PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number 11913.6003-00000		Type a plus sign (+) inside this box ≡	+

INVENTOR(s)/APPLICANT(s)

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TITLE OF INVENTION (500 characters max)

FORMULATIONS

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification: 44 Pages ☐ Drawing(s): [Number] Sheets/[Number] Figures

☐ Other: [Number] Pages; [Description]

METHOD OF PAYMENT

☒ The filing fees are submitted herewith. ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment in fees to Deposit Account Number 06-0916.	PROVISIONAL FILING FEE $250.00 Total Number of Pages of specification, drawings, sequence or computer listing, or other papers 45. If more than 100 pages, add $310 for each additional 50 pages or fraction thereof. $0 (Size Fee) Reduction by ½ For Small Entity $ TOTAL FILING FEE $250.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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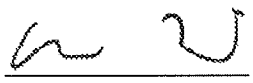
Respectfully submitted on behalf of the patent practitioners associated with Customer Number 22,852,

SIGNATURE  Date June 29, 2012

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

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FORMULATIONS

Inventor
David Goldstein

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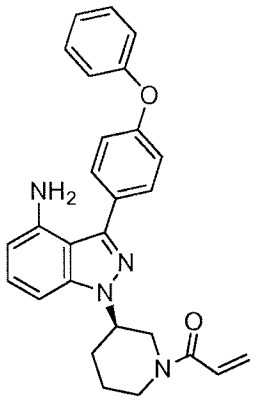
FORMULATIONS

The present disclosure provides certain oral pharmaceutical formulations of ibrutinib, certain methods for their administration, certain processes of their production, and certain uses of these formulations for the treatment of diseases treatable by ibrutinib such as cancer and autoimmune diseases.

Bruton's tyrosine kinase (BTK) is a member of the Tec tyrosine kinase family. BTK is expressed in most hematopoietic cells such as B cells, mast cells, and macrophages but not in T cells, natural killer cells, and plasma cells. Btk plays a role in the development and activation of B cells. Mutations in the human BTK gene cause the inherited disease X-linked agammaglobulinemia (XLA), with lack of peripheral B cells and low levels of serum Ig. In XLA, the primary immune deficit is B cell specific. The development of drugs which inhibit BTK can have therapeutic significance in the treatment of both B cell-related hematological cancers (e.g. non-Hodgkin lymphoma (NHL) and B cell chronic lymphocytic leukemia (B-CLL), and autoimmune diseases (e.g. rheumatoid arthritis, Sjogrens syndrome, IBD, lupus, and asthma).

PCI-32765 (ibrutinib) is disclosed in U.S. Patent No. 7,514,444, issued on April 7, 2009, and has the following structure:



Ibrutinib is an orally available drug that targets Bruton's tyrosine kinase (BTK). Ibrutinib, is an irreversible small molecule BTK inhibitor that is in Ph Ib/II of clinical trials in a variety of B-cell malignancies including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (cancer of plasma cells, a type of white blood cell present in bone marrow). At present ibrutinib is administered orally in clinical trials, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients with CLL and SLL to obtain the desired thereapeutic effect. The need for such high doses of

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ibrutinib may be due to low bioavailability (the oral bioavailability of ibrutinib is reported to be 22.8% in rats) and may be responsible for the adverse side effects associated with the use of ibrutinib such as nausea or emesis, dizziness and diarrhea. Moreover, low bioavailability results in more variable absorption and potential variability of the desired therapeutic response.

As stated above, at present ibrutinib is administered orally, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients to obtain the desired clinical benefit. It is presently disclosed that when ibrutinib is administered intraduodenally versus via the gastrointestinal tract in rats, the oral bioavailability of ibrutinib unexpectedly increased from 21 % to 100% as determined by AUC. This unexpected increase in oral bioavailability of ibrutinib can translate into a number of desirable practical benefits. The increase in oral bioavailability should enable administration of ibrutinib at a significantly lower therapeutically effective dose than is currently being used. The lower variability associated with this greater bioavailability should lead to a more reliable therapeutic response as well as more predictable drug absorption. And avoidance of exposure of Ibtrutinib to the stomach and/or use of lower therapeutically effective dose of ibrutinib can reduce or altogether eliminate potential adverse side effects of this drug such as diahrrea, nausea or emesis, and dizziness. U.S. Patent No. 7,514,444, mentioned above, discloses administration of 0.02-5000 mg/kg and1-1500 mg of ibrutinib/per day and in clinical trials 420 or 840 mg/day of ibrutinib is being administered to the patients with CLL and SLL. There is no reasonable expectation n the art that ibrutinib can be adminstered orally at lower efficacious doses to the patients with CLL and SLL, particularly as evidenced by the 420 or 840 mg/day of ibrutinib being administered in clinical trials to those patients. Moreover, other than for active agents that are unstable in the stomach or at acidic pH delivery of any active agent with low bioavailability further along in the gastrointestinal tract reduces the path length for drug absorption and would be expected to reduce bioavailability. That is a reason why it was unexpected that delivery of ibruntinib directly to the small intestine results in greater bioavailability.

Accordingly, in one aspect, the present disclosure provides a solid oral dosage form comprising:

(i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

(ii) means for release of ibrutinib in the intestine; and

(iii) at least one pharmaceutically acceptable excipient.

. In one embodiment of above aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in the small intestine. In one embodiment,, ibrutinib and/or a

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pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5, or 5, or greater than 5. In another embodiment, said ibrutinib and/or a pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5.5, or greater than about pH 5.5 or 5.5. For example, the release is in one or more of the duodenum, jejunum, ileum, and colon. In one embodiment, the release is in one or more of the duodenum, jejunum, or ileum. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings wherein the enteric coatings are choseb from polymeric coatings. When a non-enteric coating is employed, the time-delayed release dosage forms are administered in fasted state and the time-delayed release coating is designed to erode, burst, or become hightly permeable in about 0.3 to about 3 hours, and preferably in about 0.5 to about 2 hours after administration to release ibrutinib and/or a pharmaceutically acceptable salt thereof.

In a second aspect, the present disclosure provides a solid oral dosage form comprising:

(i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

(ii) means for increasing the oral bioavailability of ibrutinib, as measured by the area under the curve (AUC), as compared to when said ibrutinib and/or said pharmaceutically acceptable salt thereof are administered in an immediate release dosage form; and

(iii) at least one pharmaceutically acceptable excipient.

In one embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the ibrutinib and/or a pharmaceutically acceptable salt thereof in the intestine. In another embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the ibrutinib and/or a pharmaceutically acceptable salt thereof in the small intestine. In another embodiment of the second aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in in

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