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

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of report (Date of earliest event reported): December 7, 2020

Constellation Pharmaceuticals, Inc.
(Exact Name of Registrant as Specified in Charter)

Delaware	**001-38584**	**26-1741721**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

215 First Street, Suite 200 **Cambridge, Massachusetts** **(Address of Principal Executive Offices)**	**02142** **(Zip Code)**

Registrant's telephone number, including area code: (617) 714-0555

Not applicable
(Former Name or Former Address, if Changed Since Last Report)

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

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

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

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

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

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	CNST	Nasdaq Global Select Market

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

Emerging growth company ☒

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. ☐

Item 8.01 Other Events.

MANIFEST Trial of CPI-0610

We are currently conducting MANIFEST, a Phase 2 clinical trial of CPI-0610 as a monotherapy and in combination with ruxolitinib (marketed as Jakafi®/Jakavi®) in patients with myelofibrosis, or MF, a progressive hematological cancer. In this trial, we are treating patients who are Janus-kinase-1/2, or JAK1/JAK2-, inhibitor-naïve, a first-line, or 1L, setting, as well as patients who are refractory to or intolerant of, or have had a sub-optimal response to, ruxolitinib, a second-line, or 2L, setting. We presented preliminary clinical and translational data for CPI-0610 as a monotherapy and in combination with ruxolitinib at the Annual Meeting of the American Society of Hematology, or ASH, in December 2020, based on a September 29, 2020 data cut-off that reflected an analysis of 63 1L patients and 94 2L or later patients.

In the 1L setting, we are testing CPI-0610 in combination with ruxolitinib in JAK1/JAK2-inhibitor-naïve patients. The primary endpoint in the 1L setting is the proportion of patients who achieve at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment, or SVR35. In the 2L setting, we are stratifying patients for dependence on red-blood-cell, or RBC, transfusions. In transfusion-dependent, or TD, patients, the primary endpoint is the proportion of patients who are transfusion dependent, or TD, at baseline who convert to transfusion independence, or TI. TD, based on Gale criteria, is defined to mean two or more RBC transfusions per month during the 12 weeks prior to enrollment. TI is defined to mean an absence of RBC transfusions over any consecutive 12-week period following enrollment. For non-TD patients in the 2L setting, the primary endpoint is the proportion of patients who achieve SVR35.

In each setting, we are also measuring improvements in Total Symptom Score, or TSS, as measured by the Myelofibrosis Symptom Assessment form, version 4.0, which is a patient-reported outcome that asks patients to rate the severity of their MF symptoms. We are also measuring morphological change in bone marrow fibrosis.

We have initiated a randomized, double-blind, pivotal Phase 3 clinical trial of CPI-0610 in combination with ruxolitinib versus placebo plus ruxolitinib, called MANIFEST-2. We plan to enroll approximately 310 JAK-inhibitor-naïve patients with primary myelofibrosis or post-ET or post-PV myelofibrosis who have splenomegaly and symptoms requiring therapy. Patients will be randomized 1:1 to a CPI-0610 and ruxolitinib arm or a placebo and ruxolitinib arm. The primary endpoint is SVR35 at 24 weeks and the key secondary endpoint is TSS50 at 24 weeks.

Preliminary Data from Our MANIFEST Trial

On December 7, 2020, preliminary data from MANIFEST as of September 29, 2020 were presented in oral and poster presentations at ASH. We believe that these preliminary data from MANIFEST suggest that CPI-0610 has the potential to offer meaningful benefits beyond the current standard of care in MF and may have disease-modifying effects.

Arm 1: CPI-0610 Monotherapy in Ruxolitinib-Refractory, -Intolerant or -Ineligible Patients (2L)

In Arm 1, we are evaluating CPI-0610, as a monotherapy in ruxolitinib-refractory or -intolerant patients with MF. Patients are treated in a 21-day dosing cycle and are administered CPI-0610 starting at 125 mg once per day, which may be titrated up to 225 mg, with 14 days on treatment and seven days off treatment. The primary endpoints are the proportion of patients who achieve a SVR35 for non-TD patients and the rate at which TD patients convert to TI for the cohort of patients who were TD at baseline.

The tables below present preliminary data as of September 29, 2020 from Arm 1 of MANIFEST.

	Arm 1A: TD	**Arm 1B: non-TD**
SVR35 at 24 weeks(1)	1 of 13 evaluable (8%)	7 of 23 evaluable (30%)
SVR (%), median change at 24 weeks	-11%	-29%
TSS50 at 24 weeks(1)	1 of 13 evaluable (8%)	10 of 21 evaluable (48%)
TSS (%), median change at 24 weeks	-22%	-56%
Hemoglobin increase of at least 1.5 mg/dL(2)	N/A	10 of 20 evaluable (50%)
TD to TI conversion(3)	3 of 14 evaluable (21%)	N/A
Median duration of TI	32 weeks	N/A

(1) Patients are evaluable for SVR35 or TSS50 at week 24 if they had a week-24 assessment by the data cutoff date or discontinued treatment after having a week-12 assessment.

(2) Patients are evaluable for hemoglobin increase if they had been on treatment for at least 12 weeks and did not have any transfusions for 12 weeks prior to starting treatment.

(3) Patients are evaluable for conversion to TI if they started treatment at least 24 weeks prior to the data cutoff date or if they had been on treatment for at least 12 weeks by the data cutoff day and achieved the conversion or would have failed to achieve the conversion by week 24.

Arm 2: CPI-0610 Add-on to Ruxolitinib in Patients with Suboptimal Response to Ruxolitinib (2L)

In Arm 2, we are evaluating CPI-0610 in combination with ruxolitinib, in patients with MF with suboptimal response to ruxolitinib. CPI-0610 is added to treatment with ruxolitinib and CPI-0610 is dosed according to the schedule as in Arm 1 and patients continue treatment with ruxolitinib at their last stable dose with no titration of ruxolitinib. The primary endpoints are the proportion of patients who achieve a SVR35 for non-TD patients and the rate at which TD patients convert to TI for the cohort of patients who were TD at baseline.

The tables below present preliminary data as of September 29, 2020 from Arm 2 of MANIFEST.

	Arm 2A: TD	**Arm 2B: non-TD**
SVR35 at 24 weeks(1)	7 of 33 evaluable (21%)	6 of 21 evaluable (29%)
SVR (%), median change at 24 weeks	-19%	-17%
TSS50 at 24 weeks(1)	15 of 33 evaluable (46%)	8 of 21 evaluable (38%)
TSS (%), median change at 24 weeks	-58%	-45%
Hemoglobin increase of at least 1.5 mg/dL(2)	N/A	8 of 22 evaluable (36%)
TD to TI conversion(3)	13 of 36 evaluable (36%)	N/A
Median duration of TI	27 weeks	N/A

(1) Patients are evaluable for SVR35 or TSS50 at week 24 if they had a week-24 assessment by the data cutoff date or discontinued treatment after having a week-12 assessment.

(2) Patients are evaluable for hemoglobin increase if they had been on treatment for at least 12 weeks and did not have any transfusions for 12 weeks prior to starting treatment.

(3) Patients are evaluable for conversion to TI if they started treatment at least 24 weeks prior to the data cutoff date or if they had been on treatment for at least 12 weeks by the data cutoff day and achieved the conversion or would have failed to achieve the conversion by week 24.

Arm 3: Combination of CPI-0610 and Ruxolitinib in JAK-Inhibitor-Naïve Patients (1L)

In Arm 3, we are evaluating the combination of CPI-0610 and ruxolitinib in JAK1/JAK2-inhibitor-naïve patients with MF. Patients are treated with CPI-0610 according to the schedule as in Arm 1 and receive a starting dose of either 10 mg or 15 mg twice per day of ruxolitinib, depending on the platelet count at baseline, up to a maximum dose of 25 mg twice per day. The primary endpoint is the proportion of patients who achieve a SVR35.

The tables below present preliminary data as of September 29, 2020 from Arm 3 of MANIFEST.

	Arm 3
SVR35 at 24 weeks(1)	42 of 63 evaluable (67%)
SVR (%), median change at 24 weeks	-50%
TSS50 at 24 weeks(1)	34 of 60 evaluable (57%)
TSS (%), median change at 24 weeks	-59%

(1) Patients are evaluable for efficacy at week 24 if they had a week 24 spleen volume assessment or TSS assessment, as applicable, by the data cutoff date or discontinued prior to week 24 for any reason.

Translational Data

Patients are evaluable for improvement in bone marrow fibrosis if they have a baseline bone marrow biopsy and at least one post-baseline biopsy after 24 weeks. Bone marrow assessments were made based on a local pathology read. The translational data for change in bone marrow fibrosis is as of the September 29, 2020 data cutoff date.

In Arm 1, 6 of 29 evaluable patients (21%) with evaluable samples had at least one grade improvement in bone marrow fibrosis, and in five of these six patients (83%), the improvements occurred within six months of starting treatment in the trial. Two of the 29 evaluable patients had worsening in bone marrow fibrosis.

In Arm 2, 16 of 39 evaluable patients (41%) with evaluable samples had at least one grade improvement in bone marrow fibrosis, and in 13 of these 16 patients (81%), the improvements occurred within six months of starting treatment in the trial. Three of the 39 evaluable patients had worsening in bone marrow fibrosis.

In Arm 3, 16 of 48 evaluable patients (33%) with evaluable samples had at least one grade improvement in bone marrow fibrosis, and in 14 of these 16 patients (88%), the improvements occurred within six months of starting treatment in the trial. Two of the 48 evaluable patients had worsening in bone marrow fibrosis.

Safety Data

As of September 29, 2020, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated in each arm of the MANIFEST trial. In Arm 1, 23 patients remained on active treatment and 23 had discontinued. In Arm 2, 40 patients remained on active treatment and 38 had discontinued. In Arm 3, 66 patients remained on active treatment and 12 had discontinued.

The most common treatment-emergent adverse events, or TEAEs, of any grade irrespective of causality observed in 46 evaluable patients in Arm 1 were nausea, diarrhea, thrombocytopenia, asthenic conditions, dysgeusia, respiratory tract infections, cough, weight decrease and constipation, each of which occurred in 20% or more of patients. A total of 29 patients (63%) reported at least one grade 3 or higher TEAE. A total of 14 patients reported thrombocytopenia of any grade and seven patients reported anemia of any grade. Of the most common TEAEs, those that were grade 3 were thrombocytopenia (seven patients), diarrhea (two patients) and constipation, respiratory tract infection and weight decrease (one patient each). Other grade 3 or higher TEAEs included anemia (six patients), hyperuricemia (four patients), hyperkalemia (three patients) and dyspnea (three patients). Nine patients discontinued treatment due to TEAEs.

The most common TEAEs of any grade irrespective of causality observed in 78 evaluable patients in Arm 2 were diarrhea, thrombocytopenia, respiratory tract infections, nausea, asthenic conditions, cough and dysgeusia, each of which occurred in 20% or more of patients. A total of 35 patients reported thrombocytopenia of any grade and 11 patients reported anemia of any grade. A total of 45 patients (58%) reported at least one grade 3 or higher TEAE. Of the most common TEAEs, those that were grade 3 or grade 4 were thrombocytopenia (18 patients with grade 3 and two patients with grade 4), respiratory tract infection (four patients with grade 4), diarrhea (three patients with grade 3), asthenic conditions (three patients with grade 3) and nausea (two patients with grade 3). A total of eight patients reported anemia of grade 3 and one patient reported anemia of grade 4. Nine patients discontinued treatment due to TEAEs, including six grade 5 TEAEs. The grade 5 TEAEs consisted of acute kidney injury, traumatic subdural hematoma (patient tripped and fell), brain stem hemorrhage (no concomitant thrombocytopenia), disease progression, congestive heart failure, and transformation to AML.

The most common TEAEs of any grade irrespective of causality observed in 78 evaluable patients in Arm 3 were anemia, thrombocytopenia, diarrhea, dysgeusia, asthenic conditions, musculoskeletal pain, respiratory tract infections, nausea, abdominal pain and dizziness, each of which occurred in 15% or more of patients. A total of 26 patients reported anemia of any grade and 25 patients reported thrombocytopenia of any grade. A total of 34 patients (44%) reported at least one grade 3 or higher TEAE. Of the most common TEAEs, those that were grade 3 or grade 4 were anemia (22 patients with grade 3 and one patient with grade 4) and thrombocytopenia (four patients with grade 4 and two patients with Grade 4). Four patients discontinued treatment due to TEAEs, including two grade 5 TEAEs. The grade 5 TEAEs consisted of one patient with multiorgan failure due to sepsis secondary to bacterial endocarditis and one patient with multiorgan failure due to sepsis secondary to community acquired pneumonia.

SIGNATURES

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

CONSTELLATION PHARMACEUTICALS, INC.

Date: December 7, 2020

By: /s/ Emma Reeve
Name: Emma Reeve
Title: Chief Financial Officer