[0026] "Halofenic acid" and "CPTA" refer to the compounds of Formula (IV), i.e. 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetic acid [also referred to as 2-(4-chlorophenyl)-2-(3-(trifluoromethyl)phenoxy)acetic acid] as well as its pharmaceutically acceptable salts. The term halofenic acid and the corresponding chemical names include both the (+) and (-) enantiomer of compounds of Formula (IV) as well as mixtures thereof, unless otherwise specified.

[0027] "Hyperuricemia" refers to an elevated serum uric acid level (see above).

[0028] "Impaired renal function" refers to a medical condition in which the kidneys fail to adequately filter toxins and waste products from the blood. Impaired renal function may take the form ~~of~~ acute kidney injury or chronic kidney disease (i.e. CKD1-5).

[0029] "Moderate gout" refers to gout present in a subject having at least two gout flares in the past 12 months.

[0030] "Pharmaceutically acceptable" refers to that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable, and includes that which is acceptable for veterinary or human pharmaceutical use.

[0031] "Pharmaceutically acceptable salt" includes pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts and includes both solvated and unsolvated forms. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge *et al.*, *J. Pharma Sci.*, 66(1), 1-19 (1977), and *Remington: The Science and Practice of Pharmacy*, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0032] "Pharmaceutically acceptable acid addition salt" refers to salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0033] "Pharmaceutically acceptable base addition salt" refers to salts prepared from the addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic

level of gene exrpression of the same panel of pro-inflammatory cytokines determined. In another model, mice are injected intraperitoneally with 1 mg of MSU suspended in 0.5 ml of endotoxin free PBS. After 6 h , mice are killed and their peritoneal cavities washed and harvested for measurement of neutrophil influx by staining with a neutrophil specific antibody R-phycoerythrin conjugated rat anti mouse Ly-6G monoclonal antibody. In another model, an air pouch is introduced subcutaneously and 1 mg of MSU is injected into the pouch. Six hours after crystal injection the cells resident in the pouch are collected by lavaging with 5 ml of buffer. Neutrophil ~~infiltatation~~ is measured by staining as above. The levels of monocyte chemoatractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α), interlekin-1β, (IL-1β), interleukin-6 (IL-6) and interleukin-12 (Il-12) are also measured in the lavaged fluid isolated from the urate injected air pouch.

Example 3: Clinical Trial Comparing Effectiveness of Arhalofenate in the Reduction of Gout Flares During Initiation of and Maintenance Use of Therapy for Uric Acid Lowering

[0088] This is a double-blind, parallel group, multicenter, randomized study.

[0089] Primary Endpoint

[0090] Proportion of patients experiencing an acute gout flare overall and in the separate timeframes of weeks 0-2 of treatment, weeks 3-12 of treatment, and weeks 11-12 of treatment.

[0091] Secondary Endpoints:

[0092] a. Total number of gout flares

[0093] b. Duration of gout flares

[0094] c. Incidence of patient discontinuation due to gout flares.

[0095] d. Severity of gout flares

[0096] Treatment Regime:

[0097] Individuals are randomized into three groups: a control group (n=100) and two experimental groups (n=100 each). Subjects in the control group are administered allopurinol (300 mg) once per day. Subjects in the experimental groups are administered arhalofenate (400 mg or 600 mg) tablets once per day. All patients receive flare prophylaxis for the first two weeks of treatment. Treatment duration with blinded study drug is three months.

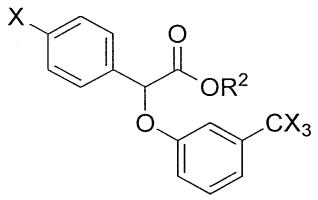
[0098] Inclusion Criteria:

[0099] Male or female, 18 years of age or older.

6. A method of providing to a subject (-)-halofenic acid with an intraday peak-to-trough ratio of about 2.0 or less, comprising administering to the subject about 100 mg to about 1000 mg per day of a compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof.

7. The method of Claim 6, wherein the compound is administered for at least about 10 days.

8. The method of any one of Claims 1 to 7, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is a compound of Formula (II)



(II)

wherein R^2 is selected from the group consisting of phenyl-lower alkyl, lower alkanamido-lower alkyl and benzamido-lower alkyl; and each X is independently a halogen; ~~and each X is independently a halogen~~;

or a pharmaceutically acceptable salt thereof.

9. The method of any one of Claims 1 to 8, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is (-)-halofenate or (-)-halofenic acid, or a pharmaceutically acceptable salt thereof.

10. The method of any one of Claims 1 to 9, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is (-)-halofenate.

11. The method of any one of Claims 1 to 10, wherein the compound is administered orally.

12. The method of any one of Claims 1 to 11, further comprising the administration of a second urate-lowering agent selected from the group consisting of a xanthine oxidase inhibitor, an inhibitor of uric acid production, a uricosuric agent and a uricase.

13. The method of Claim 12, wherein the second urate-lowering agent is a xanthine oxidase inhibitor, preferably selected from the group consisting of allopurinol, febuxostat, oxypurinol,

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administration daily and over a drug holiday of one day. In some embodiments further comprise administering to the subject arhalofenate by mouth in an oral formulation. Particular embodiments covering compositions, formulations and their method of uses are disclosed in a PCT Patent Application entitled "Methods for Treating Hyperuricemia in Patents with Gout Using Halofenate or Halofenic Acid and a Second Urate-Lowering Agent" filed concurrently with the present application, and the PCT Application is incorporated herein in its entirety. The embodiments of this application are characterized by the specification and by the features of the Claims of this application as filed, and of corresponding pharmaceutical compositions, methods and uses of these compounds.

Methods

[0073] Methods used in relation to FIGS. 1-2 showing the pharmacokinetic profile of (-)-halofenic acid were as follows:

[0074] Plasma proteins in human plasma samples containing of (-)-halofenic acid, an internal standard (I.S.) and heparin as the anticoagulant were precipitated with acetonitrile. The samples were vortex mixed, centrifuged and an aliquot was analyzed by reversed phase high performance liquid chromatography using a Phenomenex Polar RP column maintained at 45 °C. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using a tandem quadrupole mass spectrometer.

[0075] The plasma concentrations were rounded to the nearest one-tenth μg/mL before the calculations. Plasma samples with concentrations below the quantifiable limit of 1.0 μg/mL (BQL) were assigned values of zero.

[0076] Methods used in relation to FIG. 3 showing reduction in serum uric acid in subjects over time following once daily dosing with arhalofenate were as follows.

[0077] A single centre, Phase 1, placebo- and positive-controlled, double-blind, randomized, dose escalation study (MAD study, MBX102-2DM01011b) was conducted to evaluate the multiple-dose pharmacokinetics (PK) of (-)-halofenate administered as a daily dose orally for 10 days, at the protocol-specified doses in healthy adult subjects. A total of 119 subjects completed study treatment according to protocol: 6 subjects received MBX-102 100 mg/day for 10 days; 6 subjects received MBX-102 200 mg/day for 10 days; 9 subjects received MBX-102 400 mg/day for 10 days; 20 subjects received MBX-102 600 mg/day for 10 days; 10 subjects received MBX-102 600 mg Enteric Coated (EC) /day for 10 days; 9 subjects received MBX-102 800 mg EC/day

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