UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K/A
(Amendment No. 1)

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the Fiscal Year Ended December 31, 2020

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
Commission File Number: 001-38634

REVIVA PHARMACEUTICALS HOLDINGS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**85-4306526**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)
19925 Stevens Creek Blvd., Suite 100 Cupertino, CA 95014 **(Address of principal executive offices)**	95014 **(Zip code)**

(408) 501-8881
(Registrant's telephone number, including area code)

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

Title of Each Class:	**Trading Symbol**	**Name of Each Exchange on which Registered**
Common Stock, par value $0.0001 per share	RVPH	The Nasdaq Capital Market
Warrants to purchase one share of Common Stock	RVPHW	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☒	Smaller reporting company ☒ Emerging growth company ☒

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. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the closing price of a share of the registrant's common stock on June 30, 2020 as reported by the Nasdaq Global Market on such date, was approximately $33.5 million. This calculation does not reflect a determination that certain persons are affiliates of the registrant for any other purpose.

As of March 11, 2021 the number of outstanding shares of the registrant's common stock, par value $0.0001 per share, was 9,231,737.

DOCUMENTS INCORPORATED BY REFERENCE

None.

EXPLANATORY NOTE

This Amendment No. 1 on Form 10-K/A hereby amends the Registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 (the “Annual Report”), which the Registrant filed with the Securities and Exchange Commission on March 22, 2021. This amendment is being filed solely to correct the image under the heading “Company Overview” and the image under the heading “Figure 3” included in Part I – Item 1 of the Annual Report. In addition, pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), we are including with this Amendment No. 1 certain currently dated certifications. Because no financial statements have been included in this Amendment No. 1 and this Amendment No. 1 does not contain or amend any disclosure with respect to Items 307 and 308 of Regulation S-K, paragraphs 3, 4 and 5 of the certifications have been omitted. We are not including the certifications under Section 906 of the Sarbanes-Oxley Act of 2002, because no financial statements are being filed with this Amendment No. 1.

This Amendment No. 1 does not reflect events occurring after the March 22, 2021 filing of the Annual Report and, except as described above, does not affect any other parts of, or exhibits to, the Annual Report, and those unaffected parts or exhibits are not included in this Amendment. Except as described above, no other portion of the Annual Report for the fiscal year ended December 31, 2020 is amended hereby, and the Annual Report continues to speak as of the date of the original filing of the Annual Report. No modification or update is otherwise being made to any other disclosure or exhibits to such Annual Report. Accordingly, this Amendment No. 1 should be read in conjunction with such Annual Report and the Registrant's filings made with the Securities and Exchange Commission subsequent to the date of such Annual Report.

PART I

ITEM 1. BUSINESS

All references in this report to "Reviva," the "Company," "we," "us," or "our" mean Reviva Pharmaceuticals Holdings, Inc. and its subsidiaries unless we state otherwise or the context otherwise indicates.

Company Overview

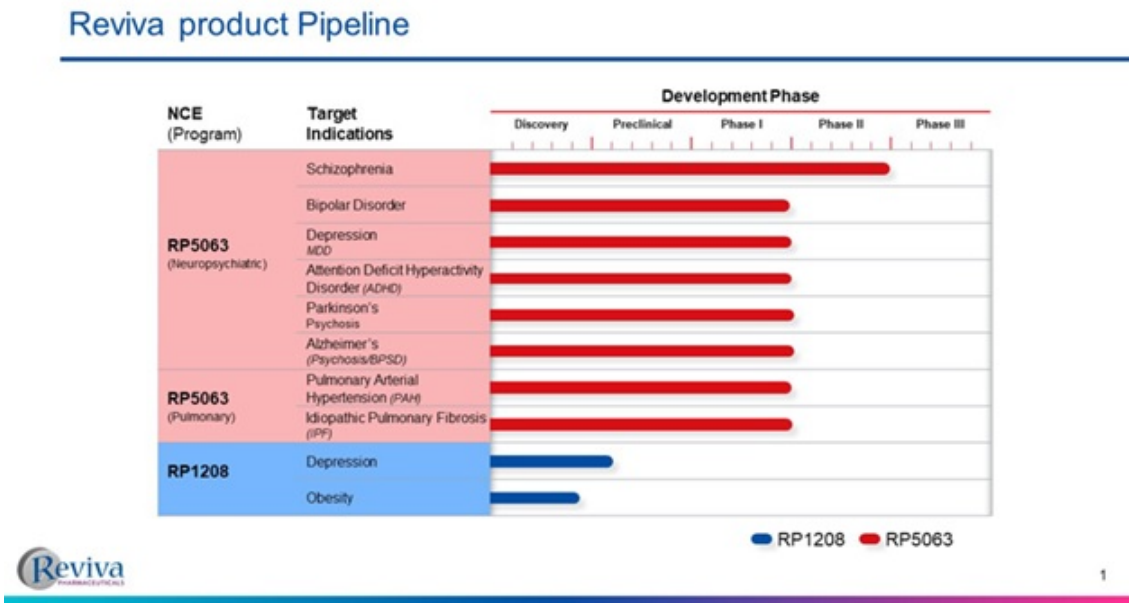
We are a clinical-stage biopharmaceutical company that discovers, develops and seeks to commercialize next-generation therapeutics for diseases representing significant unmet medical needs and burden to society, patients, and their families. Our current pipeline focuses on the central nervous system, respiratory, and metabolic diseases. We use a chemical genomics driven technology platform and proprietary chemistry to develop new medicines. Our pipeline currently has two drug candidates, RP5063 (Brilaroxazine) and RP1208. Both are new chemical entities discovered in-house. We have been granted composition of matter patents for both RP5063 and R1208 in the United States (U.S.), Europe, and several other countries.

Our lead drug candidate, RP5063, is ready for continued clinical development for multiple neuropsychiatric indications. These include schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), behavioral and psychotic symptoms, dementia or Alzheimer's disease (BPSD), Parkinson's disease psychosis (PDP), and attention deficit hyperactivity disorder (ADHD). Furthermore, RP5063 is also ready for clinical development for two respiratory indications — pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF). The U.S. Food and Drug Administration (FDA) has granted Orphan Drug designation to RP5063 for the treatment of PAH in November 2016 and IPF in April 2018.

Our primary focus is to complete the clinical development of RP5063 for the treatment of acute and maintenance schizophrenia.

Subject to the receipt of additional financing, we may also continue the clinical development of RP5063 for the treatment of BD, MDD, BPSD, PDP, ADHD, PAH and IPF. Moreover, subject to the receipt of additional financing, we may also advance the development of our second drug candidate, RP1208, for the treatment of depression and obesity.

The development status of the Reviva product pipeline is presented below:



Impact of COVID-19

In response to the spread of COVID-19, we have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees and community, including temporarily requiring employees to work remotely and suspending all non-essential travel for our employees.

As a result of the COVID-19 pandemic, we may experience disruptions that could adversely impact our business. The COVID-19 pandemic may negatively affect clinical site initiation, patient recruitment and enrollment, patient dosing, distribution of drug to clinical sites and clinical trial monitoring for our clinical trials. The COVID-19 pandemic may also negatively affect the operations of the third-party contract research organizations that we intend to rely upon to assist us in conducting our clinical trials and the contract manufacturers who manufacture our drug candidates.

We are continuing to assess the potential impact of the COVID-19 pandemic on our business and operations. For additional information on the various risks posed by the COVID-19 pandemic, refer to Part I—Item 1A—Risk Factors of this Annual Report on Form 10-K.

Business Combination and Domestication

On December 14, 2020, our predecessor company, formerly known as Tenzing Acquisition Corp., a British Virgin Islands exempted company ("Tenzing"), and Reviva Pharmaceuticals, Inc., a Delaware corporation (together with its consolidated subsidiaries, "Old Reviva"), consummated the transactions (the "Business Combination") contemplated by the Agreement and Plan of Merger, dated as of July 20, 2020 (as amended, the "Merger Agreement"), by and among Tenzing, Tenzing Merger Subsidiary Inc., a Delaware corporation and wholly-owned subsidiary of Tenzing ("Merger Sub"), Old Reviva, and the other parties thereto. Pursuant to the Merger Agreement, Merger Sub merged with and into Old Reviva, with Old Reviva surviving as our wholly owned subsidiary. We refer to this transaction as the Business Combination. In connection with and one day prior to the completion of the Business Combination, Tenzing re-domiciled out of the British Virgin Islands and continued as a company incorporated in the State of Delaware, and changed its name to Reviva Pharmaceuticals Holdings, Inc. Prior to the completion of the Business Combination, the Company was a shell company. Following the Business Combination, the business of Old Reviva is the business of the Company.

Old Reviva was incorporated in the state of Delaware on May 1, 2006 and its subsidiary, Reviva Pharmaceuticals India Pvt. Ltd., was incorporated on December 23, 2014. Tenzing was formed pursuant to the laws of the British Virgin Islands on March 20, 2018.

About RP5063

Our RP5063 drug candidate is a novel, multimodal serotonin (5HT), dopamine (DA), and nicotinic receptors modulator. Our compound displays a high affinity for 5HT2A/2B//7 and DA2/3/4 receptors and a moderate affinity for nicotinic (nACh- α4β2) receptors (Rajagopal et al., 2017). The binding affinity of RP5063 to dopamine and serotonin sub-receptors in radioligand binding assays is the following (Ki, nM): dopamine D2S (0.28), D2L (0.45), D3 (3.7), and D4.4 (6.0); Serotonin 5HT1A (1.5), 5-HT2A (2.5), 5-HT2B (0.19), 5-HT2C (39), 5-HT6 (51), and 5-HT7 (2.7). RP5063 displayed moderate binding affinity to nicotine- nAChR, α4β2 (Ki = 36.3 nM).

Radioactive and non-radioactive studies in rat and dog show that the gastrointestinal tract completely absorbs orally administered RP5063-related material, with acceptable bioavailability in rat (22%) and dog (85%) animal models. Exposure to RP5063 increased in a dose-dependent manner. Once absorbed, RP5063 rapidly and extensively distributes into various tissues. Noteworthy is the brain with a brain:plasma ratio of ~3.5, despite high plasma protein binding (>99%) characteristics. Rat and dog hepatocytes rapidly metabolize RP5063; however, human hepatocytes metabolize this compound slower. This finding suggests that this compound will show a low clearance in humans. We believe the risk of RP5063 inducing or inhibiting cytochrome P450 (CYP) at anticipated pharmacologically relevant concentrations in humans is low. Hepatic metabolism via the cytochrome P450s is the primary route of elimination with CYP3A4/5, undertaking most of the metabolism (69%), a small contribution from CYP2D6 (17%) and minor contributions by other cytochromes including extra-hepatic CYP2J2. Two metabolites in human plasma and urine display no pharmacological activity. We believe there is a low risk of inhibition and induction of human cytochromes by RP5063 at expected plasma concentrations clinically.

A full battery of regulatory compliant toxicology and safety pharmacology studies are complete. We believe the results from these tests support the chronic administration of RP5063 in clinical trials. We believe the completed safety pharmacology and toxicology studies report several significant safety findings. These include (1) RP5063 is neither genotoxic nor clastogenic, (2) does not affect the function of cardiovascular (Q.T. or blood pressure) or respiratory systems, and (3) is not phototoxic in the 3T3 *in vitro* assay.

DEVELOPMENT OF RP5063 FOR NEUROPSYCHIATRIC DISEASES

RP5063 Development for Schizophrenia

Schizophrenia is a complex, chronic, and debilitating psychiatric syndrome. As presented in 2020, the Schizophrenia and Related Disorders Alliance of America ("SARDAA") estimates schizophrenia can be found in approximately 1.1% of the world's population, regardless of racial, ethnic or economic background, with approximately 3.5 million people diagnosed in the U.S. It is a complex disease involving a mix of positive and negative symptoms, along with mood disorder and cognitive impairment. While the pathology of schizophrenia is not yet fully understood, scientists implicate the dysregulation or disruption of both dopaminergic and serotonergic functions in the development of this condition. The dysregulation of serotonergic function in the brain also contributes to schizoaffective disorders, such as bipolar, major depression, and mania. Thus, the optimal treatment for schizophrenia may not rely solely on dopamine blockade. Hypothetically, it may also include the stabilization of both the dopaminergic and serotonergic systems in the brain.

Current pharmacologic treatment involves antipsychotic therapy. There are two types of antipsychotics, typical and atypical agents. Tolerability issues (e.g., neuroleptic side effects with typical agents; metabolic and cardiovascular problems with atypical medications) limit compliance and the effectiveness of both classes of medications. Hence, compliance is poor. We estimate, pursuant to a review of multiple peer reviewed articles published between 1998 and 2015, discontinuation rates of 30 – 50% in the short-term management of acute patients and 42 – 74% in the long-term treatment. Also, both classes of antipsychotics fail to provide a broad spectrum of efficacy across the various symptom classes. Thus, we believe the optimal treatment of schizophrenia requires new compounds with broader efficacy and better safety profiles.

All approved antipsychotics in the last two decades block dopamine (D) and serotonin (5HT) receptors, particularly D2 and 5HT2A receptors. RP5063 possesses a potent binding and functional activity for both D2 and 5HT2A receptors. We believe these targets are critical for treating schizophrenia besides having potent activities for D4, 5HT1A, 5HT2B and 5HT7 receptors implicated as targets for comorbid conditions associated with schizophrenia such as negative symptoms, mood symptoms (e.g., depression, anxiety) and cognitive impairment. RP5063 also exerts a moderate activity for nicotinic (nAChR, $\alpha 4\beta 2$) receptor, implicated as a target for comorbid conditions in schizophrenia depression and cognitive impairment.

Preclinical studies define the activity, pharmacokinetic, and safety profiles of RP5063 in animals. Rodent models of pharmacologic-induced behaviors associated with schizophrenia have demonstrated that RP5063 limits both psychosis and cognitive symptoms.

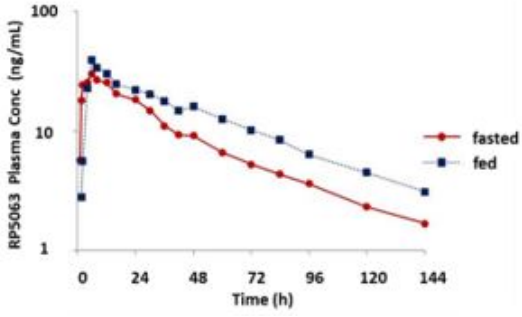
We have completed a clinical Phase 1a study in healthy subjects, a Phase 1b study in stable schizophrenia patients, and a Phase 2 study in acute schizophrenia and schizoaffective patients. We are currently focusing our efforts on initiating a pivotal Phase 3 study in acute schizophrenia.

RP5063 Phase 1 Clinical Study in Stable Schizophrenia

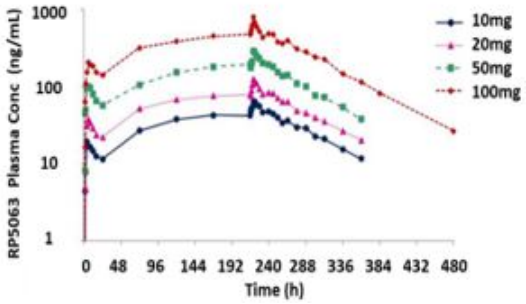
Phase 1a and 1b studies have defined the initial clinical experience with RP5063. The first-in-human study Phase 1a involved a single-dose ascending study of 24 individuals. Initially, it examined patient cohorts receiving individual doses of 10 and 15 mg fasting, followed by a food-effect cohort (food versus fasting, crossover), with a 15 mg dose (Figure 1a). The multiple-dose study Phase 1b study examined multiple doses of 10, 20, 50, and 100 mg given with food over ten days in 32 randomized patients (Figure 1b). Both studies characterized the initial safety and pharmacokinetic profiles in normal healthy volunteers (Caucasian or Japanese men, 20 – 45 years) and stable patients with schizophrenia (18 – 65 years, chronic, all types with Total Positive and Negative Syndrome Scale (PANSS) score $\leq$ 90 points). RP5063 displayed a dose-dependent Cmax at 4 to 6 h, a linear dose proportionality for both Cmax and AUC, and a half-life between 40 and 71 h. In the single-dose study, food slightly increased the extent of drug absorption. In the multiple-dose study, drug concentrations approached steady-state after 120 h (5 days) of daily dosing. Pooled data in the single-dose study indicate that the pharmacokinetic profile appeared to be comparable between Caucasians and Japanese. Study data have suggested a straightforward pharmacokinetic profile for RP5063 that we believe supports once-daily dosing as an orally administered agent for Phase 2 and Phase 3 evaluation.

Figure 1. RP5063 Phase 1 Clinical Studies, Pharmacokinetics in Healthy Subjects and Stable Schizophrenia Patients

1A. Single-dose pharmacokinetics profile of RP5063 (15 mg) in healthy subjects



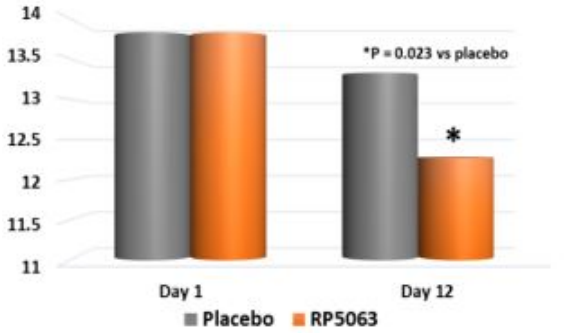
1B. Multiple-dose pharmacokinetics profile of RP5063 (10, 20, 50 or 100 mg/day) in stable schizophrenia patients for 10 days



As the multiple-dose study used patients with stable schizophrenia, the data from this study provided an early assessment of the pharmacodynamics behavior and activity of RP5063 in this population. Notable were the secondary analysis to explore the Positive and Negative Syndrome Scale ("PANSS") observations to evaluate the effect of RP5063 on positive symptoms and Trails A and B tests to assess the effect on cognition. Pooled analysis of patients' PANSS scores ≥50 at baseline showed a statistically significant reduction in positive symptoms subscale scores (Figure 2a). Furthermore, study analysis identified favorable trends in reducing PANSS total scores from baseline and in the General Psychopathology Score from baseline vs. placebo. Similarly, a pooled analysis of Trials A and B scores from baseline to day 16 showed favorable trends in the improvement of cognition in the RP5063 treatment groups vs. placebo.

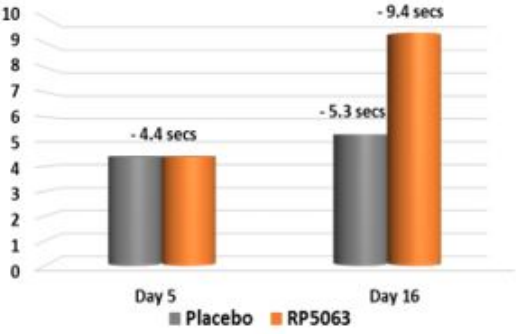
Figure 2. RP5063 Efficacy in the Phase 1B Clinical Study in Stable Schizophrenia Patients

2A. A decrease in positive symptoms in stable schizophrenia patients (PANSS positive data)



- **PANSS Baseline scores for sub-analysis: ≥50**
- **Pooled data of RP5063 (10-100mg/day), N=19**

2B. An improvement in cognition in stable schizophrenia patients (Trails A and B data)



- **PANSS Baseline scores: 39-69**
- **Pooled data of RP5063 (10-100mg/day), N=32**

The Phase 1b study in stable schizophrenia patients found that RP5063 appears to be generally well-tolerated at doses ranging from 10 – 100 mg administered over ten days. Most adverse events were mild and occurred at the higher doses 50mg and 100 mg. Notable was the lack of clinically significant changes in glucose or prolactin levels, lipid profiles, and weight or ECG findings. A pharmacodynamic analysis of the multiple-dose Phase 1b study data provided early insight regarding the clinical activity of RP5063 relevant to psychosis, along with mood and cognitive comorbidities, in patients with stable schizophrenia. Although we believe the Phase 1b study safety and efficacy findings are encouraging, it is important to recognize its power limitations due to the relatively small sample size.

RP5063 Phase 2 Clinical Study in Acute Schizophrenia

The Phase 2 clinical study involved patients with acute exacerbations of schizophrenia or schizoaffective disorder in evaluating the efficacy, safety, tolerability, and pharmacokinetics of RP5063 versus placebo. This evaluation utilized a double-blind, randomized, placebo-controlled 4-week study. Aripiprazole inclusion in the study was purely for the assay sensitivity analysis, and not as a comparator. Investigators randomized 234 eligible subjects into one of five treatment groups (15, 30, 50mg RP5063, aripiprazole 15mg, or placebo; 3:3:3:1:2, respectively). Recruitment of male and female subjects included 22 sites in the US, India, Philippines, Malaysia, and Moldova.

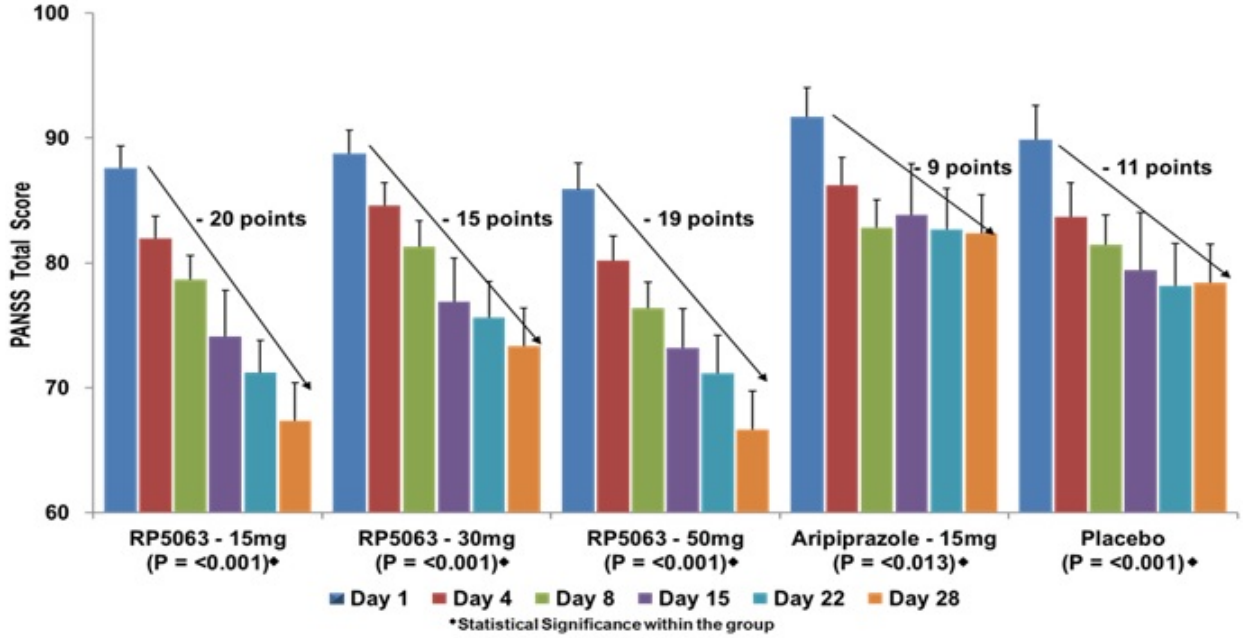
Statistical plans calculated sample sizes based on expected differences between the target dose of RP5063 and placebo 8.3 points (standard deviation of 11.3 points, effect size = 0.735) in the primary efficacy analysis (mean change from baseline in PANSS Total Score). This plan projected a sample size of 180 completing subjects (i.e., 45 subjects in each RP5063 dose group, this cohort included 15 subjects in the aripiprazole group and 30 subjects in the placebo group) to achieve at least an 85% power at an alpha level of 0.05% (two-sided). This level employed a t-test statistic for unequal group sizes, without controlling the alpha error in the pair-wise comparisons of the treatment groups with placebo. The statistical plan did not power the aripiprazole arm for statistical comparisons with other arms, as evaluation of this compound only assessed the study sensitivity; the study randomized 234 subjects to ensure that 180 would complete.

We conducted this study in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guidelines. The FDA approved the protocol, investigational review boards/independent ethics committees, and all participating subjects provided informed consent.

The primary efficacy endpoint was the change from baseline to Day 28 or End of Treatment (EOT) on PANSS Total Score. The secondary efficacy endpoints were the change from baseline to Day 4, Day 8, Day 15, Day 22 and Day 28 on the following items: PANSS Total, PANSS Positive, and Negative subscales; 20% improvement in PANSS Total Score; Improvement by at least 1 point on the Clinical Global Impression (CGI-S); cognition by trail-making Tests A and B and the Digit Symbol Substitution Test (DSST). Safety variables included adverse events (A.E.), physical examinations, vital signs, body weight, laboratory measurements (hematology, serum chemistry including prolactin, urinalysis, and pregnancy tests), and electrocardiograms (ECGs). The measurement of extrapyramidal symptoms (EPS) utilized the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BARS). The Columbia-Suicide Severity Rating Scale (C-SSRS) assessed and classified reported suicidal behavior and depression by the Calgary Depression Scale for Schizophrenia (CDSS). Investigators collected blood samples throughout the dosing period and for 220 h beyond using a sparse sampling routine. Analysis of these samples defined the population pharmacokinetics (PK) and correlated pharmacokinetic and pharmacodynamic (PK/PD) effects.

RP5063 demonstrated a sustained decrease in the total PANSS scores from Day 1 to 28 with statistically significant improvement within the group for all doses of RP5063 (p=<0.001) and aripiprazole (p=0.013), as compared with placebo (Figure 3).

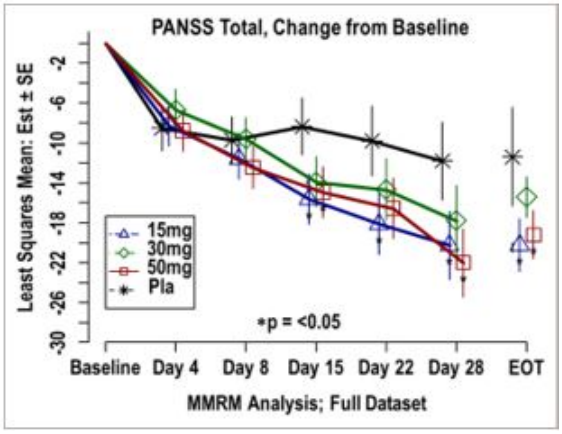
Figure 3. RP5063 Efficacy in the Phase 2 Clinical Study in Acute Schizophrenia patients, Total PANSS Scores, ITT Population (4 weeks, N = 234)



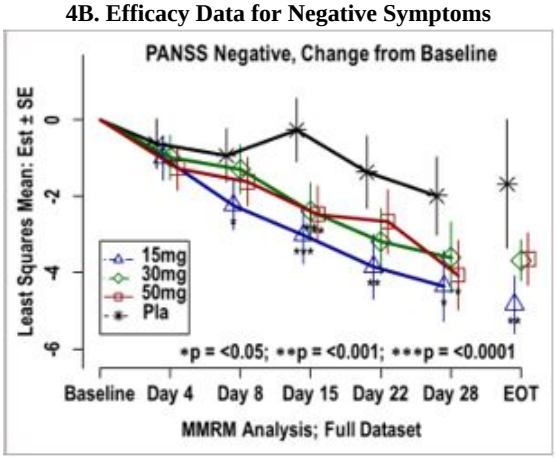
For the primary efficacy endpoint, the change in PANSS Total Score from baseline to Day 28/EOT demonstrated a statistically significant treatment difference from placebo for the RP5063 15-mg and 50-mg arms (p = 0.0212 and p = 0.0167), with a statistically significant difference versus placebo seen as early as the Day 15 assessment (mixed-effect model with repeated measures (MMRM) analyses). The 30-mg arm did not reach statistical significance (p=0.2733), although it was numerically superior. Investigators attributed the lack of significance of the RP5063 30 mg dose to a larger than normal early discontinuations (within 2-7 days) for reasons that were not related to the medication. Aripiprazole only showed efficacy in PANSS negative scores. PANSS subscales scores showed greater RP5063 improvement versus placebo in the PANSS Negative and Prosocial symptoms than the Positive symptoms (Figure 4). Both the RP5063 15-mg and 50-mg treatment groups displayed statistical significance from placebo as early as Day 15 for the PANSS Negative and Prosocial scales. The 50-mg treatment group showed statistical significance at Day 28 for PANSS Positive. All RP5063 groups were numerically superior to placebo.

Figure 4. RP5063 Phase 2 Clinical Efficacy for Acute Schizophrenia and Major Comorbid Symptoms

4A. Efficacy Data for Acute Schizophrenia



4B. Efficacy Data for Negative Symptoms



4C. Efficacy Data for Positive Symptoms

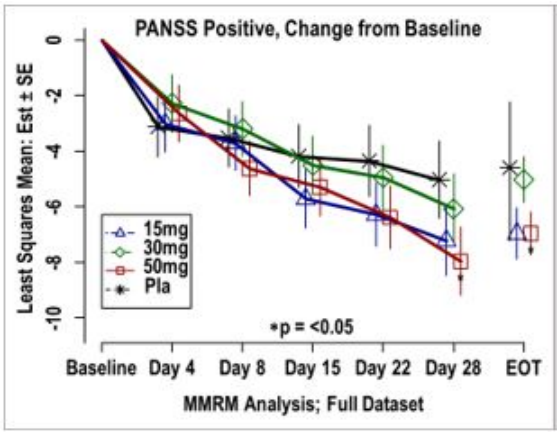
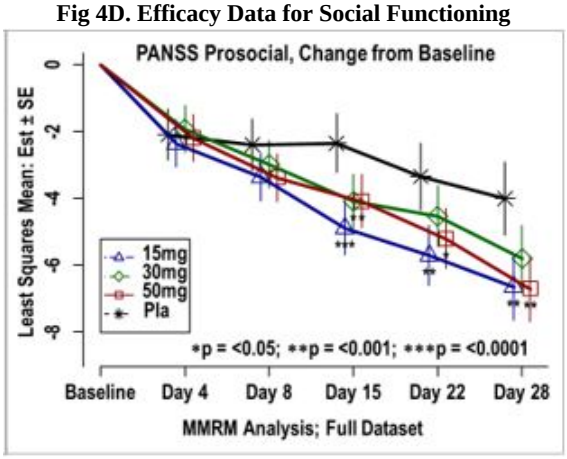


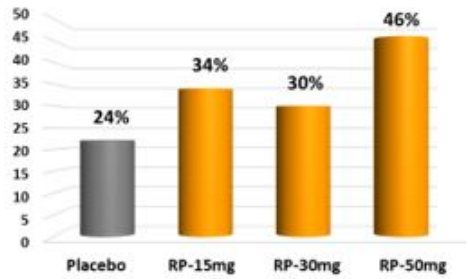
Fig 4D. Efficacy Data for Social Functioning



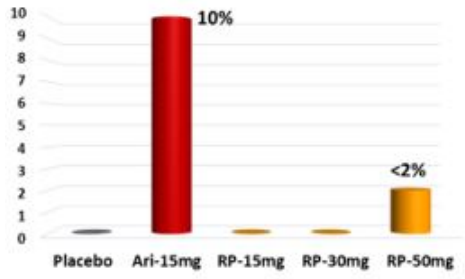
At Day 28/EOT, the frequency of a 30% improvement in total PANSS from baseline to EOT was 41%, 26%, and 39% for the respective RP5063 groups, versus 22% for the placebo cohort. RP5063 subjects improved ≥2 points on the CGI-S by Day 28/EOT at twice the frequency of those on placebo. RP5063 15-mg, 30-mg, and 50-mg groups resulted in 46%, 37%, and 40% improvements, respectively, versus placebo showing a 19% change. Further, relative to >1 point changes, the 15-mg, 30-mg, and 50-mg RP5063 groups produced 73%, 58%, and 72% improvements, respectively, in the CGI-S, as compared to placebo showing 57% change. The CGI-S changes from baseline to Day 28/EOT were statistically superior to placebo for RP5063 15 mg and 50 mg, while the change for 30 mg was numerically superior. Overall, RP5063 (15, 30, and 50mg) treated patients showed between 30-46% remission of acute schizophrenia symptoms, as compared with 22% in the placebo group (Figure 5a). As expected in a short study in patients with acute schizophrenia, there were no statistically significant differences in change from baseline for cognition scores. However, there were numerical improvements in RP5063 groups in the DSST, Trails A and Trails B scores.

Figure 5. RP5063 Phase 2 Study, Remission of Acute Schizophrenia and Discontinuation due to Side Effects

5A. Remission of Schizophrenia Symptoms



5B. Discontinuation due to Side Effects



Patients tolerated doses of RP5063 up to 50 mg with no side effect related discontinuation in the 15 mg and 30 mg dose groups. Only <2% of patients discontinued the treatment in the 50 mg dose group compared to 10% of patients in the aripiprazole 15 mg group (Figure 5b). Treatment discontinuation for any reason with 15 mg, 30 mg, and 50 mg doses of RP5063; the 15 mg dose of aripiprazole; and placebo were 14%, 25%, 12%, 35%, and 26%, respectively. Investigators attribute the higher discontinuation in the 30 mg group of RP5063 to a larger than the normal number of early discontinued patients (~10%) due to non-treatment reasons. Such early discontinuation is not uncommon in acute schizophrenia. The discontinuation rates with aripiprazole (35% for any reason, and 10% due to side effects) are consistent with findings in published clinical studies. Common treatment-emergent adverse events (TEAEs) were EPS (3%, 5%, and 9%) and akathisia (2%, 5%, and 10%), and as expected there seemed to be a dose-related increase in TEAEs in the 15, 30, and 50 mg RP5063 treatment groups, respectively (Figure 6).

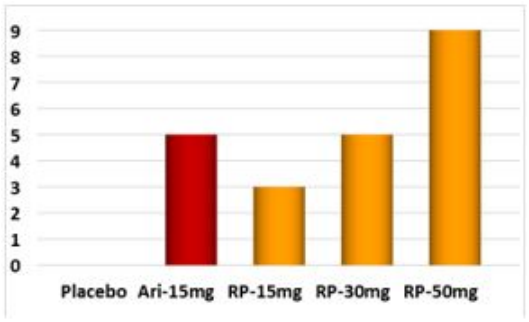
There were no clinically relevant changes from baseline in weight or body mass index (BMI); no subject had weight gain reported as a TEAE. This observation offered a clinically relevant finding because weight gain has been a common side effect of second-generation antipsychotics and identified as a key risk factor associated with increased morbidity and mortality in patients with schizophrenia with a major impact on compliance.

There were no clinically meaningful trends in laboratory parameters (including glucose, cholesterol, triglycerides or thyroid hormone T4), ECG, or vital signs. The study observed small mean decreases from baseline in prolactin levels in all treatment groups at Day 28. There were no reports of sexual side effects (Figure 6).

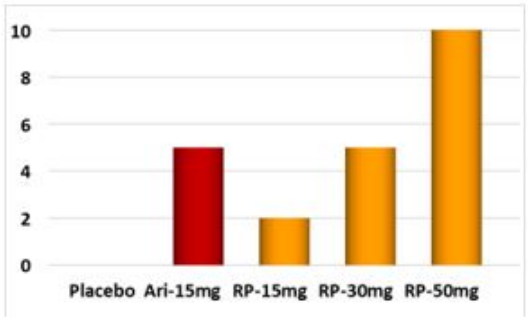
Figure 6. RP5063 Side Effect Profile in the Phase 2 Clinical Study in Acute Schizophrenia (4 weeks, N=234)

6A. CNS or Neuroleptic Side effects

Extrapyramidal Side effects (%)

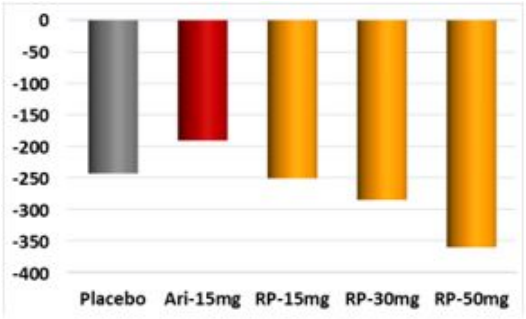


Akathisia (%)

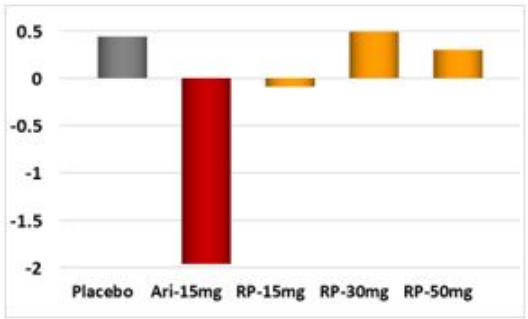


6B. Endocrine Side Effects

Change in Prolactin (mIU/L)

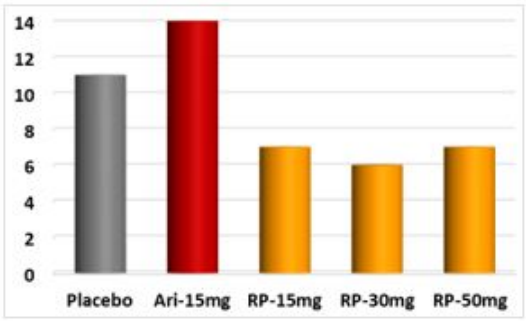


Change in Thyroid T-4 (pmol/L)

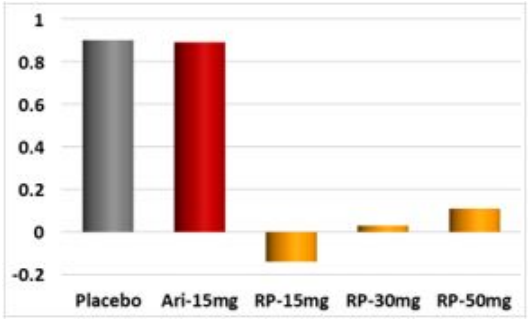


6C. Metabolic Side Effects

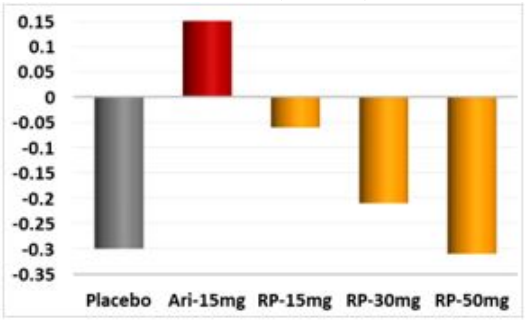
Body weight Increase (%)



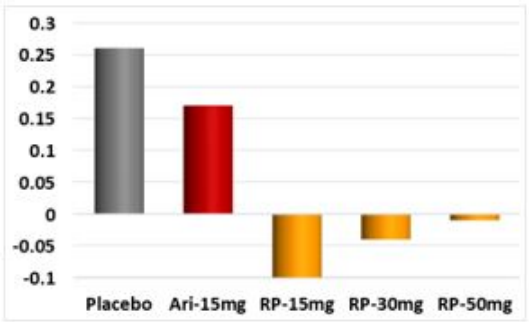
Diabetes / Blood Sugar (mmol/L)



Cholesterol (mmol/L)



Lipids/Triglyceride (mmol/L)



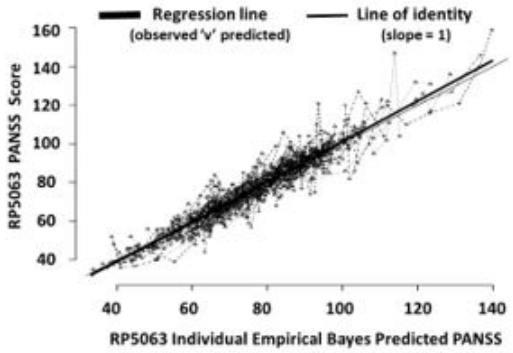
The analysis of RP5063 pharmacokinetic-pharmacodynamics relationship (PK-PD) reflected a linear, dose-proportional increase in exposure with dose and with no evidence of time dependency. Noteworthy was that of RP5063 drug exposure, reflected by Cmax and AUC. These parameters increased in direct proportion to dose irrespective of the population studied (e.g., healthy volunteers, patients with stable schizophrenia, patients with acute exacerbations of schizophrenia or schizoaffective disorder). In Phase 1 multi-dose study, drug levels approached steady-state after 120 h (5 days) of daily dosing, with doses between 10 and 100 mg with maximum steady-state concentrations of 70.1 and 696 ng/mL and AUCs of 1361 and 12526 ng*h/mL at the 10 and 100 mg dose, respectively.

We believe these findings offer important clinical benefits. We believe the lack of excessive drug accumulation should translate to a potential clinical benefit of not needing for the titration of therapy. Such might be the case with other atypical antipsychotics (e.g., aripiprazole). We believe the long half-life (~40-50 h) should translate easily to a once-daily dosing schedule. We believe this schedule is of clinical importance for the schizophrenic patient population since medication adherence, and missing doses with shorter half-life drugs can be a clinical issue leading to destabilization of clinical control. Such can lead to poor long-term functional outcomes in the treatment of schizophrenia. With RP5063, if a patient misses a single dose or two, we believe sufficient plasma concentrations remain for clinical control. Furthermore, the pharmacokinetic profile of RP5063 is independent of gender, age, ethnicity, glomerular filtration rate, smoking, concomitant medications, geographic location of the clinical site, and type of schizophrenia (acute or stable) patients treated. These observations mean that clinicians may not need dose adjustments based on the patient population (Figure 7b).

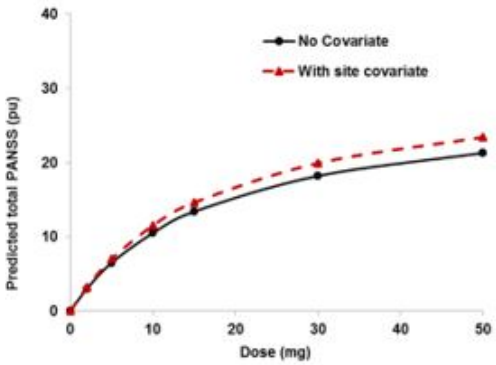
Investigators performed the PK-PD modeling correlation with actual data using the observed and predicted PANSS demonstrating high predictability with relatively low variability. As shown in the graph below, both the regression line and line of identity are very close to each other. We believe this relationship indicates that the model is providing a very good fit (Figure 7a). The regression line is the line when one plots and regresses the observed data against the data predicted from the population model. The line of identity is when there is a perfect fit of the observed and predicted data (i.e., when each of the observed data is exactly equal to those of the corresponding predicted data, so the slope of the line is in exact unity). The dose-response curve showed that the total PANSS decrease was approaching its maximum response after a dose of approximately 15 mg. Thus, we believe RP5063 doses of 15 to 50 mg daily appear to be an effective clinical range of dosing (Figure 7b).

Figure 7. RP5063 Phase 2 Clinical Study Pharmacokinetics and Pharmacodynamics Correlation

7A. Treatment PANSS vs. Predicted PANSS Scores



7B. Predicted Dose-Response Relationship



RP5063 Phase 3 Studies in Schizophrenia

The Phase 1 and Phase 2 clinical experience in multiple populations (healthy volunteers, stable schizophrenia, and acute schizophrenia and schizoaffective disorder patients) reflect the promise of RP5063 as an addition to the treatment armamentarium of this disease. Both healthy volunteers and patients tolerated RP5063 well in both Phase 1 and 2 studies. It did not produce any cardiometabolic, cardiovascular, prolactin, or neurologic effects, which would complicate current treatments. Investigators observed the early activity in Phase 1 after 10-days of dosing in stable patients and we believe that results from the Phase 2 trial may support the NDA for RP5063, as RP5063 demonstrated significance versus placebo in Total PANSS Score at Day 28 as compared to baseline. The pharmacokinetics proved to be highly predictable and consistent between Phase 1 and 2 studies, participant type (healthy volunteer, patient), and racial characteristics (Caucasian, Black, Indian, and Japanese). Analyses showed substantive and relatively rapid oral absorption, linear, dose-proportional increases in Cmax and AUC, lack of undue accumulation, and a relatively long terminal half-life over 40 hours. We believe these findings translate to a straightforward once-daily dosing regimen with no need for titration or adjustments for the type of patient. These characteristics set the stage for further evaluation in Phase 3.

As part of the Phase 3 development plan, we had a successful end of Phase 2 (EOP2) meeting with the FDA in 2013. In the EOP2 meeting, we presented the Phase 2 schizophrenia study results, discussed the Phase 3 development plans, and sought guidance from the FDA concerning a “Superior Safety Label Claim” to RP5063 for the treatment of schizophrenia. We received a favorable response from the FDA, as the agency agreed to consider granting RP5063 a “Superior Safety Label Claim” for the treatment of schizophrenia if there is a positive outcome on a relevant endpoint in a pivotal Phase 3 study in schizophrenia. Further to support the “Superior Safety Label Claim” for RP5063, the FDA agreed to waive the requirement to conduct a drug interaction clinical study with CYP2D6 inhibitors in Phase 3 development. We have accordingly planned Phase 3 development of RP5063 for acute and maintenance schizophrenia. We have completed the required regulatory compliant non-clinical studies. These include safety pharmacology studies, toxicology studies, and chemistry, manufacturing, and controls (CMC) development for initiating pivotal Phase 3 studies. Furthermore, the FDA has reviewed the results of these non-clinical studies and the Phase 3 protocols. We are currently focusing our efforts on initiating a pivotal Phase 3 study in acute schizophrenia.

RP5063 Clinical Development for Bipolar Disorder (BD) and Major Depressive Disorder (MDD)

Like schizophrenia, BD and MDD are major neuropsychiatric diseases. These neuropsychiatric diseases exhibit distinct symptoms yet share varying degrees of overlapping conditions that include psychosis, depression, and cognitive impairments. BD, a medical illness with substantial morbidity and mortality, involves episodic, recurrent mania or hypomania, and major depression. An article published in 2018 in the journal Therapeutic Advances in Psychopharmacology estimated that the global prevalence of bipolar spectrum disorders is approximately 2.4%, with approximately 0.6% for bipolar I and approximately 0.4% for bipolar II. The same journal article indicates prevalence of bipolar I in the U.S. has been found to be 1%, slightly higher than in other countries. Similarly, MDD is a common, chronic, recurrent, and debilitating psychiatric condition, leading to significant impairments in personal functional capacities. The National Institute of Mental Health (NIMH) estimated the prevalence of MDD among U.S. adults aged 18 or older at 17.3 million in 2017. NIMH also indicated the prevalence was higher among females (8.7%) compared to males (5.3%).

The clinical community also uses the antipsychotic drugs (e.g., olanzapine, risperidone, quetiapine, and aripiprazole) for the treatment of BD and/or MDD. All these antipsychotics display pharmacological activities for dopamine (D) and serotonin (5HT) receptors. The majority are selective for D2 and 5HT2A receptors, and may also be active for one or more of D4, 5HT1A, 5HT2B, and 5HT7 receptors. RP5063 exhibits potent activity for D2 and 5HT2A receptors, and each of D4, 5HT1A, 5HT2B, and 5HT7 receptors are implicated as pharmacological targets for depression and cognitive impairment conditions.

Subject to the receipt of additional financing, we may proceed with Phase 2 studies for RP5063 in BD and MDD.

RP5063 Clinical Development for Psychosis and Behavioral Symptoms in Alzheimer's Disease (BPSD), Parkinson's Disease Psychosis (PDP) and Attention Deficit Hyperactivity Disorder (ADHD)

Patients with Alzheimer's disease (AD) manifest not only progressive memory impairment, cognitive deficits, and functional alterations but also a variety of neuropsychiatric symptoms (agitation, aggression, hallucinations, delusions). An article published in 2000 in the journal Archives of General Psychiatry (now JAMA Psychiatry) states these symptoms ultimately affect up to 75% of individuals with dementia and, once present, sustain, or recur. Similarly, patients with Parkinson's disease also suffer from neuropsychiatric symptoms. There are very limited pharmacological treatment options for managing psychotic and behavioral symptoms in Alzheimer's and Parkinson's diseases. Without an approved drug, clinicians often manage the psychosis and behavioral symptoms in Alzheimer's disease with antipsychotics (e.g., quetiapine and olanzapine). Primavanserin (Nuplazid), a serotonin 5HT2A inverse agonist, is the only FDA approved treatment for the treatment of Parkinson's disease psychosis. However, clinicians do use some antipsychotics (e.g., quetiapine, and olanzapine) as an off-label treatment.

ADHD is a common developmental disorder in children and often continues into adulthood. The prevalence of ADHD in children is 5-12% worldwide, according to an article published in 2016 in the Journal of Advanced Pharmaceutical Technology & Research. ADHD has a high rate of comorbid psychiatric disorders.

Subject to the receipt of additional financing, we may also continue the clinical development of RP5063 for the treatment of BPSD, PDP, and ADHD.

DEVELOPMENT OF RP5063 FOR RESPIRATORY DISEASES

Development of RP5063 for Pulmonary Arterial Hypertension (PAH)

PAH is a progressive, debilitating condition characterized by pulmonary vascular resistance leading to right ventricular failure and death. According to an article published in 2016 in the journal The Lancet Respiratory Medicine, the global prevalence of PAH is estimated at 6.6 – 26.0 cases per million with 1.1 – 7.6 incidences per million adults per year. The same article indicates PAH is frequently diagnosed in older patients, particularly those 65 years and older. As presented in 2020, the National Organization for Rare Disorders ("NORD") estimates PAH occurs 3 – 5 times more frequently in females than in males, and it tends to affect females between the ages of 30 and 60. Pursuant to a study published in 2012, as reported by the journal Circulation: Cardiovascular Quality and Outcomes, post-diagnosis of PAH, survival rates are approximately 1 year in 87%, 3 years in 75%, and 5 years in 65% of patients, respectively.

PAH occurs when the pulmonary arteries have narrowed, thickened, or become blocked due to the constricting and remodeling of the pulmonary vasculature. Endothelial dysfunction occurs early in the disease pathogenesis. Such pathology leads to the proliferation of the endothelium and smooth muscle tissue, the remodeling of pulmonary arteriole walls, the impaired production of vasodilators, and the overexpression of vasoconstrictors. Remodeling can involve a variety of smooth muscle (e.g., hyperplasia, medial hypertrophy, perivascular fibrosis) and other extrinsic pathologic changes (e.g., microthrombosis, inflammatory cell infiltration, angioproliferative plexiform lesions).

Current treatment involves influencing smooth muscle tone: 1 — decreasing the increased expression of phosphodiesterase 5 (PDE-5) inhibition (e.g., sildenafil) and increasing nitric oxide; 2 — antagonizing endothelin (e.g., bosentan); and 3 — providing exogenous prostacyclins (e.g., epoprostenol, iloprost, treprostinil) to address the reduced production of prostaglandin I2. Such treatments can reduce symptoms, improve the performance of activities of daily living, delay disease progression, and improve survival somewhat (e.g., epoprostenol). However, they fail to stem the ongoing cytoproliferative processes that significantly modify the pulmonary vascular structure and lead to progressive disease and/or the need for lung transplantation.

Serotonin (5-hydroxytryptamine; 5HT) plays a role in both the proliferative and functional components of the pathogenesis of PAH, which involve a variety of contributing factors, including inflammatory cytokines and chemokines. Pulmonary arteries express several 5HT receptors, including the 5HT2A, 5HT2B, and 5HT7. The presence of 5HT in the pulmonary circulation activates vascular smooth muscle (VSM), 5HT2A and 5HT2B receptors, and SERT to cause constriction, the proliferation of pulmonary vascular smooth muscle cells, and fibroblast proliferation. Coupled with stimulating of the transforming growth factor β pathway, the 5HT pathway facilitates cell proliferation and vascular remodeling. These changes lead to the thickening of the medial layer. These accompany the narrowing and the remodeling of the pulmonary artery. Together these define the characteristics of PAH.

RP5063 is a novel candidate for the management of PAH. As a potent antagonist of the 5-HT receptor, it possesses a high binding affinity for several relevant targets associated with PAH. These include 5HT2A (2.5 nM), 5HT2B (0.19 nM), and 5HT7 (2.7 nM), as well as a moderate affinity for SERT (107 nM) in preclinical models.

RP5063 Preclinical Development for PAH

In November 2016, the U.S. Food and Drug Administration granted RP5063 Orphan Designation Status for clinical investigation in PAH. The agency based its decision on encouraging preclinical results with RP5063 in PAH, including disease-modifying antiproliferative effects. Two studies using the monocrotaline (MCT) and Sugen hypoxia (Su-Hx) models evaluated the effectiveness of RP5063 as monotherapy. Further, an additional study with the MCT model assessed this compound's effectiveness as an adjunct with several other standard treatments for PAH.

The monotherapy MCT-induced model involved a 28-day treatment on single-agent RP5063. On Day 0, adult male Wistar–Kyoto rats, randomized into five groups of 10 animals, received a single intravenous 60-mg/kg MCT dose. Subsequently, on Days 0 to 27, the rats were gavaged twice daily (BID) with vehicle (MCT+Veh; 5% glucose solution), RP5063 (1, 3, or 10 mg/kg), or sildenafil (50 mg/kg). On Day 28, during terminal surgery, investigators obtained blood samples, hemodynamic readings, and harvested tissues.

In this study, RP5063 produced significant functional and structural changes, as compared with those in the MCT+Veh group. Functionally, RP5063 displayed healthier pulmonary hemodynamic parameters, translating to reduced right ventricle (R.V.) hypertrophy and suggesting greater pulmonary vascular elasticity. This activity led to improved respiratory resistance and hemoglobin oxygen saturation, as compared with PAH animals without treatment. Structurally, RP5063 appeared to prevent the remodeling of the smooth muscle cells in the pulmonary vasculature. The 10 mg dose prevented vascular intimal thickening (endothelial and smooth muscle hyperplasia, and the multiplication of vascular smooth muscle cells) in the smaller vessels, mostly non-muscular in healthy animals. In exploring the cytokine response, the study found that all doses of RP5063 produced lower levels of tumor necrosis factor (TNF) α and interleukin (IL) β, and facilitated a significant reduction of IL-6 ($p<0.05$). These observations suggest an antiproliferative capacity.

In the SuHx-induced PAH study, investigators gave RP5063 treatment for 21 days. On Day 0, 4 groups of adult male Wistar–Kyoto rats received a subcutaneous injection of Sugen 5416 (20 mg/kg). Investigators kept them at FiO2 of 10% (Days 0 – 21) and 21% (Days 22 – 35). During the treatment period starting at Day 14, rats were gavaged twice daily (BID) with vehicle (SuHx+Veh; 5% glucose solution), RP5063 (10 or 20 mg/kg; RP-10 and RP-20, respectively), or sildenafil 50 mg) on Days 14 to 35. On Day 35, during terminal surgery, investigators obtained blood samples, hemodynamic readings, and harvested tissues.

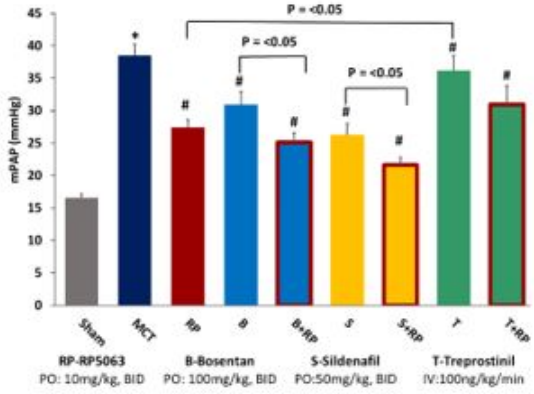
Both doses of RP5063 and sildenafil produced a significant effect on functional and structural parameters, as compared with the induced group treated with vehicle (SuHx+Veh). Functionally, RP5063 improved pulmonary hemodynamics and respiratory function, resulting in higher oxygen saturation, as compared to non-treated, Sugen-induced animals. Structurally, RP5063 decreased small-vessel wall thickness and the percentage of muscular vessels. Most significantly, RP5063 limited arterial obliteration and prevented the formation of plexiform lesions. These observations suggest that the compound might exert antiproliferative effects and, potentially, a disease-modifying capacity. Concerning the cytokine effect, both RP5063 dose groups reflect lower levels of leukotriene-B4 at Days 21, 28, and 35.

Considering the initial observations with RP5063 as a single-agent treatment in both the MCT and SuHx models in rats, we undertook an additional MCT study with this compound to evaluate its role as adjunctive therapy to standard PAH treatments (Bhat et al., 2018). In the same MCT model as previously described, investigators examined RP5063 as monotherapy and as an adjunct to current standards of PAH care (bosentan, sildenafil, treprostinil).

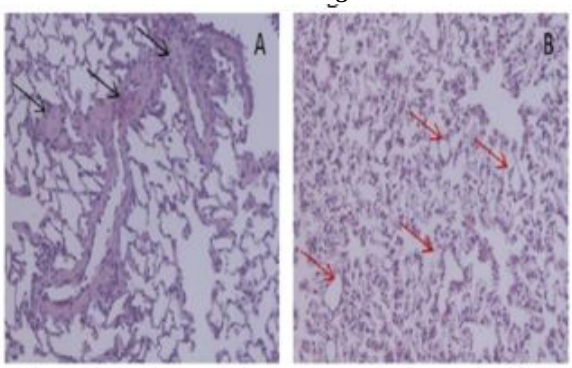
As a single agent, RP5063 produced functional and structural effects seen in the MCT+Veh group and was consistent with those seen in the initial monotherapy MCT study. Furthermore, these effects were like (and in some cases, better than) the standard treatments. As an adjunct to all treatments, RP5063 significantly ($p<0.05$) lowered mean and systolic pulmonary artery pressures and R.V. systolic pressure, and improved oxygen saturation, as compared with the untreated, induced animals. The combination of RP5063 and sildenafil displayed the most consistent and robust effects. The most notable was on pulmonary hemodynamics, respiratory parameters, and histopathologic changes.

Figure 8. Effect of RP5063 Treatment in MCT (8A) and Sugen-Hypoxia (8B) Induced PAH in Rats

8A. Treatment Effects on PAH



8B. Treatment Effects on Lung Vascular Structure



Lung photomicrograph of PAH induced rat untreated

Lung photomicrograph of PAH induced rat treated with RP5063

RP5063 Clinical Development for PAH

In November 2016, the FDA granted Orphan Drug Designation to RP5063 for the treatment of PAH. We had a successful pre-IND meeting with the FDA. In the pre-IND meeting, we presented RP5063 preclinical development data including efficacy results for PAH in rodent models, the data of regulatory compliant non-clinical studies (e.g., safety pharmacology studies, toxicology studies, and Chemistry, Manufacturing, and Controls (CMC) development), and the data of clinical Phase 1 studies. We discussed the Phase 2 clinical development plan with FDA and sought the agency's guidance for our clinical development plan for a "Disease Modifying Label Claim" based on the positive specific clinical outcome. We received a favorable response from the FDA regarding the "Disease Modifying Label Claim".

Subject to the receipt of additional financing, we may also develop the clinical protocols and proceed with a Phase 2 clinical trial for RP5063 in PAH.

Development of RP5063 for Idiopathic Pulmonary Fibrosis (IPF)

IPF is a chronic, progressive, and debilitating lung disease. In 2019, Medscape reported the worldwide prevalence of IPF is estimated at 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females. Medscape also reported that in the U.S., the prevalence among individuals aged 50 years or older ranges from 27.9 to 63 cases per 100,000. Medscape also reported, for patients suffering from IPF, the estimated mean survival is 2-5 years from the time of diagnosis and that mortality rates are estimated at 64.3 deaths per million in men and 58.4 deaths per million in women.

IPF involves chronic inflammation and progressive fibrosis of the alveoli. This pathology leads to destroyed lung architecture, reduced lung capacity, impaired oxygenation, and a decline in lung function.

Treatment involves early referral for lung transplantation, palliative care, and clinical trials. Limitations exist with various interventions, including commonly used agents (e.g., corticosteroids and immunosuppressants), and current guidelines do not support them. Two Food and Drug Administration approved treatments — Nintedanib (Ofev), and Pirfenidone (Esbriet) — are inadequate in improving functional decline and disease progression (Esbriet product Insert, 2018; Ofev Product Insert, 2018). Hence, we believe survival continues as an unmet need.

Various studies have implicated 5HT in the pathophysiology of IPF. It exerts a vasoactive effect on pulmonary arteries and stimulates lung myofibroblast actions. Pulmonary 5HT appears to mediate effects through 5-HT2A/2B/7 receptors.

RP5063 may be a new candidate for the management of IPF. As a potent antagonist of the 5HT receptor, it possesses a high binding affinity for several relevant targets associated with IPF. These include 5HT2A (2.5 nM), 5HT2B (0.19 nM), and 5HT7 (2.7 nM), as well as a moderate affinity for SERT (107 nM) in preclinical models.

RP5063 Preclinical Development for IPF

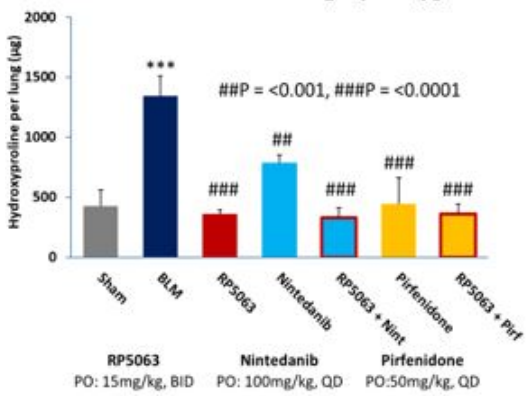
A bleomycin (BLM)-induced model involved a 21-day protocol using 34 Sprague Dawley rats divided into four groups- Group 1 (no induction, vehicle control), Group 2 (induction, vehicle control), Group 3 (induction, RP5063, 15 mg/kg, intervention at Day 1), and Group 4 (induction, RP5063, 15 mg/kg, intervention at Day 10). On Day 21, during terminal surgery, investigators obtained blood samples, hemodynamic readings, harvested tissues, and bronchoalveolar lavage fluid (BALF) samples. The histological analysis to evaluate effects on fibrosis involved several tests. Tissue stained with Masson's Trichrome and visualized using a scanner to determine the percentage of the fibrotic tissue, reflective of excessive collagen disposition in the lung. A colorimetric assay assessed the content of hydroxyproline, an amino acid for fibrillar collagens, from the right lung tissue sample. Finally, cytokine analysis of the BALF samples evaluated the effects on Macrophage inflammatory protein 1 (MIP1), Monocyte chemoattractant protein 1 (MCP1), Interleukin (IL)-6, Interferon gamma-induced protein 10 (IP10) and RANTES levels.

Compared with the bleomycin-induced vehicle group, the use of RP5063 at Day 0 and Day 10 sustained animal survival at 90.5% and 89.5%, respectively ($P<0.05$). Furthermore, animals maintained their weight with both RP5063 interventions, as compared with the vehicle group ($P<0.01$). Animals in both RP5063 groups restored cardiac output, with the Day 0 group displaying a significant effect as compared to those treated with vehicle ($P<0.01$). The Day 0 RP5063 also normalized pulse pressure.

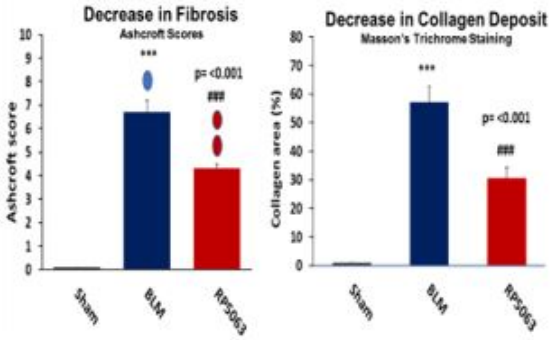
RP5063 treatment influenced multiple functional, histological, and cytokine parameters reflective of pulmonary fibrosis. Animals in the RP5063 Day 0 group displayed a significant reduction in respiratory resistance ($P<0.05$). Those in Day 10 group showed improvement ($P=0.10$). Both RP5063 interventions produced a significant diminution in the concentration of hydroxyproline ($P<0.05$, Day 0; $P<0.01$, Day 10). Lung weights, which increased in the vehicle group suggesting the presence of edema, were significantly lower in the RP5063 Day 0 group ($P<0.05$). From the BALF samples, total cell count (inflammation) was lower in both RP5063 groups ($P<0.05$), as well as total protein content (edema) in the RP5063 Day 0 group ($P<0.05$). Ashcroft Score from stained lung tissue reflected a significant reduction in the lung parenchymal fibrotic changes in the Day 0 group ($P<0.001$). Concerning the percent of fibrosis areas measured with Masson's trichrome staining, the Day 0 RP5063 group significantly reduced these changes ($P<0.001$), as compared with the vehicle group (Figure 9B). Furthermore, the Day 0 group showed significantly improved blood oxygen levels ($P<0.05$). Both groups induced a diminution of blood lactate levels ($P<0.01$, Day 0; $P<0.05$, Day 5). Finally, both RP5063 groups reduced proinflammatory and fibrotic cytokines, with significant effects on MCP-1 ($P<0.05$, Day 0), IP10 ($P<0.01$, both RP5063 interventions), and RANTES ($P<0.01$, both RP5063 interventions).

Figure 9. Effect of RP5063 as a Monotherapy and Co-administered with Standard of Care Nintedanib and Pirfenidone in Bleomycin (BLM) Induced IPF in Rats

9A. Treatment Effects on Lung Hydroxyproline



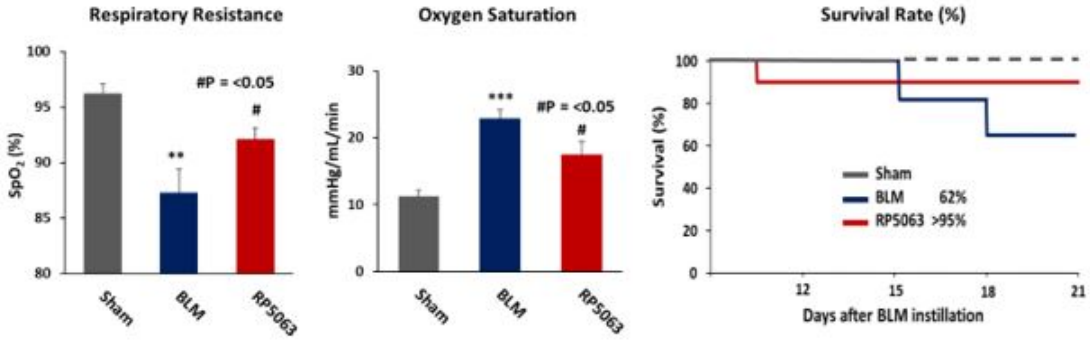
9B. Treatment Effects on Lung Alveoli Fibrosis



RP5063, PO: 15mg/kg, BID

A follow-up preclinical study utilized the same BLM-induced model and methods. This study evaluated the effect of RP5063 (15 mg/kg twice daily) in combination with either nintedanib or pirfenidone (both dosed at 100 mg/kg once daily). Both nintedanib and pirfenidone are the current standard of care for patients with IPF. Single-agent treatment with nintedanib and pirfenidone (both dosed at 100 mg/kg once daily) served as controls. Treatment started on Day 7 following BLM-induction and continued until Day 20. Terminal surgery occurred on Day 21, in which harvesting of lung tissue and collecting of BALF occurred. Similar histological investigations evaluated the effects of treatment on mitigating the development of fibrosis via BLM-induction.

Figure 10. Effect of RP5063 Treatment in Bleomycin (BLM) Induced IPF in Rats



RP5063, as an adjunct to nintedanib and pirfenidone, significantly augmented the functional and histological effects of nintedanib and pirfenidone, two standard treatments for IPF, as evidenced by reduction in hydroxyproline level (Fig 9A) and fibrosis (Fig 9B) in the lungs. The RP5063 treatment demonstrated a reduction in respiratory resistance (P<0.05), an increase in blood oxygenation P<0.05), and an improvement in survival rate (95%), as compared with vehicle control (62%) (Figure 10). Furthermore, RP5063, as an adjunct, mitigated lung fibrosis, and collagen disposition, the hallmarks of pulmonary fibrosis, as evidenced by the significantly (P<0.001) reduced concentration of hydroxyproline in the lungs produced by the treatment combinations (Figure 9A), as compared with vehicle control.

RP5063 Clinical Development for IPF

In April 2018, the FDA has granted Orphan Drug Designation to RP5063 for the treatment of IPF. We had a successful pre-IND meeting with the FDA. In the pre-IND meeting, we presented RP5063 preclinical development data including efficacy results for IPF in rodent models, the data of regulatory compliant non-clinical studies (e.g., safety pharmacology studies, toxicology studies, and Chemistry, Manufacturing, and Controls (CMC) development), and the data of clinical Phase 1 studies. We have discussed the Phase 2 clinical development plan with FDA and sought the agency's guidance for our clinical development plan for a "Disease Modifying Label Claim" based on the positive specific clinical outcome. We have received a favorable response from the FDA regarding the "Disease Modifying Label Claim."

Subject to the receipt of additional financing, we may also develop the clinical protocols and proceed with a Phase 2 clinical trial for RP5063 in IPF.

DEVELOPMENT OF RP1208 FOR DEPRESSION AND OBESITY

About RP1208

Our RP1208 drug candidate, a new chemical entity (NCE), is a novel triple reuptake inhibitor (TRI) which we believe is ready to be in IND enabling studies for depression and ready to be in animal efficacy studies for obesity, following the receipt of adequate additional financing. We possess a granted composition of matter patent for RP1208 in the USA, Europe, and several other countries.

Depression is a debilitating illness characterized by symptoms like anhedonia, depressed mood leading to suicidal thoughts, impaired cognitive functions, slowing of speech, and other actions. The NIMH estimated the prevalence of MDD among U.S. adults aged 18 or older at 17.3 million in 2017. NIMH also indicated the prevalence was higher among females (8.7%) compared to males (5.3%). Although a plethora of antidepressants exists in the market, an article published in 2015 in the journal Future Medicinal Chemistry indicates clinicians believe that approximately 30 – 40% of patients do not respond to the therapy, thus reflecting an unmet need to develop novel therapeutics to combat depression. The persistence of anhedonia originating from a depressed dopaminergic activity is one of the most treatment-resistant symptoms of depression. Currently, six major classes of antidepressant drugs, which target mainly monoamine transporters serotonin (SERT) and norepinephrine transporters (NET), are available. Therefore, though leaders have hypothesized that triple reuptake inhibitors (TRIs), with their potency to block dopamine reuptake by blocking dopamine transporter (DAT), in addition to serotonin transporter (SERT) and norepinephrine transporter (NET) should produce higher efficacy.

Triple reuptake inhibitor active compounds stimulate satiety and act as an appetite suppressant. Pharmacological studies have demonstrated that stimulated monoaminergic activity induces profound effects on feeding behaviors and, thus, energy intake. Furthermore, they have shown that agents that enhance synaptic levels of norepinephrine (NE), serotonin (5HT), or dopamine (DA) by stimulating release or reducing reuptake can decrease feeding and weight gain.

We have conducted several *in vitro* and *in vivo* studies on RP1208. In the radioligand binding assays, it has shown potent binding affinities for monoamine transporters DAT (Ki = 1.2 nM), SERT (0.8 nM), and NET (11 nM). Studies using in vitro functional assays assessed the functional activity of RP1208 for monoamine transporters. RP1208 showed potent functional inhibitory activities for monoamine transporters with IC50 values <1 nM for DAT, 6.6 nM for SERT, and 2 nM for NET. In the in vivo studies, RP1208 has shown acceptable bioavailability of 9% (t½=2.3 h) in rat and 50% (t½=13.1 h) in dog models. RP1208 rapidly and extensively distributes into tissues, including the brain with a brain:plasma ratio of ~1:1 9 (rat), despite high plasma protein binding (>99%).

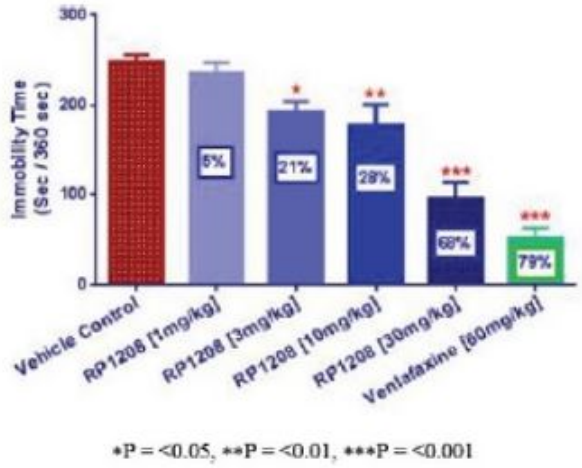
RP1208 Preclinical Studies for Depression and Obesity.

We evaluated the antidepressant activity of RP1208 in the tail-suspension test in the mouse model. The tail-suspension test is a mouse behavioral test useful in the screening of potential antidepressant drugs, and assessing other manipulations that investigators expect to affect depression-related behaviors. Mice are suspended by their tails with tape, in such a position that it cannot escape or hold on to nearby surfaces. During this test, typically six minutes in duration, the resulting escape oriented behaviors are quantified. A tail-suspension test is a valuable tool in drug discovery for high-throughput screening of prospective antidepressant compounds.

The tail-suspension test in male BALB/c mice with 1, 3, 10, and 30mg/kg doses evaluated the antidepressant activity of RP1208. Venlafaxine, an approved antipsychotic drug, 60 mg/kg, was the positive control in the study. RP1208 has shown statistically robust significant reduction in immobility time at 3 mg/kg (p = <0.05), 10 mg/kg (p = <0.01), and 30 mg/kg (p = <0.001) doses. The antidepressant activity of RP1208, as measured by reduction in immobility time at different dose levels, was dose-dependent with no adverse effects (Figure 11).

Subject to the receipt of additional financing, we may also advance the development of RP1208 for depression and obesity.

Figure 11. Effect of RP1208 in Immobility Time in Male BALB/c Mice in Tail Suspension Test

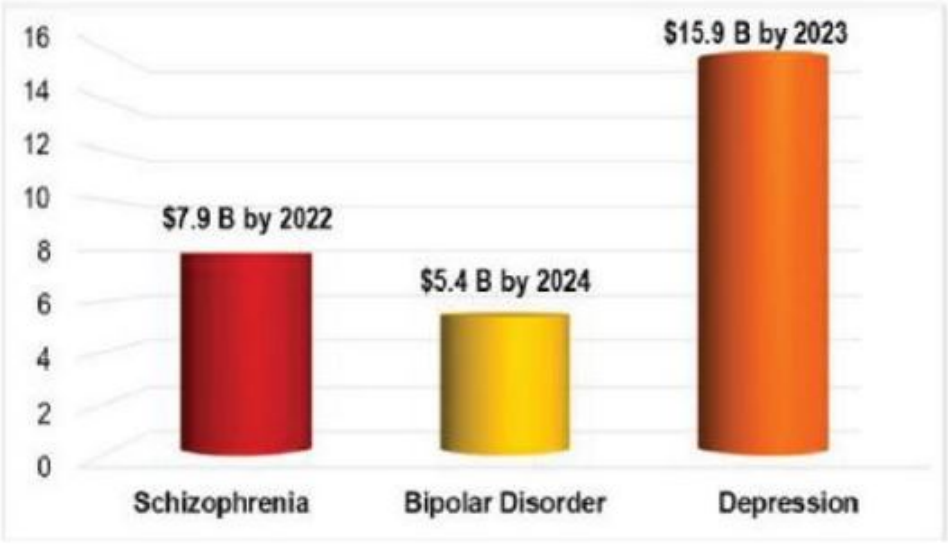


MARKET

Neuropsychiatric Diseases Schizophrenia, Bipolar Disorder (BD) and Major Depressive Disorder (MDD)

Schizophrenia, BD, and MDD are major neuropsychiatric diseases often chronic in nature. These neuropsychiatric diseases exhibit distinct symptoms yet share varying degrees of overlapping conditions that include psychosis, depression, and cognitive impairments. Schizophrenia is a complex debilitating psychiatric disease involving a mix of positive and negative symptoms, along with mood disorder (e.g. depression and anxiety) and cognitive impairment. As presented in 2020, SARDAA estimates schizophrenia can be found in approximately 1.1% of the world's population, regardless of racial, ethnic or economic background, with approximately 3.5 million people diagnosed in the U.S. Schizophrenia imposes substantial burden on patients, their families and overall society. Treatment and other economic costs due to schizophrenia are enormous, estimated by SARDAA to be between $32.5 and $65 billion annually. Antipsychotic drugs are the first-line treatment for patients with schizophrenia. Increasing awareness among patients and physicians in the field of mental health, particularly schizophrenia is likely to increase the penetration of antipsychotic drugs in the market. Currently, second and third-generation antipsychotics capture significant market share. Pipeline drugs undergoing clinical trials intend to block specific subtypes of serotonin and dopamine receptors which would help to mitigate the symptoms, and address unmet medical needs. According to a 2017 report from Grand View Research, Inc., the total estimated drugs market size for schizophrenia is anticipated to reach approximately $7.9 billion by 2022 (Figure 12).

Figure 12. Global Antipsychotics Market Insights for Schizophrenia, Bipolar Disorder (BD) and Major Depressive Disorder (MDD)



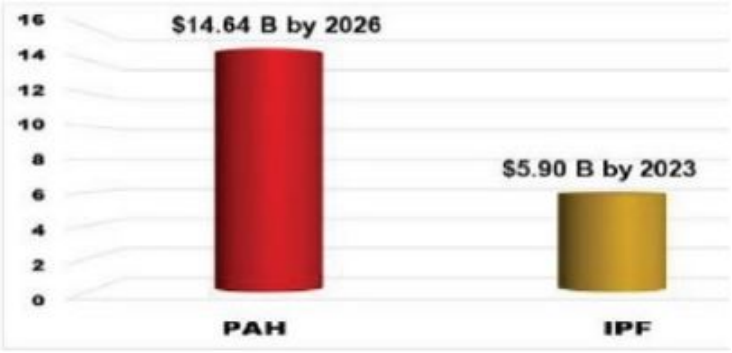
BD, a medical illness with substantial morbidity and mortality, involves episodic, recurrent mania or hypomania, and major depression. An article published in 2018 in the journal Therapeutic Advances in Psychopharmacology estimates that the global prevalence of bipolar spectrum disorders is approximately 2.4%, with approximately 0.6% for bipolar I and approximately 0.4% for bipolar II. The same journal article indicates prevalence of bipolar I in the U.S. has been found to be 1%, slightly higher than in other countries. In recent years, the general public awareness of the symptoms and treatment of BD is on the rise. Typically, the treatment for BD is for a lifetime. Antipsychotic drugs are the standard of care for patients with BD. According to a 2020 article from Market Data Forecast, the total estimated drugs market size for BD treatment is estimated to reach approximately $5.4 billion by the year 2024 (Figure 12).

MDD is a common, chronic, recurrent, and debilitating psychiatric condition, leading to significant impairments in personal functional capacities. MDD is one of the most common mental disorders in the United States. NIMH has estimated the prevalence of MDD among U.S. adults aged 18 or older at 17.3 million in 2017. NIMH also indicated the prevalence was higher among females (8.7%) compared to males (5.3%). Antipsychotic drugs are standard of care either as a monotherapy or as an adjuvant treatment for patients with MDD. According to a 2018 report from Allied Market Research, the total estimated drugs market size for the treatment of depression is estimated to reach approximately $15.9 billion by the year 2023.

Respiratory Diseases Pulmonary Arterial Hypertension (PAH) and Idiopathic pulmonary Fibrosis (IPF)

PAH and IPF are serious fatal lung diseases. Currently, there is no cure for PAH and IPF diseases. PAH is a progressive, debilitating condition characterized by pulmonary vascular resistance leading to right ventricular failure and death. According to an article published in 2016 in the journal The Lancet Respiratory Medicine, the global prevalence of PAH is estimated at 6.6 – 26.0 cases per million with 1.1 – 7.6 incidences per million adults per year. The same article indicates PAH is frequently diagnosed in older patients, particularly those 65 years and older. As presented in 2020, NORD estimates PAH occurs 3 – 5 times more frequently in females than in males, and it tends to affect females between the ages of 30 and 60. Pursuant to a study published in 2012, as reported by the journal Circulation: Cardiovascular Quality and Outcomes, post-diagnosis of PAH, survival rates are approximately 1 year in 87%, 3 years in 75%, and 5 years in 65% of patients, respectively. PAH treatment market is expected to exhibit remarkable growth as drivers accountable for the market growth are globally growing older population coupled with causative diseases including interstitial lung diseases (ILD), human immunodeficiency virus (HIV) infection, connective tissue disorders, chronic liver diseases, sedentary lifestyle and other idiopathic conditions. The presence of favorable government support in the U.S. such as Orphan Drug Act (ODA) 1983 and the Rare Disease Act (RDA) of 2002 to facilitate the development of orphan drugs with benefits including tax incentives (reduced taxes/tax credits equal to half of the development costs), clinical research subsidies, and improved patent protection and marketing rights. According to a 2018 report from Credence Research, the global PAH treatment market is projected to reach USD 14.64 billion by 2026 (Figure 13).

Figure 13. Global Market Insights for Pulmonary Arterial Hypertension (PAH) and Idiopathic Pulmonary Fibrosis (IPF)



IPF is a chronic, progressive, and fatal lung disease. In 2019, Medscape reported the worldwide prevalence of IPF is estimated at 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females. Medscape also reported that in the U.S., the prevalence among individuals aged 50 years or older ranges from 27.9 to 63 cases per 100,000. For patients suffering from IPF, the estimated mean survival is 2 – 5 years from the time of diagnosis and that mortality rates are estimated at 64.3 deaths per million in men and 58.4 deaths per million in women. IPF involves chronic inflammation and progressive fibrosis of the alveoli. This pathology leads to destroyed lung architecture, reduced lung capacity, impaired oxygenation, and a decline in lung function.

Treatment involves the FDA approved drugs Nintedanib (Ofev), and Pirfenidone (Esbriet), lung transplantation or palliative care. According to a 2018 report from iHealthcare Analyst, the total estimated drugs market size for IPF is anticipated to reach approximately $5.9 billion by 2023 (Figure 13).

Competition

The pharmaceutical industry is highly competitive and characterized by rapidly evolving technology and intense research and development efforts. We expect to compete with companies, including major international pharmaceutical companies, that have substantially greater financial, research and development, and marketing and sales capabilities, and have substantially greater experience in undertaking preclinical and clinical testing of products, obtaining regulatory approvals, and marketing and selling pharmaceutical products. We will face competition based on, among other things, product efficacy and safety, the timing and scope of regulatory approvals, product ease of use, and price.

At the highest level, our potential competitors are any company developing treatments for schizophrenia, PAH, IPF, BD, MDD, BPSD, PDP, and ADHD.

There are numerous therapies currently used to treat schizophrenia patients, including olanzapine, risperidone, quetiapine, and aripiprazole. Such products are also often used for the treatment of comorbid neuropsychiatric disorders, including BD, MDD, BPSD, PDP, and ADHD. While these offer some clinical benefit, they are associated with adverse side effects, which include neuroleptic side effects (e.g. EPS, akathisia), metabolic side effects (e.g. weight gain, obesity, type 2 diabetes, dyslipidemia) and endocrine side effects (e.g. hypothyroidism, prolactin increase leading to sexual dysfunction). Thus, we believe there is an unmet medical need for safe and effective drugs for the treatment of schizophrenia, and related comorbid neuropsychiatric disorders, that could potentially address the totality of the disorders and help patients function and feel better, with minimal side effects.

Additionally, there are numerous therapies currently used to treat PAH and IPF patients, including sildenafil, bosentan and treprostinil for PAH and nintedanib and pirfenidone for IPF. While these offer some clinical benefit, they are associated with treating the symptoms of such diseases, and not the underlying structural modification that causes the disease. Thus, we believe there is an unmet medical need for safe and effective drugs for the treatment of PAH and IPF that could potentially address the underlying cause for the disease while also treating known comorbid mental illness to potentially improve quality of life.

Sales and Marketing

We currently have no sales and marketing personnel. As a clinical stage pharmaceutical company, we currently have no customers. We intend to develop domestic and international marketing, commercial operation, distribution, market access and reimbursement capabilities, or collaborate with third parties that have such infrastructure, in connection with the potential for FDA approval for RP5063 and RP1208.

Manufacturing and Supply

We have developed and validated a good manufacturing practice ("GMP"), process to manufacture the active pharmaceutical ingredient ("API") for our RP5063 drug candidate through contract manufacturers. We have an API contract manufacturer to produce bulk batches under GMP for our anticipated clinical studies and anticipate entering into agreements to produce sufficient API required prior to submitting a New Drug Application ("NDA") filing with the FDA. We do not own or operate manufacturing facilities for the production of RP5063. We expect to depend on third-party suppliers and manufacturing organizations for all of our clinical trial quantities of raw materials and drug substance. We believe there are readily available supplies of all raw materials necessary for the manufacture of RP5063 and RP1208.

Employees

We have five full-time employees, and utilize consultants, clinical research organizations and third parties to perform our pre-clinical studies, clinical studies, manufacturing, regulatory, administrative, and financial functions. We believe our relations with our employees are good. We anticipate that the number of people we employ may grow significantly as we continue to develop our current products or if we develop new product candidates in the future.

Intellectual Property

We strive to protect our intellectual property through a combination of patent, copyright, trademark and trade secrets laws, as well as through confidentiality provisions in our contracts.

We strive to protect our intellectual property that we believe is important to our business, including our proprietary technology platform, our product candidates, and our processes. We seek patent protection in the U.S. and internationally for our products, their methods of use and processes of manufacture, and any other technology to which we have rights, where available and when appropriate. We also rely on trade secrets that may be important to the development of our business.

We also plan to seek trademark protection in the U.S. and outside of the U.S. where available and when appropriate. We intend to use these registered marks in connection with our pharmaceutical research and development as well as our product candidates.

We are the sole owner of a patent portfolio that includes issued patents and pending patent applications covering compositions of matter and methods of use of our product candidates RP5063 and RP1208, as well as related compounds. As of December 31, 2020, our portfolio of intellectual property consists of 60 granted patents and 22 pending patent applications in the United States and in 25 foreign countries.

RP5063 is our first intended commercial product. The original RP5063 patents include composition of matter, and methods of use in treating acute mania, autism, BD, depression, psychosis, and schizophrenia. One RP5063 (brilaroxazine) original patent (U.S. Patent No. 8,188,076) and its 7 divisional/continuation patents have been granted in US. The original RP5063 patents have also been granted in the following foreign countries: Australia, Brazil, Canada, Germany, Spain, France, Great Britain, Hong Kong, Israel, India, Italy, Japan, S. Korea, Liechtenstein, Mexico, Russia, and Slovakia; and pending in China, Columbia, Hong Kong, and Thailand. We believe that our patent portfolio provides good protection of RP5063. All of the US and foreign original RP5063 granted patents and pending patent applications will expire or are expected to expire in 2030, if a patent term extension is not obtained. If and when RP5063 receives regulatory approval, we intend to apply for patent term extensions on patents covering RP5063 in any jurisdiction where patent term extension is available. For example, the expiration date of the first US original RP5063 may be extendable up to 2035.

We also own additional RP5063 granted patents and pending patent applications for additional indications such as attention hyperactivity disorder (U.S. Patent No. 9,907,803, which will expire in 2036), pulmonary arterial hypertension (U.S. Patent No. 10,441,590, and pending applications in China, Hong Kong, Europe, and Japan; all of which will expire or are expected to expire in 2036), Alzheimer's Disease (pending applications in China, Hong Kong, and Europe, which are expected to expire in 2036), Parkinson's Disease (pending application in China and Hong Kong, which are expected to expire in 2036) and pulmonary fibrosis (pending applications in US and PCT, which are expected to expire in 2038).

We further own three US patents (U.S. Patent Nos. 8,207,163; 8,247,420; 8,575,185; all of which will expire in 2030) directed to composition and use of compounds related to RP5063.

We intend to continue to file patent applications to cover additional patentable aspects of RP5063 including new indications and to endeavor to exclude competitors from entering the field.

RP1208 may be our second intended commercial product. The RP1208 patents include composition of matter, and methods of use in treating depression and obesity. Three RP1208 patents have been granted in the US. RP1208 patents have also been granted in the following foreign countries: Australia, China, Columbia, Germany, Spain, France, Great Britain, Hong Kong, Italy, Mexico, Malaysia, Russia, Singapore, South Africa, and Ukraine; and are pending in Canada, Egypt, India, Philippine, and Thailand. We believe that our patent portfolio provides good protection of RP1208. The first RP1208 US patents will expire in 2033, and may be extendable up to 2038. The other two RP1208 continuation US patents will expire in 2032. All foreign RP1208 granted patents and pending patent applications will expire or are expected to expire in 2032. If and when RP1208 receives regulatory approval, we intend to apply for patent term extensions on patents covering RP1208 in any jurisdiction where patent term extension is available.

We also own two families of US patents directed to related compounds of RP1208 covering composition and use. The first family consists of US Patent No. 7,989,500 and its 5 granted continuation patents, which will expire in 2027 or 2028. The second family consists of US Patent No. 8,604,244 and its 2 granted continuation patents, which will expire in 2031.

In addition to patents, we also rely upon proprietary know-how (including trade secrets) to protect our technology and maintain and develop our competitive position. In some situations, maintaining information such as a trade secret may be more appropriate to protect the type of technology than filing a patent application. We seek to protect our confidential and proprietary information in part by confidentiality agreements, and it is our policy generally to have our employees, consultants, scientific advisors, outside scientific collaborators, sponsored researchers, investors, prospective investors and contractors execute such agreements upon the commencement of a relationship with us.

Our success will depend on 1) the ability to obtain and maintain patent and other proprietary rights in commercially important technology, inventions and know-how related to our business, 2) the validity and enforceability of our patents, 3) the continued confidentiality of our trade secrets, and 4) our ability to operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

We cannot be certain that patents will be granted with respect to any of our pending patent applications, nor can we be certain that any of our existing patents will be successful in protecting our technology. For this and more comprehensive risks related to our intellectual property, please see "Risk Factors — Risks Related to our Intellectual Property."

Regulatory Matters

The FDA and other federal, state, local and foreign regulatory agencies impose substantial requirements upon the clinical development, approval, labeling, manufacture, marketing and distribution of drug products. These agencies regulate, among other things, research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, advertising and promotion of our product candidates. The regulatory approval process is generally lengthy and expensive, with no guarantee of a positive result. Moreover, failure to comply with applicable requirements by the FDA or other requirements may result in civil or criminal penalties, recall or seizure of products, injunctive relief including partial or total suspension of production, or withdrawal of a product from the market.

The FDA regulates, among other things, the research, manufacture, promotion and distribution of drugs in the U.S. under the Federal Food, Drug and Cosmetic Act ("FDCA") and other statutes and implementing regulations. The process required by the FDA before prescription drug product candidates may be marketed in the U.S. generally involves the following:

- completion of extensive nonclinical laboratory tests, animal studies and formulation studies, all performed in accordance with the FDA's Good Laboratory Practice regulations;

- submission to the FDA of an Investigational New Drug application ("IND"), which must become effective before human clinical trials may begin;

- performance of adequate and well-controlled human clinical trials in accordance with the FDA's regulations, including Good Clinical Practices, to establish the safety and efficacy of the product candidate for each proposed indication;

- submission to the FDA of an NDA for drug products, or a Biologics License Application ("BLA"), for biologic products;

- satisfactory completion of a preapproval inspection by the FDA of the manufacturing facilities at which the product is produced to assess compliance with current GMP ("cGMP") regulations; and

- the FDA's review and approval of the NDA or BLA prior to any commercial marketing, sale or shipment of the drug.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Nonclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate toxicity in animals and other animal studies. The results of nonclinical tests, together with manufacturing information and analytical data, are submitted as part of an IND to the FDA. Some nonclinical testing may continue even after an IND is submitted. The IND also includes one or more protocols for the initial clinical trial or trials and an investigator's brochure. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to the proposed clinical trials as outlined in the IND and places the clinical trial on a clinical hold. In such cases, the IND sponsor and the FDA must resolve any outstanding concerns or questions before any clinical trials can begin. Clinical trial holds also may be imposed at any time before or during studies due to safety concerns or non-compliance with regulatory requirements. An independent Institutional Review Board ("IRB"), at each of the clinical centers proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center. An IRB considers, among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the consent form signed by the trial participants and must monitor the study until completed.

Clinical Trials

Clinical trials involve the administration of the product candidate to human subjects under the supervision of qualified medical investigators according to approved protocols that detail the objectives of the study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor participant safety. Each protocol for a U.S. study is submitted to the FDA as part of the IND.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap, or be combined.

- Phase 1 clinical trials typically involve the initial introduction of the product candidate into healthy human volunteers. In Phase 1 clinical trials, the product candidate is typically tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics.

- Phase 2 clinical trials are generally conducted in a limited patient population to gather evidence about the efficacy of the product candidate for specific, targeted indications; to determine dosage tolerance and optimal dosage; and to identify possible adverse effects and safety risks. Phase 2 clinical trials, in particular Phase 2b trials, can be undertaken to evaluate clinical efficacy and to test for safety in an expanded patient population at geographically dispersed clinical trial sites.

- Phase 3 clinical trials are undertaken to evaluate clinical efficacy and to test for safety in an expanded patient population at geographically dispersed clinical trial sites. The size of Phase 3 clinical trials depends upon clinical and statistical considerations for the product candidate and disease. Phase 3 clinical trials are intended to establish the overall risk-benefit ratio of the product candidate and provide an adequate basis for product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

Clinical testing must satisfy the extensive regulations of the FDA. Reports detailing the results of the clinical trials must be submitted at least annually to the FDA and safety reports must be submitted for serious and unexpected adverse events. Success in early-stage clinical trials does not assure success in later-stage clinical trials. We, or the FDA or an IRB, may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk.

New Drug Applications

Assuming successful completion of the required clinical trials, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of an NDA (or BLA, in the case of a biologic product). An NDA or BLA also must contain extensive manufacturing information, as well as proposed labeling for the finished product. An NDA or BLA applicant must develop information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with cGMP. The manufacturing process must be capable of consistently producing quality product within specifications approved by the FDA. The manufacturer must develop methods for testing the quality, purity and potency of the final product. In addition, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product does not undergo unacceptable deterioration over its shelf life. Prior to approval, the FDA will conduct an inspection of the manufacturing facilities to assess compliance with cGMP.

The FDA reviews all NDAs and BLAs submitted before it accepts them for filing. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA or BLA must be resubmitted with the additional information and is subject to review before the FDA accepts it for filing. After an application is filed, the FDA may refer the NDA or BLA to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers them carefully when making decisions. The FDA may deny approval of an NDA or BLA if the applicable regulatory criteria are not satisfied. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The FDA may issue a complete response letter, which may require additional clinical or other data or impose other conditions that must be met in order to secure final approval of the NDA or BLA. If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. In addition, the FDA may require us to conduct Phase 4 testing which involves clinical trials designed to further assess a drug's safety and effectiveness after NDA or BLA approval, and may require surveillance programs to monitor the safety of approved products which have been commercialized. Once issued, the FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety or efficacy questions are raised after the product reaches the market.

Section 505(b) NDAs

There are two types of NDAs: the Section 505(b)(1) NDA, or full NDA, and the Section 505(b)(2) NDA. A full NDA is submitted under Section 505(b)(1) of the FDCA, and must contain full reports of investigations conducted by the applicant to demonstrate the safety and effectiveness of the drug. A Section 505(b)(2) NDA may be submitted for a drug for which one or more of the investigations relied upon by the applicant was not conducted by or for the applicant and for which the applicant has no right of reference from the person by or for whom the investigations were conducted. A Section 505(b)(2) NDA may be submitted based in whole or in part on published literature or on the FDA's finding of safety and efficacy of one or more previously approved drugs, which are known as reference drugs. Thus, the filing of a Section 505(b)(2) NDA may result in approval of a drug based on fewer clinical or nonclinical studies than would be required under a full NDA. The number and size of studies that need to be conducted by the sponsor depends on the amount and quality of data pertaining to the reference drug that are publicly available, and on the similarity of and differences between the applicant's drug and the reference drug. In some cases, extensive, time-consuming, and costly clinical and nonclinical studies may still be required for approval of a Section 505(b)(2) NDA.

Patent Protections

An applicant submitting a Section 505(b)(2) NDA must certify to the FDA with respect to the patent status of the reference drug upon which the applicant relies in support of approval of its drug. With respect to every patent listed in the FDA's Orange Book, which is the FDA's list of approved drug products, as claiming the reference drug or an approved method of use of the reference drug, the Section 505(b)(2) applicant must certify that: (1) there is no patent information listed in the orange book for the reference drug; (2) the listed patent has expired; (3) the listed patent has not expired, but will expire on a particular date; (4) the listed patent is invalid or will not be infringed by the manufacture, use, or sale of the product in the Section 505(b)(2) NDA; or (5) if the patent is a use patent, that the applicant does not seek approval for a use claimed by the patent. If the applicant files a certification to the effect of clause (1), (2) or (5), FDA approval of the Section 505(b)(2) NDA may be made effective immediately upon successful FDA review of the application, in the absence of marketing exclusivity delays, which are discussed below. If the applicant files a certification to the effect of clause (3), the Section 505(b)(2) NDA approval may not be made effective until the expiration of the relevant patent and the expiration of any marketing exclusivity delays.

If the Section 505(b)(2) NDA applicant provides a certification to the effect of clause (4), referred to as a paragraph IV certification, the applicant also must send notice of the certification to the patent owner and the holder of the NDA for the reference drug. The filing of a patent infringement lawsuit within 45 days of the receipt of the notification may prevent the FDA from approving the Section 505(b)(2) NDA for 30 months from the date of the receipt of the notification unless the court determines that a longer or shorter period is appropriate because either party to the action failed to reasonably cooperate in expediting the action. However, the FDA may approve the Section 505(b)(2) NDA before the 30 months have expired if a court decides that the patent is invalid or not infringed, or if a court enters a settlement order or consent decree stating the patent is invalid or not infringed.

Notwithstanding the approval of many products by the FDA pursuant to Section 505(b)(2), over the last few years certain brand-name pharmaceutical companies and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged in court, the FDA may be required to change its interpretation of Section 505(b)(2) which could delay or even prevent the FDA from approving any Section 505(b)(2) NDA that we submit. The pharmaceutical industry is highly competitive, and it is not uncommon for a manufacturer of an approved product to file a citizen petition with the FDA seeking to delay approval of, or impose additional approval requirements for, pending competing products. If successful, such petitions can significantly delay, or even prevent, the approval of the new product. Moreover, even if the FDA ultimately denies such a petition, the FDA may substantially delay approval while it considers and responds to the petition.

Marketing Exclusivity

Market exclusivity provisions under the FDCA can delay the submission or the approval of Section 505(b)(2) NDAs, thereby delaying a Section 505(b)(2) product from entering the market. The FDCA provides five-year marketing exclusivity to the first applicant to gain approval of an NDA for a new chemical entity ("NCE"), meaning that the FDA has not previously approved any other drug containing the same active moiety. This exclusivity prohibits the submission of a Section 505(b)(2) NDA for any drug product containing the active ingredient during the five-year exclusivity period. However, submission of a Section 505(b)(2) NDA that certifies that a listed patent is invalid, unenforceable, or will not be infringed, as discussed above, is permitted after four years, but if a patent infringement lawsuit is brought within 45 days after such certification, FDA approval of the Section 505(b)(2) NDA may automatically be stayed until 7½ years after the NCE approval date. The FDCA also provides three years of marketing exclusivity for the approval of new and supplemental NDAs for product changes, including, among other things, new indications, dosage forms, routes of administration or strengths of an existing drug, or for a new use, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by FDA to be essential to the approval of the application. Five-year and three-year exclusivity will not delay the submission or approval of another full NDA; however, as discussed above, an applicant submitting a full NDA under Section 505(b)(1) would be required to conduct or obtain a right of reference to all of the nonclinical and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Other types of exclusivity in the United States include orphan drug exclusivity and pediatric exclusivity. The FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Seven-year orphan drug exclusivity is available to a product that has orphan drug designation and that receives the first FDA approval for the indication for which the drug has such designation. Orphan drug exclusivity prevents approval of another application for the same drug for the same orphan indication, for a period of seven years, regardless of whether the application is a full NDA or a Section 505(b)(2) NDA, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Pediatric exclusivity, if granted, provides an additional six months to an existing exclusivity or statutory delay in approval resulting from a patent certification. This six-month exclusivity, which runs from the end of other exclusivity protection or patent delay, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

Section 505(b)(2) NDAs are similar to full NDAs filed under Section 505(b)(1) in that they are entitled to any of these forms of exclusivity if they meet the qualifying criteria. They also are entitled to the patent protections described above, based on patents that are listed in the FDA's Orange Book in the same manner as patents claiming drugs and uses approved for NDAs submitted as full NDAs.

Breakthrough Therapy Designation

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act ("FDASIA"), was signed. FDASIA Section 902 provides for a new drug designation, Breakthrough Therapy. A Breakthrough Therapy is a drug:

- intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition; and

- preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Fast Track Designation

A Fast Track is a designation by the FDA of an investigational drug which:

- intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition; and
- non-clinical or clinical data demonstrate the potential to address an unmet medical need

Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The benefits of a Fast Track designation include rolling submission of portions of the NDA for the drug candidate and eligibility for priority review of the NDA. Additionally, more frequent meetings and written communication with the FDA regarding the development plan and trial design for the drug candidate are encouraged throughout the entire drug development and review process, with the goal of having earlier drug approval and access for patients.

Other Regulatory Requirements

Maintaining substantial compliance with appropriate federal, state and local statutes and regulations requires the expenditure of substantial time and financial resources. Drug manufacturers are required to register their establishments with the FDA and certain state agencies, and after approval, the FDA and these state agencies conduct periodic unannounced inspections to ensure continued compliance with ongoing regulatory requirements, including cGMPs. In addition, after approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. The FDA may require post-approval testing and surveillance programs to monitor safety and the effectiveness of approved products that have been commercialized. Any drug products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including:

- record-keeping requirements;
- reporting of adverse experiences with the drug;
- providing the FDA with updated safety and efficacy information;
- reporting on advertisements and promotional labeling;
- drug sampling and distribution requirements; and
- complying with electronic record and signature requirements.

In addition, the FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. There are numerous regulations and policies that govern various means for disseminating information to health-care professionals as well as consumers, including to industry sponsored scientific and educational activities, information provided to the media and information provided over the Internet. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label.

The FDA has very broad enforcement authority and the failure to comply with applicable regulatory requirements can result in administrative or judicial sanctions being imposed on us or on the manufacturers and distributors of our approved products, including warning letters, refusals of government contracts, clinical holds, civil penalties, injunctions, restitution and disgorgement of profits, recall or seizure of products, total or partial suspension of production or distribution, withdrawal of approvals, refusal to approve pending applications, and criminal prosecution resulting in fines and incarceration. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. In addition, even after regulatory approval is obtained, later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market.

Coverage and Reimbursement

Sales of our product candidates, if approved, will depend, in part, on the extent to which such products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage or reducing reimbursements for medical products and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Third-party payors decide which therapies they will pay for and establish reimbursement levels. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage and amount of reimbursement to be provided for any drug candidates that we develop will be made on a payor-by-payor basis. Each payor determines whether or not it will provide coverage for a therapy, what amount it will pay the manufacturer for the therapy, and on what tier of its formulary it will be placed. The position on a payor's list of covered drugs, or formulary, generally determines the co-payment that a patient will need to make to obtain the therapy and can strongly influence the adoption of such therapy by patients and physicians. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor to not cover our product candidates could reduce physician usage of our product candidates, once approved, and have a material adverse effect on our sales, results of operations and financial condition.

Other Healthcare Laws

Because of our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors, we will also be subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we will conduct our business, including our clinical research, proposed sales, marketing and educational programs. Failure to comply with these laws, where applicable, can result in the imposition of significant civil penalties, criminal penalties, or both. The U.S. laws that may affect our ability to operate, among others, include: the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; certain state laws governing the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts; the federal healthcare programs' Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs; federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent; federal criminal laws that prohibit executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members; and state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers.

In addition, many states have similar laws and regulations, such as anti-kickback and false claims laws that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, to the extent that our products are sold in a foreign country, we may be subject to similar foreign laws.

The Impact of New Legislation and Amendments to Existing Laws

The FDCA is subject to routine legislative amendments with a broad range of downstream effects. In addition to new legislation, such as the FDA Reauthorization Act of 2017 or the FDASIA in 2012, Congress introduces amendments to reauthorize drug user fees and address emerging concerns every five years. We cannot predict the impact of these new legislative acts and their implementing regulations on our business. The programs established or to be established under the legislation may have adverse effects upon us, including increased regulation of our industry. Compliance with such regulation may increase our costs and limit our ability to pursue business opportunities. In addition, the FDA's regulations, policies and guidance are often revised or reinterpreted by the agency or the courts in ways that may significantly affect our business and products.

We expect that additional federal and state, as well as foreign, healthcare reform measures will be adopted in the future, any of which could result in reduced demand for our products or additional pricing pressure.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a)(3) Exhibits

The following exhibits are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K/A.

Exhibit No.	Exhibit
2.1+	Agreement and Plan of Merger, dated as of July 20, 2020, by and among the Company, Merger Sub, Sponsor in the capacity as the Purchaser Representative, Reviva, and Dr. Bhat in the capacity as the Seller Representative (filed as Exhibit 2.1 to the Company's Current Report on Form 8-K as filed on July 24, 2020, and incorporated herein by reference).
3.1	Certificate of Corporate Domestication (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
3.2	Interim Certificate of Incorporation (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K as filed on December 14, 2020, and incorporated herein by reference).
3.3	Amended and Restated Certificate of Incorporation (filed as Exhibit 3.3 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
3.4	Bylaws of Reviva Pharmaceuticals Holdings, Inc. (filed as Exhibit 3.2 to the Company's Current Report on Form 8-K as filed on December 14, 2020, and incorporated herein by reference).
4.1	Description of Securities (filed as exhibit 4.1 to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021, and incorporated herein by reference).
4.2	Form of Assumed Warrant (filed as Exhibit 4.1 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
4.3	Specimen Warrant Certificate (filed as Exhibit 4.3 to the Company's Form S-1 (File No. 333-226263) as filed on August 16, 2018, and incorporated herein by reference).
4.4	Warrant Agreement, dated August 20, 2018, between the Company and Continental Stock Transfer & Trust Company (filed as Exhibit 4.1 to the Company's Form 8-K as filed on August 24, 2018, and incorporated herein by reference).
4.5	Specimen common stock certificate of the Company (filed as Exhibit 4.4 to the Company's Form S-4 (File No. (333-245057) as filed on November 3, 2020, an incorporated herein by reference)..
10.1#	Employment Agreement, dated as of December 14, 2020, by and between the Company and Dr. Bhat. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.2	Form of Lock-Up Agreement (General) (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K as filed on July 24, 2020, and incorporated herein by reference).
10.3	Lock-Up Agreement, dated as of July 20, 2020, by and among Dr. Bhat, Tenzing and the Purchaser Representative (filed as Exhibit 10.3 to the Company's Current Report on Form 8-K as filed on July 24, 2020, and incorporated herein by reference).

10.4	Non-Competition Agreement, dated as of July 20, 2020, by Dr. Bhat in favor of Tenzing, Reviva and their respective affiliates (filed as Exhibit 10.4 to the Company's Current Report on Form 8-K as filed on July 24, 2020, and incorporated herein by reference).
10.5++ #	Offer of Employment, dated as of October 19, 2020, by and between Narayan Prabhu and Reviva Pharmaceuticals, Inc. (filed as Exhibit 10.16 to the Company's Form S-4 (File No. (333-245057) as filed on November 6, 2020, and incorporated herein by reference).
10.6 #	Offer of Employment, dated as of December 12, 2012, by and between Marc Cantillon, MD and Reviva Pharmaceuticals, Inc. (filed as Exhibit 10.6 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.7 #	Letter Agreement, dated as of October 28, 2015, by and between Marc Cantillon, MD and Reviva Pharmaceuticals, Inc. (filed as Exhibit 10.7 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.8 #	Letter Agreement, dated as of March 15, 2016, by and between Marc Cantillon, MD and Reviva Pharmaceuticals, Inc. (filed as Exhibit 10.8 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.9 #	Form of Indemnification Agreement (filed as Exhibit 10.9 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.10 #	Saxena Indemnification Agreement (filed as Exhibit 10.10 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.11	Form of Non-Redemption Agreement, dated as of December 8, 2020, by and among the Company, Tenzing LLC and the shareholder party thereto (filed as Exhibit 10.11 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.12	Form of Registration Rights Agreement, dated as of December 14, 2020, by and between the Company and the shareholder party thereto (filed as Exhibit 10.12 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.13 #	Reviva Pharmaceuticals Holdings, Inc. 2020 Equity Incentive Plan (filed as Exhibit 10.13 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.14 #	Form of Incentive Stock Option Grant Agreement (filed as Exhibit 10.14 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.15 #	Form of Nonqualified Stock Option Grant Agreement (filed as Exhibit 10.15 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.16 #	Reviva Pharmaceuticals, Inc. 2006 Equity Incentive Plan (filed as Exhibit 10.16 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.17 #	First Amendment to Reviva Pharmaceuticals, Inc. 2006 Equity Incentive Plan (filed as Exhibit 10.17 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.18 #	Form of Assumed Option (filed as Exhibit 10.18 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.19	Form of Note Purchase Agreement, dated as of August 27, 2020, by and between the Company and the investors party thereto (filed as Exhibit 10.19 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.20	Form of Note Purchase Agreement, dated as of August 29, 2020, by and between the Company and the investors party thereto (filed as Exhibit 10.20 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.21	Letter Agreement, dated as of December 14, 2020, by and between the Company, Maxim Group LLC and Maxim Partners LLC (filed as Exhibit 10.21 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).

10.22	Letter Agreement, dated August 20, 2018, by and among the Company, its officers, its directors and the Sponsor (filed as Exhibit 10.3 to the Company's Form 8-K filed on August 24, 2018, and incorporated herein by reference).
10.23	Registration Rights Agreement, dated as of August 20, 2018, by and among Tenzing, the Sponsor, Maxim and the holders party thereto (filed as Exhibit 10.2 to the Company's Form 8-K filed on August 24, 2018, and incorporated herein by reference).
10.24	Escrow Agreement, dated as of December 14, 2020, by and among the Company, Tenzing LLC, Laxminarayan Bhat and Continental Stock Transfer & Trust Company (filed as Exhibit 10.24 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
10.25	Form of Backstop Agreement, by and among Tenzing Acquisition Corp., Reviva Pharmaceuticals, Inc., and the Investor named therein (filed as exhibit 10.1 to the Company's Form 8-K filed on October 21, 2020, and incorporated herein by reference).
10.26	Letter Agreement, dated August 20, 2018, by and among Tenzing, its officers, its directors and the Sponsor (incorporated by reference to Exhibit 10.3 of Tenzing's Form 8-K (File No. 001-38634), filed with the SEC on August 24, 2018).
10.27	Investment Management Trust Agreement, dated August 20, 2018, by and between Tenzing and Continental Stock Transfer & Trust Company, as trustee (incorporated by reference to Exhibit 10.1 of Tenzing's Form 8-K (File No. 001-38634), filed with the SEC on August 24, 2018).
10.28	Securities Purchase Agreement between Tenzing and Tenzing LLC (incorporated by reference to Exhibit 10.4 of Tenzing's Form S-1 (File No. 333-226263), filed with the SEC on July 20, 2018).
10.29	Form of Amended and Restated Unit Purchase Agreement between Tenzing and the Sponsor (incorporated by reference to Exhibit 10.4 of Tenzing's Form S-1 (File No. 333-226263), filed with the SEC on August 16, 2018).
10.30	Form of Unit Purchase Agreement between Tenzing and Maxim Group LLC (incorporated by reference to Exhibit 10.7 of Tenzing's Form S-1 (File No. 333-226263), filed with the SEC on August 16, 2018).
10.31	Promissory Note, dated February 10, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on February 14, 2020, and incorporated herein by reference).
10.32	Promissory Note, dated May 21, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on May 21, 2020, and incorporated herein by reference).
10.33	Promissory Note, dated July 24, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on July 29, 2020, and incorporated herein by reference).
10.34	Promissory Note, dated August 18, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on August 18, 2020, and incorporated herein by reference).
10.35	Promissory Note, dated September 24, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on September 25, 2020, and incorporated herein by reference).
10.36	Promissory Note, dated November 12, 2020, issued by Tenzing Acquisition Corp. to Tenzing LLC (filed as exhibit 10.1 to the Company's Form 8-K filed on November 13, 2020, and incorporated herein by reference).
21.1	List of Subsidiaries of the Company (filed as Exhibit 21.1 to the Company's Current Report on Form 8-K as filed on December 18, 2020 and incorporated herein by reference).
24.1	Power of Attorney (incorporated by reference to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).
31.1*	Certification of Chief Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a)
31.2*	Certification of Chief Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a)
32.1**	Certification of Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. Section 1350 (filed as exhibit 32.1 to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).
101.INS	XBRL Instance Document (filed as exhibit 101.INS to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

101.SCH XBRL Taxonomy Extension Schema Document (filed as exhibit 101.SCH to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

101.CAL XBRL Taxonomy Extension Calculation Linkbase Document (filed as exhibit 101.CAL to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

101.DEF XBRL Taxonomy Extension Definition Linkbase Document (filed as exhibit 101.DEF to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

101.LAB XBRL Taxonomy Extension Label Linkbase Document (filed as exhibit 101.LAB to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

101.PRE XBRL Taxonomy Extension Presentation Linkbase Document (filed as exhibit 101.PRE to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021).

* Filed herewith.

** The certifications furnished in Exhibit 32.1 (included as exhibit 32.1 to the Company's Annual Report on Form 10-K filed with the SEC on March 22, 2021) are deemed to accompany the Annual Report on Form 10-K filed with the SEC on March 22, 2021 and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the registrant specifically incorporates it by reference.

\+ The exhibits and schedules to this Exhibit have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant hereby agrees to furnish a copy of any omitted schedules to the Commission upon request.

++ Certain information in this exhibit has been omitted pursuant to Item 601(a)(6) of Regulation S-K.

\# Indicates management contract or compensatory plan.

SIGNATURES

Pursuant to the requirements of Section 13 and 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Reviva Pharmaceuticals Holdings, Inc.
(Registrant)

Date: March 24, 2021

/s/ Laxminarayan Bhat
Laxminarayan Bhat
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.1

CERTIFICATION OF THE CHIEF EXECUTIVE OFFICER
Pursuant to
Securities Exchange Act Rules 13a-14(a) and 15d-14(a),
As Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Laxminarayan Bhat, hereby certify that:

1. I have reviewed this Annual Report on Form 10-K/A (Amendment No. 1 to Annual Report on Form 10-K for the fiscal year ended December 31, 2020) of Reviva Pharmaceuticals Holdings, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report.

Dated: March 24, 2021

/s/ Laxminarayan Bhat
Laxminarayan Bhat
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF THE CHIEF FINANCIAL OFFICER
Pursuant to
Securities Exchange Act Rules 13a-14(a) and 15d-14(a),
As Adopted Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Narayan Prabhu, hereby certify that:

1. I have reviewed this Annual Report on Form 10-K/A (Amendment No. 1 to Annual Report on Form 10-K for the fiscal year ended December 31, 2020) of Reviva Pharmaceuticals Holdings, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report.

Dated: March 24, 2021

/s/ Narayan Prabhu
Narayan Prabhu
Chief Financial Officer
(Principal Financial and Accounting Officer)