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): June 12, 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**	**02142**
(Address of Principal Executive Offices)	**(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. We are enrolling MF 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. At the Annual Congress of the European Hematology Association, or EHA, in June 2020, we presented preliminary data that showed signs of activity for CPI-0610 across a broad range of parameters as both a first-line and second-line treatment for patients with MF. We plan to initiate a Phase 3 clinical trial of CPI-0610 in combination with ruxolitinib versus placebo plus ruxolitinib in MF patients who are JAK1/JAK2-, inhibitor-naïve in the second half of 2020.

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, 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 MANIFEST Trial

On June 12, 2020, updated preliminary data from MANIFEST as of April 17, 2020 were presented in posters at EHA. 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 April 17, 2020, an aggregate of 177 patients were enrolled in MANIFEST.

One poster related to Arm 1 of MANIFEST, in which we are evaluating CPI-0610, as a monotherapy in ruxolitinib-refractory or -intolerant patients with MF. A second poster related to Arm 2, in which we are evaluating CPI-0610 in combination with ruxolitinib, in patients with MF with suboptimal response to ruxolitinib. The third poster related to Arm 3 in which we are evaluating the combination of CPI-0610 and ruxolitinib in JAK1/JAK2-inhibitor-naïve patients with MF.

The updated preliminary data showed signs of clinical improvement in spleen volume reduction, patient-reported symptom improvement, hemoglobin increases and conversion to transfusion independence in transfusion-dependent patients. In Arm 1, three of 14 (21.4%) evaluable patients in Cohort 1A, which included patients who were TD at baseline, reported a conversion from TD to TI, and five of 21 (23.8%) evaluable patients in Cohort 1B, which included patients who were not TD at baseline, achieved a SVR35. In Arm 2, 11 of 32 (34.4%) evaluable patients in Cohort 2A, which included patients who were TD at baseline, reported a conversion from TD to TI, and four of 18 (22.2%) evaluable patients in Cohort 2B, which included patients who were not TD at baseline, achieved a SVR35.

In Arm 3, 19 of 30 (63.3%) evaluable patients reported a SVR35, and 17 of 29 (58.6%) evaluable patients reported at least a 50% reduction in TSS, 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, we are planning to initiate a Phase 3, randomized, double-blind, active-controlled study of CPI-0610 in combination with ruxolitinib in the 1L setting to begin in the second half of 2020.

Arm 1: CPI-0610 Monotherapy in Ruxolitinib-Refractory, -Intolerant or -Ineligible 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 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 updated preliminary data as of April 17, 2020 from Arm 1 of MANIFEST.

	Arm 1A: TD	Arm 1B: non-TD
Number of patients enrolled	16	27
SVR35 at 24 weeks[1]	0 of 10 evaluable	5 of 21 evaluable
SVR (%), median change at 24 weeks	-17.4%	-28.2%
SVR (%), median change range at 24 weeks	-38.8% to 64.7%	-51.0% to 14.4%
TSS50 at 24 weeks[1]	1 of 12 evaluable	9 of 19 evaluable
TSS (%), median change at 24 weeks	-5.8%	-55.6%
TSS (%), median change range at 24 weeks	-69.9% to 31.7%	-100% to 24.7%
Hemoglobin increase of at least 1.5 mg/dL	N/A	11 of 19
TD to TI conversion[2]	3 of 14 evaluable	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 conversion to TI if they had been on treatment for at least 24 weeks by 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 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 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 updated preliminary data as of April 17, 2020 from Arm 2 of MANIFEST.

	Arm 2A: TD	Arm 2B: non-TD
Number of patients enrolled	44	26
SVR35 at 24 weeks[1]	5 of 24 evaluable	4 of 18 evaluable
SVR (%), median change at 24 weeks	-21.9%	-15.8%
SVR (%), median change range	-53.6% to 47.9%	-89.8% to 16.3%
TSS50 at 24 weeks[1]	12 of 26 evaluable	7 of 19 evaluable
TSS (%), median change at 24 weeks	-52.8%	-45.0%
TSS (%), median change range at 24 weeks	-100% to 24.4%	-100% to 21.9%
Hemoglobin increase of at least 1.5 mg/dL	N/A	4 of 22
TD to TI conversion[2]	11 of 32 evaluable[2]	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 conversion to TI if they had been on treatment for at least 24 weeks by 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 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 endpoint is the proportion of patients who achieve a SVR35.

The tables below present updated preliminary data as of April 17, 2020 from Arm 3 of MANIFEST.

Number of patients enrolled	64
SVR35, at 12 weeks[1]	37 of 51 evaluable
SVR (%), median change at 12 weeks	-50.8%
SVR (%), median change range at 12 weeks	-90.2% to -2.8%
SVR35 at 24 weeks[2]	19 of 30 evaluable
SVR (%), median change at 24 weeks	-52.9%
SVR (%), median change range at 24 weeks	-84.4% to 23.7%
TSS50 at 24 weeks[2]	17 of 29 evaluable
TSS (%), median change at 24 weeks	-64.0%
TSS, median change range at 24 weeks	-100% to 24.2%

(1) Patients are evaluable for efficacy at week 12 if they had week 12 spleen volume assessment by the data cutoff date or discontinued prior to week 12 due to any reason.
(2) Patients are evaluable for efficacy at week 24 if they had a week 24 spleen volume assessment by the data cutoff date or discontinued due to any reason.

As of April 17, 2020, 25 of 81 evaluable patients across the three treatment arms showed evidence of improvement in bone marrow fibrosis by at least one grade, as assessed by local pathology read. 21 of the 25 patients with improvement showed these results within 24 weeks of treatment. 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 conducted by pathologists at the local study site. We plan to re-assess the results in a centralized, blinded manner and to provide updated data following central review later in 2020.

As of April 17, 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, 27 patients remained on active treatment and 16 had discontinued. In Arm 2, 44 patients remained on active treatment and 26 had discontinued, including two patients who underwent stem cell transplantation after six and 11 cycles of CPI-0610 add-on to ruxolitinib treatment, respectively. In Arm 3, 57 patients remained on active treatment and seven had discontinued, including one patient who underwent stem cell transplantation after nine cycles of CPI-0610 in combination with ruxolitinib.

Four patients in Arm 2 and two patients in Arm 3 discontinued treatment due to grade 5 (fatal) adverse events. These adverse events consisted of acute kidney injury, traumatic subdural hematoma (patient tripped and fell), brain stem hemorrhage (patient without concomitant thrombocytopenia), disease progression, multi-organ failure due to sepsis secondary to bacterial endocarditis and heart failure due to sepsis secondary to community acquired pneumonia. The relevant clinical investigator considered the acute kidney injury as possibly related to CPI-0610 and not related to ruxolitinib. The relevant clinical investigator considered the heart failure as possibly related to CPI-0610 and ruxolitinib. The relevant clinical investigators considered the other four grade 5 events as unrelated to CPI-0610.

The most common treatment-emergent adverse events, or TEAEs, of any grade irrespective of causality observed in Arm 1 included nausea, diarrhea, cough, dysgeusia, respiratory tract infections, thrombocytopenia, fatigue, vomiting, pruritus, weight decrease, constipation, abdominal distension, dizziness, pyrexia, headache, peripheral edema, back pain, dyspnea, hyperkalemia, hyperuricemia and pain in extremities, 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 thrombocytopenia (six patients), anemia (four patients), hyperuricemia (three patients), diarrhea, hyponatremia and dyspnea (two patients each). TEAEs of grade 3 or higher considered related to CPI-0610 by clinical investigator consisted of thrombocytopenia (six patients), diarrhea (two patients), acute kidney injury, anemia, blood bilirubin increase, constipation, decreased appetite, dyspnea, hyperglycemia, neutropenia, rash, taste disorder, tumor lysis syndrome and upper abdominal pain (one patient each). Six patients discontinued treatment due to TEAEs.

The most common TEAEs of any grade irrespective of causality observed in Arm 2 included diarrhea, thrombocytopenia, nausea, respiratory tract infections, cough, fatigue, dysgeusia, abdominal pain, decreased appetite, muscle spasms, vomiting, dizziness, arthralgia, pain in extremities, epistaxis, abdominal distension, pyrexia, peripheral edema, back pain, bruising, constipation, dyspnea, anemia, stomatitis, abdominal pain, chills and alanine aminotransferase increase, 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 (17 patients), anemia (six patients), fatigue (four patients), neutropenia, diarrhea and respiratory tract infections (three patients each). TEAEs of grade 3 or higher considered related to CPI-0610 by clinical investigator consisted of thrombocytopenia (15 patients), anemia (four patients), neutropenia and diarrhea (three patients each), nausea and fatigue (two patients each), abdominal pain, acute kidney injury, blood creatinine increase, lymphocyte count decrease, vomiting and white blood cell count decrease (one patient each). Seven patients discontinued treatment due to TEAEs.

The most common TEAEs of any grade irrespective of causality observed in Arm 3 included diarrhea, anemia, thrombocytopenia, nausea, respiratory tract infections, abdominal pain, dysgeusia, fatigue, headache and back pain, each of which occurred in 10% or more of patients. The most frequently observed grade 3 or higher TEAEs irrespective of causality in Arm 3 were anemia (11 patients), thrombocytopenia and respiratory tract infections (three patients each) and dyspnea (two patients). TEAEs of grade 3 or higher considered related to CPI-0610 by clinical investigator consisted of anemia (five patients), thrombocytopenia (three patients), acute myocardial infarction, cardiac failure, duodenal ulcer, hyponatremia, pneumonia, pulmonary sepsis and left ventricular dysfunction (one patient each). Four patients discontinued treatment due to TEAEs.

CPI-1205

We are conducting ProSTAR, an open-label Phase 1b/2 clinical trial of CPI-1205 for the treatment of mCRPC in combination with the ARS inhibitors enzalutamide (marketed as Xtandi®) or abiraterone acetate (marketed as Zytiga®).

Based on additional clinical data from the ProSTAR trial, we have decided to not to pursue further development of CPI-1205 in patients with mCRPC. We intend to present the full data set from the trial at a future medical meeting. We plan to further analyze the data to understand whether biomarkers may enrich for activity of EZH2 inhibitors. We plan to apply learnings from ProSTAR to CPI-0209, our second-general EZH2 inhibitor program.

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: June 15, 2020

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