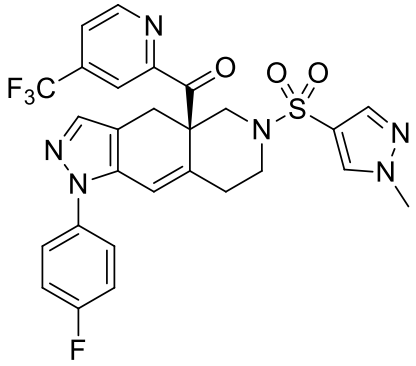
[0004] However, many GRM compounds are difficult to formulate in compositions suitable for administration to subjects in need of the compounds. Many such compounds are only sparingly soluble in water, may be incompatible with other ingredients typically used in pharmaceutical compositions, or may have other properties which make it difficult to prepare therapeutic formulations. Many GRM compounds are unstable, degrading over time, or with exposure to light or heat. Such characteristics of one heteroaryl-ketone fused azadecalin compound may differ from those of another heteroaryl-ketone fused azadecalin compound, so that a formulation suitable for one heteroaryl-ketone fused azadecalin compound may not be suitable for a different heteroaryl-ketone fused azadecalin compound.

[0005] For example, many heteroaryl-ketone fused azadecalin compounds are poorly soluble in water, and may have poor bioavailability in some formulations. Poor solubility or bioavailability necessitates the administration of large volumes of solution, large pills or tablets, or large numbers of pills or tablets in order to provide sufficient active compound for effective treatments. In addition, some heteroaryl-ketone fused azadecalin compounds, and formulations containing these compounds, may interact with capsule materials, or be incompatible with capsule materials. Such interactions, incompatibilities, and instabilities may lead to degradation of the heteroaryl-fused azadecalin compounds, reduce their bioavailability, or otherwise reduce their utility for therapeutic purposes. For these reasons, and others, pharmaceutical formulations for use in pills, tablets, solutions for injection, and other pharmaceutical formulations often may be unsuitable for therapeutic use.

[0006] Accordingly, improved formulations including heteroaryl-ketone fused azadecalin compounds having improved stability and/or bioavailability are needed.

SUMMARY

[0006a] In one aspect, the present disclosure refers to a formulation for oral administration of relacorilant, (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the following structure:



;

the formulation comprising:

about 18% to 22% relacorilant;

about 55% to 65% surfactant,

where said surfactant is selected from sorbitan surfactants, polysorbate surfactants, polyoxyl glyceride surfactants, ionic surfactants, and non-ionic surfactants;

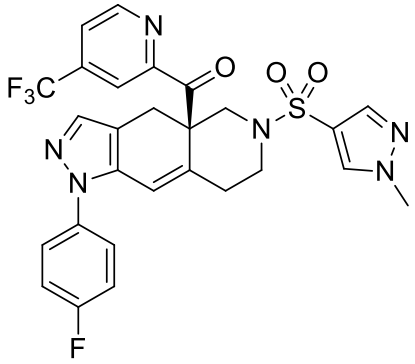
and

about 18% to 22% solubilizer,

where said solubilizer is selected from polyethylene glycols, propylene glycol esters, ethanol, propylene glycol, glycerols, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide, wherein said percentages are weight percent.

[0006b] In another aspect, the present disclosure refers to a unit dose for oral administration of relacorilant, consisting essentially of a softgel capsule containing a relacorilant formulation consisting of 20% relacorilant, 59.98% Lauroyl poloxyl-32 glycerides, 20% Propylene glycol monocaprylate, and 0.02% Butylated hydroxytoluene (BHT), wherein said percentages are weight percentages.

[0007] Applicant discloses herein formulations comprising the heteroaryl-ketone fused azadecalin (HKFA) compound (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone (Example 18 of U.S. 8,859,774), also known as “relacorilant” and as “CORT125134”, which has the following structure:



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[0008] In examples, the formulations disclosed herein are suitable for pharmaceutical use, and have improved stability and/or bioavailability as compared to prior or alternative formulations. In examples, the formulations may include relacorilant and a pharmaceutically acceptable excipient. In examples, the formulations contain relacorilant and a pharmaceutically acceptable excipient and are suitable for use in pharmaceutical compositions for oral administration of relacorilant to human patients for treating a disease or disorder, or to animals for veterinary therapeutic purposes.

[0009] In examples, the pharmaceutical formulation is suitable for the administration of an effective amount of relacorilant, e.g., in a unit dose formulation containing between about 1 and about 1000 milligrams (mg) of relacorilant, or between about 1 and about 500 mg of relacorilant. In examples, unit dose formulations contain 10 mg, or 20 mg, or 25 mg, or 50 mg, or 100 mg, or 200 mg, or 300 mg, or 400 mg, or 500 mg relacorilant. In examples, the pharmaceutical formulation is suitable for the administration of an effective amount of relacorilant, e.g., a daily dose of relacorilant of between about 1 and 100 mg/kg/day, or a daily dose of relacorilant of between about 1 and 20 mg/kg/day.

[0010] In examples, the pharmaceutical formulation comprising relacorilant is suitable for administration when encapsulated in a gelatin capsule. In examples, the pharmaceutical formulation comprising relacorilant is suitable for administration when encapsulated in a soft gelatin ("softgel") capsule.

[0011] The formulation comprising relacorilant may contain, for example, about 5 to about 35% relacorilant, about 45% to about 75% surfactant, about 5 to about 35% solubilizer, and may include an antioxidant. In examples, the formulation comprising relacorilant may contain, for example, about 10 to about 30% relacorilant, about 50% to about 70% surfactant, about 10 to

about 30% solubilizer, and may include an antioxidant. In examples, the formulation comprising relacorilant may contain, for example, about 12 to about 28% relacorilant, about 52% to about 68% surfactant, about 12 to about 28% solubilizer, and may include an antioxidant. In further examples, the formulation may have the following composition: about 15% to 25% relacorilant, about 55% to 65% surfactant, and about 15% to 25% solubilizer, optionally including an antioxidant. In yet further examples, the formulation may have the following composition: about 20% relacorilant, about 60% surfactant, about 20% solubilizer, and about 0.02% antioxidant. In particular examples, the formulation may have the following composition: about 20% relacorilant, about 60% polyoxyl glyceride, about 20% propylene glycol compound, and about 0.02% antioxidant. In further particular examples, the formulation may have the following composition: about 20% relacorilant, about 60% lauryl polyoxyl-32 glycerides, about 20% propylene glycol monocaprylate, and about 0.02% antioxidant (e.g., butylated hydroxytoluene (BHT), buylated hydroxyanisole (BHA), tert-butyl hydroquinone (TBHQ), a tocopherol, a gallate, or other antioxidant).

[0012] In examples, the capsule containing the relacorilant-containing formulation may be a softgel capsule. Softgel capsules for containing a relacorilant-containing formulation may be made of about 50% to about 75% gelatin and about 25% to about 50% of a plasticizer (e.g., a sorbitol/glycerin blend), with purified water and/or colorants included as needed; and may be made of about 58% to about 68% gelatin and about 30% to about 42% plasticizer, or may be made of about 60% to about 70% gelatin and about 30% to about 40% of a plasticizer, or about 63% to about 65% gelatin and about 35% to about 37% of a plasticizer, or about 64% gelatin and about 36% plasticizer, with purified water and/or colorants included as needed. In examples, a batch of material for making softgel capsules for containing a relacorilant-containing formulation may be made, for example, of 195.05 g gelatin and 111.46 g of a sorbitol/glycerin blend, with purified water and/or colorants included as needed.

[0013] In further exemplary examples, Applicant discloses softgel capsules containing relacorilant; the softgel capsules containing relacorilant may be any softgel capsule as disclosed herein containing any relacorilant formulation disclosed herein. In examples, the softgel capsules containing relacorilant formulations may be made of about 63% to about 65% gelatin and about 35% to about 37% of a plasticizer, or about 64% gelatin and about 36% plasticizer, with purified water and/or colorants included as needed. The plasticizer may be, for example, a

sorbitol/glycerin blend. The relacorilant held in the softgel capsule may be in any formulation described herein. In examples, the softgel capsule containing relacorilant contains a relacorilant formulation of about 15 to about 25% relacorilant, about 50% to about 70% surfactant, about 15 to about 25% solubilizer, and may include an antioxidant. In examples, the softgel capsule containing relacorilant contains a relacorilant formulation comprising about 20 relacorilant, about 60% surfactant, about 20% solubilizer, and may include an antioxidant.

[0014] In examples, the formulations disclosed herein are suitable for use in the treatment of disorders characterized by cortisol excess. In examples, the formulations disclosed herein are suitable for use in the treatment of Cushing's syndrome, including Cushing's Disease. In examples, the formulations disclosed herein are suitable for use in the treatment of other disorders. In examples of such treatment methods, pharmaceutical compositions comprising relacorilant may be administered alone, or may be administered in combination with other treatments for such diseases and disorders.

[0015] Many HKFA compounds are difficult to dissolve, difficult to formulate with pharmaceutically acceptable excipients, and are unstable (i.e., degrade by unacceptable amounts over time) in many formulations. Applicant discloses herein novel relacorilant-containing formulations and pharmaceutical compositions, with improved stability as compared to alternative formulations and compositions which are suitable for administration to human subjects. The novel formulations disclosed herein are believed to allow the safe and effective administration of relacorilant to patients suffering from diseases and disorders amenable to treatment by GRMs such as relacorilant. The formulations disclosed herein provide advantages including improved stability and compatibility with capsules suitable for oral administration, providing improved relacorilant formulations, and treatments using such improved relacorilant-containing formulations, as compared to alternative formulations and compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 shows the plasma concentration of relacorilant in healthy, fasted human subjects at times after ingestion of 150 mg relacorilant (provided in softgel capsules containing the formulation of Table III). The C_{max} was nearly 200 ng/mL at its peak about 3 hours after administration (open circles; eight subjects were tested with this composition; the subjects were fasted when they were orally administered the relacorilant formulation).