
**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): **September 8, 2014**

THERAVANCE BIOPHARMA, INC.

(Exact Name of Registrant as Specified in its Charter)

Cayman Islands
(State or Other Jurisdiction of
Incorporation)

001-36033
(Commission File Number)

Not Applicable
(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):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
 - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
 - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
 - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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Item 7.01 Regulation FD Disclosure.

The information in this Current Report (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. The information in this Current Report (including Exhibit 99.1) shall not be incorporated by reference into any registration statement or other document pursuant to the Securities Act of 1933, as amended, except as shall be expressly set forth by specific reference in such filing.

On September 8, 2014 at the European Respiratory Society International Congress in Munich, Germany, Theravance Biopharma U.S., Inc. (the “Company”) presented pharmacokinetics data from Phase 2b Study 0091 with TD-4208 as a nebulized aqueous solution in patients with chronic obstructive pulmonary disease (COPD). TD-4208 is an investigational, once-daily inhaled nebulized muscarinic antagonist discovered by Theravance Biopharma for the treatment of a subset of COPD patients that the Company believes are underserved by current hand-held products. A copy of the poster is furnished as Exhibit 99.1 to this report and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

99.1 Repeated-Dose Pharmacokinetics of Once-Daily TD-4208, a Long-acting Muscarinic Receptor Antagonist (LAMA), in Subjects with COPD

SIGNATURE

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

THERAVANCE BIOPHARMA, INC.

Date: September 8, 2014

By: /s/ Renee D. Gala
Renee D. Gala
Senior Vice President, Finance

EXHIBIT INDEX

Exhibit No.	Description
99.1	Repeated-Dose Pharmacokinetics of Once-Daily TD-4208, a Long-acting Muscarinic Receptor Antagonist (LAMA), in Subjects with COPD

ERS International Congress 2014 September 6-10, 2014

Repeated-Dose Pharmacokinetics of Once-Daily TD-4208, a Long-acting Muscarinic Receptor Antagonist (LAMA), in Subjects with COPD

David L. Bourdet, Chris N. Barnes, Wayne Yates, Edmund J. Moran, Andrew J. Nicholls, and Brett Haumann

Theravance Biopharma US Inc., South San Francisco, CA USA

ABSTRACT

Introduction

TD-4208 is a lung-selective LAMA shown to have a long duration of action and minimal systemic antimuscarinic activity in subjects with COPD after single and repeated-dose, once-daily, inhaled administration. The current study evaluates the pharmacokinetics of nebulized TD-4208 and its major metabolite (THR-195518; 10-fold lower M3 receptor potency relative to TD-4208) in subjects with moderate to severe COPD.

Methods

Fifty-nine subjects with moderate to severe COPD were randomized in a double-blind, incomplete block 5-way crossover study. TD-4208 (22, 44, 88, 175, 350, 750 µg) or matching placebo was administered via an inhalation solution by PARI nebulizer in the morning of each day for 7 days followed by a 14-day washout between each treatment period.

Results

TD-4208 demonstrated rapid absorption (median t_{max} ~15 min) followed by a steep, bi-exponential decline resulting in low systemic plasma concentrations. Metabolic conversion to THR-195518 occurred rapidly and extensively. TD-4208 and THR-195518 demonstrated linear increases in plasma exposure with dose. The metabolite-to-parent ratio ranged from 3.3 to 9.7 on Day 7. TD-4208 and THR-195518 elimination profiles were similar and were characterized by a terminal elimination half-life ranging from 22.3 to 25.3 h. Accumulation of TD-4208 and THR-195518 in plasma was limited (< 1.6-fold) and steady-state was achieved by Day 7.

Conclusions

Low systemic exposures of TD-4208 and its major metabolite were observed after inhaled administration, consistent with the lack of systemic antimuscarinic activity. TD-4208 exhibits a predictable dose-dependent plasma pharmacokinetic profile indicative of reproducible nebulized delivery of TD-4208.

INTRODUCTION

- The Global Initiative for the Treatment of Obstructive Lung Disease (GOLD) recommends the use of long-acting muscarinic antagonist (LAMA) bronchodilators as first-line therapy for subjects with persistent COPD symptoms [1]
 - There are no once-daily nebulized bronchodilators currently available for those patients for whom nebulized therapy would be appropriate
 - TD-4208 is a novel, lung selective long-acting inhaled muscarinic antagonist that is being developed as a nebulized, once daily treatment for COPD
 - Nebulized TD-4208 (350 and 700 µg) demonstrated sustained bronchodilation over 24 hours after single [350 and 700 µg] and multiple [22 – 700 µg] doses in patients with COPD. All doses were generally well-tolerated and there were no serious adverse events related to study medication reported [2], [3], [4]
 - Single dose nebulized administration of TD-4208 (350 and 700 µg) resulted in low systemic plasma exposures of both TD-4208 and its major metabolite THR-195518 [3]
 - Systemic, anti-muscarinic side effects (e.g., dry mouth or heart rate increases) resulting from antagonism of extra-pulmonary muscarinic receptors have not been observed after single dose administration and were limited after multiple-dose treatment (dry mouth <1%) with TD-4208 [2], [4]
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OBJECTIVE

- To evaluate the pharmacokinetics of nebulized TD-4208 and its major metabolite, THRX-195518, after repeated-dose administration in patients with moderate to severe COPD after once daily administration

METHODS

STUDY DESIGN

- 59 subjects diagnosed with moderate to severe COPD were enrolled in a double-blind, multiple-dose, incomplete block 5-period crossover study
- TD-4208 doses of 22, 44, 88, 175, 350 µg, and placebo were administered once daily for 7 days using a PARI LC® Sprint nebulizer
- Washout of 14 days between each treatment period

PHARMACOKINETICS

- Plasma samples were collected in each period predose and at 0.25, 0.5, 1, 2, 3, 4, and 6 hours postdose on Day 1 of dosing. On Day 7, plasma samples were collected in each period predose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose.
- TD-4208 and its major metabolite, THRX-195518, were quantified using a validated liquid chromatography with tandem mass spectrometry method. The lower limit of quantification for TD-4208 and THRX-195518 was 5 pg/mL.
- Noncompartmental TD-4208 and THRX-195518 PK parameters were calculated using Phoenix WinNonlin (Version 6.1.2; Pharsight, Sunnyvale, CA)

RESULTS

Table 1: Subject Demographics

	Dose						
	Placebo	22 µg	44 µg	88 µg	175 µg	350 µg	700 µg
n	59	40	39	39	39	39	40
Age yrs mean (SD)	63.9 (6.85)	62.6 (6.71)	63.9 (6.62)	65.4 (7.01)	63.3 (7.46)	64.5 (6.46)	64.1 (6.62)
Sex M/F	56/44	55/45	54/46	59/41	56/44	59/41	53/47
Race: Caucasian (%)	100	100	100	100	100	100	100
BMI m.kg⁻² mean (SD)	28.8 (5.92)	29.4 (6.54)	27.9 (5.18)	29.0 (5.92)	29.0 (6.44)	28.6 (4.85)	28.7 (6.38)

Table 2: Pharmacokinetic Parameters of TD-4208 and THRX-195518 (Day 7)

	PK Parameter	Dose					
		22 µg	44 µg	88 µg	175 µg	350 µg	700 µg
TD-4208	C_{max} (ng/mL)	0.0125 ± 0.006	0.0224 ± 0.009	0.0526 ± 0.0214	0.144 ± 0.049	0.243 ± 0.104	0.577 ± 0.261
	t_{max} (hr)	0.233 (0.217, 0.417)	0.233 (0.200, 0.567)	0.233 (0.200, 0.350)	0.233 (0.200, 0.450)	0.233 (0.217, 1.08)	0.233 (0.200, 0.400)
	AUC_{0-t} (ng.hr/mL)	0.0256 ± 0.0168	0.0292 ± 0.040	0.0452 ± 0.0403	0.135 ± 0.099	0.375 ± 0.175	0.755 ± 0.319
	$t_{1/2}$ (hr)	NA	NA	NA	NA	25.1 ± 7.89	23.0 ± 7.05
THRX-195518	C_{max} (ng/mL)	0.0188 ± 0.009	0.0373 ± 0.022	0.0720 ± 0.0312	0.178 ± 0.088	0.400 ± 0.180	0.948 ± 0.515
	t_{max} (hr)	0.483 (0.217, 0.650)	0.483 (0.250, 0.667)	0.483 (0.217, 0.583)	0.483 (0.300, 0.633)	0.483 (0.233, 0.617)	0.483 (0.217, 0.617)
	AUC_{0-t} (ng.hr/mL)	0.0434 ± 0.0452	0.123 ± 0.108	0.276 ± 0.137	0.559 ± 0.263	1.18 ± 0.476	2.39 ± 1.18
	$t_{1/2}$ (hr)	NA	NA	25.3 ± 11.2	23.5 ± 7.09	24.4 ± 6.10	22.3 ± 7.74

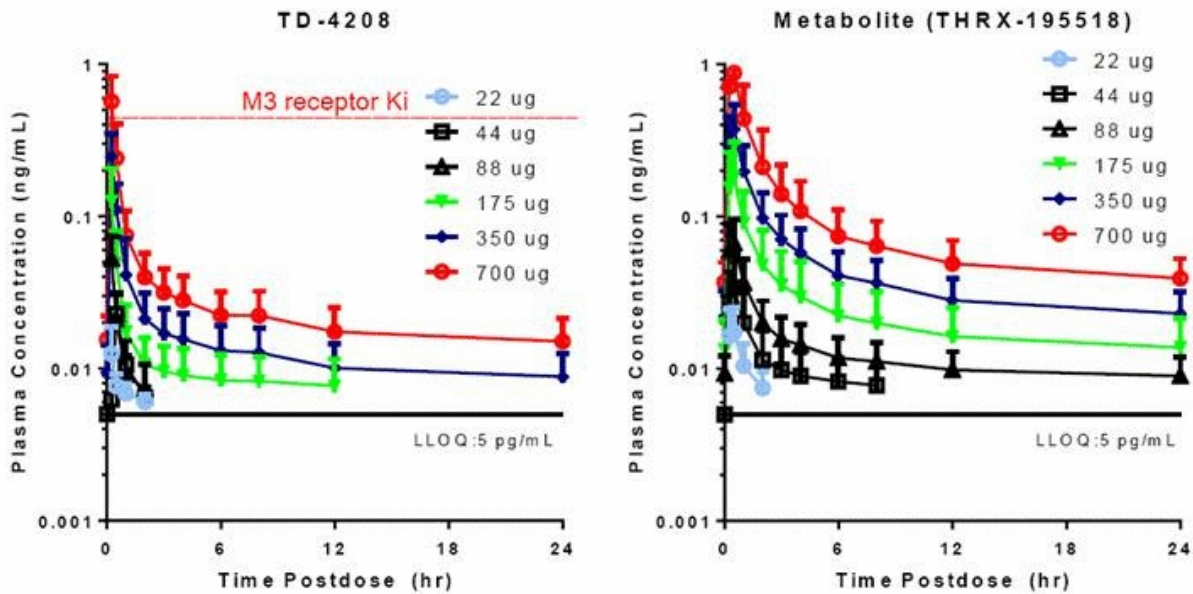
Mean values ± standard deviation

Median (min, max) presented for t_{max}

NA: Not applicable due to insufficient concentrations above the limit of quantification for determination of elimination $t_{1/2}$

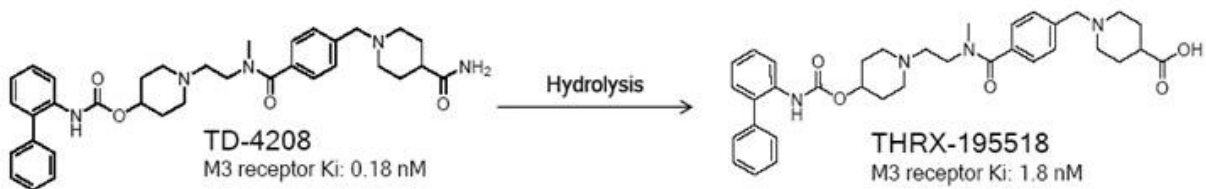
RESULTS

Figure 1: TD-4208 and THRX-195518 Plasma Pharmacokinetics (Day 7)



- Systemic TD-4208 and metabolite plasma concentrations are low and well below their respective M3 receptor K_i

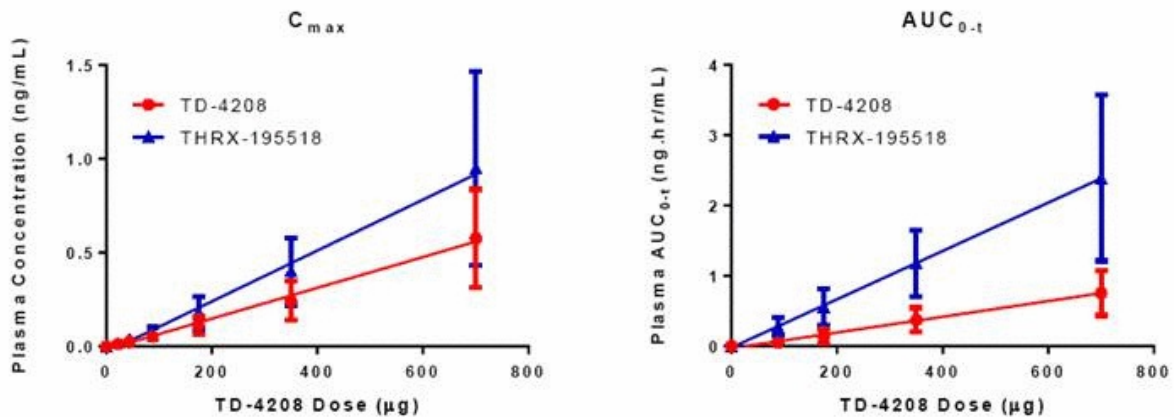
Table 3: Metabolic Conversion of TD-4208 to THRX-195518



Dose	Mean Fold Ratio of Metabolite to TD-4208 Systemic Exposure					
	22 µg	44 µg	88 µg	175 µg	350 µg	700 µg
C_{max} Ratio	1.7	1.8	1.5	1.7	1.9	1.7
AUC_{0-t} Ratio	NR	NR	9.7	5.6	3.7	3.3

NR: Not reported due to insufficient TD-4208 concentrations above the limit of quantification

Figure 2: TD-4208 and THRX-195518 Dose Proportionality (Day 7)



RESULTS

Table 4: Accumulation of TD-4208 and THRX-195518

Dose (µg)	Day 7:Day 1 C _{max} Ratio	Day 7:Day 1 AUC ₀₋₆ Ratio
22	1.1 / 1.1	0.9 / 1.2
44	1.2 / 1.1	1.0 / 1.3
88	1.2 / 1.1	1.5 / 1.3
175	1.3 / 1.1	1.6 / 1.3
350	1.1 / 1.0	1.4 / 1.2
700	1.1 / 1.0	1.3 / 1.2

Data presented as TD-4208 / THRX-195518

- Limited accumulation (< 1.6-fold) and steady-state achieved by Day 7

Safety and Tolerability Profile

- TD-4208 was generally well tolerated with rates of adverse events comparable to placebo. Headache was the most frequently reported adverse event [4]
- Limited reports of dry mouth (< 1%; TD-4208-treated) and no clinically significant changes in heart rate

CONCLUSIONS

- TD-4208 exhibits a predictable, dose-dependent plasma pharmacokinetic profile indicative of reproducible nebulized delivery of TD-4208
- TD-4208 is rapidly and extensively metabolized to a major metabolite that exhibits significantly lower affinity for M3 receptors
- TD-4208 and its major metabolite exhibit dose-proportional PK with no significant accumulation upon repeated dosing and achievement of steady-state within 7 days
- TD-4208 was generally well tolerated and did not result in significant systemic anticholinergic effects following repeat-dose administration
- TD-4208 pharmacokinetics following once daily nebulized administration demonstrate an optimal profile consistent with limited systemic TD-4208 exposure

REFERENCES

- (1) <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>
 - (2) A Randomized, Crossover Study to Examine the Pharmacodynamics and Safety of a New Antimuscarinic TD-4208 in Patients with COPD. Potgieter P.D., et al., European Respiratory Society 2012, Poster Abstract 2878.
 - (3) Single-Dose Pharmacokinetics of TD-4208, A Novel Long-Acting Muscarinic Antagonist, in Patients with COPD. Baldwin M., et al., American Thoracic Society Meeting 2013, Poster Abstract A1496.
 - (4) A Randomized, Crossover, 7-Day Study of Once-daily TD-4208, a Long-Acting Muscarinic Antagonist (LAMA) in Subjects with COPD. Nicholls A., et al., American Thoracic Society Meeting 2014, Poster Abstract A130
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