3 (2.30)

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; PBO, placebo; SALT, Severity of Alopecia Tool.
*Participants in the AT/AU category had a SALT score of 100 (complete scalp hair loss) at baseline as assessed by the investigator (regardless of the category in the AA history case report form).

Efficacy in adolescent patients at Week 24

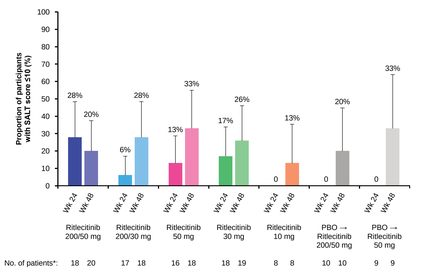
- Patients in the ritlecitinib 50- and 30-mg (± 200-mg loading dose) treatment groups achieved SALT ≤20 or SALT ≤10 at Week 24 with the proportions generally increasing through Week 48. No patients in the ritlecitinib 10-mg or placebo groups achieved SALT ≤20 or SALT ≤10 at Week 24 (**Figures 2 and 3**)

Figure 2. Response based on SALT ≤20 at Weeks 24 and 48



PBO, placebo; SALT, Severity of Alopecia Tool; Wk, Week.
Error bars are 95% CI.
*Number of patients with valid data in each subgroup at the analysis visit (non-response for missing due to reasons unrelated to COVID-19; excludes missing due to COVID-19).

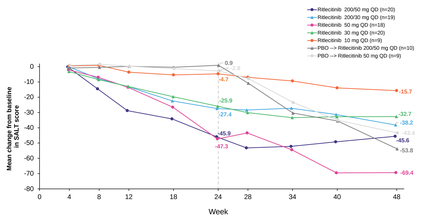
Figure 3. Response based on SALT ≤10 at Weeks 24 and 48



PBO, placebo; SALT, Severity of Alopecia Tool; Wk, Week.
Error bars are 95% CI.
*Number of patients with valid data in each subgroup at the analysis visit (non-response for missing due to reasons unrelated to COVID-19; excludes missing due to COVID-19).

- Mean change from baseline in SALT scores was greater in all treatment groups vs placebo through Week 24 and continued to improve in most ritlecitinib groups through Week 48 (**Figure 4**)
- Mean change from baseline in SALT scores was greater with ritlecitinib 50 mg (±200-mg loading dose) than with the respective 30-mg dose regimens (±200-mg loading dose) at Weeks 24 and 48 (**Figure 4**)

Figure 4. Change from baseline in SALT score to Week 48



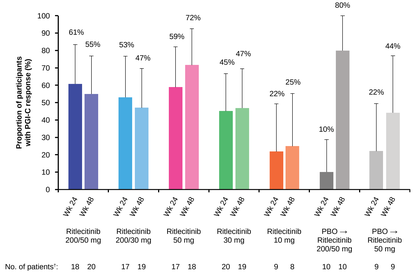
PBO, placebo; QD, once daily; SALT, Severity of Alopecia Tool.
SALT assesses the amount of scalp hair loss with scores ranging from 0 (no scalp hair loss) to 100 (complete scalp hair loss).
n = the number of patients with observed data at baseline for each treatment group.

Figure 5. Representative photos of scalp hair regrowth in an adolescent patient with alopecia universalis treated with daily ritlecitinib 50 mg



- Higher proportions of adolescents achieved PGI-C response of "moderately or greatly improved" in all treatment groups vs placebo at Week 24 and response rates were generally maintained through Week 48 (**Figure 6**)

Figure 6. Response based on PGI-C score* at Weeks 24 and 48



PGI-C, Patient Global Impression of Change.
*PGI-C response of "moderately improved" or "greatly improved".
†Number of patients with valid data at that analysis visit (non-response for missing due to reasons unrelated to COVID-19; excludes missing due to COVID-19).

Safety in adolescents up to Week 48

- Most adverse events (AEs) were mild or moderate in severity; 3 serious AEs were reported up to Week 48 (**Table 2**)
- No deaths, malignancies, major adverse cardiovascular events, pulmonary embolisms, opportunistic infections, or herpes zoster infections were reported
- The safety profile was consistent with that observed in the overall study population, with a higher proportion of adolescents reporting acne

Table 2. Safety in adolescents up to Week 48

Week 24 n (%)	Ritlecitinib 200/50 mg (n=20)	Ritlecitinib 200/30 mg (n=19)	Ritlecitinib 50 mg (n=18)	Ritlecitinib 30 mg (n=20)	Ritlecitinib 10 mg (n=9)	Placebo (n=19)
Patients with AEs	15 (75.0)	14 (73.7)	15 (83.3)	13 (65.0)	6 (66.7)	15 (78.9)
3 most common AEs overall in ≥5% of patients in any treatment group						
Headache	1 (5.0)	3 (15.8)	3 (16.7)	3 (15.0)	2 (22.2)	2 (10.5)
Acne	3 (15.0)	3 (15.8)	2 (11.1)	3 (15.0)	1 (11.1)	1 (5.3)
Nasopharyngitis	3 (15.0)	1 (5.3)	11 (9.8)	2 (11.1)	3 (15.0)	2 (22.2)
Patients with serious AEs	0	0	0	0	2 (22.2)*	0
Permanent discontinuation due to AEs	0	0	1 (5.6)†	0	1 (11.1)‡	0

Week 48 n (%)	Ritlecitinib 200/50 mg (n=20)	Ritlecitinib 200/30 mg (n=19)	Ritlecitinib 50 mg (n=18)	Ritlecitinib 30 mg (n=20)	Ritlecitinib 10 mg (n=9)	PBO → Ritlecitinib 200/50 mg (n=10)	PBO → Ritlecitinib 50 mg (n=9)
Patients with AEs	16 (80.0)	15 (78.9)	15 (83.3)	14 (70.0)	6 (66.7)	8 (80.0)	9 (100.0)
3 most common AEs overall in ≥5% of patients in any treatment group							
Headache	3 (15.0)	4 (21.1)	3 (16.7)	4 (20.0)	3 (33.3)	1 (10.0)	1 (11.1)
Acne	3 (15.0)	3 (15.8)	2 (11.1)	3 (15.0)	1 (11.1)	2 (20.0)	3 (33.3)
Nasopharyngitis	3 (15.0)	1 (5.3)	2 (11.1)	4 (20.0)	2 (22.2)	1 (10.0)	1 (11.1)
Patients with serious AEs	0	1 (5.3)§	0	0	2 (22.2)*	0	0
Permanent discontinuation due to AEs	0	0	1 (5.6)†	0	1 (11.1)‡	0	0

AE, adverse event; PBO, placebo.
*One serious AE of suicidal behavior (not considered related to study drug) and one serious AE of eczema (considered related to study drug).
†Permanent discontinuation due to urticaria.
‡Permanent discontinuation due to the serious AE of eczema.
§Appendicitis (not considered related to study drug).

CONCLUSION

- Treatment with ritlecitinib for 48 weeks demonstrated clinical efficacy and had an acceptable safety profile in adolescents with ≥50% scalp hair loss due to AA

Presented at the 47th Annual Meeting of the Society for Pediatric Dermatology; July 7-10, 2022; Indianapolis, IN

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2. Juanez-Rendon KJ, et al. *Arch Argent Pediatr* 2017;115:e404-e411.
3. King B, et al. Presented at EADV 2021.
4. Hordinsky M, et al. Presented at AAD 2022.

DISCLOSURES

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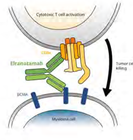
Efficacy and Safety of Elranatamab in Patients With Relapsed/Refractory Multiple Myeloma Naïve to B-cell Maturation Antigen (BCMA)-Directed Therapies: Results From Cohort A of the MagnetisMM-3 Study

Nizar Bahlis[1], Michael H. Tomasson[2], Mohamad Mohty[3], Ruben Niesvizky[4], Ajay Nooka[5], Salomon Manier[6], Christopher Maisel[7], Yogesh Jethava[8], Joaquin Martinez-Lopez[9], H. Miles Prince[10], Bertrand Arnulf [11], Paula Rodriguez-Otero[12], Guenther Koehne[13], Cyrille Touzeau[14], Noopur Raje[15], Shinsuke Iida[16], Marc-Steffen Raab[17], Eric Leip[18], Sharon Sullivan[18], Umberto Conte[19], Andrea Viqueira[20], Alexander Lesokhin[21]

[1]*Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada;* [2]*Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA;* [3]*Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France;* [4]*Weill Cornell Medical College – New York Presbyterian Hospital, New York, NY, USA;* [5]*Winship Cancer Institute, Atlanta, GA, USA;* [6]CHU *de Lille, Lille, France;* [7]Baylor *University Medical Center, Dallas, TX, USA;* [8]*Indiana Blood & Marrow Transplant, Indianapolis, IN, USA;* [9]*Hospital Universitario 12 de Octubre, Madrid, Spain;* [10]*Epworth Healthcare, Melbourne, Australia;* [11]*Hôpital Saint-Louis, Paris, France;* [12]*Clinica Universidad de Navarra, Madrid, Spain;* [13]*Miami Cancer Institute, Miami, FL, USA;* [14]*CHU de Nantes, Nantes, France;* [15]*Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA;* [16]*Department of Hematology & Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan;* [17]*Heidelberg Myeloma Center, Department of Hematology/Oncology, Heidelberg University Hospital, Heidelberg, Germany;* [18]*Pfizer Inc, Cambridge, MA, USA;* [19]*Pfizer Inc, New York, NY, USA;* [20]*Pfizer SLU, Madrid, Spain;* [21]*Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY, USA*

Background

- Elranatamab (PF-06863135) is a humanized bispecific antibody that targets both BCMA-expressing MM cells and CD3-expressing T cells[1]
- Data from the ongoing phase 1 MagnetisMM-1 study (NCT03269136) demonstrated the safety and efficacy of elranatamab in patients with RRMM[2,3]
- Here we present results from the phase 2 MagnetisMM-3 (NCT04649359) study in patients with RRMM and no prior BCMA-targeted treatment



1. Shah N, et al. Leukemia 2020;34:985-1005. 2. Bahlis NJ, et al. J Clin Oncol 2021;39(15 suppl):8006. 3. Sebag M, et al. Blood 2021;138(suppl 1):995. 4. Jakubowiak A, et al. J Clin Oncol 2022;40(16 suppl):8014. 5. Raje N, et al. Presented at ASH2022, Abstract #109.
BCMA=B-cell maturation antigen; MM=multiple myeloma; RRMM=relapsed/refractory multiple myeloma

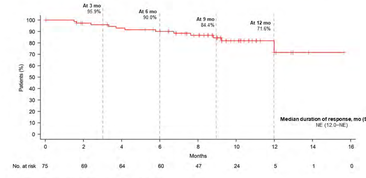
Treatment Summary and Disposition

- As of the data cut-off (October 14, 2022), median duration of follow-up was 10.4 (range, 0.2–20.1) mo
- Median duration of treatment was 5.6 (range, 0.03–19.8) mo
  - 59 (48.0%) of patients had been treated for >6 mo

	Cohort A (N=123)*
Ongoing treatment, n (%)	52 (42.3)
Duration of treatment, n (%)	
≤6 mo	64 (52.0)
>6 and ≤12 mo	41 (33.3)
>12 mo	18 (14.6)
Discontinued treatment, n (%)	71 (57.7)
Progressive disease	43 (35.0)
AE	13 (10.6)
Death	8 (6.5)
Patient withdrawal	4 (3.3)
Lack of efficacy	3 (2.4)

*Study enrollment completed January 7, 2022.
AE=adverse event

Duration of Response per BICR (Responders Only)

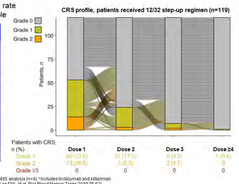


BICR=blinded independent central review; CI=confidence interval; NE=not evaluable

AEs of Special Interest: CRS and ICANS

- The step-up priming regimen successfully mitigated the rate and severity of CRS, and the CRS profile was predictable

TEAE of special interest	12/32 mg step-up regimen (n=119)* CRS	ICANS
Patients with TEAE, n (%)	67 (56.3)	4 (3.4)
Maximum Grade 1	50 (42.0)	1 (0.8)
Maximum Grade 2	17 (14.3)	3 (2.5)
Maximum Grade ≥3	0	0
Patients with >1 TEAE, n (%)	18 (15.1)	1 (0.8)
Median time to onset of TEAE, d (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, d (range)	2.0 (1.0–19.0)	2.0 (1.0–6.0)
Patients with TEAE who received tocilizumab# or steroids, n (%)		
Tocilizumab	27 (40.3)	2 (50.0)
Steroids	10 (14.9)	2 (50.0)
Permanent discontinuation due to AE, n (%)	0	0



*Patients who received 1 step-up priming dose of 44 mg in cycle 1 were excluded from this CRS and ICANS analysis (n=43).#Includes tocilizumab and siltuximab.
CRS and ICANS adverse events were graded by American Society for Transplantation and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:625).
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

MagnetisMM-3 Study

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study



[a]Refractory was defined as having disease progression while on therapy or within 60 d of last dose in any line, regardless of response
[b]By BICR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17:e328-46)
[c]By investigator assessment per IMWG response criteria
ADC=antibody drug conjugate; ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete response; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QW=once weekly; SC=subcutaneous

Objective Response Rate per BICR

- Confirmed ORR per BICR was 61.0% (95% CI, 51.8–69.6)
- Among patients who achieved an objective response (n=75), median time to response was 1.2 (range, 0.9–7.4) mo
- MRD-negativity at the threshold of 10^{-5} was achieved by 90.9% of evaluable patients (n=22)

MRD-negativity was assessed by next-generation sequencing in patients who achieved CR or sCR
BICR=blinded independent central review; CI=confidence interval; CR=complete response; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response

Progression-Free Survival per BICR

BICR=blinded independent central review; CI=confidence interval; NE=not evaluable; PFS=progression-free survival

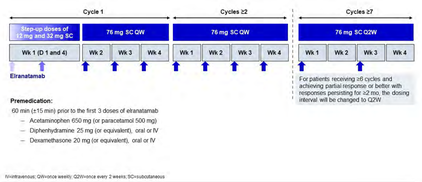
AEs of Special Interest: Infections

- Infections were reported in 66.7% (Grade 3/4, 35.0%) of patients
  - Median time to first onset of infections was 47.5 d (range, 1.0–295.0)
- COVID-19 related TEAEs were reported in 31 (25.2%) patients
  - 2 (1.6%) patients died due to COVID-19 pneumonia, both considered unrelated to treatment by the investigator
- 8 (6.5%) patients had an infection that led to permanent discontinuation of elranatamab
  - Most common infection TEAEs leading to treatment discontinuation were sepsis (n=2) and pneumonia (n=2)
- Among patients with quantitative IgG data (n=101), 76 (75.2%) patients experienced IgG level <400 mg/dL during the study
  - 50 (40.7%) patients received IVIG during the study

n (%)	Cohort A (N=123) Any grade	Grade 3/4
Infection TEAEs in ≥5% of patients		
COVID-19 related[a]	31 (25.2)	14 (11.4)
Upper respiratory tract infection	22 (17.9)	0
Pneumonia	15 (12.2)	7 (5.7)
Urinary tract infection	11 (8.9)	4 (3.3)
Sinusitis	11 (8.9)	2 (1.6)
TEAEs of interest		
Pneumocystis jirovecii pneumonia	6 (4.9)	5 (4.1)
CMV infection reactivation	6 (4.9)	2 (1.6)
CMV infection	4 (3.3)	0

[a]Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries.
Other grade 5 TEAEs: (n=6) were not treatment-related per investigator and included disease progression or recession (n=1), infections (n=2), cardiac disorders (n=2), and respiratory disorders (n=1).
≥2y were graded by Common Terminology Criteria for Adverse Events v5.0, except for CRS and ICANS, which were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:625).
TEAEs were defined as any new or worsening occurring from the start of elranatamab treatment through 30 d of the last dose or start of new anticancer therapy, whichever occurs first.
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; MedDRA=Medical Dictionary for Regulatory Activities Terminology; preferred terms; TEAE=treatment-emergent adverse event

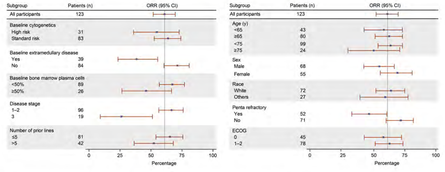
MagnetisMM-3: Elranatamab Dosing Schedule



Premedication:
60 min (±15 min) prior to the first 3 doses of elranatamab
- Acetaminophen 650 mg (or paracetamol 500 mg)
- Diphenhydramine 25 mg (or equivalent), oral or IV
- Dexamethasone 20 mg (or equivalent), oral or IV

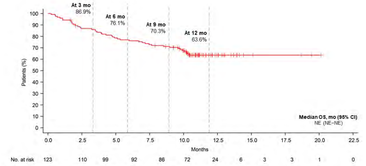
IV=intravenous; QW=once weekly; Q2W=once every 2 weeks; SC=subcutaneous

Objective Response Rate per BICR Across Subgroups



BICR=blinded independent central review; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate

Overall Survival



CI=confidence interval; NE=not evaluable; OS=overall survival

Conclusions

- Elranatamab is efficacious and well tolerated in patients with RRMM
- High response rate (ORR, 61.0%) with early, deep, and durable responses observed (9-mo DOR, 84.4%)
  - With a median follow-up of 10.4 mo, median PFS and OS have not been reached (9-mo PFS, 63.0%)
- Elranatamab toxicities were manageable
  - Step-up priming regimen with pre-medication successfully mitigated the rate and severity of CRS and ICANS
    - CRS and ICANS were limited to Grade 1/2, with no Grade 3+ events
    - CRS events occurred early, with the majority during the first week of treatment
  - Most common Grade 3/4 TEAEs were hematologic
- These results support expansion of the MagnetisMM program to evaluate elranatamab alone and in combination with other drugs for the treatment of patients with MM
  - Phase 3 MagnetisMM-5 trial in patients with RRMM (NCT05020236; abstract #1921)
  - Phase 3 MagnetisMM-7 trial in patients with newly diagnosed MM post-transplant maintenance (NCT05317416)

CRS=cytokine release syndrome; DOR=duration of response; ICANS=immune effector cell-associated neurotoxicity syndrome; MM=multiple myeloma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RRMM=relapsed/refractory multiple myeloma; TEAE=treatment-emergent adverse event

Demographics and Baseline Characteristics

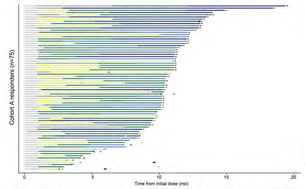
	Cohort A (N=123)*
Age, median (range), y	68 (36–89)
Male, n (%)	68 (55.3)
Race, n (%)	
White	72 (58.5)
Asian	19 (13.0)
Black or African American*	9 (7.3)
ECOG performance status, n (%)	
0	45 (36.6)
1	71 (57.7)
2	7 (5.7)
R-ISS disease stage, n (%)	
I	28 (22.8)
II	68 (55.3)
III	19 (15.4)
Unknown	8 (6.5)
Cytogenetic risk, n (%)	
Standard	83 (67.5)
High#	31 (25.2)
Missing	9 (7.3)

	Cohort A (N=123)*
Extramedullary disease by BICR, n (%)^	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class#	123 (100)
Penta-drug#	87 (70.7)
Refractory status, n (%)	
Triple-class#	119 (96.7)
Penta-drug#	52 (42.3)
Refractory to last line of therapy, n (%)	118 (95.9)

[a]Includes 64,16,14,10, and (1) chromosomal abnormalities; ^Extramedullary disease was defined as presence of any plasmacytoma (radiomedullary and/or paramedullary) with a soft-tissue component; #Triple-class refers to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody; #Penta-drug refers to at least 2 proteasome inhibitors, 2 immunomodulatory drugs, and 1 anti-CD38 antibody.
BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; R-ISS=Revised Multiple Myeloma International Staging System

* 17% (n=8/47) of patients enrolled in the United States were Black or African American

Durability of Response per BICR (Responders Only)



- At data cut-off, 77.3% (n=58/75) objective responses were ongoing

Safety Profile

TEAEs in ≥20% of patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4
Hematologic		
Anemia	59 (48.0)	45 (36.6)
Neutropenia	59 (48.0)	59 (48.0)
Thrombocytopenia	37 (30.1)	27 (22.0)
Lymphopenia	32 (26.0)	30 (24.4)
Non-hematologic		
CRS	71 (57.7)	0
Diarrhea	48 (39.0)	2 (1.6)
Fatigue	42 (34.1)	4 (3.3)
Decreased appetite	40 (32.5)	1 (0.8)
Injection site reaction	32 (26.0)	0
Nausea	32 (26.0)	0
COVID-19 related*	31 (25.2)	14 (11.4)
Pyrexia	29 (23.6)	4 (3.3)
Hypokalemia	29 (23.6)	12 (9.8)
Cough	27 (22.0)	0
Headache	27 (22.0)	0
Asthenia	23 (18.7)	6 (4.9)

- The most common TEAEs were CRS and hematologic events; non-hematologic events were predominantly Grade 1/2
- All CRS and ICANS events were Grade 1/2
- No fatal neurotoxicity events were observed
- TEAEs led to permanent elranatamab discontinuation in 19 (15.4%) patients
- TEAEs led to death in 21 patients; 2 treatment-related per investigator[b]
  - 1 grade 5 pseudomonal pneumonia
  - 1 grade 5 failure to thrive

[a]Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries.
[b]Other grade 5 TEAEs: (n=6) were not treatment-related per investigator and included disease progression or recession (n=1), infections (n=2), cardiac disorders (n=2), and respiratory disorders (n=1).
≥2y were graded by Common Terminology Criteria for Adverse Events v5.0, except for CRS and ICANS, which were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:625).
TEAEs were defined as any new or worsening occurring from the start of elranatamab treatment through 30 d of the last dose or start of new anticancer therapy, whichever occurs first.
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; MedDRA=Medical Dictionary for Regulatory Activities Terminology; preferred terms; TEAE=treatment-emergent adverse event

Acknowledgments

- We thank the MagnetisMM-3 trial patients and their families, as well as the study investigators, nurses, and site staff
- This study (NCT04649359) was sponsored by Pfizer
- Medical writing support was provided by Gemma Shay-Lowell, PhD CMPP, of Engage Scientific Solutions and was funded by Pfizer



Contact for information: Nizar Bahlis, nbahlis@ucalgary.ca

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Elranatamab, a BCMA Targeted T-cell Engaging Bispecific Antibody, Induces Durable Clinical and Molecular Responses for Patients With Relapsed or Refractory Multiple Myeloma

Noopur S. Raje, MD, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

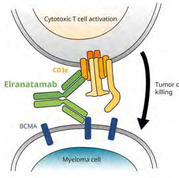
Authors for MagnetisMM-1

Noopur S. Raje, MD[1], Nizar J. Bahlis, MD[2], Caitlin L. Costello, MD[3], Bhagirathbhai Dholaria, MBBS[4], Melhem Solh, MD[5], Moshe Y. Levy, MD[6], Michael H. Tomasson, MD[7], Michael A. Damore, PhD[8], Sibo Jiang, PhD[9], Cynthia Basu, PhD[9], Athanasia Skoura, PhD[10], Edward M. Chan, MD[11], Suzanne Trudel, MD[12], Andrzej Jakubowiak, MD, PhD[13], Michael P. Chu, MD[14], Cristina Gasparetto, MD[15], Andrew Dalovisio, MD[16], Michael Sebag, MD, PhD17, Alexander M. Lesokhin, MD18

[1]*Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA;* [2]*Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada;* [3]*Moores Cancer Center, University of California San Diego, La Jolla, CA, USA;* [4]*Vanderbilt-Ingram Cancer Center, Nashville, TN, USA;* [5]*Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA, USA;* [6]*Department of Medical Oncology, Baylor Scott and White Health, Dallas, TX, USA;* [7]*Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA;* [8]*Oncology Research and Development, Pfizer Inc, San Diego, CA, USA;* [9]*Early Clinical Development, Pfizer Inc, Collegeville, PA, USA;* [10]*Oncology Research and Development, Pfizer Inc, South San Francisco, CA, USA;* [11]*Oncology Research and Development, Pfizer Inc, South San Francisco, CA, USA;* [12]*Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada;* [13]*Department of Medicine, University of Chicago Medical Center, Chicago, IL, USA;* [14]*Cross Cancer Institute, Edmonton, AB, Canada;* [15]*Department of Medicine, Duke University Cancer Institute, Durham, NC, USA;* [16]*Department of Hematology and Oncology, Ochsner Health, New Orleans, LA, USA;* [17]*Cedars Cancer Center, McGill University Health Center, Montreal, QC, Canada;* [18]*Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY, USA*

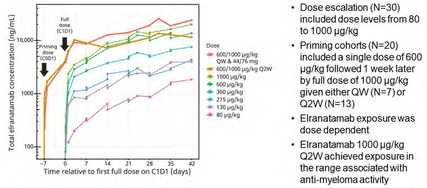
Introduction

- MM is a type of plasma cell neoplasm characterized by BCMA overexpression[1]
- Elranatamab (PF-06863135), a humanized bispecific antibody targeting BCMA on myeloma cells and CD3 on T cells, induces a selective cytotoxic T-cell response against myeloma cells[2]
- MagnetisMM-1 (NCT03269136) is the ongoing Phase 1 first-in-human study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of elranatamab for patients with RRMM
- Here, we present data for 55 patients who received elranatamab monotherapy at doses ≥215 µg/kg



1. Shah N, et al. Leukemia 2020;34:985 2. Panowski SH, et al. Blood 2019;126:383. BCMA=B-cell maturation antigen; CD3=cluster of differentiation 3; MM=multiple myeloma; RRMM=relapsed/refractory multiple myeloma.

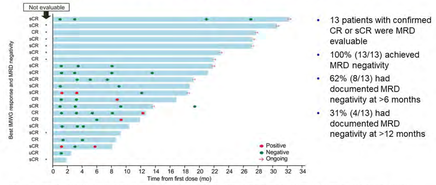
Elranatamab Pharmacokinetics



- Dose escalation (N=30) included dose levels from 80 to 1000 µg/kg
- Priming cohorts (N=20) included a single dose of 600 µg/kg followed 1 week later by full dose of 1000 µg/kg given either QW (N=7) or Q2W (N=13)
- Elranatamab exposure was dose dependent
- Elranatamab 1000 µg/kg Q2W achieved exposure in the range associated with anti-myeloma activity

Data cutoff was September 30, 2022; C=cycle; D=day; QW=weekly; Q2W=every 2 weeks.

Duration of Treatment and Molecular Response for CR/sCR Patients

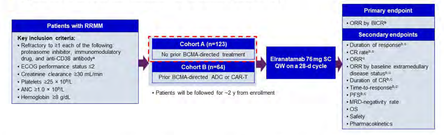


- 13 patients with confirmed CR or sCR were MRD evaluable
- 100% (13/13) achieved MRD negativity
- 62% (8/13) had documented MRD negativity at >6 months
- 31% (4/13) had documented MRD negativity at >12 months

Data cutoff was September 30, 2022. MRD status was assessed by next generation sequencing at a sensitivity of 1 x 10^-5 in accordance with IMWG criteria. Evaluable patients had a dominant variable (V)-(diversity (D)—joining (J) sequence at baseline and confirmed response of CR or better. IMWG=International Myeloma Working Group; MRD=minimal residual disease; CR=complete response; sCR=stringent complete response; unconfirmed.

MagnetisMM-3

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study



*Refractory was defined as having disease progression while on therapy or within 60 d of last dose in any line, regardless of response. †By IRCR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17:e328-46). ‡By investigator assessment per IMWG response criteria. ADC=antibody-drug conjugate; ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; IRCR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete response; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QW=weekly; SC=subcutaneous.

Methods

- Patients received elranatamab monotherapy SC at doses from 215 to 1000 µg/kg either QW or Q2W
- Safety assessments
  - TEAEs were graded by NCI CTCAE v4.03
  - CRS was graded by ASTCT criteria[1]
- Pharmacokinetics, cytokines, lymphocyte subsets, and soluble BCMA were evaluated
- Mutational profiling was performed by next-generation sequencing
- Response was assessed by IMWG criteria[2]
- MRD status was assessed by next-generation sequencing at a sensitivity of $1x10^{-5}$ in accordance with IMWG criteria for MRD assessment
- Data cutoff was September 30, 2022

1.Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625. Normal S, et al. Lancet Oncol 2016;3:e328. ASTCT=American Society for Transplantation and Cellular Therapy; BCMA=B-cell maturation antigen; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; IMWG=International Myeloma Working Group; MRD=minimal residual disease; NCI=National Cancer Institute; Q2W=every 2 weeks; SC=subcutaneous; TEAE=treatment-emergent adverse event.

Elranatamab-Induced Changes in Soluble BCMA

- Reductions in soluble BCMA were observed over time in responding patients

Data cutoff was September 30, 2022. CR=complete response; MR=minimal response; PD=progressive disease; PR=partial response; QW=weekly; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

Kaplan-Meier Plot for Progression-Free Survival – All Patients

Data cutoff was September 30, 2022. PFS=progression-free survival.

MagnetisMM-5

- MagnetisMM-5 (NCT05020236) is an ongoing, open-label, multicenter, phase 3 study

Elranatamab and daratumumab are administered by SC injection. C=cycle; D=day; DL=dose level; PI=proteasome inhibitor; SC=subcutaneous

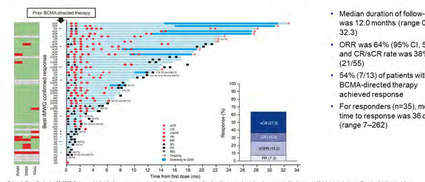
Patient Characteristics and Prior Treatments

Characteristic	Monotherapy SC (N=55)
Female, n (%)	**26 (47.3)**
Age, y, median (range)	**64.0 (42–80)**
Race, n (%)	
White	37 (67.3)
Black/African American	11 (20.0)
Asian	4 (7.3)
Not reported	3 (5.5)
Cytogenetic risk, n (%)	
High*	16 (29.1)
Standard	35 (63.6)
Unknown	4 (7.3)

Prior treatments	Monotherapy SC (N=55)
Prior anti-myeloma therapies, median (range)	**5.0 (2–14)**
Triple-class refractory, n (%)†	**50 (90.9)**
Prior PIs, n (%)	**55 (100)**
Bortezomib	52 (94.5)
Carfilzomib	47 (85.5)
Ixazomib	18 (32.7)
Prior IMiDs, n (%)	**55 (100)**
Lenalidomide	54 (98.2)
Pomalidomide	52 (94.5)
Thalidomide	9 (16.4)
CC-92480	2 (3.6)
Iberdomide	1 (1.8)
Prior anti-CD38 therapy, n (%)	**54 (98.2)**
Daratumumab	52 (94.5)
Isatuximab	4 (7.3)
Other‡	1 (1.8)
Prior BCMA-targeted therapy, n (%)	**13 (23.6)**
Anti-BCMA ADC	8 (14.5)
CAR-T	9 (16.4)

Data cutoff was September 30, 2022. Patients may have received >1 treatment within a given therapy class. *Definition of high (cytogenetic risk includes ≥1 t(4;14), t(14;16), and del(17p).† Triple-class refractory disease is refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 therapy. ‡ 1 patient treated at 300 µg/kg received prior anti-myeloma therapy with a CD3/CD20 bispecific molecule. ADC=antibody drug conjugate; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell therapy; IMiD=immunomodulatory drug; PI=proteasome inhibitor; SC=subcutaneous.

Duration of Treatment and Best Overall Response



- Median duration of follow-up was 12.0 months (range 0.3–32.3)
- ORR was 64% (95% CI, 50–75) and CR/sCR rate was 38% (21/55)
- 54% (7/13) of patients with prior BCMA-directed therapy achieved response
- For responders (n=35), median time to response was 36 days (range 7–262)

Data cutoff was September 30, 2022. 5-censor pol depicts disease assessments rolled-in to the response, confirmation of response, deepening of response, and best response. †Additional analysis was filtered on functional mutations annotated in OncoKB and normal allele frequency <1% in paired peripheral blood mononuclear cell samples. * Prior anti-BCMA ADC - Prior BCMA-targeted CAR-T. ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T-cell therapy; CR=complete response; IMWG=International Myeloma Working Group; sBCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

Most Common Treatment-Emergent Adverse Events (All Causality)

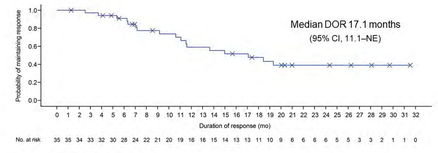
Adverse event, n (%)	Monotherapy SC (N=55)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematologic					
Neutropenia	0	2 (3.6)	14 (25.5)	25 (45.5)	41 (74.5)
Anemia	1 (1.8)	8 (14.5)	28 (50.9)	0	37 (67.3)
Lymphopenia	0	1 (1.8)	3 (5.5)	25 (45.5)	29 (52.7)
Thrombocytopenia	6 (10.9)	6 (10.9)	5 (10.9)	10 (18.2)	28 (50.9)
Non-hematologic					
CRS*	28 (50.9)	20 (36.4)	0	0	48 (87.3)
Injection site reaction	27 (49.1)	4 (7.3)	0	0	31 (56.4)
Fatigue	7 (12.7)	12 (21.8)	4 (7.3)	0	23 (41.8)
Diarrhea	12 (21.8)	8 (14.5)	2 (3.6)	0	22 (40.0)
Dry skin	18 (32.7)	2 (3.6)	0	0	20 (36.4)
Hypophosphatemia	0	6 (10.9)	13 (23.6)	1 (1.8)	20 (36.4)
Decreased appetite	11 (20.0)	7 (12.7)	1 (1.8)	0	19 (34.5)
Nausea	6 (10.9)	10 (18.2)	3 (5.5)	0	19 (34.5)

With 44 mg step-up priming plus premedication, overall incidence of CRS was 67% CRS was further mitigated by 12/32 mg step-up priming in Phase 2 study (MagnetisMM-3)

Adverse Event of Clinical Interest: Infection Grade 3 and 4 occurred in 21.8% (12/55) and 5.5% (3/55) of patients respectively, and 1 patient had Grade 5 adenovirus infection assessed by investigator as possibly related to study treatment.

Data cutoff was September 30, 2022. * 23 patients received no priming or pre-medication, 23 patients received priming only, and 15 patients received priming plus pre-medication. In the group that received priming plus premedication, the overall incidence of CRS was 67% and incidents Grade 1 (33%) or Grade 2 (33%) with 7 patients (47%) receiving tocilizumab. Grading of TEAEs based on NCI CTCAE version 4.03, except for CRS, which is based on ASTCT consensus. Supported (S19.2f.525). CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; SC=subcutaneous; TEAE=treatment-emergent adverse event.

Kaplan-Meier Plot for Duration of Response – Responders



Data cutoff was September 30, 2022. DOR=duration of response; NE=not estimable.

Conclusions for MagnetisMM-1

- Elranatamab showed a manageable safety profile for patients with RRMM
  - The 12/32 mg step-up priming dose regimen successfully mitigated CRS in MagnetisMM studies (Abstract 159 [MagnetisMM-3] and Abstract 3192 [pooled analysis from MagnetisMM studies])
- Elranatamab demonstrated a dose-dependent increase in exposure and reduced soluble BCMA over time in responding patients
- Confirmed ORR was 64% (95% CI, 50–75), and CR/sCR rate was 38%
- For responders (n=35), median DOR was 17.1 months (95% CI, 11.1–NE)
- All evaluable patients achieved MRD negativity, and 62% had documented MRD negativity at >6 months
- For all patients (N=55), median PFS was 11.8 months (95% CI, 6.0–19.1)
- Elranatamab induced durable clinical and molecular responses for patients with RRMM
- Along with emerging data from MagnetisMM-3 (NCT0469359) and MagnetisMM-5 (NCT05020236), these results support further development of elranatamab for patients with MM

Data cutoff was September 30, 2022. BCMA=B-cell maturation antigen; CR=complete response; DOR=duration of response; MM=multiple myeloma; MRD=minimal residual disease; NE=not estimable; ORR=objective response rate; PFS=progression-free survival; RRMM=relapsed/refractory multiple myeloma; sCR=stringent complete response.

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- **Funding:** This study was sponsored by Pfizer.

- **Contact for information:** Noopur S Raje, nraje@mgh.harvard.edu

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TALAPRO-1: Phase 2 Study of Talazoparib in Patients With DNA Damage Repair Alterations and Metastatic Castration-Resistant Prostate Cancer

Johann S. de Bono,[1] Niven Mehra,[2] Celestia S. Higano,[3] Fred Saad,[4] Consuelo Buttigliero,[5] Inge M. van Oort,[6] Marielena Mata,[7] Hsiang-Chun Chen,[7] Cynthia G. Healy,[8] Akos Czibere,[9] Karim Fizazi[10]

[1]The Institute of Cancer Research and Royal Marsden Hospital, London, UK; [2]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [3]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [4]Division of Urology, Centre Hospitalier de l'Université de Montréal (CHUM/CRCHUM), Montréal, Quebec, Canada; [5]Department of Oncology, University of Turin, San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy; [6]Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands; [7]Pfizer Inc., La Jolla, CA, USA; [8]Pfizer Inc., Collegeville, PA, USA; [9]Pfizer Inc., Cambridge, MA, USA; [10]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

Background

- Inhibition of poly(ADP-ribose) polymerase (PARP) is synthetically lethal in cells with homozygous deletions and/or deleterious alterations in DNA damage response (DDR) genes involved in homologous recombination repair.[1,2]
- Alterations in homologous recombination DDR genes have been identified in ~23–27 % of patients with prostate cancer;[3-5] these alterations are linked with a poor prognosis and worse clinical outcome.[6-8]
- Talazoparib inhibits PARP catalytic activity and effectively traps PARP on DNA, preventing DNA replication and transcription as well as contributing to the accumulation of double-strand DNA breaks, leading to cell death.[9-12]
- TALAPRO-1 (NCT03148795) is a multinational Phase 2 trial evaluating talazoparib monotherapy in heavily pretreated men with metastatic castration-resistant prostate cancer (mCRPC) and DDR alterations.[a] Here we report antitumor activity and tolerability results (data cut-off September 4, 2020).

[a]DDR alterations are defined as known/likely pathogenic variants or homozygous deletions.

Methods

STUDY DESIGN

- TALAPRO-1[13] enrolled men with progressive mCRPC and measurable soft tissue disease[b] per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) per independent central review or investigator assessment.
  - All patients had homozygous or heterozygous DDR core gene alterations likely to sensitize to PARP inhibition (DDR tumor core genes: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*) determined by prospective testing of de novo or archival tumor tissue using FoundationOne® CDx (Foundation Medicine, Cambridge, MA).
  - Patients must have received 1–2 chemotherapy regimens (⩾1 taxane-based) in the metastatic setting (castration-sensitive or -resistant), and progressed on ⩾1 novel hormonal therapy (NHT; enzalutamide and/or abiraterone acetate) given in the mCRPC setting (**Table S1 and Supplemental Appendix accessed via QR code**).
- Oral talazoparib 1 mg/day (0.75 mg/day if moderate renal impairment) was taken until radiographic progression, unacceptable toxicity, investigator decision, withdrawal of consent, or death.

[b]23 patients were enrolled under the original study protocol with non-measurable disease; however, a protocol amendment required all subsequent patients to have measurable disease.

STUDY ENDPOINTS

- The primary endpoint was confirmed objective response rate (ORR) by blinded independent central review (BICR), with objective response defined as a best overall soft tissue response of complete or partial responses.
  - Soft tissue responses were confirmed ⩾4 weeks later by computed tomography or magnetic resonance imaging with no evidence of confirmed bone progression per Prostate Cancer Working Group 3 (PCWG3) criteria on repeat bone scan ⩾6 weeks later.
- Secondary endpoints were time to objective response per BICR, duration of objective response per BICR, proportion of patients with prostate-specific antigen (PSA) decline ⩾50 %, proportion of men with conversion of circulating tumor cell (CTC) count (decrease from ⩾5 to <5 per 7.5 mL of blood, decrease from ⩾1 to 0 per 7.5 mL of blood, or any increase from <5 per 7.5 mL of blood), time to PSA progression, radiographic progression-free survival (rPFS) per BICR, overall survival (OS), and safety.

STATISTICAL ANALYSES

- The safety population included all patients who received ⩾1 dose of talazoparib, including a subset of patients with non-measurable disease enrolled under an earlier version of the protocol **(Supplemental Appendix)** and DDR gene alterations assessed using an expanded DDR gene panel.
- Antitumor assessments were performed in the DDR-deficient measurable disease population (ie, **efficacy population**) defined as all patients who had measurable soft tissue disease at screening per central review or investigator assessment, had predefined tumor DDR gene alterations in the core DDR gene panel, and had received ⩾1 dose of talazoparib.
- All antitumor activity endpoints were analyzed by DDR groups (*BRCA1/2*, *PALB2*, *ATM*, others), where patients are separated hierarchically by DDR gene alterations, with *BRCA1/2* ascendant over *PALB2*, *PALB2* ascendant over *ATM*, and *ATM* ascendant over all other alterations.

Results

PATIENTS

- 128 patients were enrolled between July 4, 2017 and March 20, 2020 (**Figure S1**).
- Baseline characteristics for the safety population (N = 127) and the efficacy population (N = 104) were similar (**Table 1** and **Table S2**; populations defined in statistical analyses section). The patient population was heavily pretreated, with 48 % of patients having received >1 prior taxane.
- Of 104 patients in the efficacy population, 4 (3.8 %) had a *BRCA1* alteration alone, 52 (50.0 %) had a *BRCA2* alteration alone, 15 (14.4 %) had an *ATM* alteration alone, 4 (3.8 %) had a *PALB2* alteration alone, and 22 (21.2 %) had other DDR gene alterations; 7 patients had co-occurring DDR gene alterations (2 had *BRCA2/PALB2* alterations; 1 each had *ATM/BRCA2*, *ATM/FANCA*, *ATM/RAD51C*, *BRCA2/CHEK2*, and *BRCA2/MLH1* alterations [**Figure S2**]). When separated by the predefined hierarchy (see Methods), 61 patients had a *BRCA1/2* alteration, 57 had a *BRCA2* alteration, 4 had a *PALB2* alteration, 17 had an *ATM* alteration, and 22 had other alterations.
- Median (range) duration of talazoparib treatment was 6.1 (0.4–24.9) months in the safety population and 6.2 (0.5–22.2) months in the efficacy population.

ANTITUMOR ACTIVITY

- In the efficacy population, the confirmed ORR by BICR was 29.8 % (31/104 patients; 95 % CI, 21.2–39.6) (**Table 2**).
  - Confirmed ORR (BICR) by DDR gene alteration group was *BRCA2*, 45.6 % (26/57 patients); *BRCA1*, 50.0 % (2/4 patients); *PALB2*, 25.0 % (1/4 patients); *ATM*, 11.8 % (2/17 patients) (**Table 2**).
- Most patients in the efficacy population demonstrated a reduction in tumor burden (67/84 patients; **Figure 1A**), PSA (69/96 patients; **Figure 1B**), and CTC count (37/45 patients; **Figure S3**), with the highest rates seen with *BRCA1/BRCA2* alterations.
  - Many patients with *PALB2* or *ATM* alterations also showed a reduction in tumor burden (*PALB2*, 3/3 patients; *ATM*, 9/13 patients; **Figure 1A**), PSA (*PALB2*, 3/4 patients; *ATM*, 11/15 patients; **Figure 1B**), and CTC counts (*PALB2*, 1/2 patients; *ATM*, 6/6 patients; **Figure S3**).
  - Some clinical benefit was seen in many patients regardless of DDR11 alteration germline/somatic origin or zygosity. However, when zygosity was evaluable, tumor shrinkage ⩾30 % or decreases in PSA were primarily observed with homozygous alterations (**Figure 1**).
    - Of note, the exploratory DDR11 alteration germline/somatic origin and zygosity analysis was limited to short variants, and tumors otherwise evaluable for such analyses (eg, evaluable saliva samples or adequate tumor purity for zygosity analysis).
  - PSA ⩾50 % results are shown in **Table 2**. Of the patients with a baseline PSA value, a ⩾30 % reduction in PSA response was seen in 70.5 % (43/61) of patients with *BRCA1/2* alterations and 48.1 % (50/104) of patients in the overall efficacy population, respectively.
  - A composite response was observed in 72.1 % of patients with *BRCA1/2* alterations and 51.0 % of patients in the total efficacy population (**Table 2**).
  - The clinical benefit rate was 37.5 % for the overall efficacy population, 55.7 % for *BRCA1/2* alterations, 25.0 % for *PALB2* alterations, and 23.5 % for *ATM* alterations (**Table 2**).
- Time to and duration of confirmed objective response by BICR is shown in **Figure 2A**, with the longest confirmed objective responses seen with *BRCA2* alterations. There were multiple patients with non-*BRCA1/2* gene alterations who showed prolonged stable disease, most notably in those with *ATM* alterations (**Figure 2B**).
  - In the efficacy population, median time to response (range) was 3.4 (1.6–7.5) months and median duration of response (95 % CI) was 12.8 (6.5–not evaluable [NE]) months (12 patients had an ongoing response at data cut-off).
- Median rPFS by BICR was 5.6 (95 % CI, 3.7–8.8) months for all patients (**Figure 3**), 11.2 (7.5–19.2) months for patients with *BRCA1/BRCA2* alterations, 3.5 (1.8–3.7) months for patients with non-*BRCA* alterations, 5.6 (3.7–7.4) months for patients with *PALB2* alterations, and 3.5 (1.7–8.3) months for patients with *ATM* alterations. A similar trend was observed for OS (**Figure S4A**) and time to PSA progression (**Figure S4B**).

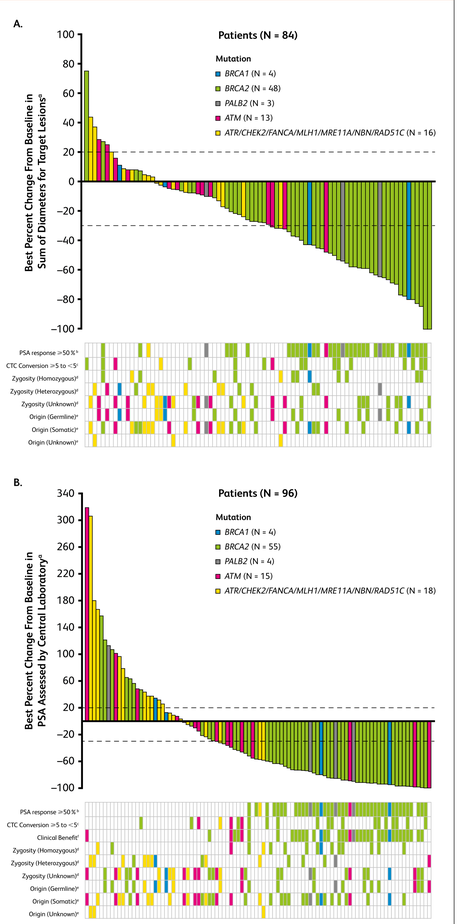
Talazoparib demonstrated substantial and durable antitumor activity in heavily pretreated men with DDR-mutated advanced mCRPC who received prior taxane therapy/NHT. The most common all-grade TEAEs were anemia, nausea, decreased appetite, and asthenia. Few patients permanently discontinued talazoparib because of TEAEs.

Table 1. Baseline Patient Characteristics (Safety and Efficacy Populations)[a]

	Safety Population (N = 127)	Efficacy Population					
		BRCA1/2 (n = 61)	*BRCA2* (n = 57)	*PALB2* (n = 4)	*ATM* (n = 17)	Other (n = 22)[b]	Total (N = 104)
Age, median (range), y	69.0 (46.0–84.0)	69.0 (46.0–83.0)	69.0 (46.0–83.0)	72.5 (51.0–79.0)	67.0 (53.0–81.0)	71.0 (57.0–82.0)	69.0 (46.0–83.0)
Baseline PSA[c], mean (SD)	303.0 (524.1)	277.7 (499.5)	236.7 (349.1)	150.4 (143.2)	450.2 (739.5)	378.8 (615.6)	322.4 (560.2)
Baseline CTC count[d], mean (SD)	82.9 (196.2)	68.6 (174.2)	71.9 (177.8)	168.7 (278.3)	101.1 (203.9)	78.3 (260.6)	79.7 (200.6)
Disease site, no. (%)							
Visceral	41 (32.3)	18 (29.5)	17 (29.8)	3 (75.0)	5 (29.4)	10 (45.5)	36 (34.6)
Non-visceral	86 (67.7)	43 (70.5)	40 (70.2)	1 (25.0)	12 (70.6)	12 (54.5)	68 (65.4)
ECOG PS, no. (%)							
0	52 (40.9)	24 (39.3)	22 (38.6)	0	8 (47.1)	9 (40.9)	41 (39.4)
1	63 (49.6)	31 (50.8)	29 (50.9)	4 (100.0)	8 (47.1)	10 (45.5)	53 (51.0)
2	12 (9.4)	6 (9.8)	6 (10.5)	0	1 (5.9)	3 (13.6)	10 (9.6)
Prior taxanes, no. (%)							
Docetaxel only	65 (51.2)	35 (57.4)	32 (56.1)	1 (25.0)	9 (52.9)	9 (40.9)	54 (51.9)
Docetaxel and cabazitaxel	61 (48.0)	26 (42.6)	25 (43.9)	3 (75.0)	8 (47.1)	12 (54.5)	49 (47.1)
Not reported	1.0 (0.8)	0	0	0	0	1 (4.5)	1 (1.0)
Prior NHT, no. (%)							
Abiraterone only	45 (35.4)	28 (45.9)	27 (47.4)	2 (50.0)	3 (17.6)	4 (18.2)	37 (35.6)
Enzalutamide only	46 (36.2)	20 (32.8)	19 (33.3)	2 (50.0)	8 (47.1)	7 (31.8)	37 (35.6)
Abiraterone and enzalutamide	34 (26.8)	12 (19.7)	10 (17.5)	0	6 (35.3)	10 (45.5)	28 (26.9)
Not reported	2 (1.6)	1 (1.6)	1 (1.8)	0	0	1 (4.5)	2 (1.9)

[a]Alterations categorized using gene hierarchy (see Methods); [b]Other: *ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *RAD51C*; [c]μG/L; [d]cells/7.5 mL of blood; PS, performance status.

Figure 1. Best Change From Baseline in A) Sum of Diameters for Target Lesions by BICR and B) PSA (Efficacy Population)

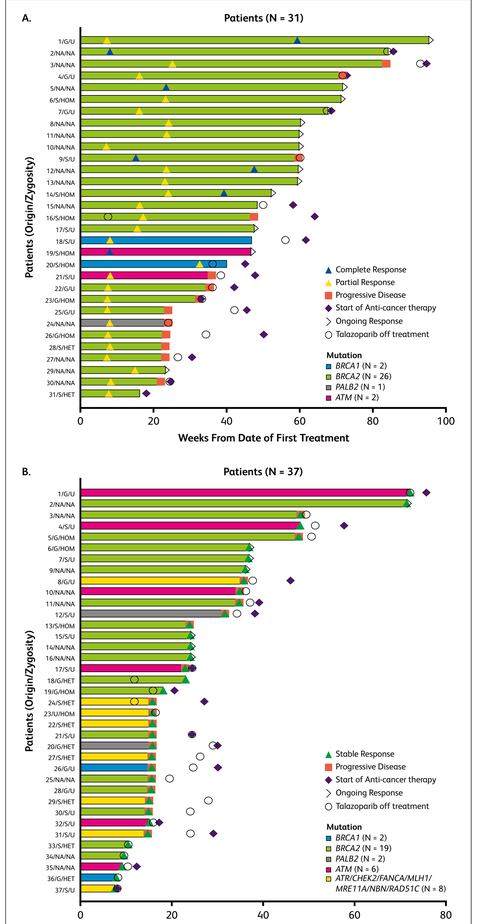


[a]Excludes patients who did not have baseline/post-baseline assessments; [b]PSA response ⩾50 % was defined as a decline from baseline by ⩾50 % and was confirmed by a second consecutive value ⩾3 weeks later; [c]CTC conversion ⩾5 to <5; patients with a CTC count of ⩾5 CTC per 7.5 mL of blood at study entry that decreased to <5 CTC per 7.5 mL of blood anytime on study. Only patients with a baseline CTC assessment and ⩾1 post-baseline CTC assessment; [d]Predicted DDR11 mutational zygosity per SGZ; [e]Patient DDR11 mutation origin based on comparison with saliva; [f]Clinical benefit is defined as complete or partial response, or stable disease for ⩾6 months.

Exploratory analyses of alteration origin and zygosity were based on tumor tissue sample(s) recorded under the latest screening attempt and accessible only for short variants. Alterations categorized using gene hierarchy (see Methods).

SGZ, somatic-germline-zygosity.

Figure 2. A) Time to and Duration of Confirmed Objective Response by BICR and B) Stable Disease (Efficacy Population)



Origin: G, germline; S, somatic; U, unknown; NA, not evaluable.

Zygosity: HOM, homozygous; HET, heterozygous; U, unknown; NA, not evaluable.

DDR11 alteration origins are shown for patients evaluable for both germline (saliva) and tumor DDR alterations. Tumor DDR11 alteration zygosity was predicted by SGZ analysis of tumors with adequate purity. Alterations categorized using gene hierarchy (see Methods).

NA, not evaluable for tumor alteration origin/zygosity due to type of alteration (only short variants were amenable to these analyses), lack of matched saliva data (origin), and/or inadequate tumor purity (zygosity).

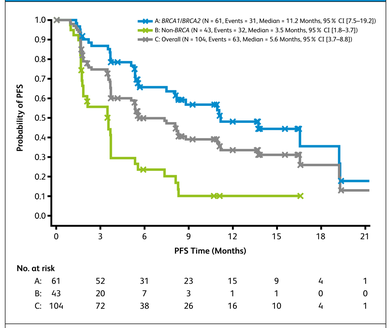
Table 2. Efficacy Assessments by BICR (Efficacy Population)[a,b]

% (Response/n)	*BRCA1/2* (n = 61)	*BRCA2* (n = 57)	*PALB2* (n = 4)	*ATM* (n = 17)	Other (n = 22)[c]	Total (N = 104)
Best overall response[d]						
Confirmed CR	9.8 (6/61)	10.5 (6/57)	0.0 (0/4)	5.9 (1/17)	0.0 (0/22)	6.7 (7/104)
Confirmed PR	36.1 (22/61)	35.1 (20/57)	25.0 (1/4)	5.9 (1/17)	0.0 (0/22)	23.1 (24/104)
SD (any duration)	34.4 (21/61)	33.3 (19/57)	50.0 (2/4)	35.3 (6/17)	36.4 (8/22)	35.6 (37/104)
SD ⩾6 months	9.8 (6/61)	10.5 (6/57)	0.0 (0/4)	11.8 (2/17)	0.0 (0/22)	7.7 (8/104)
Non-CR/non-PD	6.6 (4/61)	7.0 (4/57)	0.0 (0/4)	0.0 (0/17)	0.0 (0/22)	3.8 (4/104)
PD	6.6 (4/61)	7.0 (4/57)	0.0 (0/4)	47.1 (8/17)	45.5 (10/22)	21.2 (22/104)
NE	6.6 (4/61)	7.0 (4/57)	25.0 (1/4)	5.9 (1/17)	18.2 (4/22)	9.6 (10/104)
Objective response[e]	45.9 (28/61)	45.6 (26/57)	25.0 (1/4)	11.8 (2/17)	0.0 (0/22)	29.8 (31/104)
PSA response ⩾50% [1][e]	66.1 (39/59)	67.3 (37/55)	75.0 (3/4)	6.7 (1/15)	5.6 (1/18)	45.8 (44/96)
PSA response ⩾50% [2][f]	63.9 (39/61)	64.9 (37/57)	75.0 (3/4)	5.9 (1/17)	4.5 (1/22)	42.3 (44/104)
CTC conversion ⩾5 to <5[g]	81.0 (17/21)	81.0 (17/21)	0.0 (0/1)	50.0 (3/6)	20.0 (1/5)	63.6 (21/33)
Median PFS (95% CI), months	11.2 (7.5–19.2)	11.2 (7.5–19.2)	5.6 (3.7–7.4)	3.5 (1.7–8.3)	1.8 (1.7–3.7)	5.6 (3.7–8.8)
Composite response[h]	72.1 (44/61)	73.7 (42/57)	75.0 (3/4)	23.5 (4/17)	9.1 (2/22)	51.0 (53/104)
Clinical benefit rate[d,i]	55.7 (34/61)	56.1 (32/57)	25.0 (1/4)	23.5 (4/17)	0.0 (0/22)	37.5 (39/104)

[a]Gene(s) altered were reported using Foundation Medicine results generated either under protocol or by historical results; [b]All endpoints were analyzed using gene hierarchy (see Methods); [c]*ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *RAD51C*; [d]Only patients with measurable disease per BICR or investigator; [e]PSA response ⩾50% in patients with a baseline and ⩾1 post-baseline PSA assessment; [f]PSA response ⩾50% in patients with a baseline PSA assessment; [g]CTC count ⩾5 CTC per 7.5 mL of blood at study entry that decreased to <5 CTC per 7.5 mL of blood anytime during the study. Only patients with a baseline CTC assessment and ⩾1 post-baseline CTC assessment; [h]Composite response is defined as patients with objective response and/or PSA response and/or CTC conversion; [i]Clinical benefit is defined as complete or partial response, or stable disease for ⩾6 months.

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. rPFS (BICR; Efficacy Population)



Alterations categorized using gene hierarchy (see Methods). Non-*BRCA*: *ATM*, *ATR*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *RAD51C*, *PALB2*.

rPFS, radiographic progression-free survival.

SAFETY

- Of 127 patients (safety population), 95.3 % reported any all-causality treatment-emergent adverse events (TEAEs; **Table 3**).
- Anemia (48.8 %), nausea (33.1 %), decreased appetite (28.3 %), and asthenia (23.6 %) were the most common all-grade TEAEs (**Table 3**).
- The most common Grade 3/4 TEAEs (⩾5 %) were anemia, thrombocytopenia, and neutropenia (**Table 3**). No Grade 4 anemia or neutropenia was observed.
  - Grade 3 or 4 hematologic TEAEs were reported in 41 (32.3 %) and 5 (3.9 %) patients, respectively, and considered treatment-related in 40 (31.5 %) and 4 (3.1 %) patients, respectively.
- Serious TEAEs were reported in 43 (33.9 %) patients.
  - Most common all-cause serious AEs (in >1 patient) comprised pulmonary embolism (n = 8 [6.3 %]), anemia (n = 5 [3.9 %]), disease progression (n = 4 [3.1 %]), urinary tract infection and pneumonia (each n = 3 [2.4 %]), and general physical health deterioration, pain, pyrexia, subdural hematoma, and platelet count decreased (each n = 2 [1.6 %]). No deaths were related to talazoparib. No patients had myelodysplastic syndrome or acute myeloid leukemia either while on trial or by the end of follow-up.
- TEAEs that led to dose reductions and dose interruptions are listed in the **Supplemental Appendix**. Few patients permanently discontinued talazoparib because of TEAEs (11.8 %, 15/127 patients).

Table 3. TEAEs (⩾15%; Safety Population, N = 127)

No. (%)	Grade 1–2	Grade 3–4[a]	Total[b]
Any TEAE	50 (39.4)	61 (48.0)	121 (95.3)
Nonhematologic TEAEs			
Nausea	39 (30.7)	3 (2.4)	42 (33.1)
Decreased appetite	32 (25.2)	4 (3.1)	36 (28.3)
Asthenia	25 (19.7)	5 (3.9)	30 (23.6)
Fatigue	23 (18.1)	2 (1.6)	25 (19.7)
Constipation	22 (17.3)	1 (0.8)	23 (18.1)
Diarrhea	21 (16.5)	0 (0.0)	21 (16.5)
Peripheral edema	20 (15.7)	1 (0.8)	21 (16.5)
Hematologic TEAEs[c]			
Any TEAE	22 (17.3)	46 (36.2)	68 (53.5)
Anemia	23 (18.1)	39 (30.7)	62 (48.8)
Thrombocytopenia	13 (10.2)	11 (8.7)	24 (18.9)
Neutropenia	11 (8.7)	10 (7.9)	21 (16.5)

[a]Grade 4 TEAEs included thrombocytopenia (4/127 patients; 3.1%), lymphopenia (2/127 patients; 1.6%), gamma-glutamyltransferase increased (1/127 patients; 0.8%), and sepsis (1/127 patients; 0.8%).

[b]Grade 5 TEAEs included death due to disease progression (4 patients), general physical health deterioration (1 patient), pulmonary embolism (1 patient), subdural hematoma (1 patient), malignant neoplasm progression (1 patient), neoplasm progression (1 patient), and cardio-respiratory arrest (1 patient); no Grade 5 TEAEs were related to the study drug.

[c]Anemia = anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased; Thrombocytopenia = thrombocytopenia, platelet count decreased; Neutropenia = neutropenia, neutrophil count decreased.

TEAE, treatment-emergent adverse event.

Conclusions

- TALAPRO-1 met its primary objective with a confirmed ORR of 29.8% in the efficacy population.
- Antitumor effects were most notable in patients with *BRCA1/2* alterations, with a confirmed ORR of 45.9% and a median rPFS of 11.2 months.
- Objective responses, PSA responses, or stable disease were also observed in patients with non-*BRCA* DDR gene alterations, including *PALB2* or *ATM* alterations.
- The observed antitumor activity and tolerability profile demonstrate talazoparib is a promising therapy for patients with prostate cancer.

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Disclosure information for all authors can be found in the **Supplemental Appendix.**

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TPS5089

TALAPRO-2: A Phase 3 Randomized Study of Enzalutamide (ENZA) Plus Talazoparib (TALA) vs Placebo in Patients With New Metastatic Castration-resistant Prostate Cancer (mCRPC)

Neeraj Agarwal,[1] Arun Azad,[2] Neal D. Shore,[3] Joan Carles,[4] Andre P. Fay,[5] Curtis Dunshee,[6] Lawrence I. Karsh,[7] Maria Luisa Paccagnella,[8] Nicola Di Santo,[9] Mohamed Elmeliegy,[10] Xun Lin,[10] Alexander Niyazov,[11] Akos Czibere,[12] Karim Fizazi[13]

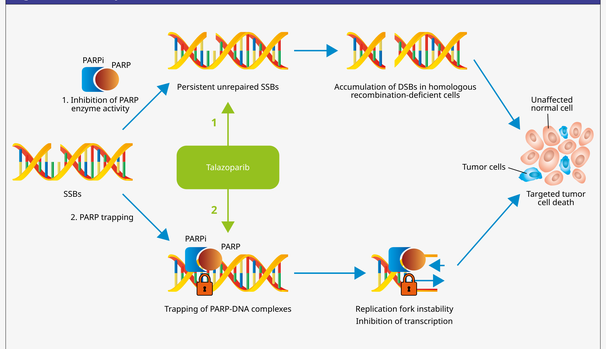
[1]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [4]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [5]PUCRS School of Medicine Grupo Oncoclínicas, Porto Alegre, Brazil; [6]Urological Associates of Southern Arizona, Tucson, AZ, USA; [7]The Urology Center of Colorado, Denver, CO, USA; [8]Pfizer Inc., Groton, CT, USA; [9]Pfizer Inc., Durham, NC, USA; [10]Pfizer Inc., La Jolla, CA, USA; [11]Pfizer Inc., New York, NY, USA; [12]Pfizer Inc., Cambridge, MA, USA; [13]Institut Gustave Roussy, University of Paris Saclay, Villejuif, France

Background

- Current standard-of-care therapies for metastatic castration-resistant prostate cancer (mCRPC) include taxanes, novel hormonal therapies that target the androgen receptor (AR) or androgen signaling, such as enzalutamide and abiraterone, sipuleucel-T, or targeted alpha therapy[1]*
- Responses in mCRPC can be short in duration, and progression usually reflects reactivation of the AR signaling pathway.[1] Patients, therefore, often require additional therapeutic approaches, and rational combination therapies could minimize resistance mechanisms
- Approximately 23-27% of men with mCRPC harbor somatic and/or germline deletions and/or deleterious alterations in DNA damage response (DDR) genes involved, directly or indirectly, in homologous recombination repair (HRR) (eg, *BRCA1/2*, *ATM*, *FANCA*, *CHEK2*).[2,3] *BRCA2* alterations may be associated with poor prognosis in mCRPC[4]
- Talazoparib blocks poly(ADP-ribose) polymerase (PARP) activity and traps PARP on single-strand DNA breaks, preventing DNA repair (Figure 1)[5,6]
  - Talazoparib kills tumor cells with DDR/HRR pathway defects, including germline *BRCA1/2* alterations[7†]
  - Based on the Phase 3 EMBRACA clinical trial, talazoparib has been approved in multiple countries as monotherapy for the treatment of patients with germline *BRCA1/2*-mutated human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer[7-9]

*The National Comprehensive Cancer Network® (NCCN), NCCN Guidelines Version 2.2021 Prostate Cancer have been revised to state: "Consider inclusion of olaparib in men who have an HRRm [homologous recombination repair mutation] and have progressed on prior treatment with enzalutamide and/or abiraterone regardless of prior docetaxel therapy."[1] The updated guidelines emphasize that clinical trials of olaparib and other PARP inhibitors to assess the overall net clinical benefit are ongoing in men with CRPC and that, at present, no PARP inhibitor is approved for use in prostate cancer.[10]
†DDR alterations are defined as known/likely pathogenic variants or homozygous deletions.

Figure 1. Dual Cytotoxic Mechanisms of PARP Inhibitors



Abbreviations: DSBs=double-strand breaks; PARP=poly(ADP-ribose) polymerase; PARPi=PARP inhibitor; SSBs=single-strand breaks.

- Nonclinical/translational evidence suggests a potential for synergistic benefit when PARP inhibitors and AR signaling inhibitors are combined
  - AR signaling supports homologous recombination through maintaining DDR/HRR gene expression[11]
  - Disruption of AR signaling suppresses DDR/HRR gene expression (ie, inducing a "*BRCA*ness" phenotype) and activates PARP[12,13]
  - Furthermore, PARP activity has been shown to support AR function. PARP inhibition is expected to reduce AR signaling and complement the effect of AR-directed therapies[14]
  - Clinical resistance to AR blockade is also associated with co-deletion of *retinoblastoma tumor suppressor* gene and *BRCA2*, which is in turn associated with PARP inhibitor sensitivity[15]
- Combining enzalutamide with a PARP inhibitor may, therefore, be efficacious regardless of DDR/HRR alteration status[16]

Methods

STUDY DESIGN

- TALAPRO-2 (NCT03395197) is a multinational Phase 3, 2-part study to evaluate the efficacy, safety, pharmacokinetics (PK), and patient-reported outcomes of talazoparib in combination with enzalutamide
  - Part 1 was an open-label, nonrandomized study to confirm the starting dose of talazoparib (initially 1 mg/day prior to dose reduction to 0.5 mg/day based on safety and PK data) to be given in combination with enzalutamide (160 mg/day) in mCRPC
  - Part 2 is a randomized, double-blind, placebo-controlled study comparing talazoparib (0.5 mg/day) plus enzalutamide (160 mg/day) vs placebo plus enzalutamide in mCRPC (Table 1; Table 2; Table 3; Figure 2)
  - Randomization is stratified by prior novel hormonal therapy or taxane for castration-sensitive prostate cancer (CSPC; yes/no), and DDR/HRR alteration status (deficient vs nondeficient/unknown)

ENROLLMENT

- The enrollment goal for this study is 1037 patients (19 patients in the part 1 dose-finding study; 1018 in the part 2 placebo-controlled study)
  - Enrollment is planned or ongoing at 223 sites in 26 countries including 32 states across the US (Figure 3)

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TALAPRO-2 is a randomized, double-blind, placebo-controlled, multinational study comparing talazoparib plus enzalutamide vs placebo plus enzalutamide in patients unselected for DDR/HRR status and DDR/HRR-deficient patients

Patient recruitment is ongoing in multiple regions including US, Europe/Eastern Europe, Israel, South America, South Africa, and Asia-Pacific region

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Presenting author: Neeraj Agarwal

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Table 1. Key Inclusion Criteria*

Demographics	Additional Criteria
• Male, aged ⩾18 years†	• ECOG performance status ⩽1 • Life expectancy ⩾12 months per investigator assessment • Prospective assessment of DDR/HRR mutation status by a gene mutation biomarker panel using tissue or blood (liquid biopsy)
Prostate Cancer Status	
• Histologically/cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features	
• Bilateral orchiectomy or ongoing ADT with a GnRH agonist/antagonist, with serum testosterone ⩽50 ng/dL (⩽1.73 nmol/L) at screening; ADT must continue throughout the study for patients who have not undergone bilateral orchiectomy	
• Asymptomatic or mildly symptomatic mCRPC (<4 on BPI-SF question #3)	
• Progressive disease at study entry, defined by ⩾1 of the following 3 criteria: – PSA progression (⩾2 rising PSA values from 3 consecutive assessments with ⩾7 days between assessments) – Soft tissue disease progression per RECIST v.1.1 (CT or MRI) – Bone disease progression per PCWG3, with ⩾2 new metastatic bone lesions on whole body radionuclide bone scan	

Abbreviations: ADT=androgen deprivation therapy; BPI-SF=Brief Pain Inventory Short Form; CT=computed tomography; DDR=DNA damage response; ECOG=Eastern Cooperative Oncology Group; GnRH=gonadotropin-releasing hormone; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; PCWG3=Prostate Cancer Working Group 3; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors version 1.1.
*Country-specific protocols may differ; †≥20 years in Japan.

Table 2. Key Exclusion Criteria

Prior Treatment	Clinically Significant Disease
• Systemic life-prolonging treatment initiated in the nonmetastatic CRPC or mCRPC disease state* • Prior treatment with second-generation AR inhibitors (enzalutamide, apalutamide, and darolutamide), a PARP inhibitor, cyclophosphamide, or mitoxantrone for prostate cancer • The following agents are NOT exclusionary if received for CSPC: docetaxel, biologic therapy (eg, sipuleucel-T), or radionuclide therapy, if discontinued 28 days prior to randomization; hormonal therapy (eg, bicalutamide, nilutamide, flutamide, estrogens) or abiraterone, if discontinued prior to randomization • Prior treatment with platinum-based therapy ⩽6 months (from the last dose) or any history of disease progression on platinum-based therapy ⩽6 months (from the last dose) • Any investigational agent ⩽4 weeks before randomization • Prior treatment with opioids for pain related to either primary prostate cancer or metastasis ⩽28 days before randomization • Major surgery, defined by the investigator, ⩽2 weeks before randomization, or palliative localized radiation therapy ⩽3 weeks before randomization • Use of potent P-gp inhibitors ⩽7 days before randomization	• Cardiovascular disease • Renal: eGFR <30 mL/min/1.73 m^2 by the MDRD equation • Hepatic: total serum bilirubin >1.5×ULN or >3×ULN in patients with Gilbert syndrome or with suspected extrahepatic source of elevation; AST or ALT >2.5×ULN (>5×ULN if liver function abnormalities are due to hepatic metastasis); or albumin <2.8 g/dL (at screening) • Neurologic: known or suspected brain metastasis or active leptomeningeal disease; symptomatic or impending spinal cord compression or cauda equina syndrome; seizure risk; history of loss of consciousness or TIA ⩽12 months before randomization • Hematologic: ANC <1500/µL, platelets <100,000/µL, or hemoglobin <9 g/dL; no growth factors or blood transfusions ⩽14 days before screening hematology values • Gastrointestinal: disorders affecting absorption • Prior cancers: including MDS and AML, with the exception of carcinoma in situ or nonmelanoma skin cancers, any prior malignancies ⩾3 years before randomization with no subsequent evidence of recurrence/progression regardless of stage, or AJCC stage 0/1 cancer <3 years before randomization that has a remote possibility of recurrence/progression in the opinion of the investigator

Abbreviations: ADT=androgen deprivation therapy; AJCC=American Joint Committee on Cancer; ALT=alanine aminotransferase; AML=acute myeloid leukemia; ANC=absolute neutrophil count; AR=androgen receptor; AST=aspartate aminotransferase; CRPC=castration-resistant prostate cancer; CSPC=castration-sensitive prostate cancer; eGFR=estimated glomerular filtration rate; mCRPC=metastatic castration-resistant prostate cancer; MDRD=Modification of Diet in Renal Disease (available at www.mdrd.com); MDS=myelodysplastic syndrome; PARP=poly(ADP-ribose) polymerase; P-gp=P-glycoprotein; TIA=transient ischemic attack; ULN=upper limit of normal.
*ADT and first-generation antiandrogens received for CRPC are NOT exclusionary; prior docetaxel and abiraterone in castration-sensitive (CSPC) setting is allowed.

Table 3. Part 2 Study Endpoints

Co-primary Endpoints

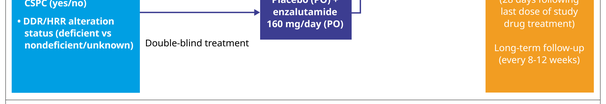
- Radiographic PFS (rPFS) by BICR per RECIST v.1.1 (soft tissue disease) and PCWG3 (bone disease) in patients unselected for DDR/HRR status (all-comers population; Cohort 1). rPFS by BICR per RECIST v.1.1 (soft tissues disease) and PCWG3 (bone disease) in patients with DDR/HRR alterations (Cohort 2)
  - rPFS is defined as time from randomization to first evidence of radiographic progression by BICR or death, whichever occurs first
  - Efficacy will be assessed by radiography every 8 weeks up to Week 25 and every 12 weeks thereafter
  - rPFS will be compared between the two arms by a 1-sided stratified log-rank test

Secondary Endpoints

- OS based on time from randomization to death from any cause
- Proportion of patients with measurable soft tissue disease at baseline with objective response per RECIST v.1.1
- Duration of soft tissue response per RECIST v.1.1
- Proportion of patients with PSA response ⩾50%
- Time to PSA progression
- Time to initiation of cytotoxic chemotherapy
- Time to initiation of antineoplastic therapy
- Time to first symptomatic skeletal event (fracture, spinal cord compression, surgery, radiation to the bone)
- PFS on second-line therapy (defined as time from randomization to the start of second subsequent treatment after disease progression, or death from any cause, whichever occurs first)
- Time to opiate use for prostate cancer pain
- Incidence of AEs and SAEs by type and severity (NCI CTCAE version 4.03)
- PK characterized by predose trough and postdose plasma concentrations of talazoparib, enzalutamide, and its N-desmethyl metabolite
- PROs:
  - Change from baseline in patient-reported pain symptoms and time to deterioration in pain symptoms per BPI-SF
  - Change from baseline in patient-reported general health status per EQ-5D-5L
  - Change from baseline and time to definitive deterioration in patient-reported cancer-specific global health status/QoL, functioning and symptoms per EORTC QLQ-C30
  - Time to definitive deterioration in disease-specific urinary symptoms per EORTC QLQ-PR25

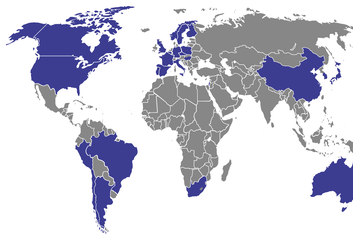
Abbreviations: AE=adverse event; BICR=blinded independent central review; BPI-SF=Brief Pain Inventory Short Form; CTCAE=Common Terminology Criteria for Adverse Events; DDR=DNA damage response; EORTC=European Organisation for Research and Treatment of Cancer (QLQ-C30=Quality of Life Questionnaire C30; QLQ-PR25=Quality of Life Questionnaire Prostate Cancer Module PR25); EQ-5D-5L=EuroQOL 5-dimension, 5-level scale; HRR=homologous recombination repair; NCI=National Cancer Institute; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcome; PSA=prostate-specific antigen; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious adverse event.

Figure 2. Part 2 Study Design



Abbreviations: CSPC=castration-sensitive prostate cancer; DDR=DNA damage response; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; PO=per oral.
*Dose of talazoparib 0.5 mg/day (0.35 mg/day if moderate renal impairment) plus enzalutamide 160 mg/day was determined in Part 1 as providing the same talazoparib exposure as talazoparib 1.0 mg/day monotherapy.
†Remain on blinded treatment until radiographic progression and no longer clinically benefiting as per investigator opinion, the occurrence of an adverse event leading to permanent discontinuation, patient decision to discontinue treatment, or death.

Figure 3. Countries Participating in the TALAPRO-2 Study



Countries With Investigative Centers	
Argentina	Italy
Australia	Japan
Belgium	New Zealand
Brazil	Norway
Canada	Peru
Chile	Poland
China	Portugal
Czech Republic	Republic of Korea
Finland	South Africa
France	Spain
Germany	Sweden
Hungary	United Kingdom
Israel	United States

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Disclosures: NA reports consulting or advisory roles with Astellas Pharma, AstraZeneca, AVEO, Bayer, Bristol-Myers Squibb, Calithera Biosciences, Eisai, EMD Serono, Exelixis, Foundation Medicine, Foundation One Inc., Genentech, Janssen Oncology, Lilly, Medivation/Astellas, MEI Pharma, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics; and research funding to his institution from Active Biotech, Amgen, AstraZeneca, Bavarian Nordic, Bayer, BN ImmunoTherapeutics, Bristol-Myers Squibb, Calithera Biosciences, Celldex, Eisai, Exelixis, Genentech, GlaxoSmithKline, Immunomedics, Janssen, Merck, Newlink Genetics, Novartis, Pfizer, Prometheus, Rexahn Pharmaceuticals, Sanofi, Takeda, and TRACON Pharma. **AA** reports honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Noxopharm, Pfizer, Sanofi, Telix, and Tolmar; speakers' bureau for Amgen, Astellas, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, Merck Serono, and Novartis; research funding from Aptevo Therapeutics (institutional), Astellas (institutional), Astellas (investigator), AstraZeneca (institutional), AstraZeneca (investigator), Bionomics (institutional), Bristol-Myers Squibb (institutional), GlaxoSmithKline (institutional), Ipsen (institutional), MedImmune (institutional), Merck Serono (investigator), Novartis (institutional), Pfizer (institutional), Sanofi Aventis (institutional), Synthorx (institutional); and travel, accommodation, and expenses from Amgen, Astellas, Janssen, Merck Serono, Novartis, Pfizer, and Tolmar. **NDS** reports leadership of a Large Urology Group Practice Association and a consulting or advisory role for Amgen, AstraZeneca, Bayer, Dendreon, Ferring, Genentech/Roche, Janssen Scientific Affairs, Medivation/Astellas, Myovant Sciences, Pfizer, Sanofi, and Tolmar. **JC** reports consulting and scientific advisory board attendee for Amgen, Astellas, Bayer, Bristol-Myers Squibb, Johnson & Johnson, Merck Sharp & Dohme, Pfizer, and Sanofi. He also reports a speaker bureau for Asofarma, Astellas, Bayer, Johnson & Johnson, and Sanofi. **APF** reports honoraria from AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, and Roche. He also reports a consulting or advisory role for AstraZeneca, Merck Sharp & Dohme, Novartis, Pfizer, and Roche. **CD** reports a consulting or advisory role for Pfizer; and research funding to his institution from AstraZeneca, BHR Pharmaceuticals, Churchill Pharmaceuticals, Dendreon, Eleven Biotherapeutics, Exact Sciences, Ferring, Janssen Oncology, Medivation/Astellas, Myovant Sciences, Pfizer, Siemens, and TesoRX Pharma. **LIK** reports stock and ownership interests in Swan Valley Medical; consulting or honoraria from Astellas, AstraZeneca, Bayer, Clovis, Dendreon, Ferring, Genentech/Roche, Janssen, Merck and Myovant, Pfizer, UroGPO, and Vaxxion; speakers' bureau for Astellas, AstraZeneca, Bayer, Dendreon, Janssen, Myovant, and Pfizer; and research funding to his institution from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Dendreon, Epizyme, Exact Sciences, Exelixis, Ferring, FKD, Genentech/Roche, Hinova, Janssen, Merck, Pfizer, and Vaxxion. **MLP**, **NDS**, **ME**, **XL**, **AN**, and **AC** are employees of Pfizer and hold Pfizer stock/stock options. **KF** reports consulting or advisory roles with Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Curevac, ESSA, Janssen Oncology, Orion Pharma GmbH, and Sanofi; travel, accommodations, and expenses from Janssen and Merck Sharp & Dohme; and honoraria from Astellas Pharma, Bayer, Janssen, and Sanofi.

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TALAPRO-3: A Phase 3, Double-blind, Randomized Study of Enzalutamide (ENZA) Plus Talazoparib vs Placebo Plus ENZA in Patients With DDR Gene Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

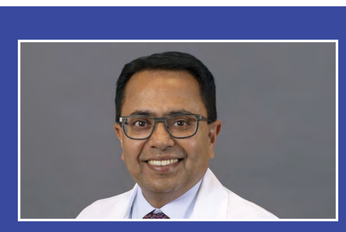
Neeraj Agarwal,[1] Fred Saad,[2] Arun A. Azad,[3] Joaquin Mateo,[4] Nobuaki Matsubara,[5] Neal D. Shore,[6] Jayeta Chakrabarti,[7] Hsiang-Chun Chen,[8] Silvana Lanzalone,[9] Alexander Niyazov,[10] Karim Fizazi,[11] for the TALAPRO-3 investigational group

[1]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA; [2]University of Montréal Health Center, Montréal, Québec, Canada; [3]Peter MacCallum Cancer Centre, Melbourne, Australia; [4]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [7]Pfizer Ltd., Surrey, UK; [8]Pfizer Inc., La Jolla, CA, USA; [9]Pfizer Oncology, Milan, Italy; [10]Pfizer Inc., New York, NY, USA; [11]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

TALAPRO-3 is a randomized, double-blind, placebo-controlled, multinational Phase 3 trial comparing the combination of talazoparib (0.5 mg) plus ENZA (160 mg) vs placebo plus ENZA (160 mg) in men with mCSPC and DDR-HRR alterations. Patient recruitment is planned or ongoing in multiple regions, including the United States, Canada, Europe, South America, South Africa, Australia, and Asia-Pacific countries

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Presenting author: Neeraj Agarwal

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For more information about this clinical trial, please call 1-800-718-1021 or email clinicaltrials.gov_inquiries@pfizer.com

Trial identifier: NCT04821622

@PfizerOncMed

Background

- Despite combination treatment with androgen deprivation therapy (ADT) and an androgen axis inhibitor, such as enzalutamide (ENZA), many patients with metastatic castration-sensitive prostate cancer (mCSPC) can progress to metastatic castration-resistant prostate cancer (mCRPC) over time,[1,2] highlighting the need for novel therapeutic strategies that prolong the time to developing mCRPC and increase overall survival (OS)
- Alterations of germline or somatic origin in DNA damage response (DDR) genes involved directly or indirectly in homologous recombination repair (HRR; eg, *BRCA1/2*, *ATM*, *PALB2*, *CHEK2*) are commonly found in 23–27% of metastatic prostate cancers,[3] with some alterations (eg, in *BRCA2*) associated with poor prognosis and rapid progression to mCRPC[4-6]
- DDR-HRR alterations have been shown to sensitize patients to poly(ADP-ribose) polymerase (PARP) inhibitors, such as talazoparib[7]
  - Talazoparib both inhibits PARP activity and traps PARP on single-strand DNA breaks, preventing DNA repair (Figure S1) and leading to synthetic lethality in cancer cells[7,8]
- TALAPRO-1, a recent Phase 2 study of talazoparib monotherapy, demonstrated robust antitumor activity in heavily pretreated men with mCRPC and DDR-HRR alterations[9]
- Androgen receptor (AR) signaling continues to be active in most men with mCSPC, despite ADT[10]
- ENZA is an AR inhibitor that has demonstrated significant improvement in men with mCSPC by slowing progression to mCRPC and is considered a standard-of-care option in combination with ADT for the treatment of mCSPC[1,11-14]
- There is potential for synergistic interactions between PARP inhibitors and ENZA
  - Models show that PARP-1 activity is required for AR function; therefore, PARP inhibition may sensitize prostate cancer cells to AR-directed therapies[15]
  - In addition, AR blockade downregulates DDR-HRR gene expression, which may induce a "*BRCA*ness" phenotype and increase sensitivity to PARP inhibitors[16-18]
  - Clinical resistance to AR blockade is sometimes associated with the deletion of *BRCA2*, which also confers sensitivity to PARP inhibitors[19]
  - In the United States, olaparib is currently recommended for the treatment of men with mCRPC and DDR-HRR alterations following treatment with ENZA or abiraterone acetate[20]
- Therefore, combining ENZA with talazoparib may significantly improve clinical outcomes for men with mCSPC and DDR-HRR alterations

Methods

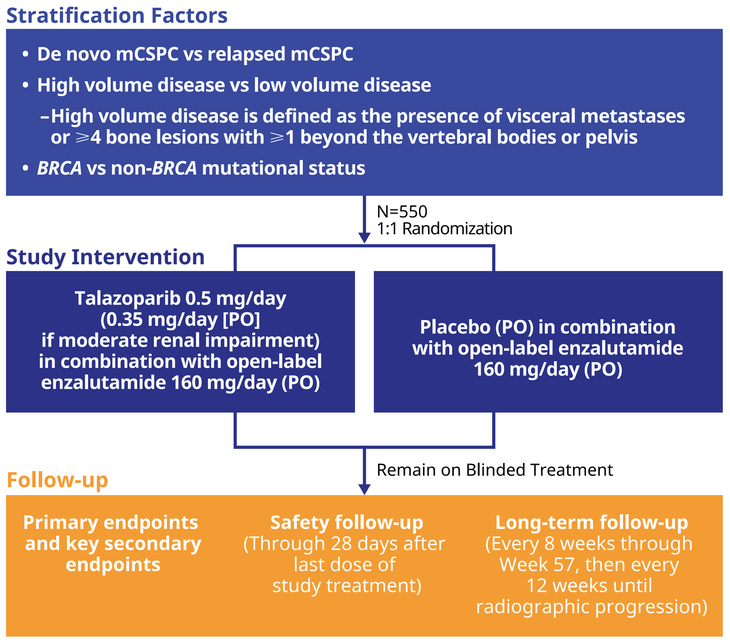
TRIAL DESIGN

- The Phase 3, double-blind, randomized trial, TALAPRO-3 (NCT04821622), will compare the combination of talazoparib plus ENZA vs placebo plus ENZA in men with mCSPC with DDR-HRR alterations (Figure 1)

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Figure 1. Study Design



Abbreviations: *BRCA*=breast cancer susceptibility gene; mCSPC=metastatic castration-sensitive prostate cancer; PO=per oral.

ENROLLMENT

- ~550 patients with mCSPC harboring DDR-HRR alterations will be randomized to receive talazoparib (0.5 mg once daily) plus ENZA (160 mg once daily), or talazoparib-matching placebo (once daily) plus ENZA (160 mg once daily)
  - It is anticipated that enrollment will be ~25 participants per month for an accrual duration of ~22 months
  - A total of 158 radiographic progression-free survival (rPFS) events will provide ~80% power to detect a target hazard ratio of 0.63, using a 2-sided log-rank test with a 5% significance level
  - The median rPFS in the control arm is assumed to be ~47.7 months. Assuming an exponential distribution for rPFS with proportional hazards, it is expected that the experimental arm will result in an increase in median rPFS to ~75.8 months
- Key eligibility criteria: men age ⩾18 years (⩾20 years in Japan; ⩾19 years in the Republic of Korea); histological diagnosis of prostate cancer; alterations in one or more DDR-HRR genes (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*); metastatic disease (no brain metastases) (Table 1; Table S1)
- Primary endpoint is rPFS (time to radiographic progression in soft tissue per RECIST 1.1, or in bone per PCWG3 criteria by investigator, or death) (Table 2)
- Secondary and exploratory endpoints include OS, safety, biomarkers, and patient-reported outcomes (Table 2)
- Patient recruitment is planned or ongoing at approximately 285 sites in 27 countries, including in the United States, Canada, Europe, South America, South Africa, Australia, and Asia-Pacific countries (Figure 2)

Table 1. Key Inclusion Criteria

• Men ⩾18 years old (⩾20 years in Japan; ⩾19 years in the Republic of Korea)*
• Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, small cell, or signet cell features*
• Confirmation of DDR-HRR gene alteration status by prospective or historical analysis of blood (FoundationOne Liquid CDx) and/or de novo or archival tumor tissue (FoundationOne CDx)
• Metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue)
• ECOG performance status ⩽1
• Adequate organ function within 28 days before the first study treatment on Day 1
• Prior therapy allowed for mCSPC; ⩽3 months of ADT (chemical or surgical) with or without approved NHT* in mCSPC, if required prior to randomization, with no radiographic evidence of disease progression or rising PSA levels prior to Day 1*

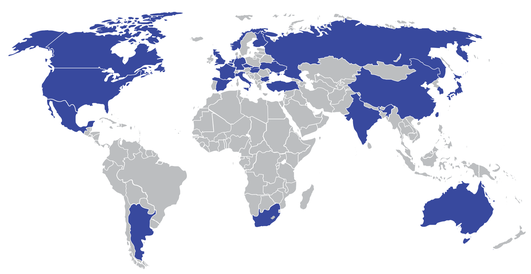
Abbreviations: ADT=androgen deprivation therapy; CT=computed tomography; DDR=DNA damage response; ECOG=Eastern Cooperative Oncology Group; HRR=homologous recombination repair; mCSPC=metastatic castration-sensitive prostate cancer; MRI=magnetic resonance imaging; NHT=novel hormonal therapy; PSA=prostate-specific antigen.
*According to Protocol Amendment 1.

Table 2. Study Endpoints

Primary Endpoint	Secondary Endpoints
• rPFS based on investigator assessment per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) – rPFS is defined as time from randomization to first evidence of radiographic progression by investigator, or death, whichever occurs first – Efficacy will be assessed by radiography every 8 weeks through Week 57, and every 12 weeks thereafter – rPFS will be compared between the two arms by a 2-sided stratified log-rank test	• OS, defined as the duration from the date of randomization until the date of death from any cause • Objective response (in participants with measurable soft tissue disease)* • Duration of soft tissue response* • Time to first symptomatic skeletal event (spinal cord compression, symptomatic pathologic bone fracture, or radiation or surgery to bone)* • ⩾50% decline in PSA from baseline, confirmed ⩾21 days later • Time to PSA progression • Time to initiation of antineoplastic therapy • Time to opioid use for prostate cancer pain • AEs (graded by NCI CTCAE version 4.03) • PK of talazoparib, ENZA, and its *N*-desmethyl metabolite • ctDNA burden at baseline and on study • Patient-reported outcomes: – Change from baseline in PGI-S, participant-reported pain symptoms (BPI-SF), general health status (EQ-5D-5L), cancer-specific global health status/QoL, functioning, and symptoms (EORTC QLQ-C30) – Time to deterioration in BPI-SF, global health status/QoL (EORTC QLQ-C30), and disease-specific urinary symptoms (EORTC QLQ-PR25)

Abbreviations: AE=adverse event; BPI-SF=Brief Pain Inventory Short Form; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; DDR=DNA damage response; ENZA=enzalutamide; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQoL 5-dimension, 5-level scale; HRR=homologous recombination repair; mCSPC=metastatic castration-sensitive prostate cancer; NCI=National Cancer Institute; OS=overall survival; PCWG3=Prostate Cancer Working Group 3; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetics; PSA=prostate-specific antigen; QLQ-C30=Quality of Life Questionnaire C30; QLQ-PR25=Quality of Life Questionnaire Prostate Cancer Module PR25; QoL=quality of life; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; rPFS=radiographic progression-free survival.
*Per RECIST 1.1.

Figure 2. Countries Participating in the TALAPRO-3 Study



Countries With Investigative Centers	
Argentina	Mexico
Australia	Netherlands
Belgium	Norway
Bulgaria	Republic of Korea
Canada	Russian Federation
China	Slovakia
Czech Republic	South Africa
Finland	Spain
France	Taiwan
Germany	Turkey
Hungary	Ukraine
India	United Kingdom
Italy	United States
Japan	

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Disclosures: NA reports consultancy or advisory roles with Astellas, AstraZeneca, AVEO, Bayer, Bristol Myers Squibb, Calithera Biosciences, Eisai, EMD Serono, Exelixis, Foundation Medicine, Foundation One Inc., Genentech, Janssen Oncology, Lilly, Medivation/Astellas, MEI Pharma, Merck, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics; and research funding to his institution from Active Biotech, Amgen, AstraZeneca, Bavarian Nordic, Bayer, BN ImmunoTherapeutics, Bristol Myers Squibb, Calithera Biosciences, Celldex, Eisai, Exelixis, Genentech, GlaxoSmithKline, Immunomedics, Janssen, Merck, Newlink Genetics, Novartis, Pfizer, Prometheus, Rexahn Pharmaceuticals, Sanofi, Takeda, and TRACON Pharma. Full disclosure information for all authors is available on the ASCO meeting site.

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Efficacy, safety and tolerability of danuglipron (PF-06882961) over 12 weeks in Phase 2a study in adults with Type 2 diabetes mellitus

Donal N Gorman[1], Aditi R Saxena[2], Juan Frias[3], Rene N Lopez4, Nikolaos Tsamandouras[2], Morris J Birnbaum[2]*

[1]*Pfizer Worldwide Research and Development, Cambridge, UK;* [2]*Pfizer Worldwide Research, Development, and Medical, Cambridge, MA, USA;* [3]*Velocity Clinical Research, Los Angeles, CA, USA;* [4]*Pfizer Inc, Groton, CT, USA.*

**At the time of the study*

#588, Presented at the European Association for the Study of Diabetes (EASD) Annual Meeting, September 20, 2022, Stockholm, Sweden

Danuglipron 12-Week Phase 2a Study Overview

- **Danuglipron:** an oral small molecule GLP-1R agonist being investigated for T2D and/or obesity
- **Objectives and study design:** phase 2a, randomised, double-blind, placebo-controlled, parallel-group study to assess the tolerability, safety and pharmacodynamic effects over 12 weeks of different danuglipron dose escalation schemes in adults with T2D treated with metformin (NCT04617275)
- **Endpoints:** tolerability (primary) and changes from baseline in HbA1c, FPG and body weight at Week 12
- Study was conducted in the US during the pandemic, January 2021 to November 2021

Study week			≤4 weeks	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13-16
Danuglipron target dose (BID)	Dose escalation schedule*	Participants	Screening	Placebo run-in	Randomised, double-blind treatment 5 parallel groups, with prespecified dose escalation													Follow-up
Placebo (n=16)	–	T2D			Placebo													
80 mg (n=20)	LS	T2D			5	10		20		40		60		80				
80 mg (n=22)	HS	T2D			10		20		40		60		80					
120 mg (n=22)	LF	T2D			5	10	20	40	60	80	100		120					
120 mg (n=22)	HF	T2D			10	20	40	60	80	100		120						
200 mg (n=21)	HF	T2D			10	20	40	60	80	100	120	140	160	180	200			
Placebo (n=6)	–	Obesity			Placebo													
200 mg (n=22)	HF	Obesity			10	20	40	60	80	100	120	140	160	180	200			

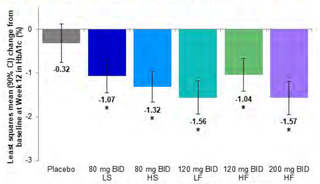
Randomisation

* Danuglipron dose escalation to target dose (80 mg BID, 120 mg BID, or 200 mg BID) using low (L, 5 mg BID), or high (H, 10 mg BID) starting dose and HF, 1 week or faster (E, 2 weeks) titration rates.
BID, twice daily; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, glycated haemoglobin; T2D, type 2 diabetes; US, United States.

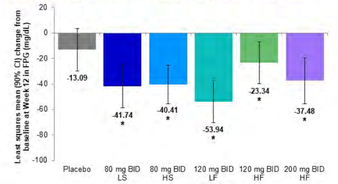
Declines in HbA1c and FPG with Danuglipron at Week 12 in T2D

Statistically significant reductions from baseline in HbA1c in all Danuglipron groups, and FPG across most groups, at Week 12 were demonstrated compared with placebo

HbA1c: Change from baseline at week 12 in T2D



FPG: Change from baseline at week 12 in T2D



† Pressure fixed-anchored P<0.05, mandatorily significant continuous control, linked model, repeated measure analysis including treatment, time, strata (defined as main vs. female) and the treatment-by-time interaction as fixed effects; baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect.
BID, twice daily; CI, confidence interval; E, fast; FPG, fasting plasma glucose; H, high; HbA1c, glycated haemoglobin; L, low; S, slower; T2D, type 2 diabetes.

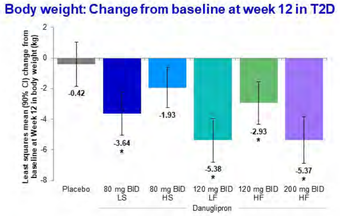
Tolerability and Safety of Danuglipron in 12 Week Phase 2 Study

- Majority of AEs were mild, with nausea, vomiting and diarrhoea most commonly reported; incidence of nausea and vomiting was generally greater at higher doses

	T2D						Obesity without T2D	
Participants, n (%)	Placebo (n=16)	Danuglipron 80 mg BID LS (n=20)	Danuglipron 80 mg BID HS (n=22)	Danuglipron 120 mg BID LF (n=22)	Danuglipron 120 mg BID HF (n=22)	Danuglipron 200 mg BID HF (n=21)	Placebo (n=6)	Danuglipron 200 mg BID HF (n=22)
Participants who discontinued study medication due to AE	1 (6.3)	6 (30.0)	4 (18.2)	6 (27.3)	7 (31.8)	8 (38.1)	0	12 (54.5)
Participants with ≥1 AE	8 (50.0)	12 (60.0)	14 (63.6)	16 (72.7)	15 (68.2)	14 (66.7)	4 (66.7)	18 (81.8)
Participants with ≥1 AE (preferred tem)								
Nausea	2 (12.5)	4 (20.0)	5 (22.7)	6 (27.3)	8 (36.4)	10 (47.6)	0	13 (59.1)
Vomiting	2 (12.5)	5 (25.0)	4 (18.2)	6 (27.3)	9 (40.9)	6 (28.6)	0	10 (45.5)
Diarrhoea	2 (12.5)	2 (10.0)	1 (4.5)	5 (22.7)	5 (22.7)	1 (4.8)	0	1 (4.5)
Dyspepsia	0	1 (5.0)	1 (4.5)	2 (9.1)	5 (22.7)	1 (4.8)	0	1 (4.5)
Abdominal pain upper	1 (6.3)	1 (5.0)	3 (13.6)	2 (9.1)	1 (4.5)	0	0	3 (13.6)
Constipation	0	1 (5.0)	1 (4.5)	1 (4.5)	1 (4.5)	2 (9.5)	0	2 (9.1)
Gastro-oesophageal reflux disease	1 (6.3)	2 (10.0)	1 (4.5)	1 (4.5)	0	1 (4.8)	0	1 (4.5)
Abdominal pain	0	2 (10.0)	2 (9.1)	0	0	1 (4.8)	0	0
Eructation	0	1 (5.0)	2 (9.1)	0	1 (4.5)	0	0	0
Abdominal distension	0	1 (5.0)	0	0	0	2 (9.5)	0	1 (4.5)

Declines in Body Weight with Danuglipron at Week 12

Body weight: Change from baseline at week 12 in T2D



- **T2D**
  - Statistically significant reductions in body weight in all Danuglipron groups at Week 12 were demonstrated compared with placebo (except for Danuglipron 80 mg BID HS)
- **Obesity without T2D**
  - Least squares mean difference did not reach statistical significance (one-sided P=0.0826)
  - Observed (mean ± SD) reductions from baseline at Week 12:
    - **Danuglipron 200 mg BID**: **–7.17** ± 7.24 kg (n=6 who completed double-blind treatment)
    - **Placebo**: **–0.30** ± 2.19 kg (n=5)

† Pressure fixed-anchored P<0.05, mandatorily significant continuous control, linked model, repeated measure analysis including treatment, time, strata (defined as main vs. female) and the treatment-by-time interaction as fixed effects; baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and participant as a random effect.
BID, twice daily; CI, confidence interval; E, fast; FPG, fasting plasma glucose; H, high; HbA1c, glycated haemoglobin; L, low; S, slower; T2D, type 2 diabetes.

Summary of Danuglipron Phase 2 Data

- These Phase 2 clinical data with an oral small molecule GLP-1R agonist demonstrate that danuglipron was generally safe, with a tolerability profile consistent with the mechanism of action[1,2]
- Danuglipron reduced HbA1c, FPG and body weight in T2DM at multiple dose levels at Weeks 12-16, compared with placebo, and was administered without fasting restrictions
  - Declines in HbA1c up to -1.57% and body weight up to -5.38 kg were observed in T2D over this duration
- Adverse events (AEs) were generally mild in nature, and the most common AEs were gastrointestinal and consisted of nausea, diarrhea and vomiting
- The efficacy and safety data are in line with Phase 1 data for danuglipron[3] and Phase 2 data for peptidic GLP-1R agonists over similar durations of time[4-6]

Oral small molecule GLP-1 receptor agonist danuglipron (PF-06882961) results in glucose lowering and body weight loss over 16 weeks in aPhase 2b study in adults withType 2 diabetes mellitus

Aditi R Saxena[1], Juan Frias[2], Lisa S Brown[3], Donal N Gorman[4], Nikolaos Tsamandouras[1], Morris J Birnbaum[1]*

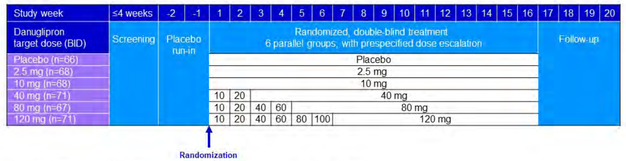
[1]*Pfizer Worldwide Research, Development, and Medical, Cambridge, MA, USA;* [2]*Velocity Clinical Research, Los Angeles, CA, USA;* [3]*Pfizer Worldwide Research and Development, Collegeville, PA, USA;* [4]*Pfizer Worldwide Research and Development, Cambridge, UK*

**At the time of the study*

#589, Presented at the European Association for the Study of Diabetes (EASD) Annual Meeting, September 20, 2022, Stockholm, Sweden

Introduction, Objectives and Study Design

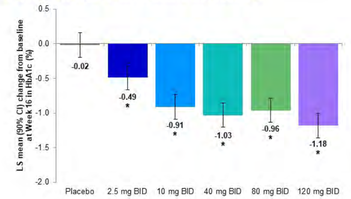
- **Objectives and study design:** Phase 2b, randomized, placebo-controlled, parallel group, dose-ranging study to examine the effect of danuglipron on efficacy, safety, tolerability and pharmacokinetics over 16 weeks in adults with T2D (NCT03985293)
- **Primary efficacy endpoint:** change from baseline in HbA1c at Week 16
- **Key secondary endpoints:** changes from baseline in FPG and body weight at Week 16
- Study was conducted during the early stages of the pandemic, July 2020 to July 2021
- 411 participants were randomized and dosed, and 316 (77%) completed double-blind treatment



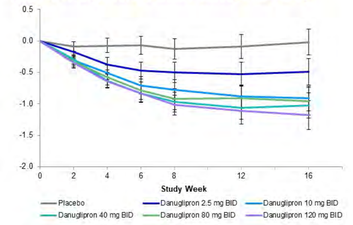
Significant, Dose-responsive Declines in HbA1c

All danuglipron groups demonstrated statistically significant dose-responsive declines from baseline in HbA1c at Week 16 compared with placebo (all P<0.0001, except 2.5 mg BID which was P<0.01)

HbA1c: Change from Baseline at Week 16



HbA1c: Change from Baseline Through the Study

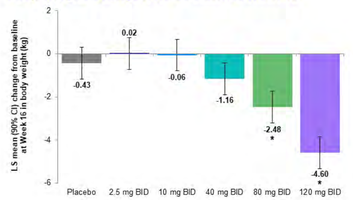


*Prespecified two-sided P<0.1 (statistically significant) versus placebo, mixed model repeated measures analysis including treatment, time, sima metformin vs dasiforxosec, and treatment-time interaction as fixed effects, sasenra as covariate, and baseline-time interaction with time fitted as a repeated effect and participant as a random effect.
BID, twice daily; CI, confidence interval; HbA1c, glycated haemoglobin; LS, least squares.

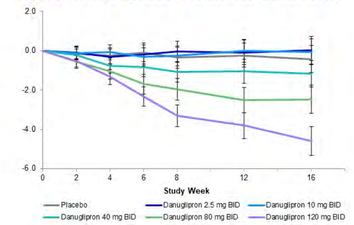
Significant Decline in Body Weight Over 16 Weeks

Body weight was statistically significantly reduced at Week 16 in the Danuglipron 80 mg BID and 120 mg BID groups (both P<0.001), compared with placebo

Body Weight: Change from Baseline at Week 16



Body Weight: Change from Baseline Through the Study



*Prespecified two-sided P<0.1 (statistically significant) versus placebo, mixed model repeated measures analysis including treatment, time, sima metformin vs dasiforxosec, and treatment-time interaction as fixed effects, sasenra as covariate, and baseline-time interaction with time fitted as a repeated effect and participant as a random effect.
BID, twice daily; CI, confidence interval; LS, least squares.

Eligibility Criteria and Baseline Characteristics

Key Eligibility Criteria

- T2D treated with diet and exercise, with or without metformin
- HbA1c ≥7% and ≤10.5%
- Stable body weight
- Body mass index[b] 24.5–45.4 kg/m^2

Demographics and Baseline Characteristics of the Overall Population[a]

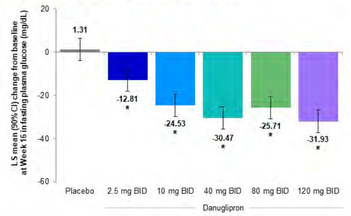
- **Age:** 58.6 ± 9.33 years
- **Female:** 49.1%
- **Race:** White 83.5%, other 16.5%
- **Ethnicity:** Hispanic or Latino 31.1%, other 68.9%
- **Duration of T2D:** 8.8 ± 6.68 years
- **Metformin use:** 91.5%
- **HbA1c:** 8.07 ± 0.92%
- **FPG:** 169.3 ± 41.65 mg/dL
- **Body weight:** 91.3 ± 17.89 kg
- **Body mass index:** 32.8 ± 5.25 kg/m^2

[a] Treated participants (n=411) randomized and dosed. [b] Calculated as weight (kg) / height (m)^2. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

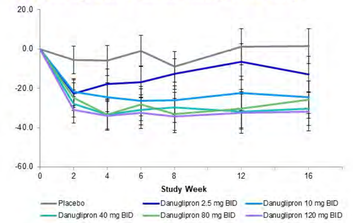
Significant Reduction in Fasting Plasma Glucose Over 16 weeks

At Week 16, FPG was statistically significantly reduced with all Danuglipron doses compared with placebo (P<0.001 for all doses ≥10 mg BID; P<0.1 for 2.5 mg BID)

FPG: Change from baseline at Week 16



FPG: Change from Baseline Through The Study



*Prespecified two-sided P<0.1 (statistically significant) versus placebo, mixed model repeated measures analysis including treatment, time, sima metformin vs dasiforxosec, and treatment-time interaction as fixed effects, sasenra as covariate, and baseline-time interaction with time fitted as a repeated effect and participant as a random effect.
BID, twice daily; CI, confidence interval; FPG, fasting plasma glucose; LS, least squares.

Safety & Tolerability Profile Consistent with Mechanism

- The majority of AEs were mild, with nausea, diarrhoea and vomiting most common
- No episodes of severe hypoglycemia
- No clinically significant, adverse trends in laboratory measures, electrocardiogram or vital sign abnormalities

Participants, n (%)	Placebo (n=66)	Danuglipron 2.5 mg BID (n=68)	Danuglipron 10 mg BID (n=68)	Danuglipron 40 mg BID (n=71)	Danuglipron 80 mg BID (n=67)	Danuglipron 120 mg BID (n=71)	Total (N=411)
Participants who discontinued study medication due to AE	5 (7.6)	2 (2.9)	3 (4.4)	8 (11.3)	15 (22.4)	24 (33.8)	57 (13.9)
Participants with ≥1 AE	32 (48.5)	32 (47.1)	31 (45.6)	42 (59.2)	43 (64.2)	44 (62.0)	224 (54.5)
Participants with ≥1 AE							
Nausea	2 (3.0)	5 (7.4)	5 (7.4)	11 (15.5)	22 (32.8)	23 (32.4)	68 (16.5)
Diarrhoea	2 (3.0)	3 (4.4)	4 (5.9)	8 (11.3)	12 (17.9)	7 (9.9)	36 (8.8)
Vomiting	0	0	1 (1.5)	5 (7.0)	11 (16.4)	18 (25.4)	35 (8.5)
Dyspepsia	0	4 (5.9)	3 (4.4)	2 (2.8)	9 (13.4)	2 (2.8)	20 (4.9)
Gastro-oesophageal reflux disease	0	1 (1.5)	2 (2.9)	2 (2.8)	4 (6.0)	5 (7.0)	14 (3.4)
Abdominal distension	1 (1.5)	0	1 (1.5)	4 (5.6)	3 (4.5)	2 (2.8)	11 (2.7)

Treatment-emergent AEs, all causality. Participants counted once per treatment per event. Includes all data collected since the first dose of double-blind study medication. Participants who discontinued study medication might still have continued in the study. Gastrointestinal AEs (preferred terms with ≥5% incidence in any treatment arm are shown.
AE, adverse event; BID, twice daily.

Once-daily oral small molecule GLP-1R agonist PF-07081532 robustly reduces glucose and body weight within 4-6 weeks in a Phase 1b in adults with Type 2 diabetes and non-diabetic adults with obesity

Clare Buckeridge[1], Nikolaos Tsamandouras[1], Santos Carvajal-Gonzalez[1], Lisa S Brown[2], Kristin L Chidsey[1], Aditi R Saxena[1]

[1]*Pfizer Worldwide Research, Development, and Medical, Cambridge, MA, USA*; [1]*Pfizer Worldwide Research, Development, and Medical, Collegeville, PA, USA*

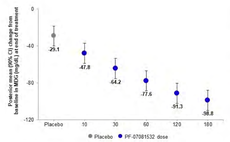
#114, Presented at the European Association for the Study of Diabetes (EASD) Annual Meeting, September 21, 2022, Stockholm, Sweden

Study Design Overview

- Inpatient study (NCT05158244) conducted at 2 clinical research units in the United States
- 6 cohorts were enrolled: 5 cohorts of participants with T2D and 1 cohort with obesity
- PF-07081532 or placebo administered once daily, with breakfast
- Rapid titration used to achieve higher doses
- Dosing took place during the early stages of the COVID-19 pandemic: mid-2020 to mid-2021



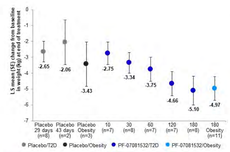
Robust Declines in Mean Daily Glucose with Once-daily PF-07081532 in Participants with T2D



Observed mean reductions from baseline in MDG were dose-dependent

Each of the PF-07081532 doses were statistically significantly different to placebo

Dose-responsive Weight Reduction with Once-daily PF-07081532 for 4 to 6 Weeks



While longer duration of intervention is required to assess the effect of treatment on body weight, reductions were observed following dosing with PF-07081532 for 4 to 6 weeks: mean decreases from baseline of up to approx. -5.5% in participants with T2D and approx. -5.2% in participants with obesity

Phase 1b Data with PF-07081532 Over 4-6 Weeks in T2D and Obesity Support Potential Best-in-Class in Efficacy and Tolerability

- Dose-dependent reductions from baseline in MDG, FPG and HbA1c in participants with T2D
- Declines in body weight, with higher doses of PF-07081532 demonstrating greater reductions
- Tolerability profile consistent with the mechanism of action
- Pharmacokinetic profile suitable for once-daily dosing
- Plasma concentrations of PF-07081532 increased approximately dose-proportionally, with similar plasma exposure observed in participants with T2D and participants with obesity

Population and Key Endpoints

Adult Participants

With type 2 diabetes:
- T2D (stable metformin ≥ 500 mg)
- HbA1c 7%–10.5%
- BMI 24.5–45.5 kg/m^2

With obesity:
- HbA1c < 6.5%
- BMI 30.5–45.5 kg/m^2

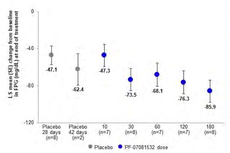
Key Safety and Tolerability Endpoints

- Adverse events (AEs), discontinuations due to AEs
- Laboratory tests, vital signs, 12-lead ECGs

Other Assessments

- Change from baseline in mean daily glucose and fasting plasma glucose
- Change from baseline in HbA1c and body weight over 4–6 weeks
- Pharmacokinetic parameters

Fasting Plasma Glucose Approaching Non-diabetic Thresholds with Once-daily PF-07081532 in Participants with T2D



Observed average reductions from baseline in FPG were up to -79 mg/dL over 28 days and up to -102 mg/dL over 42 days

By Day 28, all PF-07081532 treatment groups >10 mg had observed average fasting plasma glucose levels of ≤126 mg/dL

Observed Adverse Effect Profile of PF-07081532 in Phase 1b Study is Consistent with the Mechanism of Action

Adverse Events: Most events (87% for T2D; 94% for obesity) were reported as mild in intensity, with gastrointestinal disorders most common across groups, in line with the mechanism of action. None of the events listed below were severe or serious

Safety Laboratory, ECG, Vitals: No clinically significant adverse trends

	T2D 28 days					T2D 42 days		Obesity 42 days	
	Placebo	10 mg	30 mg	60 mg	120 mg	Placebo	180 mg	Placebo	180 mg
Randomised (n)	9	7	8	8	8	2	9	3	12
Discontinued study drug due to AE (n)	0	0	0	1	1	0	0	0	1
Participants with AE (n)	7	5	7	8	8	2	9	3	11
Number (%) of participants with all-causality treatment-emergent AEs of interest, by Preferred Term									
Nausea	2 (22.2)	0	2 (25.0)	4 (50.0)	5 (62.5)	1 (50.0)	8 (88.9)	1 (33.3)	7 (58.3)
Diarrhoea	2 (22.2)	1 (14.3)	4 (50.0)	2 (25.0)	4 (50.0)	0	2 (22.2)	1 (33.3)	5 (41.7)
Constipation	2 (22.2)	0	1 (12.5)	2 (25.0)	4 (50.0)	1 (50.0)	3 (33.3)	2 (66.7)	6 (50.0)
Headache	2 (22.2)	0	2 (25.0)	4 (50.0)	3 (37.5)	0	3 (33.3)	1 (33.3)	2 (16.7)
Vomiting	1 (11.1)	0	1 (12.5)	3 (37.5)	3 (37.5)	0	2 (22.2)	1 (33.3)	3 (25.0)
Decreased Appetite	0	1 (14.3)	0	3 (37.5)	2 (25.0)	0	3 (33.3)	1 (33.3)	4 (33.3)

Key Baseline Demographic and Disease Characteristics

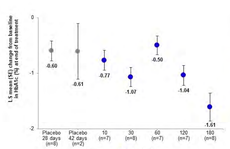
A total of 66 participants were randomised

T2D: 51 participants; 40 for dosing duration of 28 days and 11 for dosing duration of 42 days

Obesity: 15 participants for dosing duration of 42 days

	T2D	Obesity
Age, years	58.6 (8.3)	53.3 (9.1)
Male, %	52.9	53.3
T2D duration, years	10.7 (5.4)	N/A
MDG, mg/dL	207.8 (36.9)	N/A
FPG, mg/dL	194.1 (38.7)	N/A
HbA1c, %	8.6 (1.0)	5.6 (0.5)
Body weight, kg	89.7 (19.3)	98.2 (12.2)
BMI, kg/m^2	32.1 (5.8)	32.9 (6.9)

HbA1c Reduction with Once-daily PF-07081532 for 4 to 6 Weeks in Participants with T2D



While longer duration of intervention is required to assess the effect of treatment on HbA1c, reductions were observed following dosing with PF-07081532, with modelled mean decreases of up to -1.61% in 6 weeks

PF-07081532 Pharmacokinetic Profile Following Last Dose

- PF-07081532 exposure (AUC24 and Cmax) generally increased in an approximately dose-proportional manner across the dose range studied
- Observed half-life is supportive of once-daily administration
- No substantial differences in exposure observed between participants with T2D and those with obesity

	Participants with T2D					Participants with Obesity
	10 mg (n=7)	30 mg (n=8)	60 mg (n=8)	120 mg (n=8)	180 mg (n=9)	180 mg (n=12)
AUC_{24}, ng.hr/mL	26380 (23)	78930 (20)	177000 (58)	265400 (62)	496500 (44)	521300 (38)
C_{max}, ng/mL	2263 (19)	5631 (26)	12860 (51)	18520 (47)	30600 (33)	35000 (37)
T_{max}, hr	2.0 (2.0–4.0)	4.0 (1.0–12.0)	4.0 (1.0–10.0)	4.0 (4.0–12.0)	8.0 (6.0–12.0)	4.0 (1.0–12.0)
$t_{1/2}$, hr	26.5 (4.6)	26.4 (6.3)	23.7 (3.8)	24.5 (5.4)	23.1 (5.9)	20.7 (4.4)

Pharmacodynamic Results from Phase 1 Studies of GBT021601, a Next-Generation HbS Polymerization Inhibitor for Treatment of Sickle Cell Disease

Modupe Idowu, MD[1]; Thinh Nguyen, MD[2]; Erin Buckley, PhD[3]; Rowan Brothers, BS[3]; Kobina Dufu, PhD[4]; Eleanor Lisbon, MD, MPH[4]

[1]*University of Texas, McGovern Medical School, Houston, TX, USA;* [2]*Visionaries Clinical Research, Atlanta, GA, USA;* [3]*Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA;* [4]*Global Blood Therapeutics, South San Francisco, CA, USA*

Presented at the 64th American Society of Hematology Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, USA.

Introduction

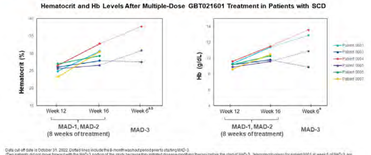
- SCD is an inherited, lifelong disorder characterized by HbS polymerization, resulting in RBC sickling, hemolytic anemia, vaso-occlusion, and end-organ damage.
- Voxelotor is an approved, first-in-class HbS polymerization inhibitor that reduces sickling and improves RBC deformability.[1] In patients with SCD, voxelotor 1500 mg once daily resulted in rapid and robust improvements in Hb concentrations and reductions in markers of hemolysis that were maintained up to week 72.[2]
- GBT021601 is a next-generation HbS polymerization inhibitor, that also stabilizes Hb in the oxygenated state and has potential to be a best-in-class therapy.
- **Here we explore the use of novel biomarkers to provide insights into the pharmacokinetics and pharmacodynamics of GBT021601 in patients with SCD.**

Hb, hemoglobin; Hbss, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

1. Dufu K, et al. *Clin Hemorheol Microcirc.* 2018;70(1):95-107.2 Howard J, et al. *Lancet Haematol.* 2021;8(1):e023-e033.

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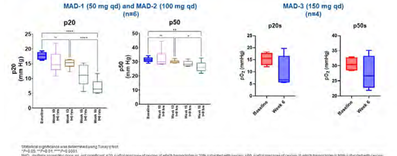
Improvements in Hematocrit and Hb Levels Over Time with GBT021601 in Patients with Sickle Cell Disease



Cells cut off date is October 31, 2022. Dotted lines include the 6-month washout period prior to starting MAD-3.
[A]Hematocrit values for patient 0001 at week 6 of MAD-3 were missing due to lost blood sample.
Hb, hemoglobin; MAD, multiple ascending dose; SCD, sickle cell disease.

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p20 and p50 Values Observed with GBT021601 in Patients with Sickle Cell Disease



Wilcoxon signed-rank test was performed using Tukey's test.
*P<0.05; **P<0.01; ***P<0.001.
MAD, multiple ascending dose; n=, not significant; p20, partial pressure of oxygen of which hemoglobin is 20% saturated with oxygen; p50, partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen; pO2, partial pressure of oxygen; qd, once daily; SCD, sickle cell disease.

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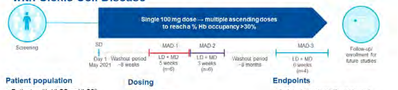
Safety Overview: Treatment-Emergent Adverse Events and Serious Adverse Events

Overview of adverse events	Single dose, MAD-1 (50 mg qd), and MAD-2 (100 mg qd) (n=6)	MAD-3 (150 mg qd) (n=4)[A]
Number of TEAEs	33	6
Number of participants with at least 1 TEAE, n (%)	6 (100)	3 (75)
Number of TEAEs grade ≥3	7	0
Number of drug-related TEAEs	4	1
Number of participants with at least 1 drug-related TEAE, n (%)	2 (33.3)	1 (25)
Number of TEAEs leading to study drug discontinuation	0	0
Number of SAEs	3	0

Data cutoff date is October 31, 2022.
[A]Two patients started dose titration with the MAD-3 portion of the study because they initiated disease-modifying therapy before the start of MAD-3.
MAD, multiple ascending dose; qd, once daily; SAE, serious adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

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Study GBT021601-012: Phase 1 Study in Patients with Sickle Cell Disease



Patient population
- Patients with HbSS or HbSβ⁰, aged 18 to 60 years
- Baseline Hb ≥5.5 g/dL and ≤10.5 g/dL
- No recent VOCs[a] or transfusions[a]
- Background HU allowed if dose has been stable for ≥90 days[a]

Dosing
- SD: 100 mg
- MAD-1: LD and 50 mg daily maintenance
- MAD-2: LD and 100 mg daily maintenance
- MAD-3: LD and 150 mg daily maintenance

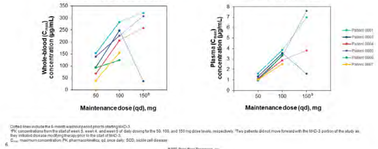
Endpoints
- Safety and tolerability (primary)
- PK
- Relationship between time-matched GBT021601 concentrations and the changes in clinical measures of anemia and hemolysis from baseline

[a]No hospitalizations for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF or within 28 days before day 1 of study treatment.
No transfusions within 60 days of signing the ICF or at any time during the screening period.
Hb, hemoglobin; HbSS, homozygous for HbS; HU, hydroxyurea/hydroxycarbamide; ICF, informed consent form; LD, loading dose; MAD, multiple ascending dose; MD, maintenance dose; PK, pharmacokinetic; SAD, single ascending dose; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

ClinicalTrials.gov identifier: NCT04482284; Accessed Mar 2, 2022. http://clinicaltrials.gov/ct2/show/NCT04482284

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Individual Dose Response: GBT021601 PK Concentration[a] in Patients with Sickle Cell Disease

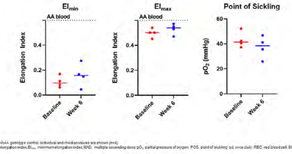


Dotted lines include the 6-month washout period prior to starting MAD-3.
[a]Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 12, 24, and 48 hours after the first dose of study dosing for the 50, 100, and 150 mg dose levels, respectively. Preliminary analysis based on apparent C_{max}. Two patients started dose titration with the MAD-3 portion of the study, because they initiated disease-modifying therapy before the start of MAD-3.
C_{max}, maximum concentration; PK, pharmacokinetics; qd, once daily; SCD, sickle cell disease.

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Improvement in POS and RBC Deformability with GBT021601 in Patients with Sickle Cell Disease

Results from MAD-3 (150 mg qd)



AA, dioxybenzenesulfonate; genotype, patient individual and medium used as shown (mM).
EI_{min}, maximum elongation index; EI_{max}, minimum elongation index; MAD, multiple ascending dose; pO2, partial pressure of oxygen; POS, point of sickling; qd, once daily; RBC, red blood cell; SCD, sickle cell disease.

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Conclusions

- In adults with SCD, treatment with GBT021601 loading doses followed by maintenance doses of 100 mg and 150 mg led to a mean Hb occupancy >30%, increased hematocrit, and increased Hb levels.
- Daily maintenance doses of GBT021601 at 150 mg were well tolerated in adults with SCD.
- Results from hemoximetry, ektacytometry, and peripheral blood smears suggest that GBT021601 maintenance doses of 100 mg and 150 mg improve RBC health.

Hb, hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

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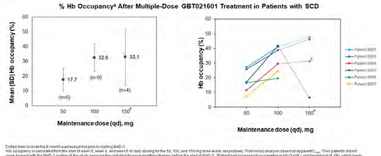
Baseline Characteristics and Hb Levels of Patients with Sickle Cell Disease

Parameter	Single dose, MAD-1 (50 mg qd) and MAD-2 (100 mg qd) (n=6)	MAD-3 (150 mg qd) (n=4)
Mean age, years (minimum, maximum)	20.2 (18.0, 23.0)	19.8 (18.0, 23.0)
Male, n (%)	4 (66.7)	2 (50.0)
Race, n (%)		
Black or African American	5 (83.3)	3 (75.0)
Other	1 (16.7)	1 (25.0)
HbSS genotype, n (%)	6 (100)	4 (100)
Hb level, g/dL, mean (SD), range	8.2 (0.4), 7.7 8.1	9.2 (0.4), 8.6 9.6
Current hydroxyurea use, n (%)	6 (100)	4 (100)
Number of VOCs within 12 months of screening, n (%)		
0	2 (33.3)	2 (50.0)
1	1 (16.7)	1 (25.0)
2	3 (50.0)	1 (25.0)
Number of transfusions within 12 months of screening, n (%)		
0	4 (66.7)	3 (75.0)
1	2 (33.3)	1 (25.0)

Hb, hemoglobin; HbSS, homozygous for SCD; qd, once daily; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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Dose-Related Increases with GBT021601: Hb Occupancy in Patients with Sickle Cell Disease

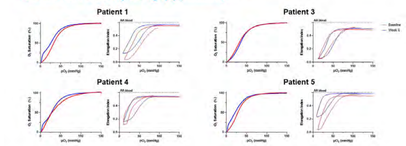


Dotted lines include the 6-month washout period prior to starting MAD-3.
[a]Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 12, 24, and 48 hours after the first dose of study dosing for the 50, 100, and 150 mg dose levels, respectively. Preliminary analysis based on apparent C_{max}. Two subjects rolled from cohort 0003 at 100 mg were excluded due to lack of adherence. Two patients started dose titration with the MAD-3 portion of the study, because they initiated disease-modifying therapy before the start of MAD-3. Whole-blood concentrations in baseline were 0 (1 gdc) and hemolytic (0.1%), which bias the occupancy value.
C_{max}, maximum concentration; Hb, hemoglobin; qd, once daily; SCD, sickle cell disease.

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Improvement in POS and RBC Deformability with GBT021601 in Patients with Sickle Cell Disease

Results from MAD-3 (150 mg qd) *(continued)*



AA, dioxybenzenesulfonate; genotype, patient individual and medium used as shown (mM).
MAD, multiple ascending dose; O_2, oxygen; pO2, partial pressure of oxygen; POS, point of sickling; qd, once daily; RBC, red blood cell; SCD, sickle cell disease.

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Acknowledgments

We thank the patients with SCD, their families, caregivers, physicians, research nurses, study coordinators, and support staff who contributed to this study, including
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- Mira Patel, Eric Zimmerman, Wai Chin, Clark Brown (Global Blood Therapeutics, Inc.)
- Mariam M. Akbar and Sydney E. Triplett (Dr Erin Buckley's Laboratory)

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SCD, sickle cell disease.

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Dose-Related Increases with GBT021601: Hb Occupancy in Patients with Sickle Cell Disease

Dotted lines include the 6-month washout period prior to starting MAD-3.
[a]Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 12, 24, and 48 hours after the first dose of study dosing for the 50, 100, and 150 mg dose levels, respectively. Preliminary analysis based on apparent C_{max}. Hb occupancy data from cohort 0003 at 100 mg were excluded due to lack of adherence. Two patients started dose titration with the MAD-3 portion of the study, because they initiated disease-modifying therapy before the start of MAD-3. Whole-blood concentrations in baseline were 0 (1 gdc) and hemolytic (0.1%), which bias the occupancy value.
C_{max}, maximum concentration; Hb, hemoglobin; qd, once daily; SCD, sickle cell disease.

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Summary of Changes in Percentage of Sickled RBCs for all Patients per Time Point

Data cutoff date is October 31, 2022. Individual and median values are shown.
[A]Baseline was at day 1 of MAD-3. Patients were not re-baselined. Washed 100011 is a one time blood spec of sickled cells at baseline.
Hb, hemoglobin; RBC, red blood cell.

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Real-World Effectiveness of Voxelotor for the Treatment of Sickle Cell Disease

Group and Pediatric Subgroup Analyses of Effects on Transfusions, Vaso-occlusive Crises, and Hospitalizations

Nirmish Shah, MD[1]; Thokozeni Lipato, MD[2]; Thomas E. Delea, MSIA[3]; Alexander Lonshteyn, PhD[3]; Derek Weycker, PhD[3]; Andy Nguyen, PhD[4]; Anne Beaubrun, PhD[4]; Ofelia Alvarez, MD[5]

[1]Duke University School of Medicine, Durham, NC, USA; [2]VCU Health, Richmond, VA, USA; [3]Policy Analysis Inc. (PAI), Brookline, MA, USA; [4]Global Blood Therapeutics, Inc., South San Francisco, CA, USA; [5]University of Miami, Miami, FL, USA

Presented at the 64th American Society of Hematology Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, USA.

Introduction

- SCD is characterized by **chronic hemolytic anemia**, **acute painful VOCs**, and **progressive multisystem end-organ damage**.[1]
- The condition requires **comprehensive**, **life-long management**,[2] including relatively frequent **hospitalizations** (usually involving VOCs) and **blood transfusions**.[3-5]
- **Voxelotor** is a first-in-class sickle hemoglobin polymerization inhibitor that targets the underlying pathophysiology of SCD.[6]
  - Voxelotor is approved in the United States for the treatment of SCD in patients aged ≥4 years, and in the United Arab Emirates, Oman, and Kuwait for patients aged ≥12 years; voxelotor is approved in the European Union and Great Britain for the treatment of hemolytic anemia in patients with SCD aged ≥12 years.[7,8]
- Clinical studies and RWE indicate that voxelotor **increases hemoglobin** and **reduces markers of hemolysis**,[9-11] and there are emerging data being evaluated to assess voxelotor's impact on the clinical symptoms of SCD, the rates of VOCs, and the need for transfusions.[11-13]

RWE, real-world evidence; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Kato GJ, et al. *Nat Rev Dis Primers*. 2018;4:18010. 2. Bender MA. *Genet Med Rev*. 2013;27(6):279-87. 3. Wilkes-Frederick S, et al. Accessed October 6, 2022. https://www.medicaid.gov/medicaid/quality-of-care/downloads/sickcell-qm-2021.pdf. 4. Finger K, et al. Accessed October 2, 2019. https://hcup-us.ahrq.gov/reports/statbriefs/sb231-Sickle-Cell-Disease-Stays-2016.jsp. 5. Chou ST. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):579-83. 6. Global Blood Therapeutics, Inc. Accessed August 1, 2021. https://ir.gbt.com/news-releases/news-release-details/fda-approves-oxbryta®-voxelotor-first-medicine-specifically. 7. Global Blood Therapeutics, Inc. July 29, 2022. Accessed July 29, 2022. https://ir.gbt.com/news-releases/news-release-details/mohap-grants-marketing-authorization-gbts-oxbryta-voxelotor-use. 8. Data on file. Global Blood Therapeutics, Inc., South San Francisco, CA. 9. Vichinsky E, et al. *N Engl J Med*. 2019;381(6):509-519. 10. Estepp JH, et al. *Pediatr Blood Cancer*. 2022;69(6):e29710. 11. Abuchowski A, et al. *Eur J Haematol*. 2022;109(2):164-161. 12. Shah N, et al. *Expert Rev Hematol*. 2022;15(2):167-173. 13. Enzhelier MB. *Transfusion*. 2020;60(12):2866-2867.

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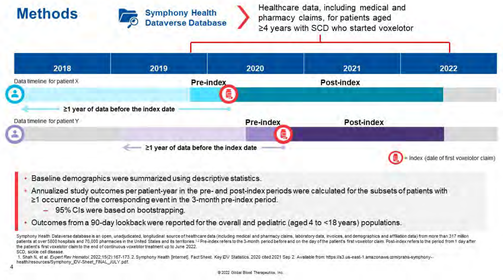
Objective

To examine the real-world rates of transfusions, VOCs, and hospitalizations among patients with SCD who initiate voxelotor treatment.

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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Methods



- Baseline demographics were summarized using descriptive statistics.
- Annualized study outcomes per patient-year in the pre- and post-index periods were calculated for the subsets of patients with ≥1 occurrence of the corresponding event in the 3-month pre-index period.
  - 95% CIs were based on bootstrapping.
- Outcomes from a 90-day lookback were reported for the overall and pediatric (aged 4 to <18 years) populations.

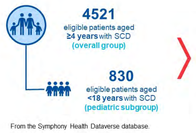
Symphony Health Dataverse database is an open, unadjudicated, longitudinal source of healthcare data (including medical and pharmacy claims, laboratory data, invoices, and demographics and affiliation data) from more than 317 million patients at over 5000 hospitals and 70,000 pharmacies in the United States and its territories. Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022.
SCD, sickle cell disease.

1. Ataga KI, et al. *Expert Rev Hematol*. 2022;15(2):167-173. 2. Symphony Health [Internet]. Fact Sheet. Key IDV Statistics. 2020 cited 2021 Sep 2. Available from: https://s3.us-east-1.amazonaws.com/prara-symphony-healthmisc/surface/Symphony_IDV-Sheet_FINAL_JULY.pdf.

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Study Population

Included in analysis:



From the Symphony Health Dataverse database.

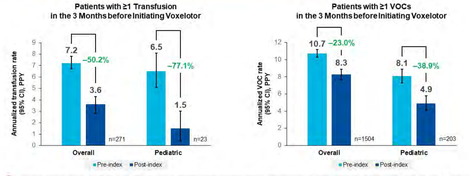
Baseline Patient Demographics and Duration of Follow-up

	Overall N=4521	Pediatric n=830
Age, mean (range), years	33.4 (4-80)	13.2 (4-17)
Age group, n (%)		
4 to 11 years	170 (3.8)	170 (20.5)
12 to 17 years	660 (14.6)	660 (79.5)
18+ years	3691 (81.6)	0 (0)
Sex, n (%)		
Female	2658 (58.8)	434 (52.3)
Male	1863 (41.2)	396 (47.7)
Follow-up, median (Q1,Q3), days	78 (45, 157)	82 (45, 159)
Follow-up length >1 year, n (%)	321 (7.1)	67 (8.1)

Data cutoff: June 2022.
Q, quartile; SCD, sickle cell disease.

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Change in Number of Transfusions and VOCs

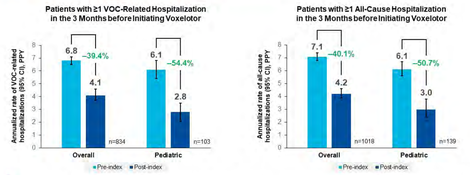


Compared with those in the 3-month pre-index period, lower annualized rates of transfusions and VOCs were observed in the post-index period for the overall population and the pediatric subgroup.

Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022.
PPPY, per patient-year; VOC, vaso-occlusive crisis.

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Change in Number of Hospitalizations

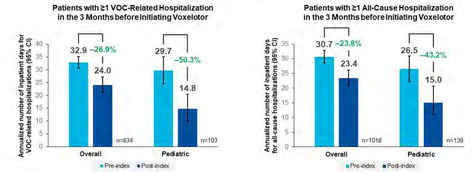


Compared with the 3-month pre-index period, lower annualized rates of hospitalizations were observed in the post-index period for the overall population and the pediatric subgroup.

Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022.
PPPY, per patient-year; VOC, vaso-occlusive crisis.

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Change in Number of Inpatient Days



Compared with the 3-month pre-index period, lower annualized mean number of inpatient days were observed in the post-index period for the overall population and the pediatric subgroup.

Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022.
VOC, vaso-occlusive crisis.

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Study Limitations

Limitations of this analysis include:

- No control group to compare effect observed in study
- Open claims data: patients may have received care outside of the data captured by Symphony
- Study time frame: the study's initial look-back period is pre-pandemic, and the look-forward period is post-pandemic; healthcare utilization was greatly decreased during the initial phase of the pandemic
- That only the subgroup of patients who had a transfusion, VOC, or hospitalization within the 90-day pre-index period were included in the analyses for the corresponding event
- Limited time frame for follow-up
- That annualized clinical outcomes may not be consistent over time
- Limitations associated with administrative claims data such as:
  - Missing or incomplete data
  - Diagnosis on claims that may not be sensitive or specific to clinical conditions
- Residual confounding factors, such as treatment adherence and medication utilization driven by any potential medication side effects

VOC, vaso-occlusive crisis.

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Conclusions

In these subgroup analyses of patients with SCD, voxelotor treatment was associated with a reduction in frequency of transfusions, VOCs, and hospitalizations and a decrease in inpatient days.

Compared with those for the overall study population, reductions in outcomes (frequencies of transfusions, VOCs, and hospitalizations and length of inpatient days) were numerically greater for pediatric patients.

- One potential explanation for this difference is that younger patients may have accumulated fewer SCD-related complications than adults,[1] enabling a greater clinical response.
- Other potential explanations for this difference include the smaller pediatric sample size and the historically greater treatment adherence seen among pediatric patients.[2]

Overall, this real-world evidence provides support for the clinical use of voxelotor to treat SCD, including in pediatric patients.

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Ware RE. *Blood*. 2010;115(26):5300-5311.2. Campbell-Lee SK, et al. *Pediatric Drugs*. 2020;22(5):501-509.

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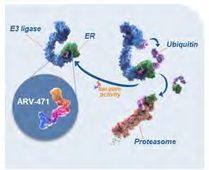
ARV-471, a PROTAC® estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study

Sara A Hurvitz,[1] Anne F Schott,[2] Cynthia Ma,[3] Erika P Hamilton,[4] Rita Nanda,[5] George Zahrah,[6] Natasha Hunter,[7] Antoinette R Tan,[8] Melinda L Telli,[9] Jesus Anampa Mesias,[10] Rinath Jeselsohn,[11] Pamela Munster,[12] Haolan Lu,[13] Richard Gedrich,[13] Cecile Mather,[13] Janaki Parameswaran,[13] Hyo S Han[14]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [2]Rogel Cancer Center, University of Michigan Health, Ann Arbor, MI; [3]Washington University, St Louis, MO; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]University of Chicago Medicine, Chicago, IL; [6]Norwalk Hospital, Norwalk, CT; [7]Seattle Cancer Care Alliance, Seattle, WA; [8]Levine Cancer Institute, Atrium Health, Charlotte, NC; [9]Stanford University School of Medicine, Stanford, CA; [10]Albert Einstein College of Medicine, Bronx, NY; [11]Dana-Farber Cancer Institute, Boston, MA; [12]University of California San Francisco, San Francisco, CA; [13]Arvinas Operations, Inc, New Haven, CT; [14]Moffitt Cancer Center, Tampa, FL

Background

- ARV-471 is a selective, orally administered PROTAC® protein degrader that targets wild-type and mutant ER[1]
- ARV-471 directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation
  - In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- Limitations of the SERD fulvestrant include its intramuscular route of administration[3] and only 40%–50% ER protein degradation at its optimal dose[4,5]
- ARV-471 treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]



ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera; SERD=selective estrogen receptor degrader

1. Flanagan, JJ, et al. *Cancer Research*. 2019;79(4 Suppl):P5-04.
2. Hanker AB, et al. *Cancer Cell*. 2020;37(4):496-513.
3. Nathan MR and Schmid P. *Oncol Ther*. 2017;5:17-29.
4. Kuter I, et al. *Breast Cancer Res Treat*. 2012;133(1):227-236.
5. Robertson JFR, et al. *Breast Cancer Res*. 2013;15(2):R18.

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Phase 1/2 Study Design[a]

First-in-human, open-label, 3-part study of ARV-471 alone or in combination with palbociclib in patients with ER+/HER2- locally advanced/metastatic breast cancer

Phase 1 dose escalation (Part A)	Phase 2 cohort expansion (Part B; VERITAC)	Phase 1b combination (Part C)
Treatment • ARV-471 orally	**Treatment** • ARV-471 orally	**Treatment** • ARV-471 plus palbociclib orally
Primary objective • Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds	**Primary objective** • Assess the antitumor activity of ARV-471	**Primary objective** • Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D of the combination

[a]ClinicalTrials.gov: NCT04072952
ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose

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Phase 1 ARV-471 Dose Escalation Results[1]

Phase 1 dose escalation (Part A)

Treatment
- ARV-471 orally

Primary objective
- Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds

- As of September 30, 2021, 60 patients received ARV-471
  - Total daily doses ranged from 30–700 mg
- ARV-471 was well tolerated at all doses, with no DLTs or grade ≥4 TRAEs; most TRAEs were grade 1/2
- The CBR[a] was 40% (95% CI: 26–56) in 47 evaluable patients
- 3 patients had confirmed PRs
- Preliminary PK data showed dose-related increases for AUC_{24} and C_{max} from 30–500 mg daily doses
- At the 200-mg and 500-mg doses, mean exposure on day 15 exceeded the nonclinical efficacious range by >2-fold and >5-fold, respectively[2]
- ER degradation up to 89% was observed; median and mean ER degradation across dose levels was 67% and 64%, respectively

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff.
AUC_{24}=area under the curve from 0 to 24 hours; CBR=clinical benefit rate; C_{max}=maximum plasma concentration; DLT=dose-limiting toxicity; ER=estrogen receptor; MTD=maximum tolerated dose; PK=pharmacokinetic; PR=partial response; RP2D=recommended phase 2 dose; TRAE=treatment-related adverse event

1. Hamilton E, et al. Presented at SABCS; Dec7-10, 2021; Poster PD13-08.
2. Snyder LB, et al. Presented at AACR; April 10-15, 2021; Oral Presentation 44.

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Phase 2 (VERITAC) Cohort Expansion Design

Phase 2 cohort expansion (Part B; VERITAC)

Key eligibility criteria
- Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
- Measurable or nonmeasurable disease per RECIST criteria v1.1
- ≥1 prior endocrine regimen (≥1 regimen for ≥6 months in the locally advanced or metastatic setting)
- ≥1 prior CDK4/6 inhibitor
- ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting

ARV-471 200 mg orally QD[a] (n=35)

ARV-471 500 mg orally QD[a] (n=36)

Primary endpoint
- CBR (rate of confirmed CR or PR or SD ≥24 weeks)[b]

Secondary endpoints
- ORR, DOR, PFS, and OS
- AEs and laboratory abnormalities
- PK parameters

Exploratory endpoints
- *ESR1* mutational status
- ER protein levels

Data cutoff date for this analysis
- June 6, 2022

[a]Enrollment in the 200-mg QD cohort began before enrollment in the 500-mg QD cohort
[b]Analyzed in patients enrolled ≥24 weeks prior to the data cutoff.
AE=adverse event; CBR=clinical benefit rate; CDK=cyclin-dependent kinase; CR=complete response; DOR=duration of response; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

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Patient Baseline Characteristics (VERITAC)

Characteristic	Total (N=71)
Sex, n (%)	
Female	69 (97.2)
Median age, y (range)	60 (41–86)
ECOG PS, n (%)[a]	
0	47 (66.2)
1	23 (32.4)
Visceral disease, n (%)	39 (54.9)
Sites of metastasis, n (%)	
Bone	49 (69.0)
Liver	32 (45.1)
Lung	17 (23.9)
Other	5 (7.0)

Characteristic	Total (N=71)
Baseline *ESR1* status, n (%)[b]	
Mutant	41 (57.7)
Wild-type	25 (35.2)
Median no. of prior regimens (range)	
Any setting	4 (1–10)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	71 (100)
Aromatase inhibitor	64 (90.1)
Fulvestrant	56 (78.9)
Chemotherapy	
Any setting	52 (73.2)
Metastatic setting	32 (45.1)

[a]Baseline ECOG PS status was unknown in 1 patient. [b]Baseline *ESR1* status was unknown or missing in 5 patients
CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene

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Treatment-Emergent Adverse Event Summary (VERITAC)

n (%)	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
TEAEs			
Any grade	32 (91)	30 (83)	62 (87)
Grade 3/4	9 (26)	6 (17)	15 (21)
Grade 5[a]	1 (3)	0	1 (1)
Leading to discontinuation	1 (3)	2 (6)	3 (4)
Leading to dose reduction	0	3 (8)	3 (4)

- Dose reductions due to TEAEs
  - 500-mg QD cohort (to 400 mg QD)
    - ALT increased (n=1)
    - Neutropenia (n=1)
    - Fatigue (n=1)
- Discontinuations due to TEAEs
  - 200-mg QD cohort
    - QT prolongation (n=1)[b]
  - 500-mg QD cohort
    - ECG T-wave abnormality (n=1)[c]
    - Back pain/spinal cord compression (n=1)

[a]Acute respiratory failure in the setting of disease progression and unrelated to ARV-471 treatment.
[b]Patient had QT prolongation at baseline, received a concomitant QT-prolonging drug during ARV-471 treatment, and had hypokalemia
[c]Patient had an uncertified, partial response
ALT=alanine aminotransferase; ECG=electrocardiogram; QD=once daily; TEAE=treatment-emergent adverse event

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TRAEs Reported in ≥10% of Patients Overall (VERITAC)

	200 mg QD (n=35)			500 mg QD (n=36)			Total (N=71)		
n (%)	Grade 1	Grade 2	Grade 3/4[a]	Grade 1	Grade 2	Grade 3/4[b]	Grade 1	Grade 2	Grade 3/4
Any TRAE	13 (37)	13 (37)	2 (6)	11 (31)	9 (25)	3 (8)	24 (34)	22 (31)	5 (7)
Fatigue	8 (23)	6 (17)	0	7 (19)	2 (6)	1 (3)	15 (21)	8 (11)	1 (1)
Nausea	2 (6)	3 (9)	0	6 (17)	1 (3)	0	8 (11)	4 (6)	0
Arthralgia	4 (11)	0	0	5 (14)	0	0	9 (13)	0	0
Hot flush	6 (17)	0	0	1 (3)	0	0	7 (10)	0	0
AST increased	3 (9)	1 (3)	0	2 (6)	1 (3)	0	5 (7)	2 (3)	0

[a]Grade 3/4 TRAEs in the 200-mg QD cohort were grade 3 QT prolonged (n=1; same TEAE that led to discontinuation as shown in the prior slide) and grade 3 thrombocytopenia and grade 4 hyperbilirubinemia (n=1)
[b]Grade 3/4 TRAEs in the 500-mg QD cohort were grade 3 fatigue, decreased appetite, and neutropenia (n=1 each)
AST=aspartate aminotransferase; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

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Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; QD=once daily

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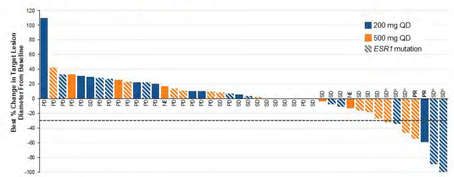
Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks
CBR=clinical benefit rate; QD=once daily

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Tumor Response[a] (VERITAC)



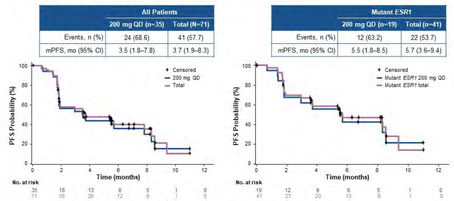
[a]Includes patients with measurable disease (n=44); 1 patient with measurable disease at baseline and PD as best overall response was excluded due to lack of complete set of target lesion measurements on-study
[b]Patient had an unconfirmed, partial response
ESR1=estrogen receptor 1 gene; NE=not evaluable due to missing data for best overall response; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease

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Progression-Free Survival[a] (VERITAC)

All Patients	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)

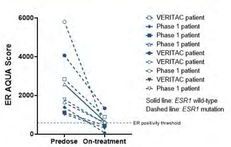
Mutant *ESR1*	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



[a]Limited follow-up in 200-mg QD cohort led to ≥50% of patients censored for PFS (curve not shown)
ESR1=estrogen receptor 1 gene; mPFS=median progression-free survival; PFS=progression-free survival; QD=once daily

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ER Degradation[a] With 200 mg QD ARV-471 (Phase 1/VERITAC)



- Median ER degradation was 69% (range: 28%–95%)
- Mean ER degradation was 71%

[a]ER immunoreactivity analyzed by QIF using the AQUA method, and ER positivity threshold derived by examining AQUA scores and visually inspecting all samples in the dataset to determine a cut point for ER positivity; *ESR1* mutation status determined from tumor biopsy (n=7) or circulating tumor DNA (n=8)
AQUA=multiplexed quantitative analysis; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; QD=once daily; QIF=quantitative immunofluorescence

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Conclusions

- ARV-471 showed clinical activity in the VERITAC expansion cohorts of heavily pretreated patients (4 median prior regimens, 100% with prior CDK4/6 inhibitors, and 79% with prior fulvestrant) with ER+/HER2- advanced breast cancer
  - CBR was 37.1% and 38.9% in the 200- and 500-mg QD cohorts, respectively
  - Clinical benefit was also observed in the *ESR1* mutation subgroup (CBR of 47.4% and 54.5% in the 200- and 500-mg QD cohorts, respectively)
- ARV-471 had a manageable AE profile; most AEs were grade 1/2
- ARV-471 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy, favorable tolerability, and robust ER degradation

AE=adverse event; CBR=clinical benefit rate; CDK=cyclin-dependent kinase; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; QD=once daily

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Phase 3 VERITAC-2 Trial

Key eligibility criteria
- Women or men aged ≥18 years
- Confirmed ER+/HER2- advanced breast cancer
- 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy
- ≤1 additional endocrine therapy
- Most recent endocrine treatment given for ≥6 months prior to disease progression
- No prior fulvestrant
- No prior chemotherapy for locally advanced/metastatic disease
- Radiological progression during or after the last line of therapy

RANDOMIZE 1:1

Treatment (N=560)

ARV-471 200 mg orally once daily

Fulvestrant 500 mg intramuscularly days 1 and 15 of cycle 1 and day 1 of subsequent cycles

Stratification factors
- *ESR1* mutant (yes vs no)
- Visceral disease (yes vs no)

Primary endpoint
- PFS by BICR in
  - ITT population
  - *ESR1* mutant population

Secondary endpoints include:
- OS, ORR, DOR, and CBR[a]
- AEs
- QoL measurements

[a]Rate of confirmed complete response or partial response or stable disease ≥24 weeks

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Thank You

