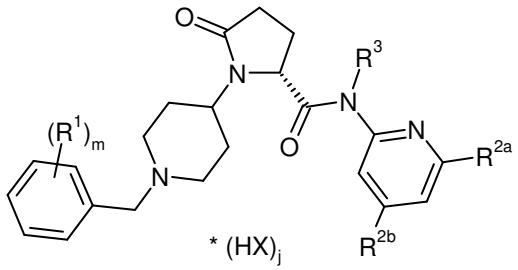
context) endothelial cells of the retinal vasculature, and studies on rodents have shown promise in alleviating retinal disease-associated neovascularization.

[0009] Despite this promise, there has been a failure in the industry to develop a CCR3 antagonist for human treatment of retina-associated disease. However, the compounds, co-crystals, salts, and formulations disclosed herein, which specifically modulate/antagonize CCR3, are effective at improving the visual acuity of a significant number of subjects, even while effects on neovascularization are insignificant.

SUMMARY

[0010] In a first aspect, the present disclosure refers to use of a compound that is a co-crystal of Formula 2

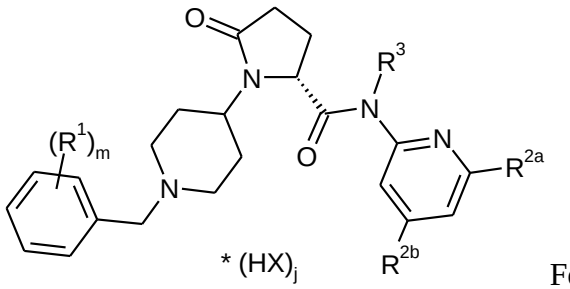


Formula 2

wherein R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, halogen; m is 1, 2 or 3; R^{2a} and R^{2b} are each independently selected from H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, or halogen; $R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl; $R^{2b.2}$ is H, or C_{1-6}-alkyl; or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom R^3 is H, or C_{1-6}-alkyl; X is an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, benzoate, citrate, salicylate, fumarate, tartrate, dibenzoyltartrate, oxalate, succinate, benzoate and p-toluenesulphonate; j is 0, 0.5, 1, 1.5 or 2; with a co-crystal former selected from the group consisting of orotic acid, hippuric acid, L-pyroglutamic acid, D-pyroglutamic acid, nicotinic acid, L-(+)-ascorbic acid, saccharin, piperazine, 3-hydroxy-2-naphtoic acid, mucic (galactaric) acid, pamoic (embonic) acid, stearic acid, cholic acid, deoxycholic acid, nicotinamide, isonicotinamide, succinamide, uracil, L-lysine, L-proline, D-valine, L-arginine, glycine, in the manufacture of a medicament for improving visual acuity in a subject diagnosed with a retina-associate disease, wherein the compound that is a co-crystal of Formula 2 is to be administered orally. In a first example, the present disclosure

What is claimed:

1. Use of a compound that is a co-crystal of Formula 2



Formula 2

wherein

R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, halogen;

m is 1, 2 or 3;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, or halogen;

$R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-6}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom

R^3 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, benzoate, citrate, salicylate, fumarate, tartrate, dibenzoyltartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

j is 0, 0.5, 1, 1.5 or 2;

with a co-crystal former selected from the group consisting of orotic acid, hippuric acid, L-pyroglutamic acid, D-pyroglutamic acid, nicotinic acid, L-(+)-ascorbic acid, saccharin, piperazine, 3-hydroxy-2-naphtoic acid, mucic (galactaric) acid, pamoic

(embonic) acid, stearic acid, cholic acid, deoxycholic acid, nicotinamide, isonicotinamide, succinamide, uracil, L-lysine, L-proline, D-valine, L-arginine, glycine,

in the manufacture of a medicament for improving visual acuity in a subject diagnosed with a retina-associate disease, wherein the compound that is a co-crystal of Formula 2 is to be administered orally.

2. The use of claim 1, wherein

R^{2a} is H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, O-C_{1-6}-alkyl, or $CONR^{2a.1}R^{2a.2}$;

$R^{2a.1}$ is H, C_{1-6}-alkyl, or C_{1-6}-haloalkyl;

$R^{2a.2}$ is H, or C_{1-6}-alkyl;

R^{2b} is H, C_{1-6}-alkyl, C_{1-6}-alkenyl, C_{1-6}-alkynyl, C_{3-6}-cycloalkyl, COO-C_{1-6}-alkyl, O-C_{1-6}-alkyl, $CONR^{2b.1}R^{2b.2}$, or halogen;

$R^{2b.1}$ is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-6}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom.

3. The use of claim 1, wherein

R^1 is C_{1-6}-alkyl, C_{1-6}-haloalkyl, O-C_{1-6}-haloalkyl, or halogen;

m is 1 or 2;

R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-4}-haloalkyl;

$R^{2b.2}$ is H, or C_{1-4}-alkyl;

or $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom

R^3 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride or dibenzoyltartrate, and

j is 1 or 2.

4. The use of claim 1, wherein

R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-alkyl;

$R^{2b.2}$ is C_{1-4}-alkyl.

5. The use of claim 1, wherein

R^{2a} is H, or C_{1-4}-alkyl;

R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{0-4}-alkyl-C_{3-6}-cycloalkyl;

$R^{2b.2}$ is H, or C_{1-4}-alkyl.

6. The use of claim 1, wherein

R^{2a} is H, or C_{1-4}-alkyl;

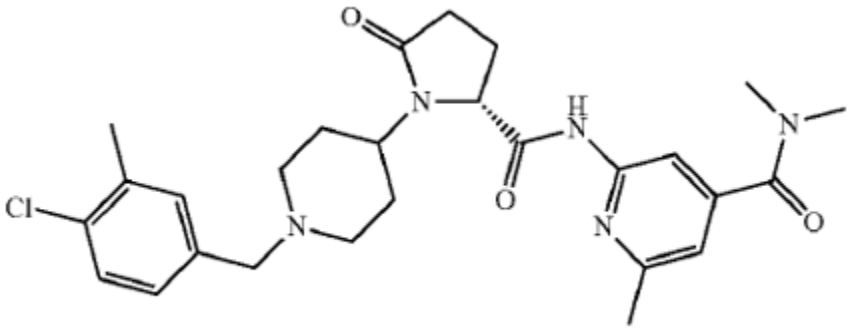
R^{2b} is H, or $CONR^{2b.1}R^{2b.2}$;

$R^{2b.1}$ is C_{1-4}-haloalkyl;

$R^{2b.2}$ is H, C_{1-4}-alkyl.

7. The use of claim 1, wherein the compound is a co-crystal of the formula according to claim 1, wherein $R^{2b.1}$ and $R^{2b.2}$ are together a C_{3-6}-alkylene group forming with the nitrogen atom a heterocyclic ring, wherein optionally one carbon atom or the ring is replaced by an oxygen atom.

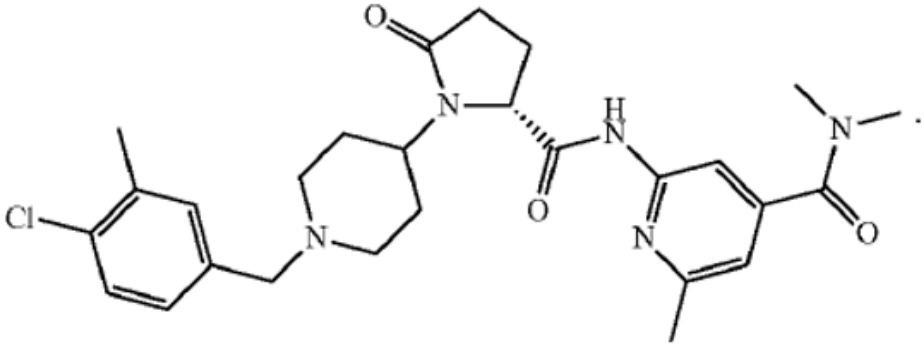
8. The use of claim 1, wherein the compound that is a co-crystal of Formula 2 is,



*$(HX)_j$

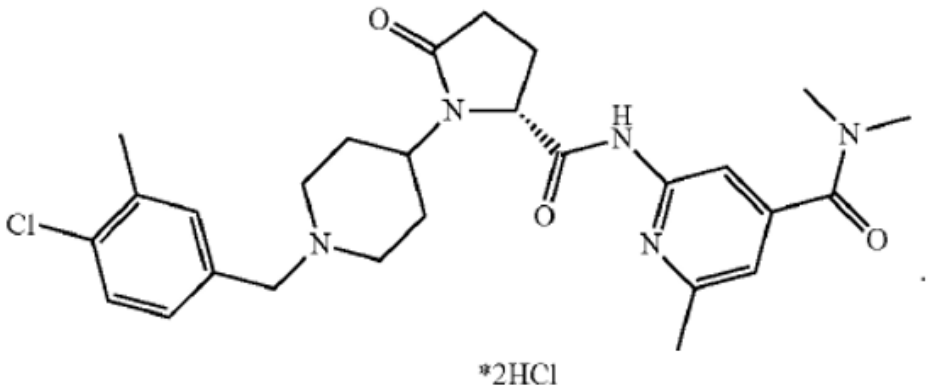
wherein j is 0.

9. The use of claim 1, wherein the compound that is a co-crystal is a crystalline salt of the formula below,



*dibenzoyltartrate

10. The use of claim 1, wherein the compound that is a co-crystal is a crystalline salt of the formula below,



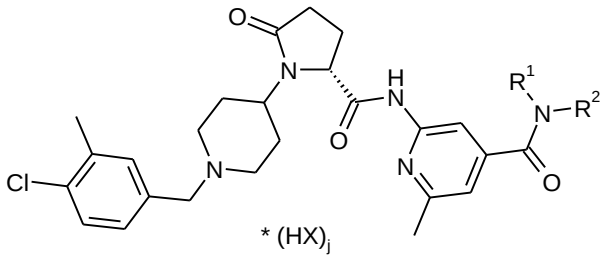
11. The use of claim 9, wherein the crystalline salt is characterized in that the four highest X-ray powder diffraction peaks occur at 3.72, 13.60, 16.89, and 19.34 degrees 2Θ (±0.05 degrees 2Θ) when measured using CuKα radiation.

12. The use of claim 10, wherein the crystalline salt is characterized in that the four highest X-ray powder diffraction peaks occur at 16.02, 16.86, 19,45, and 19.71 degrees 2Θ (±0.05 degrees 2Θ) when measured using CuKα radiation.

13. The use of claim 1, wherein the co-crystal of Formula 2 is to be administered with a pharmaceutically acceptable carrier.

14. The use of claim 1 or 2, wherein the co-crystal of Formula 2 is to be administered in the form of the individual optical isomers, a mixture of the individual enantiomers, a racemate or in the form of the enantiomerically pure compounds.

15. The use of claim 1 or 2, wherein the co-crystal of Formula 2 is to be administered orally as a pharmaceutical composition comprising as an active ingredient one or more compounds that is a co-crystal of the formula below,



1

wherein

R^1 is H, C_{1-6}-alkyl, C_{0-4}-alkyl-C_{3-6}-cycloalkyl, or C_{1-6}-haloalkyl;

R^2 is H, or C_{1-6}-alkyl;

X is an anion selected from the group consisting of chloride or ½ dibenzoyltartrate; and

j is 1 or 2, and

a first diluent, a second diluent, a binder, a disintegrant and a lubricant.

16. The use of claim 15 wherein the pharmaceutical composition is characterized in that

R^1 is H, or Methyl;

R^2 is H, or Methyl;

X is an anion selected from the group consisting of chloride or ½ dibenzoyltartrate; and

j is 1 or 2

17. The use of claim 15, wherein the pharmaceutical composition is characterized in that X is chloride and j is 2.

18. The use of any one of claims 15-17, wherein the pharmaceutical composition further comprises an additional disintegrant.

19. The use of any one of claims 15-17, wherein the pharmaceutical composition further comprises a glidant.

20. The use of any one of claims 15-17, wherein the diluent of the pharmaceutical composition further comprises cellulose powder, dibasic calcium phosphatae anhydrous, dibasic calcium phosphate dehydrate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelantinized starch, or xylitol.

21. The use of any one of claims 15-17, wherein the lubricant of the pharmaceutical composition is talc, polyethyleneglycol, calcium behenate, calcium stearate, hydrogenated castor oil or magnesium stearate.

22. The use of any one of claims 15-17, wherein the binder of the pharmaceutical composition is copovidone (copolymerisates of vinylpyrrolidon with other vinylderivates), hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidon (Povidone).

23. The use of any one of claims 15-22, wherein the disintegrant of the pharmaceutical composition according to claim is corn starch.

24. The use of any one of claims 19 or 23, wherein the glidant of the pharmaceutical composition is colloidal silicon dioxide.

25. The use of claim 15, wherein the pharmaceutical composition comprises

10-90 %	active ingredient
5-70 %	diluent 1,
5-30 %	diluent 2,
0-30 %	binder,
1-12 %	disintegrant, and
0.1-3 %	lubricant.

26. The use of claim 15, wherein the pharmaceutical composition comprises

30-70 %	active ingredient
20-75 %	diluent 1,

5-30 %	diluent 2,
2-30 %	binder,
0,5-20 %	buffering agent,
1-12 %	disintegrant, and
0.1-3 %	lubricant.

27. The use of claim 18, wherein the additional disintegrant of the pharmaceutical composition is crospovidone.

28. The use of claim 15, wherein the pharmaceutical composition is in the dosage form of a capsule, a tablet, or a film-coated tablet.

29. The use of claim 28, wherein the pharmaceutical composition further comprises a 2-4% film coat.

30. The use of claim 29, wherein the film coat comprises a film-forming agent, a plasticizer, a glidant, and optionally one or more pigments.

31. The use of claim 30, wherein the film coat comprises Polyvinyl alcohol (PVA) or hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide and iron oxide.

32. The use of any of the preceding claims, further comprising that a therapeutically effective amount of an anti-VEGF therapy is to be administered.

33. The use of any of the preceding claims, wherein the retina-associated disease is from the group consisting of dry age-related macular degeneration, wet age-related macular degeneration, central retinal vein occlusion, retinopathy of prematurity, and diabetic retinopathy.