

METHODS OF TREATING INFLAMMATORY DISEASES

Technical Field of the Invention

This invention generally relates to method of treating inflammatory diseases, for
5 example Crohn's Disease (CD), utilizing anti-IL-23A antibodies.

Background of the Invention

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the
gastrointestinal tract characterized by abdominal pain, fever, and bloody or mucus-
10 containing diarrhea. The disease affects the gastrointestinal tract discontinuously from
mouth to anus, but most commonly the ileum and colon (40%), followed by the small
bowel only (30%), and the colon only (25%). It occurs in a relatively young population
and there is no marked sex difference.

The incidence of CD seems to be increasing with more recent estimates varying from
15 7.9 to 20.2 cases/100,000, and a prevalence of 161 to 319 cases/100,000 in North
America and Europe. Mucosal lesions may be complicated by perforation and fistula
formation, which may require hospitalization for medical or surgical management.

There is a need for treatment options for inflammatory diseases, in particular Crohn's
Disease, that lead to favorable outcomes for patients, for example in terms of efficacy,
20 safety and/or tolerability of the treatment.

Summary

The present disclosure addresses the above needs and provides methods for treating
inflammatory diseases, in particular methods comprising administering an anti-IL-23A
25 antibody to a patient in certain amounts and/or at certain intervals. In one embodiment,
a method of the present disclosure is for the treatment of Crohn's Disease. In one
embodiment, a method of the present disclosure is for the treatment of ulcerative colitis.
The methods of the present disclosure provide the advantage of enabling patients to
experience clinical improvement while receiving fewer administrations of the anti-IL-23A
30 antibody.

- In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one embodiment for treating Crohn's Disease, comprising (a) administering to a patient a dose of an anti-IL-23A antibody at week 0, at week 4 and at week 8 by intravenous infusion, wherein the doses of the anti-IL-23A antibody comprise 200 mg or 600 mg of the antibody. In one embodiment, the method further comprises (b) administering to the patient three doses of the anti-IL-23A antibody, for example at week 14, at week 18 and at week 22 by intravenous infusion, wherein the doses of the anti-IL-23A antibody comprise 600 mg of the antibody. In one embodiment, the method further comprises (c) administering to the patient one or more doses of the anti-IL-23A antibody at 8 weeks intervals by subcutaneous injection, for example four doses of the anti-IL-23A antibody at 8 weeks intervals by subcutaneous injection, for example at week 26, at week 34, at week 42 and at week 50, wherein the one or more doses of the anti-IL-23A antibody comprise 180 mg of the antibody.
- 15 In one embodiment, at week 12, a patient is evaluated for deep remission, for example defined as reaching clinical remission (CDAI score <150) and endoscopic remission ($CDEIS \leq 4$). In one embodiment, for a patient with initial isolated ileitis endoscopic remission is defined by $CDEIS \leq 2$.
- 20 In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one embodiment for treating Crohn's Disease, comprising (a) administering to a patient a dose of an anti-IL-23A antibody at week 0, at week 4 and at week 8 by intravenous infusion, wherein the doses of the anti-IL-23A antibody comprise 200 mg or 600 mg of the antibody. In one embodiment, the method further comprises (b) administering to the patient one or more doses of the anti-IL-23A antibody at 8 weeks intervals by subcutaneous injection, for example four doses of the anti-IL-23A antibody at 8 weeks intervals by subcutaneous injection, for example at week 26, at week 34, at week 42 and at week 50, wherein the one or more doses of the anti-IL-23A antibody comprise 180 mg of the antibody.

In one embodiment, at week 12, a patient is evaluated for deep remission, for example defined as reaching clinical remission (CDAI score <150) and endoscopic remission ($\text{CDEIS} \leq 4$). In one embodiment, for a patient with initial isolated ileitis endoscopic remission is defined by $\text{CDEIS} \leq 2$.

In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one embodiment for treating Crohn's Disease, comprising administering to a patient 180 mg of the anti-IL-23A antibody at 8 weeks intervals by subcutaneous injection.

In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one embodiment for treating Crohn's Disease, comprising administering to a patient an anti-IL-23A antibody, said method comprising administering at least one induction dose of the anti-IL-23A antibody to the patient, wherein said induction dose comprises 200 to 1,200 mg of the anti-IL-23A antibody, for example 450 to 1,200 mg of the anti-IL-23A antibody. In one aspect, the present disclosure provides use of an anti-IL-23A antibody in the manufacture of a medicament for the treatment of Crohn's Disease in a patient, wherein: a) at least one induction dose of said anti-IL-23A antibody is to be administered to the patient, and wherein said induction dose comprises 200 to 1,200 mg of said anti-IL-23A antibody. In one embodiment, the induction dose comprises 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of the anti-IL-23A antibody. In one embodiment, 1, 2 or 3 induction doses are administered to the patient. In one embodiment, 2 or 3 inductions doses are administered, for example at 4 weeks intervals. In one embodiment, the induction dose(s) is administered by intravenous infusion.

In one embodiment, the induction doses comprise 200 mg of the anti-IL-23A antibody and three inductions doses are administered to the patient at 4 weeks intervals. In one embodiment, the induction doses comprise 450 mg of the anti-IL-23A antibody and three inductions doses are administered to the patient at 4 weeks intervals. In one embodiment, the induction doses comprise 600 mg of the anti-IL-23A antibody and three inductions doses are administered to the patient at 4 weeks intervals.

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In one embodiment, the induction doses comprise 900 mg of the anti-IL-23A antibody and three induction doses are administered to the patient at 4 weeks intervals.

In one embodiment, the induction doses comprise 1,200 mg of the anti-IL-23A antibody and three induction doses are administered to the patient at 4 weeks intervals.

In one embodiment, at least one additional induction dose of the anti-IL-23A antibody is administered to the patient after the last induction dose above. In one embodiment, an additional induction dose comprises 200 to 1,200 mg of the anti-IL-23A antibody, for example 450 to 1,200 mg of the anti-IL-23A antibody. In one embodiment, an additional induction dose comprises 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of the anti-IL-23A antibody. In one embodiment, 1, 2 or 3 additional induction doses are administered to the patient. In one embodiment, 2 or 3 additional induction doses are administered, for example at 4 weeks intervals. In one embodiment, the additional induction dose(s) is administered by intravenous infusion.

In one embodiment, the patient has a CDAI score of 220-450 before the administration of the first induction dose.

In one embodiment, the patient achieves clinical remission after the administration of the one or more induction doses. In one embodiment, the patient achieves a CDAI score of less than 150 after the administration of the one or more induction doses. In one embodiment, the patient achieves a PRO-2 score equal to or less than 75 after the administration of the one or more induction doses. In one embodiment, the patient achieves a CDAI score of less than 150 and a PRO-2 score equal to or less than 75 after the administration of the one or more induction doses.

In one embodiment, the present disclosure further provides a method for inducing clinical remission of Crohn's Disease in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein. In one aspect, the present disclosure provides use of an anti-IL-23A antibody in the manufacture of a medicament for inducing remission of Crohn's Disease in a patient, wherein: a) said anti-IL-23A antibody is to be administered in at least one induction dose to the patient, and wherein said induction dose comprises 200 to 1,200 mg of said anti-IL-23A antibody.

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In one embodiment, the present disclosure further provides a method for inducing clinical response to Crohn's Disease in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein.

In one embodiment, the method further comprises administering a first maintenance dose of the anti-IL-23A antibody to the patient after the last induction dose is administered and administering at least one additional maintenance dose to the patient 4 to 12 weeks after said first maintenance dose is administered. In one embodiment, the first maintenance dose is administered 2 to 8 weeks, for example 4 to 6 weeks, for example 2 weeks, 4 weeks, 6 weeks or 8 weeks, after the last induction dose is administered. In one embodiment, the at least one additional maintenance dose is administered to the patient 4, 8 or 12 weeks after the first maintenance dose is administered.

In one embodiment, the first maintenance dose comprises 150 to 300 mg of the anti-IL-23A antibody. In one embodiment, the first maintenance dose comprises 150 mg, 225 mg or 300 mg of the anti-IL-23A antibody. In one embodiment, the first maintenance dose comprises 180 mg or 270 mg of the anti-IL-23A antibody.

In one embodiment, the at least one additional maintenance dose comprises 150 to 300 mg of the anti-IL-23A antibody. In one embodiment, the at least one additional maintenance dose comprises 150 mg, 225 mg or 300 mg of the anti-IL-23A antibody. In one embodiment, the at least one additional maintenance dose comprises 180 mg or 270 mg of the anti-IL-23A antibody.

In one embodiment, the first maintenance dose and the at least one additional maintenance dose comprise 150 to 300 mg of the anti-IL-23A antibody. In one embodiment, the first maintenance dose and the at least one additional maintenance dose comprise 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose and the at least one additional maintenance dose comprise 180 mg or 270 mg of said anti-IL-23A antibody. In one embodiment, a maintenance dose is administered by subcutaneous injection.

In one embodiment, the maintenance doses comprise 150 mg of the anti-IL-23A antibody and are administered to the patient at 4 weeks intervals.

In one embodiment, the maintenance doses comprise 150 mg of the anti-IL-23A antibody and are administered to the patient at 8 weeks intervals.

In one embodiment, the maintenance doses comprise 225 mg of the anti-IL-23A antibody and are administered to the patient at 8 weeks intervals.

In one embodiment, the maintenance doses comprise 225 mg of the anti-IL-23A antibody and are administered to the patient at 12 weeks intervals.

In one embodiment, the maintenance doses comprise 300 mg of the anti-IL-23A antibody and are administered to the patient at 8 weeks intervals.

In one embodiment, the maintenance doses comprise 300 mg of the anti-IL-23A antibody and are administered to the patient at 12 weeks intervals.

In one embodiment, the patient maintains clinical remission after the administration of the one or more maintenance doses. In one embodiment, the patient maintains a CDAI score of less than 150 after the administration of the one or more maintenance doses. In one embodiment, the patient maintains a PRO-2 score equal to or less than 75 after the administration of the one or more maintenance doses. In one embodiment, the patient maintains a CDAI score of less than 150 and a PRO-2 score equal to or less than 75 after the administration of the one or more maintenance doses.

In one embodiment, the present disclosure further provides a method for maintaining clinical remission of Crohn's Disease in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein.

In one embodiment, the present disclosure further provides a method for maintaining clinical response to Crohn's Disease in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein.

In one embodiment, the present disclosure further provides a method for treating Crohn's Disease by inducing and maintaining clinical remission in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein.

In one embodiment, the present disclosure further provides a method for maintaining endoscopic remission of Crohn's Disease in a patient comprising administering to the patient an anti-IL-23 antibody as described above or herein.

In one embodiment, the present disclosure provides a method for inducing clinical remission of Crohn's Disease comprising administering to a patient an anti-IL-23A antibody, said method comprising administering at least one induction dose of said anti-IL-23A antibody to the patient, wherein said induction dose comprises 200 to 1,200 mg of said anti-IL-23A antibody. In one embodiment, the induction dose comprises 450 to 1,200 mg of said anti-IL-23A antibody. In one embodiment, the induction dose comprises 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of said anti-IL-23A antibody. In one embodiment, 1, 2 or 3 induction doses are administered to the patient. In one embodiment, 2 or 3 induction doses are administered at 4 weeks intervals. In one embodiment, the induction dose(s) is/are administered by intravenous infusion. In one embodiment, the patient has a CDAI score of 220-450 before said administration. In one embodiment, the patient achieves a CDAI score of less than 150. In one embodiment, the patient achieves a PRO-2 score equal to or less than 75.

In one embodiment, the method further comprises maintaining clinical remission of Crohn's disease, said method further comprising administering a first maintenance dose of said anti-IL-23A antibody to the patient after the last induction dose is administered, and administering at least one additional maintenance dose to the patient 4 to 12 weeks after said first maintenance dose is administered. In one embodiment, the first maintenance dose is administered 2 to 8 weeks, for example 4 to 6 weeks, for example 2 weeks, 4 weeks, 6 weeks or 8 weeks, after the last induction dose is administered. In one embodiment, the at least one additional maintenance dose is administered to the patient 4, 8 or 12 weeks after said first maintenance dose is administered. In one embodiment, the first maintenance dose comprises 150 to 300 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose comprises 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose comprises 180 mg or 270 mg of said anti-IL-23A antibody. In one embodiment, the at least one additional maintenance dose comprises 150 to 300 mg of said anti-IL-23A

antibody. In one embodiment, the at least one additional maintenance dose comprises 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody. In one embodiment, the at least one additional maintenance dose comprises 180 mg or 270 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose and said at least one additional maintenance dose comprise 150 to 300 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose and said at least one additional maintenance dose comprise 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody. In one embodiment, the first maintenance dose and said at least one additional maintenance dose comprise 180 mg or 270 mg of said anti-IL-23A antibody. In one embodiment, the maintenance dose is administered by subcutaneous injection. In one embodiment, the patient maintains a CDAI score of less than 150. In one embodiment, the patient maintains a PRO-2 score equal to or less than 75.

In one embodiment, the present disclosure provides a method for treating an inflammatory disease, in one embodiment for treating Crohn's Disease, comprising administering to a patient 150 to 1,200 mg of an anti-IL-23A antibody. In one aspect, the present disclosure provides use of 150 to 1,200 mg of an anti-IL-23A antibody in the manufacture of a medicament for the treatment of Crohn's Disease. In one embodiment, the method comprises administering to a patient 200 mg to 1,200 mg of an anti-IL-23A antibody, for example 450 to 1,200 mg of an anti-IL-23A antibody. In one embodiment, the method comprises administering to a patient 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of an anti-IL-23A antibody. In one embodiment, the method comprises administering to a patient 150 to 300 mg of an anti-IL-23A antibody. In one embodiment, the method comprises administering to a patient 150 mg, 225 mg or 300 mg of an anti-IL-23A antibody. In one embodiment, the method comprises administering to a patient 180 mg or 270 mg of an anti-IL-23A antibody.

In one embodiment, in any one of the methods above, the anti-IL-23A antibody is Antibody A, Antibody B, Antibody C or Antibody D.

In one embodiment, in any one of the methods above, the method is for treating Crohn's Disease, for example moderately to severely active Crohn's Disease. In one embodiment, in the context of a method of the present disclosure a patient is naïve to, or was previously

treated with anti-TNF therapy. In one embodiment, in the context of a method of the present disclosure a patient was previously treated with one, two, three or more TNF antagonist(s). In one embodiment, the patient is a patient who had an inadequate response with, was intolerant to, or demonstrated dependence on corticosteroids. In one embodiment, the patient is a patient who had an inadequate response with, lost response, or was intolerant to an immunomodulator, a TNF α inhibitor (or TNF antagonist) or an integrin inhibitor. In one embodiment, the treatment is by inducing and maintaining clinical remission, corticosteroid-free remission, endoscopic remission and mucosal healing.

In one embodiment, a patient to be treated by a method according to the present disclosure has a CDAI score of 220-450.

In one embodiment, in any one of the methods above, the patient is an adult patient.

In one embodiment, in any one of the methods above, the method is for treating ulcerative colitis.

In one embodiment, the present disclosure provides an anti-IL-23A antibody for use in the treatment of a disease, for example an inflammatory disease, for example Crohn's Disease, by administration in certain amounts and/or at certain intervals as described
5 herein. In one embodiment, the inflammatory disease is ulcerative colitis.

In one embodiment, the present disclosure provides for the use of an anti-IL-23A antibody for the preparation of a medicament for the treatment of a disease, for example an inflammatory disease, for example Crohn's Disease, by administration in certain amounts and/or at certain intervals as described herein. In one embodiment, the
10 inflammatory disease is ulcerative colitis.

In one embodiment, in any one of the methods or uses above, the anti-IL-23A antibody is disclosed below.

In one embodiment, the present disclosure provides a method for detecting the presence or absence of a beneficial response in a patient after administration of an IL-23A antagonist, comprising: a) obtaining a biological sample from the patient; b) measuring in said sample the level of expression of one or more genes; c) comparing the level in b) to the level of expression of the one or more genes in a control; and d) determining whether or not the difference in levels between the sample and the control reflects a beneficial response in the patient, wherein the one or more genes is one or more genes described herein. In one embodiment, the patient suffers from Crohn's Disease. In one embodiment, the biological sample is a colon tissue or a ileum tissue. In one embodiment, the biological sample is taken from the upper gastrointestinal (GI) tract, for example the stomach or the esophagus. In one embodiment, the IL-23A antagonist is an anti-IL-23A antibody or an antigen binding fragment thereof, for example Antibody A, Antibody B, Antibody C or Antibody D.

Brief Description of the Figures

Figure 1: Trial Design. Deep remission, defined as achieving clinical remission (CDAI score < 150) and CDEIS remission (CDEIS score ≤ 4 or 2 or less in patients with initial isolated ileitis).

Figure 2A and 2B: Proportion of patients with clinical remission (A) or clinical response (B) at week 4, week 8 and week 12. Clinical remission is defined as a CDAI score <150. Clinical response is either a CDAI score <150 or a CDAI reduction from baseline of ≥ 100 points. Patients in which prohibited concomitant medication to treat Crohn's disease was used prior to Week 12 were considered as treatment failures. Full analysis set was used for these analyses. * $p < 0.05$ versus placebo, ** $p < 0.005$ versus placebo, *** $p < 0.001$ versus placebo.

Figure 3A-D: Median CDAI scores over time (A), median CRP over time (B), median percent change in FCP from baseline (C), median percent change in IL-22 from baseline (D). * $p < 0.001$, Bonferroni adjusted p-value for 600 mg Antibody A versus placebo.

** $p < 0.05$, Bonferroni adjusted p-value for 600 mg Antibody A versus placebo.

Claims

1. Use of an anti-IL-23A antibody in the manufacture of a medicament for inducing remission of Crohn's Disease in a patient, wherein:
 - a) said anti-IL-23A antibody is to be administered in at least one induction dose to the patient, and wherein said induction dose comprises 200 to 1,200 mg of said anti-IL-23A antibody.
2. The use according to claim 1, wherein said induction dose comprises 450 to 1,200 mg of said anti-IL-23A antibody.
3. The use according to claim 1, wherein said induction dose comprises 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of said anti-IL-23A antibody.
4. The use according to any one of claims 1 to 3, wherein 1, 2 or 3 induction doses are to be administered to the patient.
5. The use according to any one of claims 1 to 4, wherein 2 or 3 induction doses are to be administered at 4 weeks intervals.
6. The use according to any one of claims 1 to 5, wherein said induction dose is to be administered by intravenous infusion.
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7. The use according to any one of claims 1 to 6, wherein said patient has a CDAI score of 220-450 before administration of said induction dose.
8. The use according to any one of claims 1 to 7, wherein said patient achieves a CDAI score of less than 150.
9. The use according to any one of claims 1 to 8, wherein said patient achieves a PRO-2 score equal to or less than 75.

10. The use according to any one of claims 1 to 9, wherein
 - b) said anti-IL-23A antibody is to be administered as a first maintenance dose to the patient after the last induction dose is administered; and
 - c) at least one additional maintenance dose is to be administered to the patient 4 to 12 weeks after said first maintenance dose is administered.
11. The use according to claim 10, wherein said first maintenance dose is to be administered 2 to 8 weeks, for example 4 to 6 weeks, for example 2 weeks, 4 weeks, 6 weeks or 8 weeks, after the last induction dose is administered.
12. The use according to any one of claims 10 or 11, wherein said at least one additional maintenance dose is to be administered to the patient 4, 8 or 12 weeks after said first maintenance dose is administered.
13. The use according to any one of claims 10 to 12, wherein said first maintenance dose comprises 150 to 300 mg of said anti-IL-23A antibody.
14. The use according to any one of claims 10 to 13, wherein said first maintenance dose comprises 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody.
15. The use according to any one of claims 10 to 14, wherein said first maintenance dose comprises 180 mg or 270 mg of said anti-IL-23A antibody.
16. The use according to any one of claims 10 to 15, wherein said at least one additional maintenance dose comprises 150 to 300 mg of said anti-IL-23A antibody.
17. The use according to any one of claims 10 to 16, wherein said at least one additional maintenance dose comprises 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody.

18. The use according to any one of claims 10 to 17, wherein said at least one additional maintenance dose comprises 180 mg or 270 mg of said anti-IL-23A antibody.
19. The use according to any one of claims 10 to 18, wherein said first maintenance dose and said at least one additional maintenance dose comprise 150 to 300 mg of said anti-IL-23A antibody.
20. The use according to any one of claims 10 to 19, wherein said first maintenance dose and said at least one additional maintenance dose comprise 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody.
21. The use according to any one of claims 10 to 20, wherein said first maintenance dose and said at least one additional maintenance dose comprise 180 mg or 270 mg of said anti-IL-23A antibody.
22. The use according to any one of claims 10 to 21, wherein said maintenance dose is to be administered by subcutaneous injection.
23. The use according to anyone of claims 10 to 22, wherein said patient maintains a CDAI score of less than 150.
24. The use according to anyone of claims 10 to 23, wherein said patient maintains a PRO-2 score equal to or less than 75.
25. Use of 150 to 1,200 mg of an anti-IL-23A antibody in the manufacture of a medicament for the treatment of Crohn's Disease.
26. The use according to claim 25, comprising 200 to 1,200 mg of said anti-IL-23A antibody.

27. The use according to claim 25, comprising 450 to 1,200 mg of said anti-IL-23A antibody.
28. The use according to claim 25, comprising 200 mg, 450 mg, 600 mg, 900 mg or 1,200 mg of said anti-IL-23A antibody.
29. The use according to claim 25, comprising 150 to 300 mg of said anti-IL-23A antibody.
30. The use according to claim 25, comprising 150 mg, 225 mg or 300 mg of said anti-IL-23A antibody.
31. The use according to claim 25, comprising 180 mg or 270 mg of said anti-IL-23A antibody.
32. Use of an anti-IL-23A antibody in the manufacture of a medicament for the treatment of Crohn's Disease in a patient, wherein:
 - a) at least one induction dose of said anti-IL-23A antibody is to be administered to the patient, and wherein said induction dose comprises 200 to 1,200 mg of said anti-IL-23A antibody.
33. The use according to claim 32, wherein:
 - b) a first maintenance dose of said anti-IL-23A antibody is to be administered to the patient after the last induction dose is administered; and
 - c) at least one additional maintenance dose is to be administered to the patient 4 to 12 weeks after said first maintenance dose is administered.
34. The use according to claim 33, wherein said first maintenance dose comprises 150 to 300 mg of said anti-IL-23A antibody.

35. The use according to claim 33 or 34, wherein said at least one additional maintenance dose comprises 150 to 300 mg of said anti-IL-23A antibody.
36. The use according to any one of claims 1 to 35, wherein said anti-IL-23A antibody is Antibody A, Antibody B, Antibody C or Antibody D.
37. The use according to any one of claims 1 to 36, wherein said use is for treating moderate to severe active Crohn's Disease.