UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 8-K

Current Report Pursuant
to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event Reported): **June 18, 2019**

THERAVANCE BIOPHARMA, INC.

(Exact Name of Registrant as Specified in its Charter)

Cayman Islands	**001-36033**	**Not Applicable**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

PO Box 309
Ugland House, South Church Street
George Town, Grand Cayman, Cayman Islands KY1-1104
(650) 808-6000
(Addresses, including zip code, and telephone numbers, including area code, of principal executive offices)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Ordinary Share $0.00001 Par Value	TBPH	NASDAQ Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company o

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. o

Item 7.01. Regulation FD Disclosure.

On June 18, 2019, Theravance Biopharma presented new data from its Phase 2 clinical trial of ampreloxetine (TD-9855) in patients with neurogenic orthostatic hypotension (nOH) in a poster presentation at the 2019 International Association of Parkinsonism and Related Disorders (IAPRD) World Congress. The poster is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

The information in this Item 7.01 and in Item 9.01 of this Current Report on Form 8-K, including Exhibit 99.1, is being furnished and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Securities Exchange Act of 1934"), or otherwise subject to the liabilities of that Section, nor shall it be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

99.1	Poster entitled Efficacy, Durability, and Safety of Ampreloxetine, a Norepinephrine Reuptake Inhibitor, Given Once-Daily to Treat Neurogenic Orthostatic Hypotension (nOH) in Subjects With Primary Autonomic Failure

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

THERAVANCE BIOPHARMA, INC.

Date: June 18, 2019

By: /s/ Bradford J. Shafer
Bradford J. Shafer
Executive Vice President, General Counsel and Secretary

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Efficacy, Durability, and Safety of Ampreloxetine, a Norepinephrine Reuptake Inhibitor, Given Once-Daily to Treat Neurogenic Orthostatic Hypotension (nOH) in Subjects With Primary Autonomic Failure

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Background

- Neurogenic orthostatic hypotension (nOH) is due to failure of the autonomic nervous system to increase norepinephrine (NE) and to maintain blood pressure (BP) adequately in the upright position. nOH is common to all types of primary autonomic failure (eg, Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF])[1]
- Orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure (SBP) of ≥20 mmHg or diastolic blood pressure (DBP) of ≥10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table[2]
- Resultant cerebral hypoperfusion causes symptoms of dizziness, lightheadedness, generalized weakness, nausea, blurred vision, fatigue, headaches, and loss of consciousness/syncope, with reduction in quality of life, increase in falls and hospitalizations[1]
- Drugs that inhibit the reuptake of NE (NE reuptake inhibitors [NRIs]) could augment tonically released NE at the vascular synaptic neuroeffector junction, resulting in increase in BP in the upright position, and reduction in symptoms of nOH[1]
- Ampreloxetine (TD-9855) is a novel, selective NRI that is being investigated for the treatment of nOH[3]
- In a phase 2, multicenter study, the efficacy, durability, and safety of once-daily oral ampreloxetine were evaluated for the treatment of nOH in subjects with primary autonomic failure

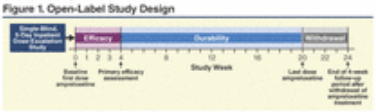
Objectives

- To determine the efficacy and durability on symptom improvement with ampreloxetine in the treatment of nOH in subjects with primary autonomic failure (using Question 1 of the Orthostatic Hypotension Symptom Assessment [OHSA #1; dizziness, lightheadedness, feeling faint, or feeling like you might black out])
- To characterize the efficacy and durability of the pressor effect of ampreloxetine in the treatment of nOH in subjects with primary autonomic failure
- To evaluate the safety and tolerability of ampreloxetine in the treatment of nOH in subjects with primary autonomic failure

Methods

Study Design

Figure 1. Open-Label Study Design



- **Single-blind, 5-day inpatient dose-escalation study** Day 1, placebo; Day 2, ampreloxetine 2.5 mg; Day 3, 5 mg; Day 4, 10 mg; Day 5, 20 mg
  - A subset of 10 patients from the dose-escalation study received single-dose ampreloxetine versus placebo to assess pressor effect (results reported elsewhere)
- **Open-label, outpatient study:** Subjects with a documented pressor response in the dose-escalation study were eligible to enroll in the open-label study, and receive once-daily ampreloxetine for up to 5 months (20 weeks) with a 4-week follow-up period after ampreloxetine treatment withdrawal
  - On Day 1 of the open-label study, subjects were given 50% of the highest tolerated dose of ampreloxetine from the dose-escalation study for that subject or a lower dose
  - Ampreloxetine dosing was flexible throughout the open-label study and could be increased or decreased based on potential benefit and safety/tolerability (maximum dose, 20 mg)
  - Efficacy was assessed from the day of the first dose of ampreloxetine to the end of Week 4; durability of efficacy was assessed from the end of Week 4 to the end of Week 20; and effect of withdrawal of ampreloxetine treatment was assessed from the end of Week 20 to the end of Week 24.
- Only results of the open-label study and 4-week follow up period after withdrawal of ampreloxetine treatment are presented

Study Criteria

Key Inclusion Criteria
- Male or female at least 40 years of age
- Diagnosed with symptomatic nOH due to: PD, MSA, or PAF
- Diagnostic criteria for moderate-to-severe OH (eg, ≥30 mmHg drop in SBP within 5 minutes of standing, associated with symptoms of dizziness, lightheadedness, or fainting when standing)
- Absence of other identifiable causes of autonomic neuropathy
- Subjects with a documented pressor response in the dose-escalation study were eligible to enter the 20-week, open-label ampreloxetine study

Key Exclusion Criteria
- Systemic illnesses known to produce autonomic neuropathy (eg, diabetes mellitus)
- Known intolerance to other NRIs or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Pre-existing sustained hypertension (sitting BP ≥150/100 mmHg)
- Concomitant vasoconstrictors, antihypertensive medications, or monoamine oxidase inhibitors (fludrocortisone was permitted but limited to 0.1 mg daily)
- Major cardiovascular or cerebrovascular event in the past 6 months

BP, blood pressure; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; NRI, norepinephrine reuptake inhibitor; OH, orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson's disease; SBP, systolic blood pressure.

Key Efficacy Measures

Orthostatic Hypotension Questionnaire (OHQ)

Orthostatic Hypotension Symptom Assessment (OHSA)
6 items rated 0 (none)–10 (worst possible) symptoms); 7-week recall
1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out (OHSA #1)
2. Problems with vision
3. Weakness
4. Fatigue
5. Trouble concentrating
6. Headneck discomfort

Orthostatic Hypotension Daily Activity Scale (OHDAS)
4 items 0 (no interference)–10 (complete interference); 7-week recall
1. Activities that require standing for a short time
2. Activities that require standing for a long time
3. Activities that require walking for a short time
4. Activities that require walking for a long time

Orthostatic Standing Test
SBP/DBP/HR
- Supine 5, 10 minutes (torso and head-elevated 30° from horizontal)
- Seated 5, 10 minutes
- Standing 1, 3, 5, 10 minutes
- Total duration of standing

BP, blood pressure; DBP, diastolic BP; HR, heart rate; OHSA #1, OHSA Question 1; SAE, serious adverse event; SBP, systolic BP.

Key Efficacy and Safety Endpoints

Primary Efficacy
- Mean change from baseline to end of Week 4 in OHSA #1 score

Secondary Efficacy
(all timepoints of open-label treatment period [to end of Week 20] and follow-up period after ampreloxetine treatment withdrawal [Weeks 22 and 24])
- Mean change from baseline in OHSA #1 score
- Mean change from baseline in OHSA, OHDAS, and OHQ composite scores (OHQ composite score, mean of OHSA and OHDAS composite scores)
- Mean change from baseline in duration of standing
- Mean change from baseline in SBP at 1, 3, 5, and 10 minutes post-standing

Safety
- Treatment-emergent adverse events (TEAEs, %)
- Serious adverse events (SAEs, %)
- Vital signs (BP, HR)
- ECG
- Laboratory evaluations

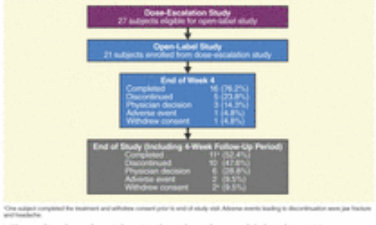
BP, blood pressure; ECG, electrocardiogram; HR, heart rate; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHQ, Orthostatic Hypotension Questionnaire; OHSA, Orthostatic Hypotension Symptom Assessment; OHSA #1, OHSA Question 1; SBP, systolic BP.

Statistical Analysis

- Descriptive summary of OHSA #1, OHSA, OHDAS, and OHQ scores are presented by timepoint
  - No imputation for missing values was done

Results

Figure 2. Subject Disposition



*One subject completed the treatment and withdrew consent prior to end of study visit. Adverse events leading to discontinuation were jaw fracture and headache.

- The median dose of ampreloxetine throughout the open-label study was 10 mg

Table 1. Demographics and Subject Characteristics

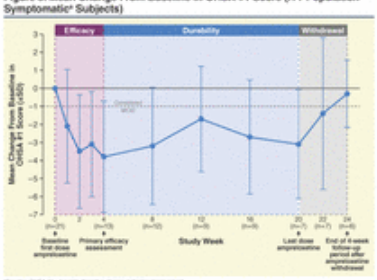
Characteristics	Total (N=21)
Age, years, mean (SD)	64.1 (7.91)
Sex, male, n (%)	12 (57.1%)
Race, white, n (%)	18 (85.7%)
BMI, kg/m², mean (SD)	26.4 (4.67)
MSA; PAF; PD; n (%)	12 (57.1%); 4 (19.0%); 5 (23.8%)
Symptomatic (OHSA #1 >4 pts) at baseline, n (%)[a]	17 (81.0%)
OHSA Question #1, pts, mean (SD) (min, max)	6.6 (3.12) (0, 10)
OHSA Composite Score, pts, mean (SD) (min, max)	4.3 (2.62) (0, 8)
OHDAS Composite Score, pts, mean (SD) (min, max)	6.7 (2.73) (0.5, 10)
OHQ Composite Score, pts, mean (SD) (min, max)	5.5 (2.48) (0.3, 8.7)
Supine SBP, mmHg, mean (SD) (min, max)	130.4 (24.42) (91, 186)
Seated SBP, mmHg, mean (SD) (min, max)	107.4 (24.69) (58, 147)
SBP at 3 mins standing, mmHg, mean (SD) (min, max)	94.9 (23.86) (59, 144)
Duration of standing, minutes, mean (SD) (min, max)	5.5 (4.36) (0, 10.7)

[a]Symptomatic MSA n=9, PAF n=4, PD n=4; non-symptomatic MSA n=3, PAF n=0, PD n=1.
BMI, body mass index; MSA, multiple system atrophy; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHQ, Orthostatic Hypotension Questionnaire; OHSA, Orthostatic Hypotension Symptom Assessment; OHSA #1, OHSA Question 1; PAF, pure autonomic failure; PD, Parkinson's disease; pts, points; SBP, systolic blood pressure; SD, standard deviation.

- Of the 21 subjects enrolled in the open-label study, demographics and subject characteristics generally reflected patient populations of MSA, PD, and PAF seen in clinical practice
  - Mean age 64 years, ~60% male, predominantly white, ~80% symptomatic, mean baseline OHSA #1 score 6.6, OH confirmed
  - The predominance of MSA subjects (~60%) reflected study enrollment from specialty autonomic centers where MSA is more predominant than in the general population

Efficacy

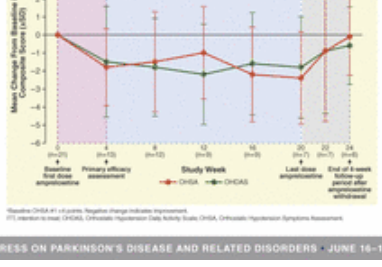
Figure 3. Mean Change From Baseline in OHSA #1 Score (ITT Population—Symptomatic[a] Subjects)



[a]Baseline OHSA #1 >4 points. Negative change indicates improvement.
ITT, intention-to-treat; MCID, minimal clinically important difference; OHSA #1, Orthostatic Hypotension Symptom Assessment Question 1; SE, standard deviation.

- In symptomatic subjects (baseline OHSA #1 score >4 points), mean change from baseline in OHSA #1 at the end of Week 4 was –3.8 points
  - Overall (symptomatic and non-symptomatic subjects), mean change from baseline at the end of Week 4 in OHSA #1 score was –2.4 points
  - Improvement in OHSA #1 from baseline was demonstrated as early as Week 1
- Mean change from baseline in OHSA #1 score was sustained in most patients from the end of Week 4 through the end of Week 20
  - Improvement in OHSA #1 score was –3.1 points at the end of Week 20
  - Only 1 subject had 1 point worsening in OHSA #1 score from baseline at the end of Week 20
    - At the end of the 4-week follow-up period after withdrawal of ampreloxetine treatment (end of Week 24), OHSA #1 score returned to baseline with mean change of –0.3 points
  - 1 subject had ≥1 point worsening in OHSA #1 score from baseline, and 5 subjects had ≥1 point worsening in OHSA #1 score from the end of Week 20

Figure 4. Mean Change From Baseline in OHSA and OHDAS Composite Scores (ITT Population—Symptomatic Subjects[a])



[a]Baseline OHSA #1 >4 points. Negative change indicates improvement.
ITT, intention-to-treat; OHDAS, Orthostatic Hypotension Daily Activity Scale; OHSA, Orthostatic Hypotension Symptoms Assessment.

- Similar trend as in OHSA #1 score was observed in composite scores for OHSA, OHDAS, and OHQ throughout the 20-week, open-label study, with worsening in all measures after ampreloxetine treatment withdrawal

Table 2. Standing SBP at 3 min (ITT Population)

Pre-Lunch Measurement at Each Study Visit		Efficacy: Day 1 (n=14)	Efficacy: Week 4 (n=12)	Durability: Week 12 (n=12)	Durability: Week 20 (n=10)	Follow-Up: Week 22 (n=8)	Follow-Up: Week 24 (n=7)
Change from baseline[a]	Mean (SD), mmHg	–	7.6 (22.37)	23.0 (19.21)	31.0 (44.03)	23.2 (43.64)	47.2 (52.18)
	≥80 mmHg, n (%)	9 (64.3%)	8 (66.7%)	9 (75.0%)	7 (70.0%)	7 (77.8%)	5 (71.4%)

[a]Baseline defined as pre-breakfast measurement on day of first dose.
ITT, intention-to-treat population; SBP, systolic blood pressure.

- Mean standing SBP increased at all visits and at all timepoints (1, 3, 5, and 10 mins; data at 3 mins shown)
  - At the end of Week 4, the mean increase in SBP from baseline at 3 mins standing was 7.6 mmHg
  - From the end of Week 4 to the end of Week 20, approximately 67–78% of subjects maintained ≥80 mmHg SBP at 3 mins standing (baseline, 64%)
  - The increase in mean standing SBP from baseline was higher at the end of Week 4 and after withdrawal of ampreloxetine treatment (after treatment withdrawal, subjects restarted their usual pressor agents; there was one outlier, who received both midodrine and droxidopa during the withdrawal period, with a 3-min standing SBP of 205 mmHg at the end of Week 24)

Safety

Table 3. Summary of Adverse Events (AEs)

Subjects With Any Treatment-Emergent Adverse Event	Total, n (%) (N=21)
Adverse Event	18 (85.7%)
Moderate or severe adverse event	13 (61.9%)
Adverse event related to study drug	8 (38.1%)
Moderate or severe adverse event related to study drug	6 (28.6%)
Serious adverse event[a]	5 (23.8%)
Serious adverse event related to study drug	0
Adverse events leading to permanent study drug discontinuation[b]	2 (9.5%)
Adverse events leading to temporary interruption/dose reduction of study drug[c]	7 (30.3%)
Death during study	0

Only TEAEs summarized: post first dose through 7 days post last dose. [a]Urinary tract infection (n=3), jaw fracture (n=1), meniscus injury (n=1), pain in extremity (n=1), all not related to study drug; [b]jaw fracture (n=1, serious AE, severe, not related to study drug), headache (n=1, moderate AE, related to study drug); [c]Protocol-mandated a temporary interruption (3 days) for dose reductions (n=7).
TEAE, treatment-emergent adverse event.

- Most subjects had an observed AE
  - From the first dose of ampreloxetine to the end of Week 4
    - 4 subjects had moderate, drug-related AEs; all others were mild
    - No subject had an SAE related to study drug
  - From the end of Week 4 to the end of Week 20 (7 days after the last dose of ampreloxetine was given)
    - 4 additional subjects with AE and moderate/severe AE
    - 1 additional SAE and AE leading to discontinuation

Table 4. Adverse Events Occurring More Than Twice in the Open-Label Study

≥2 Events	Total, n (%) (N=21)
Subjects With Any Treatment-Emergent Adverse Event	18 (85.7%)
Urinary tract infection	5 (23.8%)
Hypertension	4 (19.0%)
Headache	3 (14.3%)
Chest discomfort	2 (9.5%)
Dizziness	2 (9.5%)
Hematuria	2 (9.5%)
Laceration	2 (9.5%)
Musculoskeletal pain	2 (9.5%)
Nausea	2 (9.5%)
Syncope	2 (9.5%)

Only TEAEs summarized: post first dose through 7 days post last dose. Single event AEs by preferred term, included asthenia, back pain, blood pressure increased, bronchitis, cough, deep vein thrombosis, diplopia, dysgeusia, dysuria, ear canal injury, ear pain, erythema, fall, flushing, gastroesophageal reflux disease, hypothermia, jaw fracture, joint injury, localized infection, loss of consciousness, meniscus injury, muscular weakness, neck pain, orthostatic hypotension, pain in extremity, peripheral swelling, sleep apnea syndrome, solar lentigo, urinoxyprocine to stimul, urine analysis abnormal, vision blurred, vomiting.
TEAE, treatment-emergent adverse event.

- From the first dose of ampreloxetine to the end of Week 20, the most frequently reported AEs were urinary tract infection (23.8%), hypertension (19.0%), and headache (14.3%)
- A small increase in SBP from baseline was observed in Weeks 1, 2, and 3 (mean [SD] supine SBP, mmHg: baseline, 136.0 [23.91]; Week 1, 140.2 [24.66]; Week 2, 142.8 [23.15]; Week 3, 151.3 [24.77])
  - At the end of Week 4, no increase in supine SBP from baseline was observed (mean [SD] supine SBP, mmHg: 135.4 [17.02])
- No issues were observed in vital signs, ECG, or laboratory evaluations throughout the open-label study

Summary of Findings

- Of the 21 subjects who entered the open-label study, 12 (57%) completed 20 weeks of open-label ampreloxetine treatment
- Median dose of ampreloxetine was 10 mg throughout the study
- At the primary assessment timepoint (end of Week 4), mean improvement in OHSA #1 was –3.8 points in symptomatic subjects (–2.4 overall), which is greater than the mean improvement of –1 point considered a Minimal Clinically Important Difference
  - Mean improvement was sustained until the end of the open-label study (end of Week 20) and deteriorated after withdrawal of ampreloxetine treatment
- Ampreloxetine resulted in a mean increase in standing SBP at all visits and all timepoints during the open-label study
  - At the end of Week 4, the mean increase from baseline at 3 mins standing was >7 mmHg and ≥20 mmHg at subsequent assessment timepoints
- No safety concerns were identified during the 20-week, open-label study

Overall Conclusions

- In subjects with nOH and primary autonomic failure, ampreloxetine demonstrated clinically meaningful symptomatic improvement in OHSA #1, which was sustained for up to 5 months of treatment, and deteriorated after withdrawal of ampreloxetine treatment
- These improvements in symptoms of nOH were associated with increase in standing SBP
- Ampreloxetine was generally well-tolerated
- Once-daily oral ampreloxetine demonstrated symptomatic and objective efficacy, with durability over 20 weeks of treatment, and a favorable safety profile in the treatment of nOH in subjects with primary autonomic failure

References 1. Freeman R, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72. 2. Mtinder M, et al. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. J Neurol. 2013;260(9):2212-2218. 3. Hoban C, et al. Norepinephrine transporter blockade with atomoxetine reduces hypotension in patients with impaired autonomic function. Hypertension. 2007;50(3):47-53. 4. Hegde S et al. Preclinical cardiovascular sympathomimetic effects of TD-9855, a novel norepinephrine transporter (NET) inhibitor in development for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in patients with primary autonomic failure. 2018 International Congress of Parkinson's Disease and Movement Disorders. Abstract 1412.

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