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 9, 2019

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

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. The U.S. Food and Drug Administration, or FDA, granted orphan drug designation to CPI-0610 for the treatment of MF on November 20, 2019.

We are enrolling MF patients who are Janus-kinase-, or JAK-, 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. In the 1L setting, we are testing CPI-0610 in combination with ruxolitinib in JAK-inhibitor-naïve patients with the aim of measuring spleen volume reduction and symptom improvement, among other relevant parameters. In the 2L setting, we are stratifying patients for dependence on red-blood-cell, or RBC, transfusions. In transfusion-dependent, or TD, patients, we are measuring conversion to transfusion independence, or TI, in addition to spleen volume reduction and symptom improvement, among other relevant parameters. In non-TD patients, we are measuring spleen volume reduction and symptom improvement, among other relevant parameters.

The primary endpoints of MANIFEST are the reduction in spleen volume from baseline measured by MRI, or SVR, and the rate at which patients that are TD at baseline convert to 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. Secondary endpoints of the trial include change in patient-reported outcomes. We are 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, and Patient Global Impression of Change, or PGIC, which is an assessment of patient's perception of change in their MF symptoms over time. We are also measuring morphological change in bone marrow fibrosis.

Updated Preliminary Data from Our Ongoing MANIFEST Trial

On December 9, 2019, updated preliminary data from MANIFEST were presented at the Annual Meeting of the American Society of Hematology, or 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. As of October 17, 2019, an aggregate of 120 patients were enrolled in MANIFEST.

One presentation related to Arms 1 and 2 of MANIFEST, in which we are evaluating CPI-0610, either as a monotherapy (Arm 1) or in combination with ruxolitinib (Arm 2) in ruxolitinib-refractory or -intolerant patients with MF. The second presentation related to Arm 3, in which we are evaluating the combination of CPI-0610 and ruxolitinib in JAK-inhibitor-naïve patients with MF.

The presentation relating to Arms 1 and 2 included updated preliminary data as of October 17, 2019 that showed signs of clinical improvement in spleen volume reduction, patient-reported symptom improvement, hemoglobin increases, bone marrow fibrosis score improvement and conversion to transfusion independence in transfusion-dependent patients. As of October 17, 2019, in Arm 2, six of 14 ruxolitinib-refractory or -intolerant patients who were TD at baseline had converted to TI. Neither of the two ruxolitinib-refractory or -intolerant patients in Arm 1 who were TD at baseline had converted to TI as of October 17, 2019.

The presentation relating to Arm 3 included updated preliminary data as of October 17, 2019 that showed signs of CPI-0610 clinical activity in JAK-inhibitor-naïve patients. As of October 17, 2019, 12 of 15 evaluable JAK-inhibitor-naïve patients treated with a combination of CPI-0610 and ruxolitinib for at least 12 weeks experienced at least a 35% reduction in spleen volume from baseline, or SVR35, and ten of 14 evaluable patients reported at least a 50% reduction in Total Symptom Score, or TSS50, both of which are measures of clinical activity that have been the basis for approval of other existing MF treatments.

As a result of preliminary data in JAK-inhibitor-naïve patients and in TD ruxolitinib-refractory or -intolerant patients, we have expanded enrollment in Arms 2 and 3. We expanded Arm 3 for JAK-inhibitor-naïve patients from 43 patients to up to 101 patients. We expanded the cohort in Arm 2 for TD patients being treated with CPI-0610 + ruxolitinib from 16 to up to 60 patients. We are planning for a potential pivotal trial in the 1L setting that we expect to begin in 2020.

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

In this arm, 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 at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment for non-TD patients and the rate at which TD patients convert to TI.

The tables below present updated preliminary data as of October 17, 2019 from Arm 1 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	36
Number of patients evaluable for efficacy	15
SVR35, best response	1 of 13 evaluable[1]
SVR35 at 24 weeks	0 of 9 evaluable[2]
SVR	11 of 13 evaluable[1]
SVR (%), median best change	-26.8%
SVR (%), median best change range	-57.5% to 10.8%
TSS50, best response	6 of 10 evaluable[1]
TSS50 at 24 weeks	3 of 6 evaluable[2]
TSS (%), median best change	-58.3%
TSS (%), median best change range	-90.1% to 13.4%
PGIC improvement, number of patients	14 of 15 evaluable[1]
PGIC much / very much improved	10 of 15 evaluable[1]
Hemoglobin increase of at least 1.5 mg/dL	6 of 11
Improvement in bone marrow fibrosis	2 of 9 evaluable[2]
TD to TI conversion	0 of 2 evaluable

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for≥ 12 weeks
(2) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for≥ 24 weeks
(3) quantification of bone marrow cellularity is scored to one of four grade categories based on a review by a pathologist

Arm 2: CPI-0610 Add-on to Ruxolitinib in Ruxolitinib-Refractory or -Intolerant Patients (2L)

In this arm, 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 at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment for non-TD patients and the rate at which TD patients convert to TI.

The tables below present updated preliminary data as of October 17, 2019 from Arm 2 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	54
Number of patients evaluable for efficacy	33
SVR35, best response	5 of 32 evaluable[1]
SVR35 at 24 weeks	3 of 25 evaluable[2]
SVR	29 of 32 evaluable[1]
SVR (%), median best change	-17.1%
SVR (%), median best change range	-53.6% to 4.7%
TSS50, best response	19 of 31 evaluable[1]
TSS50 at 24 weeks	12 of 26 evaluable[2]
TSS (%), median best change	-61.8%
TSS (%), median best change range	-100% to 0.9%
PGIC improvement	30 of 33 evaluable[1]
PGIC much / very much improved	23 of 33 evaluable[1]
Hemoglobin increase of at least 1.5 mg/dL	2 of 15
Improvement in bone marrow fibrosis	10 of 23 evaluable[3]
TD to TI conversion	6 of 14 evaluable

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for≥ 12 weeks
(2) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for≥ 24 weeks
(3) quantification of bone marrow cellularity is scored to one of four grade categories based on a review by a pathologist

In Cohort 2A, which enrolled patients that were TD at baseline, three of 12 evaluable patients had a SVR35 response at week 24 and the evaluable patients had a median best percent change in spleen volume of -24.9%. Seven of 13 evaluable patients had a TSS50 response at week 24 and the evaluable patients had a median best percent change in TSS of -58.8% and nine of 12 evaluable patients reported PGIC improvement at 24 weeks. For the patients in this cohort evaluable after 12 weeks, five of 17 evaluable patients had a SVR35 response at any time (best response) and the evaluable patients had a median best percent change in spleen volume of -21.2%. 13 of 17 evaluable patients had a TSS50 response at any time (best response) and the evaluable patients had a median best percent change in TSS of -71% and 16 of 18 evaluable patients reported PGIC improvement.

In Cohort 2B, which enrolled patients that were not TD at baseline, no evaluable patients (0 of 13) had a SVR35 response at week 24 and the evaluable patients had median best percent change in spleen volume of -10.9%. Five of 13 evaluable patients had a TSS50 response at week 24 and the evaluable patients had a median best percent change in TSS of -44.1% and nine of 13 evaluable patients reported PGIC improvement at 24 weeks. For the patients in this cohort evaluable after 12 weeks, no patients (0 of 15) had a SVR35 response at any time (best response) and the evaluable patients had a median best percent change in spleen volume of -15.8%. Six of 14 evaluable patients had a TSS50 response at any time (best response) and the evaluable patients had a median best percent change of -49% and 14 of 15 evaluable patients reported PGIC improvement.

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

In this arm, patients are treated with CPI-0610 according to the schedule as in Arm 1 and receive either 10 mg or 15 mg twice per day of ruxolitinib, depending on the platelet count at baseline, up to a maximum dose of 20 mg twice per day. The primary endpoints are the proportion of patients who achieve at least a 35% reduction in spleen volume from baseline after 24 weeks of treatment.

The tables below present updated preliminary data as of October 17, 2019 from Arm 3 of MANIFEST.

	As of October 17, 2019
Number of patients enrolled	30
Number of patients evaluable for efficacy	15 (SVR35) / 14 (TSS50)
SVR35, at 12 weeks	12 of 15 evaluable[1]
SVR (%), median change at 12 weeks	-49.7%
SVR (%), median change range at 12 weeks	-80.8% to -17.0%
TSS50, 12 weeks	10 of 14 evaluable[1]
TSS (%), median change at 12 weeks	-60.3%
TSS (5), median change range at 12 weeks	-100% to 90.2%

(1) evaluable patients had a scan at baseline and at least one post-baseline scan or assessment available, received treatment for≥ 12 weeks

As of October 17, 2019, CPI-0610, both as monotherapy and in combination with ruxolitinib, was generally well tolerated in each arm of the MANIFEST trial. In Arm 1, 34 patients remained active on treatment and two had discontinued. In Arm 2, 41 patients remained on active treatment and 13 had discontinued, including one patient who was initially transplant ineligible, who underwent stem cell transplantation after six cycles of CPI-0610 add-on to ruxolitinib treatment. All 30 patients in Arm 3 remained active on treatment as of October 17, 2019.

Three patients in Arm 2 discontinued treatment due to grade 5 (fatal) adverse events. These adverse events consisted of acute kidney injury, traumatic subdural hematoma (patient tripped and fell) and brain stem hemorrhage (patient without concomitant thrombocytopenia). We assessed the acute kidney injury as unlikely related to CPI-0610 and unlikely related to ruxolitinib. The clinical investigator assessed the acute kidney injury as possibly related to CPI-0610 and not related to ruxolitinib. We believe the acute kidney injury event was likely related to the concomitant use of other medications and possibly due to progression of disease. We and the relevant clinical investigator assessed the two other deaths as unrelated to CPI-0610.

The most common treatment-emergent adverse events, or TEAEs, of any grade observed in Arm 1 included diarrhea, nausea, headache, cough, vomiting, thrombocytopenia, dysgeusia, back pain, upper respiratory tract infection and hyperuricemia, each of which occurred in 10% or more of patients. The most frequently observed grade 3 or higher TEAEs irrespective of causality in Arm 1 were dyspnea (three patients), anemia (two patients), diarrhea (two patients), thrombocytopenia (two patients), hyponatremia (two patients) and neutropenia (two patients). TEAEs of grade 3 or higher considered related to CPI-0610 consisted of diarrhea and thrombocytopenia (two patients each), constipation, decreased appetite, diarrhea, dyspnea, neutropenia, rash, taste disorder and upper abdominal pain (one patient each).

The most common TEAEs of any grade observed in Arm 2 included diarrhea, thrombocytopenia (including platelet count decrease), nausea, fatigue, cough, upper respiratory tract infection, vomiting, constipation, pain in extremity, peripheral edema, contusion, abdominal distension, decreased appetite, paresthesia and arthralgia, each of which occurred in 10% or more of patients. The most

frequently observed grade 3 or higher TEAEs irrespective of causality in Arm 2 were thrombocytopenia (including platelet count decrease) (seven patients), anemia (four patients), fatigue (three patients) and pneumonia (three patients). TEAEs of grade 3 or higher considered related to CPI-0610 by clinical investigator consisted of thrombocytopenia (including platelet count decrease) (seven patients), anemia (three patients), diarrhea and fatigue (two patients each), acute kidney injury, blood creatinine increase, nausea, neutropenia and vomiting (one patient each).

The most common TEAEs of any grade observed in Arm 3 included diarrhea, anemia, nausea, thrombocytopenia (including platelet count decrease), dizziness, muscle spasms, constipation, dyspnea and mouth ulceration, each of which occurred in 10% or more of patients. There were three patients with grade 3 anemia and one patient with grade 4 thrombocytopenia who required a dose interruption for three weeks.

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 9, 2019

By: /s/ Karen Valentine
Name: Karen Valentine
Title: Chief Legal Officer and General Counsel