such drugs do not address the multiple symptoms of d-IBS including pain and abdominal discomfort and, thus, are not long-term options. (See H. R. Mertz, N Engl J Med 2003, 349: 2136-2146). There is a need for improved therapeutics for the treatment of dIBS that address the multiple symptoms of d-IBS including pain and abdominal discomfort.

[0007] U.S. Patent Nos. 5,211,944 and 5,494,661 to Tempesta disclose the use of a proanthocyanidin polymeric composition isolated from Croton spp. or Calophyllum spp. for the treatment of viral infections. Rozhon et al., U.S. Patent Publication No. 2005/0019389, disclose the use of a proanthocyanidin polymeric composition isolated from Croton spp. or Calophyllum spp. for the treatment of secretory or traveler's diarrhea. PCT application PCT/US00/02687, published as WO 00/47062, discloses a method of manufacturing a proanthocyanidin polymeric composition isolated from Croton spp. or Calophyllum spp. D. DiCesare et al., The American journal of Gastroenterology, October 2002, 97:2585-2588 disclose a clinical trial of crofelemer as a treatment for traveler's diarrhea compared to placebo. Dosages used in this study were 500 mg/day (125 four times a day); 1000 mg/day (250 mg four times a day); and 2000 mg/day (500 mg four times a day) for two days. The study showed that the composition was useful for the amelioration of stool frequency and gastrointestinal symptoms in patients with traveler's diarrhea.

[0008] Citation or identification of any reference in this section or any other section of this application shall not be construed as an admission that such reference is available as prior art for the present application.

SUMMARY OF THE INVENTION

[0008a] In one aspect of the present invention, there is provided a use of crofelemer in the manufacture of a medicament for the treatment of pain associated with d-IBS, or abdominal discomfort associated with d-IBS, wherein said crofelemer is formulated for administration at a dosage of 50 mg per day to 750 mg per day.

[0009] The present ~~invention~~disclosure relates to methods for treating at least one symptom of diarrhea-predominant irritable bowel syndrome (d-IBS) by administering a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule). Exemplary inhibitor molecules are those that inhibit secretion of chloride ions through the cystic fibrosis

transmembrane conductance regulator chloride-ion channel (CFTR). Other exemplary inhibitor molecules include potassium ion channel openers. Exemplary symptoms of d-IBS include pain, abdominal discomfort, diarrhea, abnormal stool frequency, abnormal stool consistency and the presence of urgency. Thus, in one ~~embodiment~~example, the ~~invention~~disclosure provides a ~~method for~~ the treatment of one or more symptoms of d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat the one or more symptoms of d-IBS. In ~~preferred embodiments~~some examples, the dosage of the inhibitor molecule is bioequivalent to orally administered enteric coated crofelemer at a dosage of about 50 mg per day to about 750 mg per day. In one ~~embodiment~~example, bioequivalency is a sufficient dose of an inhibitor molecule to produce a similar therapeutic effect as seen with another inhibitor molecule at a particular dosage, e.g., crofelemer at a dosage of about 50 mg per day to about 750 mg per day. In another ~~embodiment~~example, bioequivalency is as defined by, or is as determined in accordance with methods approved by, the U.S. Food and Drug Administration. In a particular ~~embodiment~~example, the inhibitor molecule is co-administered with a compound that inhibits COX-2, and preferably selectively inhibits COX-2 over COX-1, which compound is preferably not systemically absorbed. Such compounds include 5-ASA, sulfasalazine, mesalamine, APAZA, as well as other commercially available COX-2 inhibitors such as celecoxib and rofecoxib.

In another aspect of the present invention, there is provided a use of an amount of enterically-protected crofelemer in the manufacture of a medicament for the treatment of pain or abdominal discomfort associated with d-IBS, in which the amount is be- tween 50 mg per day and 750 mg per day and the medicament is formulated for oral administration.

[0010] In a particular ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating pain and diarrhea associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat pain and diarrhea associated with d-IBS. In another ~~embodiment~~example, the present invention is directed to a method of treating abdominal discomfort and diarrhea associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell

(inhibitor molecule) effective to treat abdominal discomfort and diarrhea associated with d-IBS. In another particular ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating pain associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat pain associated with d-IBS. In another ~~embodiment~~example, the present invention is directed to a method of treating abdominal discomfort associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat abdominal discomfort associated with d-IBS. Optionally, analgesic or antiinflammatory agents can be co-administered with the inhibitor molecule. In particular, the agent is formulated or is modified such that it is not systemically absorbed.

[0011] In another ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating diarrhea associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat the diarrhea associated with d-IBS, with the proviso that the inhibitor molecule is not a polymeric proanthocyanidin composition isolated from Croton spp. or Calophyllum spp. or that the inhibitor molecule is not crofelemer. In yet another ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a molecule that inhibits secretion of chloride ions from a cell (inhibitor molecule) effective to treat the abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS, with the proviso that the inhibitor molecule is not a polymeric proanthocyanidin composition isolated from Croton spp. or Calophyllum spp. or that the inhibitor molecule is not crofelemer.

[0012] In another ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating diarrhea associated with d-IBS comprising orally administering to a patient in need of such treatment, an amount of enterically-protected crofelemer (CAS 148465-45-6) effective to treat the diarrhea associated with d-IBS, in which said amount is between about 50 mg per day and about 750mg per day. In yet another ~~embodiment~~example, the present ~~invention~~ disclosure is directed to a method of treating abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS comprising orally administering to a patient in need of such treatment, an amount of enterically-protected crofelemer effective to treat the abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS, in which said amount is between about 50 mg per day and about 750 mg per day. In certain ~~embodiments~~examples where corfelemer is otherwise formulated, for example, in a controlled release formulation (not enterically protected), the dosage of crofelemer administered is bioequivalent to a dosage of about 50 mg per day to about 750 mg per day of orally administered enterically-protected crofelemer.

[0013] In another ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating diarrhea associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a polymeric proanthocyanidin composition isolated from Croton spp. or Calophyllum spp. effective to treat the diarrhea associated with d-IBS, in which said amount is bioequivalent to an orally administered dose of about 50 mg per day to about 750 mg per day of crofelemer. In yet another ~~embodiment~~example, the present ~~invention~~disclosure is directed to a method of treating abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS comprising administering to a patient in need of such treatment, an amount of a polymeric proanthocyanidin composition isolated from Croton spp. or Calophyllum spp. effective to treat the abnormal stool frequency, abnormal stool consistency or presence of urgency associated with d-IBS, in which said amount is