deficient), could enhance atrial energetics to reduce P-wave duration/dispersion and thereby prevent or treat AF.

An aspect of the invention discloses the use of iron for the reduction of P-wave dispersion/duration for the prevention and treatment of AF where the AF is either paroxysmal, persistent, long-standing, or chronic.

SUMMARY

In one aspect, the present disclosure refers to the use of iron isomaltoside for the manufacture of a medicament for treating iron deficiency in a subject, wherein the treatment of iron deficiency reduces the incidence of, or risk for, a cardiovascular adverse event in the subject, which use comprises that an effective amount of the iron isomaltoside is to be administered, wherein the subject is: (A) a subject being at risk of a cardiovascular adverse event; (B) a subject having a history of congestive heart failure (CHF); or (C) a subject having a history of congestive heart failure (CHF) and being at risk of a cardiovascular adverse event.

In another aspect, the present disclosure refers to the use of an iron agent for the manufacture of a medicament for reducing P-wave dispersion/duration for the prevention or treatment of atrial fibrillation (AF) or disorders that predispose to AF in an animal suffering from such a condition which comprises that a therapeutically effective amount of the iron agent is to be administered to such an animal.

In one example of this disclosure, iron deficiency is treated in a subject being at risk of a cardiovascular adverse event. Accordingly, subjects are selected for treatment with iron isomaltoside not only based on the criteria commonly used to define eligibility for parenteral iron, i.e. diagnosis of ID or IDA and/or a potential lack of the ability to tolerate or absorb oral iron, but also based on their risk of experiencing a cardiovascular adverse event.

In a second example of this disclosure, the treatment of iron deficiency reduces the incidence of, or risk for, a cardiovascular adverse event in the subject. Accordingly, the subjects that are selected for treatment with iron isomaltoside based on the criteria commonly used to define eligibility for parenteral iron, i.e. diagnosis of ID or IDA and/or a potential lack of the ability to tolerate or absorb oral iron and based on their risk of experiencing a cardiovascular adverse event, benefit from a reduction of the incidence of, or risk for, a cardiovascular adverse event in the subject.

A third example of the disclosure relates to the treatment of particular groups of subjects, as defined herein, to reduce the incidence of, or risk for, a cardiovascular adverse event, as defined herein.

In line with these examples, the present disclosure in particular relates to therapeutic methods of treating iron deficiency which comprise administering iron isomaltoside to selected subgroups of subjects; and combinations of iron isomaltoside 1000 with other drugs that are either used to treat subjects at risk of cardiovascular adverse events or increase the risk of such cardiovascular adverse events.

In an example of said first example, the present disclosure relates to a method of treating iron deficiency in a subject being at risk of a cardiovascular adverse event, which comprises administering an effective amount of iron isomaltoside.

In a number of examples of said first example, subjects being at risk of a cardiovascular adverse event are subjects having one or more of the following risk factors:

(xx) subjects having hereditary iron refractory iron deficiency anemia.

In a particular example of said first example, the present disclosure relates to a method of treating iron deficiency in a subject having a history of congestive heart failure (CHF), which comprises administering an effective amount of iron isomaltoside. According to one example, the subject also has a history of myocardial infarction (MI) and/or a history of stroke. According to a preferred example, CHF is heart failure with reduced ejection fraction (HFrEF).

In a further particular example of said first example, the subject being at risk of a cardiovascular adverse event or having a history of congestive heart failure has chronic kidney disease (CKD). In another particular example of said first example, the subject being at risk of a cardiovascular adverse event or having a history of congestive heart failure does not have chronic kidney disease (CKD). In another particular example of said first example, the subject being at risk of a cardiovascular adverse event is a subject having chronic kidney disease (CKD) and a history of congestive heart failure (CHF).

According to one example, the subject having a history of congestive heart failure has HFrEF. According to another example the subject having a history of congestive heart failure has congestive heart failure in New York Heart Association (NYHA) class II-IV, in particular HFrEF-type congestive heart failure in New York Heart Association (NYHA) class II-IV. According to another example the subject has congestive heart failure in NYHA class I.

In an example of said second example, the present disclosure relates to a method of treating iron deficiency in a subject being at risk of a cardiovascular adverse event wherein the treatment of iron deficiency reduces the incidence of, or risk for, a cardiovascular adverse event in the subject, which method comprises administering an effective amount of iron isomaltoside.

In one example of said second example, the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is selected from the group consisting of events that affect the heart (cardiac adverse events); events that affect the peripheral vasculature (peripheral vascular adverse events); events that affect the cerebral vasculature (cerebrovascular adverse events); respiratory, thoracic and mediastinal adverse events; general adverse events; and infections and infestations. According to one example, the cardiac adverse events are selected from the group consisting of congestive heart failure,

atrial fibrillation, cardiac arrest, atrioventricular block, cardiac failure, sinus node dysfunction, acute myocardial infarction, bradycardia, angina pectoris, myocardial ischemia, and ventricular extrasystoles; the peripheral vascular adverse events are selected from the group consisting of hypertension, increased systolic blood pressure, increase blood pressure, increased troponin, and hypotension; the cerebrovascular adverse events are selected from the group consisting of cerebrovascular accident, cerebral infarction, and transient ischemic attack; the respiratory, thoracic and mediastinal adverse events are selected from the group consisting of dyspnea and pulmonary edema; the general adverse events are selected from the group consisting of chest pain and death; and the infections and infestations are septic shock.

In a preferred example of this second example of the disclosure, the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is selected from the group consisting of events that affect the heart (cardiac adverse events); events that affect the peripheral vasculature (peripheral vascular adverse events); events that affect the cerebral vasculature (cerebrovascular adverse events); and death. According to a preferred example, the events that affect the heart (cardiac adverse events) are congestive heart failure, myocardial infarction, unstable angina, and arrhythmia; events that affect the peripheral vasculature (peripheral vascular adverse events) are hypertension; and events that affect the cerebral vasculature (cerebrovascular adverse events) is stroke.

In a particularly preferred example of this second example of the disclosure, the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is selected from the group consisting of congestive heart failure, myocardial infarction, unstable angina, arrhythmia, hypertension, hypotension, stroke, and death.

In a further particularly preferred example of this second example of the disclosure, the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is congestive heart failure, atrial fibrillation, hypertension, and/or cardiac arrest.

According to one example, specific cardiovascular adverse events related to congestive heart failure are hospitalization or death due to congestive heart failure. In one example, a specific cardiovascular adverse event related to congestive heart failure is hospitalization due to worsening congestive heart failure. The present disclosure is in particular directed to those CV adverse events where the CV adverse event is CHF.

In an example of said third example, the present disclosure relates to a method of treating iron deficiency in a subject, wherein the treatment of iron deficiency reduces the incidence of, or risk for, a cardiovascular adverse event in the subject, which method comprises administering an effective amount of iron isomaltoside,

wherein the subject is:

(A) a subject being at risk of a cardiovascular adverse event;

(B) a subject having a history of congestive heart failure (CHF); or

(C) a subject having a history of congestive heart failure (CHF) and being at risk of a cardiovascular adverse event, and

wherein the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is:

(a) selected from the group consisting of congestive heart failure, myocardial infarction, unstable angina, arrhythmia, hypertension, hypotension, stroke, and death;

(b) congestive heart failure;

(c) atrial fibrillation;

(d) hypertension; or

(e) cardiac arrest.

In a preferred example of this third example of the disclosure, the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is congestive heart failure.

In a further preferred example of this third example of the disclosure, the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is atrial fibrillation.

In a further preferred example of this third example of the disclosure, the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest.

In a further preferred example of this third example of the disclosure, the subject is a subject having a history of congestive heart failure and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest or congestive heart failure or both.

In a further preferred example of this third example of the disclosure, the subject is a subject having a history of congestive heart failure (CHF) and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is atrial fibrillation.

In a further preferred example of this third example of the disclosure, the subject is a subject having a history of congestive heart failure (CHF) and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest.

In particular example of this third example of the disclosure, the subject defined herein is a subject being at risk of a cardiovascular adverse event and/or having a history of congestive heart failure, wherein the subject has chronic kidney disease (CKD).

In another particular example of this third example of the disclosure, the subject defined herein the subject is a subject being at risk of a cardiovascular adverse event and/or having congestive heart failure, wherein the subject does not have chronic kidney disease (CKD).

In these examples, chronic kidney disease (CKD) is preferably non-dialysis dependent chronic kidney disease (NDD-CKD).

In still further preferred examples of this third example of the disclosure, the subject having a history of congestive heart failure has HFrEF, congestive heart failure in NYHA class II-IV, or both.

According to another example the subject has congestive heart failure in NYHA class I.

In a particularly preferred example of this third example of the disclosure, the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiovascular death and/or hospitalization due to worsening congestive heart failure.

According to the disclosure, iron deficiency is preferably defined as TSAT < 20% and/or ferritin < 100 µg/L. In one example of the disclosure, the iron deficiency is iron-deficiency anemia.

In a further example of the disclosure, the subject to be treated has chronic iron loss or malabsorption. In a further example of said first example, the subject does not tolerate oral iron or for whom oral iron is not effective.

The preferred iron carbohydrate complex for use in the disclosure is an iron isomaltoside, especially ferric derisomaltose.

In another example the disclosure relates to a method of reducing P-wave dispersion/duration for the prevention or treatment of AF or disorders that predispose to AF (e.g., heart valve disease, hypertension, heart failure, coronary artery disease, obesity, and diabetes mellitus) in an animal suffering from such a condition which comprises administering to such an animal a therapeutically effective amount of an iron agent. The animal is preferably a mammal and most preferably a human.

The AF treated may be paroxysmal, persistent, long-standing, or chronic.

According to one example, the iron agent may be administered via the oral, intramuscular, or intravenous route.

According to other examples the animal, preferably human, may or may not be iron deficient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG 1. is a flow chart of a randomized double-blind placebo-controlled trial on which an analysis was performed to evaluate the effect of intravenous iron on P-wave dispersion in patients with heart failure.

FIG 2. is an example of a surface electrocardiogram with P-wave duration measured in each lead. P-wave dispersion is then calculated as the difference between the longest and shortest recorded P-wave duration.

FIG 3. represents the baseline data of intravenous iron vs saline control patients.

FIG 4. represents the results for all endpoints showing that P-wave dispersion is significantly reduced by iron.

FIG 5. represents the results for P-wave dispersion with changes in each individual patient given. P-wave dispersion remains unchanged in the saline placebo group but is shortened in the iron group with an analysis of covariance (ANCOVA) P-value of 0.007 which is significant.

Figure 6 is a table summarizing the analysis of the incidence of adjudicated and confirmed treatment-emergent composite cardiovascular (CV) adverse events with incidence $\geq 0.25\%$ by preferred term for study CKD-04, study IDA-03, and the combined studies CKD-04/IDA-03.

Claims:

1. Use of iron isomaltoside for the manufacture of a medicament for treating iron deficiency in a subject, wherein the treatment of iron deficiency reduces the incidence of, or risk for, a cardiovascular adverse event in the subject, which use comprises that an effective amount of the iron isomaltoside is to be administered,

wherein the subject is:

(A) a subject being at risk of a cardiovascular adverse event;

(B) a subject having a history of congestive heart failure (CHF); or

(C) a subject having a history of congestive heart failure (CHF) and being at risk of a cardiovascular adverse event.

2. The use of claim 1, wherein the cardiovascular adverse event, the incidence of, or risk for, which reduced is:

(a) selected from the group consisting of congestive heart failure, myocardial infarction, unstable angina, arrhythmia, hypertension, hypotension, stroke, and death;

(b) congestive heart failure;

(c) atrial fibrillation;

(d) hypertension; or

(e) cardiac arrest.

3. The use of claim 1 or 2, wherein the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is congestive heart failure.

4. The use of claim 1 or 2, wherein the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is atrial fibrillation.

5. The use of claim 1 or 2, wherein the subject is a subject being at risk of a cardiovascular adverse event and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest.

6. The use of claim 1 or 2, wherein the subject is a subject having a history of congestive heart failure and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest or congestive heart failure or both.

7. The use of claim 1 or 2, wherein the subject is a subject having a history of congestive heart failure (CHF) and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is atrial fibrillation.

8. The use of claim 1 or 2, wherein the subject is a subject having a history of congestive heart failure (CHF) and the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiac arrest.

9. The use of any one of claims 1 -8, wherein the subject is a subject being at risk of a cardiovascular adverse event and/or having a history of congestive heart failure, wherein the subject has chronic kidney disease (CKD).

10. The use of any one of claims 1 -8, wherein the subject is a subject being at risk of a cardiovascular adverse event and/or having congestive heart failure, wherein the subject does not have chronic kidney disease (CKD).

11. The use of claim 9 or 10, wherein the chronic kidney disease (CKD) is non-dialysis dependent chronic kidney disease (NDD-CKD).

12. The use of any one of claims 1 or 2, or 6-11, wherein the subject having a history of congestive heart failure has HFrEF.

13. The use of any one of claims 1 or 2, or 6-12, wherein the subject having a history of congestive heart failure has congestive heart failure in NYHA class II-IV.

14. The use of any one of claims 1-13, wherein the cardiovascular adverse event, the incidence of, or risk for, which is reduced, is cardiovascular death and/or hospitalization due to worsening congestive heart failure.

15. The use of any one of claims 1-14, wherein the iron deficiency is defined as TSAT < 20% and/or ferritin < 100 µg/L.

16. The use of any one of claims 1-15, wherein the iron isomaltoside is ferric derisomaltose.

17. The use of any one of claims 1-16, wherein the subject is also being treated with another agent used to treat or prevent cardiovascular adverse events including but not limited to congestive heart failure (CHF), cardiac arrest, congestive heart failure (CHF), myocardial infarction, unstable angina, arrhythmia, hypertension, hypotension, stroke, and atrial fibrillation.

18. Use of an iron agent for the manufacture of a medicament for reducing P-wave dispersion/duration for the prevention or treatment of atrial fibrillation (AF) or disorders that predispose to AF in an animal suffering from such a condition which comprises that a therapeutically effective amount of the iron agent is to be administered to such an animal.

19. The use of claim 18, wherein said disorders that predispose to AF are selected from heart valve disease, hypertension, heart failure, coronary artery disease, obesity, and diabetes mellitus.

20. The use of claim 18 or claim 19, wherein said iron agent is an intravenous injection or infusion and said intravenous injection or infusion comprises high molecular weight iron dextran, low molecular weight iron dextran, iron sucrose, ferrous gluconate, ferric carboxymaltose, or iron isomaltoside.