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(54) **METHOD OF ESCALATING SOTALOL HYDROCHLORIDE DOSING**

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(57) **ABSTRACT**

This disclosure provides a method of safely and rapidly initiating or escalating oral sotalol therapy by administering an intravenous dosage of sotalol followed by oral sotalol twice daily.

11 Claims, 2 Drawing Sheets

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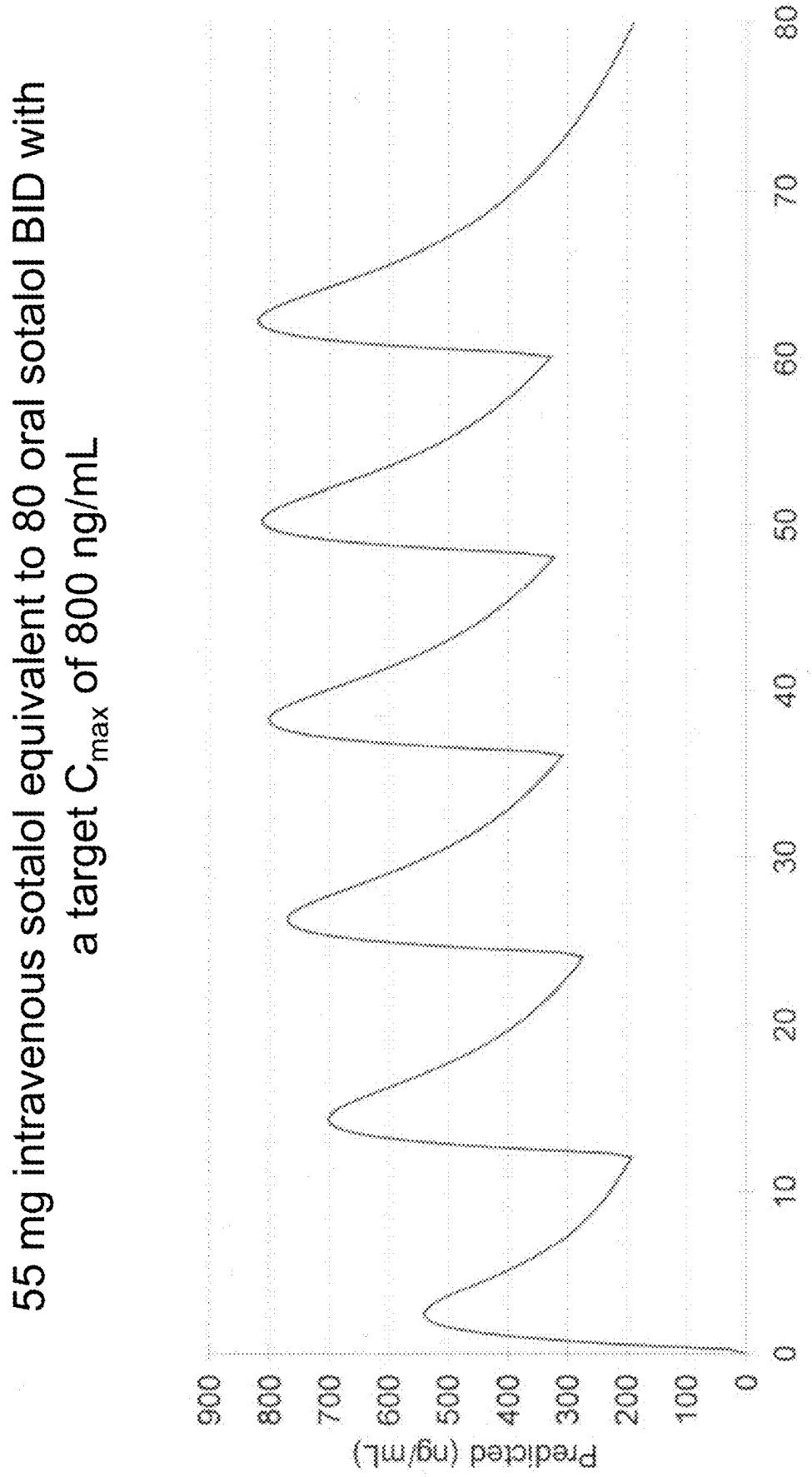
55 mg intravenous sotalol equivalent to 80 oral sotalol BID with a target C_{max} of 800 ng/mL
Predicted (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
80
Time (hr)

FIGURE 1

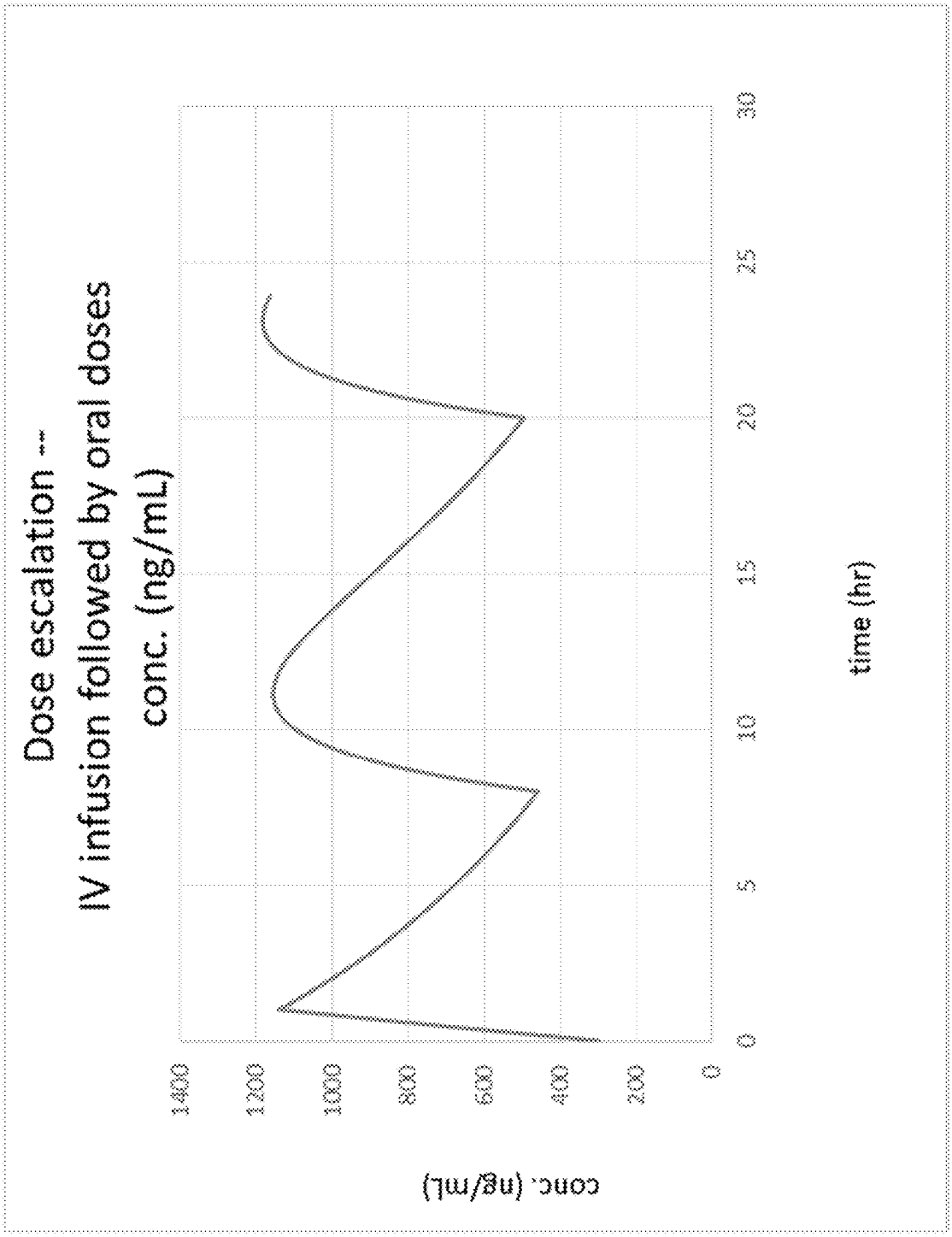
Dose escalation --
IV infusion followed by oral doses
conc. (ng/mL)
conc. (ng/mL)
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
time (hr)

FIGURE 2

METHOD OF ESCALATING SOTALOL HYDROCHLORIDE DOSING

FIELD

This disclosure provides methods of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof comprising intravenously administering sotalol hydrochloride to subject in need thereof.

BACKGROUND

Sotalol hydrochloride ("sotalol") is Vaughan Williams Class III anti-arrhythmic drug that prolongs cardiac action potential duration by blocking the outward potassium channel IKr (rapid potassium rectifier current), thereby prolonging repolarization time.

Although sotalol is effective at treating or preventing atrial fibrillation, atrial flutter, and combinations thereof, sotalol's mechanism of action is both anti-arrhythmic and pro-arrhythmic. Too much sotalol too fast can lead to excessive prolongation of repolarization time giving rise to life threatening arrhythmias, especially Torsade de Pointes ventricular tachycardia (Tdp). Thus, it is well understood in the art, that during sotalol's initial loading, or in a dose escalation intervention, it is critical to monitor a subject's QTc interval to avoid excessive QTc prolongation.

Due to sotalol's potential to induce arrhythmia, the FDA has mandated in-hospital QTc monitoring for at least three days upon initial sotalol hydrochloride loading and for dose escalation. Although this extended hospital stay is effective at reducing subject risk, maintaining the subject in a telemetry unit for three days is extremely expensive, making sotalol a less desirable treatment choice in a managed care environment. A need therefore exists to develop methods of reducing the length of hospital stay required to safely and efficaciously administer sotalol to subjects in need thereof.

BRIEF SUMMARY

The present disclosure provides methods of safely intravenously administering sotalol hydrochloride to subjects in need thereof over a significantly reduced period of time, such as about 1 hour. In particular, the present disclosure provides a method of achieving a sotalol steady state C_{max} after about 1 hour of intravenous administration equal to the sotalol steady state C_{max} typically achieved after BID PO sotalol administration for three days.

In one embodiment, this disclosure provides a method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes.

In some embodiments, the method further comprises discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 750 ng/mL and about 850 ng/mL in the subject.

In some embodiments, the method further comprises orally administering to the subject 80 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, the method further comprises initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

Also provided is a method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride over a period of about 60 minutes.

In some embodiments, the method further comprises discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

In some embodiments, the method further comprises orally administering to the subject 120 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, the method further comprises initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

Also provided is a method of treating atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.65 mg/min to about 2.35 mg/min of sotalol hydrochloride over a period of about 60 minutes.

In some embodiments, the method further comprises discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is

greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

In some embodiments, the method further comprises orally administering to the subject 160 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, the method further comprises initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

Also provided is a method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes, wherein the subject received an administration of sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration.

In some embodiments, the subject received an oral administration of 80 mg of oral sotalol hydrochloride between about 12 and about 24 hours before the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

In some embodiments, the method further comprises orally administering to the subject 120 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, the method further comprises initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

Also provided is a method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.05 mg/min and 1.47 mg/min of sotalol hydrochloride over a period of about 60 minutes, wherein the subject received an administration of sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration.

In some embodiments, the subject received an oral administration of 120 mg of oral sotalol hydrochloride between about 12 and about 24 hours before the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

In some embodiments, the method further comprises orally administering to the subject 160 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, the method further comprises discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, the method further comprises initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

BRIEF DESCRIPTION OF THE DRAWINGS

The above-mentioned features and objects of this disclosure will become more apparent with reference to the following description taken in conjunction with the accompanying drawings.

FIG. **1** is a line graph depicting initiation of an intravenous dose of 55 mg of sotalol hydrochloride to achieve an estimated steady state C_{max} equivalent to the steady state C_{max} achieved via chronic oral twice daily dosing of 80 mg sotalol hydrochloride in a subject with normal renal function.

FIG. **2** is a line graph depicting dose escalation from 80 mg twice a day to 120 mg twice a day of oral sotalol hydrochloride via the intravenous administration of 55 mg of sotalol hydrochloride in 1 hour.

DETAILED DESCRIPTION

Definitions

As used in this disclosure, the term "or" is defined as a logical disjunction (i.e., and/or) and does not indicate an exclusive disjunction unless expressly indicated as such with the terms "either," "unless," "alternatively," and words of similar effect.

As used herein, the term "about" means+/−10% of the value specified. By way of example only, "about 50" means from 45 to 55.

The term "C_{max}" refers to the maximum blood concentration shown on the curve that represents changes in blood concentrations of an active pharmaceutical ingredient (e.g., sotalol hydrochloride), or a metabolite of the active pharmaceutical ingredient, over time.

The term "steady state C_{max}" refers to the state, wherein the post dose maximum plasma concentration of sotalol hydrochloride does not differ from one dose to another. In some embodiments, the method described herein provides a steady state C_{max} of sotalol hydrochloride concentration in a range between about 800 ng/mL and about 1600 ng/mL, depending upon the amount of sotalol dosed.

The term "QT" refers to a telltale measurement seen on an electrocardiogram (ECG). The QT interval is measured from the start of the Q wave or the QRS complex, to the end of the T wave, where the Q wave corresponds to the beginning of ventricular depolarization and the T wave end corresponds to the end of ventricular repolarization.

The term "QTc" refers to a calculated interval that represents the QT interval corrected for heart rate. The QTc interval may be derived by simple mathematical correlation of the QT interval and the heart rate. In preferred embodiments, and for purposes of the present disclosure, the QTc interval is measured using the Bazett formula. Other methods, however, are known in the art, such as the nomogram method, the Frederica formula, or the linear regression equation.

The term "ΔQTc" refers to the difference between a QTc measurement taken prior to intravenous sotalol hydrochloride administration and a QTc measured after intravenous sotalol hydrochloride administration.

The term "PO" stands for "per os" and refers to an oral dosing regimen.

The term "BID" stands for "bis in die" and means twice a day.

The term "subject" refers to a human subject.

An "effective amount" of a drug necessary to achieve a therapeutic effect may vary according to factors such as the age, sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response.

The terms "treat," "treating," and "treatment" refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the subject; slowing in the rate of degeneration or decline; or improving a subject's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

Intravenous sotalol was approved by the FDA in 2009. Although FDA guidance requires a slow infusion over five hours coupled with multi-day cardiac monitoring, it has now been surprisingly discovered that it is possible to safely reach a sotalol steady state C_{max} in a subject equal to the sotalol steady state C_{max} typically achieved after BID PO sotalol administration for three days at various sotalol dosage strengths, after about 1 hour of intravenous administration. The ability to reach a steady state C_{max} equal to the steady state C_{max} achieved via oral dosing is surprising because rapid, intravenous sotalol administration was thought to result in high sotalol serum concentration, excessive QT interval prolongation, and on occasion, Torsade de Pointes ventricular tachycardia. See, Somberg, et. al., *Am. J. Ther.* 17(4):365-72 (2010).

Sotalol Initiation Protocol in Naïve Subjects

It has been surprisingly discovered that an about 55 mg to about 64 mg intravenous load of sotalol can be safely delivered over about 1 hour to reach a projected steady state C_{max} of about 800 ng/mL (corresponding to the steady state C_{max} achieved after three days of PO BID dosing of 80 mg sotalol hydrochloride) in sotalol naive subjects. It has likewise been surprisingly discovered that an about 82 mg to about 96 mg intravenous load of sotalol hydrochloride delivered over about 1 hour can safely provide a projected steady state C_{max} of about 1200 ng/mL (corresponding to the steady state C_{max} achieved after three days of PO BID dosing of 120 mg sotalol hydrochloride) in sotalol naïve subjects and that an about 110 mg to about 128 mg intravenous load of sotalol hydrochloride delivered over about 1 hour can safely provide a projected steady state C_{max} of about 1600 ng/mL (corresponding to the steady state C_{max} achieved after three days of PO BID dosing of 160 mg sotalol hydrochloride) in naïve subjects. In each of these cases, intravenous administration of sotalol hydrochloride can be followed at appropriate intervals by oral sotalol hydrochloride to maintain the steady state C_{max} for efficacious treatment or prevention of a given condition.

By administering sotalol according to the dosing protocol described herein, a subject can be discharged from the hospital from about 18 hours to about 24 hours after initiation of intravenous sotalol administration. During the 18-24 hour period, the subject typically experiences at least two sotalol concentration peaks: one following intravenous sotalol hydrochloride administration and one following subsequent oral sotalol hydrochloride administration. In some embodiments, the subject experiences two sotalol concentration peaks over a period of about 15 hours to about 18 hours. In each instance, the subject's peak plasma concentration will approach the steady state C_{max} observed during chronic dosing. As a result, it is possible to assess the QTc interval of a subject corresponding to the full concentration effect of sotalol hydrochloride over an 18-24 hour period and to determine within that period, if the subject can tolerate the dose.

Accordingly, in some embodiments, this disclosure provides a method of safely administering sotalol hydrochloride to a subject in need thereof, the method comprising intravenously administering sotalol hydrochloride over a period of about 60 minutes to reach a sotalol steady state C_{max} in the subject, wherein the subject has a QTc interval during the intravenous administration of sotalol hydrochloride that is less than or equal to 480 msec to 500 msec; and wherein the subject has a ΔQTc during sotalol hydrochloride administration that is less than 20% of the subject's QTc prior to intravenous sotalol administration. In some embodiments, this disclosure provides a method of safely administering sotalol hydrochloride to a subject in need thereof, the method comprising intravenously administering sotalol hydrochloride over a period of about 60 minutes to reach a sotalol steady state C_{max} in the subject, wherein the subject

has a QTc interval during the intravenous administration of sotalol hydrochloride that is less than or equal to 480 msec; and wherein the subject has a ΔQTc during sotalol hydrochloride administration that is less than 20% of the subject's QTc prior to intravenous sotalol administration. In other embodiments, this disclosure provides a method of safely administering sotalol hydrochloride to a subject in need thereof, the method comprising intravenously administering sotalol hydrochloride over a period of about 60 minutes to reach a sotalol steady state C_{max} in the subject, wherein the subject has a QTc interval during the intravenous administration of sotalol hydrochloride that is less than or equal to 500 msec; and wherein the subject has a ΔQTc during sotalol hydrochloride administration that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

In some embodiments, about 49.5 to about 70.4 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 800 ng/mL. In a particular embodiment, about 55 mg to about 64 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of 800 ng/mL. In some embodiments, about 55 mg to about 64 mg of intravenous sotalol hydrochloride administered over about a 60 minute period can provide a sotalol steady state C_{max} of between about 600 ng/mL and about 1000 ng/mL, between about 600 ng/mL and about 900 ng/mL, between about 600 ng/mL and about 850 ng/mL, between about 600 ng/mL and about 800 ng/mL, between about 600 ng/mL and about 750 ng/mL, between about 600 ng/mL and about 700 ng/mL, between about 700 ng/mL and about 1000 ng/mL, between about 700 ng/mL and about 900 ng/mL, between about 700 ng/mL and about 850 ng/mL, between about 700 ng/mL and about 800 ng/mL, between about 700 ng/mL and about 750 ng/mL, between about 750 ng/mL and about 1000 ng/mL, between about 750 ng/mL and about 900 ng/mL, between about 750 ng/mL and about 850 ng/mL, between about 750 ng/mL and about 800 ng/mL, between about 800 ng/mL and about 1000 ng/mL, between about 800 ng/mL and about 900 ng/mL, between about 800 ng/mL and about 850 ng/mL, between about 850 ng/mL and about 1000 ng/mL, between about 850 ng/mL and about 900 ng/mL, or between about 900 ng/mL and about 1000 ng/mL. In particular embodiments, an about 55 mg to about 64 mg intravenous load of sotalol hydrochloride administered over about 60 minutes can provide a steady state C_{max} of between about 750 ng/mL and about 850 ng/mL.

In some embodiments, between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride can be intravenously administered over the about 60 minute period to achieve the desired steady state C_{max}.

In another embodiment, about 73.8 to about 105.6 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1200 ng/mL. In a particular embodiment, about 82 mg to about 96 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1200 ng/mL. In some embodiments, about 82 mg to about 96 mg of intravenous sotalol hydrochloride administered over about 60 minutes can provide a steady state C_{max} of between about 1000 ng/mL and about 1400 ng/mL, between about 1000 ng/mL and about 1300 ng/mL, between about 1000 ng/mL and about 1250 ng/mL, between about 1000 ng/mL and about 1200 ng/mL, between about 1000 ng/mL and about 1150 ng/mL, between about 1000 ng/mL and about 1100 ng/mL, between about 1100 ng/mL and about 1400 ng/mL, between about 1100 ng/mL and about 1300 ng/mL, between about 1100 ng/mL and about 1250 ng/mL, between about 1100 ng/mL and about 1200 ng/mL, between about 1100 ng/mL and about 1150 ng/mL, between about 1150 ng/mL and about 1400 ng/mL, between about 1150 ng/mL and about 1300 ng/mL, between about 1150 ng/mL and about 1250 ng/mL, between about 1150 ng/mL and about 1200 ng/mL, between about 1200 ng/mL and about 1400 ng/mL, between about 1200 ng/mL and about 1300 ng/mL, between about 1200 ng/mL and about 1250 ng/mL, between about 1250 ng/mL and about 1400 ng/mL, between about 1250 ng/mL and about 1300 ng/mL, or between about 1300 ng/mL and about 1400 ng/mL. In particular embodiments, about 82 mg to about 96 mg of sotalol hydrochloride administered intravenously over about 60 minutes can provide a steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL.

In some embodiments, an intravenous dose of between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride can be administered over a period of about 60 minutes to achieve the desired steady state C_{max}.

In yet another embodiment, about 99 to 140.8 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1600 ng/mL. In a particular embodiment, about 110 mg to about 128 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1600 ng/mL. In some embodiments, about 110 mg to about 128 mg of intravenous sotalol hydrochloride administered over a period of about 60 minutes can provide a steady state C_{max} of between about 1400 ng/mL and about 1800 ng/mL, between about 1400 ng/mL and about 1700 ng/mL, between about 1400 ng/mL and about 1650 ng/mL, between about 1400 ng/mL and about 1600 ng/mL, between about 1400 ng/mL and about 1550 ng/mL, between about 1400 ng/mL and about 1500 ng/mL, between about 1500 ng/mL and about 1800 ng/mL, between about 1500 ng/mL and about 1700 ng/mL, between about 1500 ng/mL and about 1650 ng/mL, between about 1500 ng/mL and about 1600 ng/mL, between about 1500 ng/mL and about 1550 ng/mL, between about 1550 ng/mL and about 1800 ng/mL, between about 1550 ng/mL and about 1700 ng/mL, between about 1550 ng/mL and about 1650 ng/mL, between about 1550 ng/mL and about 1600 ng/mL, between about 1600 ng/mL and about 1800 ng/mL, between about 1600 ng/mL and about 1700 ng/mL, between about 1600 ng/mL and about 1650 ng/mL, between about 1650 ng/mL and about 1800 ng/mL, between about 1650 ng/mL and about 1700 ng/mL, or between about 1700 ng/mL and about 1800 ng/mL. In some embodiments, about 110 mg to about 128 mg of sotalol hydrochloride administered intravenously over about 60 minutes can provide a steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL.

In some embodiments, between about 1.65 mg/min and about 2.35 mg/min of sotalol hydrochloride can be intravenously administered over the about 60 minute period.

Typically, for each of the embodiments described above, the QTc interval of a subject is measured 5 to 15 minutes prior to sotalol initiation and subsequently at 15 minute intervals during intravenous sotalol administration and for about 90 minutes after intravenous administration of sotalol hydrochloride is complete. In other embodiments, the QTc interval of a subject is monitored continuously via telemetry upon intravenous administration of sotalol hydrochloride up to about 90 minutes following complete administration of the drug. It is within the skill of an ordinarily skilled

cardiologist to calculate ΔQTc based on these measurements and to increase or decrease sotalol administration appropriately.

In some embodiments, where a subject has been initiated on about 55 mg to about 64 mg of intravenous sotalol over about a 60 minute period, 80 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours after the completion of the intravenous administration of the about 55 mg to about 64 mg of sotalol hydrochloride. In some embodiments, 80 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between about 2 hours and about 3 hours, between about 3 hours and about 6 hours, between about 3 hours and about 5 hours, between about 3 hours and about 4 hours, between about 4 hours and about 6 hours, between about 4 hours and about 5 hours, or between about 5 hours and about 6 hours after the completion of the intravenous administration of about 55 mg to about 64 mg of sotalol hydrochloride.

In some embodiments, between about 2 hours and 5 hours after oral administration of 80 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In some embodiments, between about 2 hours and 5 hours after oral administration of 80 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In other embodiments, between about 2 hours and 5 hours after oral administration of 80 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

Alternatively, and in another embodiment, a BID regimen of PO 80 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after the initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In some embodiments, a BID regimen of PO 80 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after the initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In other embodiments, a BID regimen of PO 80 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after the initial oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

In another embodiment, such when the subject exhibits impaired renal function, i.e. a glomerular filtration rate (GFR) of between about 45-60 mL/min, the maintenance dose of oral sotalol can be administered over a longer dosing interval. For example, a once daily regimen of 80 mg PO sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of 80 mg of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

In some embodiments, where a subject has been initiated on about 82 mg to about 96 mg of intravenous sotalol over about a 60 minute period, 120 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours after completion of the intravenous administration of the about 82 mg to about 96 mg of sotalol hydrochloride. In some embodiments, 120 mg of sotalol hydrochloride is administered orally between about 2 hours and about 6 hours, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between about 2 hours and about 3 hours, between about 3 hours and about 6 hours, between about 3 hours and about 5 hours, between about 3 hours and about 4 hours, between about 4 hours and about 6 hours, between about 4 hours and about 5 hours, or between about 5 hours and about 6 hours after completion of the intravenous administration of about 82 mg to about 96 mg of sotalol hydrochloride.

In some embodiments, between about 2 hours and 5 hours after oral administration of 120 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to initial oral administration of sotalol hydrochloride. In a particular embodiment, between about 2 hours and 5 hours after oral administration of 120 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to initial oral administration of sotalol hydrochloride. In another embodiment, between about 2 hours and 5 hours after oral administration of 120 mg of sotalol hydrochloride, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to initial oral administration of sotalol hydrochloride.

Alternatively, and in another embodiment, a BID regimen of PO 120 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In a particular embodiment, a BID regimen of PO 120 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In another embodiment, a BID regimen of PO 120 mg sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

In another embodiment, such when the subject exhibits impaired renal function, i.e. a glomerular filtration rate (GFR) of between about 45-60 mL/min, the maintenance dose of oral sotalol can be administered over a longer dosing interval. For example, a once daily regimen of 120 mg PO sotalol hydrochloride can be initiated when the subject has

a QTc interval at between about 2 hours and about 3 hours after initial oral administration of 120 mg of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

In some embodiments, where a subject has been initiated on about 110 mg to about 128 mg of intravenous sotalol over about a 60 minute period, 160 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours after completion of the intravenous administration of about 110 mg to about 128 mg of sotalol hydrochloride. In some embodiments, 160 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours, between about 2 and about 5 hours, between about 2 and about 4 hours, between about 2 hours and about 3 hours, between about 3 hours and about 6 hours, between about 3 hours and about 5 hours, between about 3 hours and about 4 hours, between about 4 hours and about 6 hours, between about 4 hours and about 5 hours, or between about 5 hours and about 6 hours after completion of the intravenous administration of about 110 mg to about 128 mg of sotalol hydrochloride.

In some embodiments, between about 2 hours and 5 hours after initial oral administration of 160 mg of sotalol hydrochloride, further oral administration can be discontinued or reduced when the subject has a QTc interval that is greater than 480 to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In one embodiment, between about 2 hours and 5 hours after initial oral administration of 160 mg of sotalol hydrochloride, further oral administration can be discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In another embodiment, between about 2 hours and 5 hours after initial oral administration of 160 mg of sotalol hydrochloride, further oral administration can be discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

Alternatively, and in another embodiment, a BID regimen of PO of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 480 to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In a particular embodiment, a BID regimen of PO of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In another embodiment, a BID regimen of PO of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

In another embodiment, such when the subject exhibits impaired renal function, i.e. a glomerular filtration rate (GFR) of between about 45-60 mL/min, the maintenance dose of oral sotalol can be administered over a longer dosing interval. For example, a once daily regimen of 160 mg PO sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of 160 mg of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

Dose Escalation Protocol

The method of rapid sotalol introduction described herein can also be applied to dose escalation, for example when a subject needs to transition from 80 mg BID PO to 120 mg BID PO; or from 120 mg BID PO to 160 mg BID PO.

For example, subjects receiving 80 or 120 mg BID PO sotalol hydrochloride can be safely transitioned to 120 or 160 mg BID PO sotalol hydrochloride, respectively, via the administration of an intravenous infusion about 12 hours after the last oral dose of sotalol hydrochloride, i.e. when the concentration of sotalol hydrochloride is at a trough (steady state C_{min}).

Dose Escalation to from 80 mg to 120 mg Oral Sotalol Hydrochloride

In some embodiments, about 49.5 to about 70.4 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1200 ng/mL. In a particular embodiment, about 55 mg to about 64 mg of sotalol hydrochloride can be safely administered intravenously over a period of about 60 minutes to provide an average sotalol steady state C_{max} of about 1200 ng/mL (corresponding to the steady state C_{max} achieved after three days of PO BID dosing of 120 mg sotalol hydrochloride) in a subject dosed with 80 mg of oral sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration. In some embodiments, the sotalol hydrochloride can be administered to the subject at a rate between about 0.825 mg/min and about 1.17 mg/min over a period of about 60 minutes.

In some embodiments, during administration of between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In a particular embodiment, during administration of between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In another embodiment, during administration of between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

Alternatively, and in other embodiments, 120 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours after the completion of the intravenous administration of about 55 mg to about 64 mg of sotalol hydrochloride. In some embodiments, 120 mg of sotalol hydrochloride is administered orally between about 2 hours and about 6 hours, between about 2 and about 5 hours, between about 2 and about 4 hours, between about 2 hours and about 3 hours, between about 3 hours and about 6 hours, between about 3 hours and about 5 hours, between about 3 hours and about 4 hours, between about 4 hours and about 6 hours, between about 4 hours and about 5 hours, or

between about 5 hours and about 6 hours after the completion of the intravenous administration of about 55 mg to about 64 mg of sotalol hydrochloride.

In some embodiments, oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to the oral administration of sotalol hydrochloride. In a particular embodiment, oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to the oral administration of sotalol hydrochloride. In another embodiment, oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to the oral administration of sotalol hydrochloride.

In other embodiments, BID PO administration of 120 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of 120 mg of sotalol hydrochloride that is less than or equal to 480 msec to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In a particular embodiment, BID PO administration of 120 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of 120 mg of sotalol hydrochloride that is less than or equal to 480 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In another embodiment, BID PO administration of 120 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of 120 mg of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

Subjects with impaired renal function safely transitioned to the higher dose can take 120 mg sotalol once daily as discussed elsewhere herein.

Dose Escalation from 120 mg to 160 mg Oral Sotalol Hydrochloride

In some embodiments, about 63 to about 88 mg of sotalol hydrochloride can be administered intravenously over about 60 minutes to provide an average sotalol steady state C_{max} of about 1600 ng/mL. In a particular embodiment, about 70 mg to about 80 mg of sotalol hydrochloride can be safely administered intravenously over a period of about 60 minutes to provide an average sotalol steady state C_{max} of about 1600 ng/mL (corresponding to the steady state C_{max} achieved after three days of PO BID dosing of 160 mg sotalol hydrochloride) in a subject dosed with 120 mg of oral sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration. In some embodiments, the sotalol hydrochloride can be administered to the subject at a rate between about 1.05 mg/min and about 1.47 mg/min over a period of about 60 minutes.

In some embodiments, during administration of between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In one embodiment, during administration of between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In another embodiment, during administration of between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride over a period of about 60 minutes, intravenous administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

Alternatively, and in other embodiments, 160 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours after the completion of the intravenous administration of about 70 mg to about 80 mg of sotalol hydrochloride. In some embodiments, 160 mg of sotalol hydrochloride can be administered orally between about 2 hours and about 6 hours, between about 2 hours and about 5 hours, between about 2 hours and about 4 hours, between about 2 hours and about 3 hours, between about 3 hours and about 6 hours, between about 3 hours and about 5 hours, between about 3 hours and about 4 hours, between about 4 hours and about 6 hours, between about 4 hours and about 5 hours, or between about 5 hours and about 6 hours after the completion of the intravenous administration of about 70 mg to about 80 mg of sotalol hydrochloride.

In some embodiments, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec to 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In one embodiment, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 480 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In another embodiment, further oral administration is discontinued or reduced when the subject has a QTc interval that is greater than 500 msec; or when the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In other embodiments, BID PO administration of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In some embodiments, BID PO administration of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 480 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration. In other embodiments, BID PO administration of 160 mg of sotalol hydrochloride can be initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after initial oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or when the subject has a ΔQTc that is less than 20% of the subject's QTc prior to sotalol administration.

Subjects with impaired renal function safely transitioned to the higher dose can take 160 mg sotalol once daily as discussed elsewhere herein.

Method of Reducing Hospital Stay

In some embodiments, the disclosure provides a method of reducing a hospital stay in a subject in need of treatment

or prevention of atrial fibrillation, atrial flutter, or a combination thereof, the method comprising introducing a subject to sotalol hydrochloride administered intravenously over a period of about 60 minutes in the absence of further sotalol administration for a period of about 2 hours to about 6 hours after the period of about 60 minutes.

In some embodiments, about 0.825 mg/min to about 1.17 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period. In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 750 ng/mL and about 850 ng/mL in the subject.

In some embodiments, about 1.23 mg/min to about 1.76 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period. In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

In some embodiments, about 1.65 mg/min to about 2.35 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period. In some embodiments, the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

In some embodiments, where the subject received 80 mg oral sotalol hydrochloride about 12 hours to about 24 hours before the intravenous administration, about 0.825 mg/min to about 1.17 mg/min of sotalol hydrochloride can be intravenously administered over the about 60 minute period to safely escalate sotalol hydrochloride dosing to 120 mg oral sotalol hydrochloride.

In yet another embodiment, where the subject received 120 mg oral sotalol hydrochloride about 12 hours to about 24 hours before the intravenous administration, between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride can be intravenously administered over the about 60 minute period to safely escalate sotalol hydrochloride dosing to 160 mg oral sotalol hydrochloride.

In any of the embodiments described above, the intravenous administration of sotalol hydrochloride can be discontinued or reduced when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 480 msec to 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. In any of the embodiments described above, the intravenous administration of sotalol hydrochloride can be discontinued or reduced when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 480 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration. Alternatively, in any of the embodiments described above, the intravenous administration of sotalol hydrochloride can be discontinued or reduced when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

In some embodiments, sotalol hydrochloride is orally administered between about 2 hours and about 6 hours after completion of the intravenous administration.

In some embodiments, 80 mg of sotalol hydrochloride can be orally administered between about 2 and about 6 hours after completing intravenous administration of about 0.825 mg/min to about 1.17 mg/min of sotalol hydrochloride.

In some embodiments, 120 mg of sotalol hydrochloride can be orally administered between about 2 hours and about 6 hours after completing intravenous administration of about 1.23 mg/min to about 1.76 mg/min of sotalol hydrochloride.

In some embodiments, 160 mg of sotalol hydrochloride can be orally administered between about 2 hours and about 6 hours after completing intravenous administration of about 1.65 mg/min to about 2.35 mg/min of sotalol hydrochloride.

In some embodiments, the oral administration of sotalol hydrochloride is discontinued or reduced when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration. In a particular embodiment, the oral administration of sotalol hydrochloride is discontinued or reduced when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is greater than 480 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration. In another particular embodiment, the oral administration of sotalol hydrochloride is discontinued or reduced when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

As described elsewhere herein, when a subject has a QTc interval that is acceptable and/or wherein the subject has a ΔQTc that is less than or equal to 20% of the subject's QTc prior to intravenous sotalol administration, the subject can be transitioned to BID PO dosing, or QD (once daily) PO dosing, as appropriate for the subject's renal function.

Embodiments

In addition to the various embodiments described above, the present disclosure includes the following specific embodiments numbered E1 through E27. This list of embodiments is presented as an exemplary list and the application is not limited to these embodiments.

E1. A method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes.

E2. The method of E1, further comprising discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E3. The method of E1, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 750 ng/mL and about 850 ng/mL in the subject.

E4. The method of E3, further comprising orally administering to the subject 80 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E5. The method of E4, further comprising discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject

has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E6. The method of E4, further comprising initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

E7. A method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride over a period of about 60 minutes.

E8. The method of E7, further comprising discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E9. The method of E7, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

E10. The method of E9, further comprising orally administering to the subject 120 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E11. The method of E10, further comprising discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E12. The method of E10, further comprising initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

E13. A method of treating atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.65 mg/min and about 2.35 mg/min of sotalol hydrochloride over a period of about 60 minutes.

E14. The method of E13, further comprising discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E15. The method of E13, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

E16. The method of E15, further comprising orally administering to the subject 160 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E17. The method of E16, further comprising discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E18. The method of E16, further comprising initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

E19. A method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride over a period of about 60 minutes, wherein the subject received an administration of sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration.

E20. The method of E19, wherein the subject received an oral administration of 80 mg of oral sotalol hydrochloride between about 12 and about 24 hours before the intravenous administration.

E21. The method of E19, further comprising discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E22. The method of E19, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

E23. The method of E22, further comprising orally administering to the subject 120 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E24. The method of E23, further comprising discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E25. The method of E23, further comprising initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

E26. A method of treating or preventing atrial fibrillation, atrial flutter, or a combination thereof in a subject in need thereof, the method comprising intravenously administering to the subject between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride over a period of about 60 minutes, wherein the subject received an administration of sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration.

E27. The method of E26, wherein the subject received an oral administration of 120 mg of oral sotalol hydrochloride between about 12 and about 24 hours before the intravenous administration.

E28. The method of E26, further comprising discontinuing or reducing intravenous administration of sotalol hydrochloride when the subject has a QTc interval after intrave-

nous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E29. The method of E26, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

E30. The method of E29, further comprising orally administering to the subject 160 mg of sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E31. The method of E30, further comprising discontinuing or reducing oral administration of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and about 5 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E32. The method of E30, further comprising initiating an oral BID administration regimen of sotalol hydrochloride when the subject has a QTc interval at between about 2 hours and 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% the subject's QTc prior to intravenous sotalol administration.

E33. A method of reducing a hospital stay of a subject in need of treatment or prevention of atrial fibrillation, atrial flutter, or a combination thereof, the method comprising stabilizing a subject on sotalol hydrochloride administered intravenously over a period of about 60 minutes in the absence of further sotalol administration for a period of about 2 hours to about 6 hours after the period of about 60 minutes.

E34. The method of E33, wherein the hospital stay is reduced to between about 18 hours and about 24 hours.

E35. The method of E33, wherein the hospital stay is reduced to between about 20 hours and about 24 hours.

E36. The method of E33, wherein between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E37. The method of E33, wherein between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E38. The method of E33, wherein between about 1.65 mg/min and about 2.35 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E39. The method of E33, wherein the subject received oral sotalol hydrochloride between about 12 hours and about 24 hours before the intravenous administration.

E40. The method of E39, wherein between about 0.825 mg/min about 1.17 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E41. The method of E39, wherein between about 1.05 mg/min and about 1.47 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E42. The method of E33, wherein the intravenous administration of sotalol hydrochloride is discontinued or reduced when the subject has a QTc interval after intravenous sotalol hydrochloride initiation that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to sotalol administration.

E43. The method of E36, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 750 ng/mL and about 850 ng/mL in the subject.

E44. The method of E37, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1150 ng/mL and about 1250 ng/mL in the subject.

E45. The method of E38, wherein the intravenous administration of sotalol hydrochloride results in a sotalol steady state C_{max} of between about 1550 ng/mL and about 1650 ng/mL in the subject.

E46. The method E33, further comprising orally administering to the subject sotalol hydrochloride between about 2 hours and about 6 hours after completion of the intravenous administration.

E47. The method of E33, wherein 80 mg of sotalol hydrochloride is orally administered between about 5 and about 8 hours after completion of intravenous administration of between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride.

E48. The method of E33, wherein 120 mg of sotalol hydrochloride is orally administered between about 2 hours and about 6 hours after completion of intravenous administration of between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride.

E49. The method of E33, wherein 160 mg of sotalol hydrochloride is orally administered between about 2 hours and about 6 hours after completion of intravenous administration of between about 1.65 mg/min and about 2.35 mg/min of sotalol hydrochloride.

E50. The method of E46, wherein the oral administration of sotalol hydrochloride is discontinued or reduced when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is greater than 500 msec; or wherein the subject has a ΔQTc that is greater than or equal to 20% of the subject's QTc prior to intravenous sotalol administration.

E51. The method of E46, wherein an oral administration BID regimen of sotalol hydrochloride is initiated when the subject has a QTc interval at between about 2 hours and about 3 hours after oral administration of sotalol hydrochloride that is less than or equal to 500 msec; or wherein the subject has a ΔQTc that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

E52. A method of administering sotalol hydrochloride to a subject in need thereof, the method comprising intravenously administering sotalol hydrochloride over a period of about 60 minutes to reach a sotalol steady state C_{max} in the subject, wherein the subject has a QTc interval during the intravenous administration of sotalol hydrochloride that is less than or equal to 500 msec; and wherein the subject has a ΔQTc during sotalol hydrochloride administration that is less than 20% of the subject's QTc prior to intravenous sotalol administration.

E53. The method of E52, wherein the sotalol steady state C_{max} is between about 750 ng/mL and about 850 ng/mL.

E54. The method of E52, wherein the steady sotalol state C_{max} is between about 1150 ng/mL and about 1250 ng/mL.

E55. The method of E52, wherein the steady sotalol state C_{max} is between about 1550 ng/mL and about 1650 ng/mL.

E56. The method of E52, wherein between about 0.825 mg/min and about 1.17 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E57. The method of E52, wherein between about 1.23 mg/min and about 1.76 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E58. The method of E52, wherein between about 1.65 mg/min and about 2.35 mg/min of sotalol hydrochloride is intravenously administered over the about 60 minute period.

E59. A method to administer a loading dose of Sotalol entirely intravenously to a target maximum serum concentration that a subject is expected to be exposed in the course of chronic oral dosing of Sotalol.

E60. A method to administer sotalol intravenously to a target concentration in order to see the maximum QTc interval increment that can be expected to be expressed by a subject in the course of chronic oral therapy, while maximizing subject safety during initial loading process.

E61. A method permitting the targeting of the projected maximum concentration of sotalol hydrochloride that may be attained on chronic dosing in a period of one hour, permitting the adjustment of the dosing, or its cessation for subject safety dependent on QTc interval prolongation.

E62. A way to initiate sotalol hydrochloride therapy in a subject with an indication to receive chronic sotalol therapy employing an intravenous infusion.

E63. The use of an intravenous infusion to obtain sotalol hydrochloride steady state C_{max} concentration to the level obtained with chronic oral sotalol hydrochloride dosing.

E64. A way to obtain steady state C_{max} to observe changes in cardiac repolarization such that the increase in QTc is not greater than specified in guidelines and thus, not risking the development of life threatening ventricular arrhythmias.

E65. A method of administering sotalol hydrochloride, observing the changes in QTc such that if the QTc increases beyond acceptable parameters, the infusion can be terminated immediately, enhancing subject safety.

E66. A method of increasing sotalol hydrochloride dose from low dose oral therapy to higher dose oral therapy using an intravenous infusion.

E67. A method of dose escalation of sotalol hydrochloride such that the infusion obtains the projected steady state C_{max} and thus maximum QTc changes in a brief period of time, avoiding changes in QTc in excess of those expected to be experienced by a subject receiving an appropriate dose of sotalol and thus reducing the risk of drug induced arrhythmias.

E68. A method of dose initiation and dose escalation employing intravenous sotalol hydrochloride in subjects with renal dysfunction. Providing the attainment of steady state C_{max} and thus, the full exposure of QTc changes under electrocardiographic observation within 24 hours of exposure.

EXAMPLES

The following examples are illustrative and non-limiting, of the methods described herein. Suitable modifications and adaptations of the variety of conditions, formulations, and other parameters normally encountered in the field and which are obvious to those skilled in the art in view of this disclosure are within the spirit and scope of the invention.

Example 1: IV Sotalol

A subject with a QTc interval of 405 msec is to receive 80 mg of oral sotalol hydrochloride by mouth twice a day (PO BID) with a steady state serum concentration reached in 3-5 days with a steady state C_{max} of 800 ng/mL. With the relationship of QTc to serum concentration on average of 0.024:

$$QTc\,\max = QTc\ \text{baseline} + (0.024 \times 800\ \text{ng/mL})$$

$$= 424\ \text{msec}^{*}$$

*Within the prescribed FDA guideline of remaining under a maximum QTc of 500 msec.

Dose Initiation: To attenuate the time required to achieve steady state Cmax, one can administer sotalol hydrochloride IV as an infusion. For example, 55 mg (projected to equate to 80 mg by mouth twice a day) of IV sotalol hydrochloride can be administered over 1-2 hours, the steady state C_{max} estimated for an average person's serum sotalol concentration 800 ng/mL would be achieved, which would transpose to a QTc prolongation of an average of 427 msec.

Example 2: IV Sotalol

A subject with an initial QTc of 405 msec (average for a 70 kg person) starts receiving a sotalol hydrochloride IV infusion of 55 mg/mL and after 45 minutes the QTc is measured to be 456 msec. The infusion can be halted and the dose of sotalol hydrochloride selected for chronic administration can be reduced, the dosing interval can be prolonged, or the physician can decide not to use sotalol hydrochloride and instead turn to an alternative anti-arrhythmic therapy.

IV loading could safely expose the subject to the expected maximum sotalol hydrochloride concentration and thus maximum QTc prolongation that would be expected to occur with chronic dosing. If under observation, the QTc prolongs to a significantly greater degree, the infusion can be stopped, the dose reduced, or the subject deemed too sensitive to sotalol hydrochloride dosing and another antiarrhythmic drug could be evaluated for efficacy and safety in that particular subject. This approach would be a major safety factor for subjects, since with oral loading or oral and IV loading, the absorption continues once a pill is taken and the overshoot in QTc will continue, placing the subject at greater risk. An infusion thus provides greater safety, since the infusion can be stopped with no further significant increase in QTc.

Example 3: IV Sotalol

A 70 kg subject presents with intermittent atrial fibrillation (AF). His physician wants to place the subject on oral sotalol hydrochloride 80 mg PO BID. He has never taken sotalol before. He is admitted to the hospital and receives an infusion of IV sotalol hydrochloride (55 mg) over 1 hour. This infusion achieves a target serum concentration of 800 ng/mL. Following the infusion the QTc is checked 30 minutes after administration. If the QTc is within guidelines (less than 20% increase, or under 500 msec) an interval of 2-6 hours is left to elapse to reach the predicted trough and then 80 mg orally is given to subject, which will predictably peak in 2-4 hours and QTc will be measured again hourly (at 4-5 hours). If QTc is within guidelines, then dosing will continue orally, 80 mg every 12 hours.

The subject will thus have been exposed to a serum sotalol hydrochloride concentration predicted to be reached with chronic dosing (predicted C_{max}) twice in the 16 hours of observation and can be discharged safely in 24 hours knowing that the QTc will not at maximum predicted concentration exceed guidelines. Thus, in a timeframe of between 6-23 hours, sotalol hydrochloride could be fully evaluated for repolarization safety with the maximum QTc expected at a given chronic dose.

That some subjects respond unpredictably to sotalol hydrochloride, or other QT prolonging drugs is well-known. This can be explained in the case of sotalol hydrochloride by an abnormality in the potassium channel. Genetic conditions can cause mild abnormalities in protein structure of the potassium channel. These abnormalities can be dormant and only seen as marked QT prolongation when subjects are

exposed to a potassium channel blocker such as sotalol hydrochloride. In these subjects with a channelopathy, the QTc may markedly increase with ensuing life threatening ventricular arrhythmias and possibly sudden cardiac death. Having a way to rapidly access the QTc effect of sotalol hydrochloride by administering an intravenous infusion when the drug administration could be halted at any time will greatly enhance subject safety. As can be seen in FIG. **1**, the exposure to sotalol through an IV infusion over several hours can achieve steady state Cmax and the maximum QTc in a short period of time (less than 24 hours). Thus, permitting evaluation in hospital over 24 hours as opposed to the 3 day hospitalization currently needed to achieve steady state C_{max} levels with oral sotalol hydrochloride dosing.

Another critical factor in the dosing of sotalol hydrochloride to observe maximum QTc effect is the relation of the serum concentration and QTc prolongation based on time. The phenomenon is called hysteresis: the delay between a change in a marker affected by an exposure to an agent causing its change. This can be due to delay of the drug reaching the receptor or channel or changes in the receptor or channel needed over time to be fully expressed. Information on sotalol concentration and QTc prolongation is known from the work of Somberg and colleagues. In Somberg, J. C., et al., *Am. J. Ther.* 17(4):365-72 (2010) 15 normal individuals received sotalol hydrochloride infused intravenously and then at a later date administered orally. The infusion was over a 2.5 hour duration and thus the serum concentration would be at a maximum at the end of infusion (2.5 hours). The maximum QTc was seen at 2.25 hours. Thirty minutes later at hour 3, the QTc had decreased. Thus, the hysteresis between sotalol hydrochloride concentration and QTc cannot be longer than 30 minutes. Therefore, a period of 30 minutes is recommended to observe the maximum QTc effect after the completion of the infusion, to observe and then act upon the maximum QTc observed.

Dose Escalation

In an analogous manner a subject on a maintenance dose of 80 mg PO BID sotalol hydrochloride, or 120 mg PO BID could be increased to the next standard increment in oral dosing. A subject could be brought in to the hospital at the time before the next dosing interval, nadir of serum concentration, and administered an infusion over 1-2 hours of IV sotalol hydrochloride to attain the projected next highest concentration level (steady state C_{max}) and thus the maximum concentration the subject would be exposed to, resulting in the maximum QTc predicted exposure. This could be done in hospital in less than 24 hours such that the full risk to the subject of that serum sotalol hydrochloride concentration could be observed as shown in FIG. **2**. If arrhythmias occur, cardiac resuscitation measures could be initiated, offering the subject maximal safety. If the infusion is given intravenously, the infusion could be terminated if the QTc increases beyond acceptable parameters recommended by FDA in the sotalol hydrochloride product label.

Example 4: IV Sotalol

A subject on 80 mg PO BID is brought to hospital at end of dosing interval before the next oral dose and then, receives an IV infusion of sotalol hydrochloride. Trough concentration of sotalol hydrochloride given at 80 mg PO BID can be estimated to be 400 ng/mL. The steady state C_{max} of a 120 mg PO BID dose would be 1200 ng/mL. Thus, an infusion of 55 mg sotalol hydrochloride would achieve a target concentration of approximately 1200 ng/mL, exposing the subject to the maximal predicted QTc prolongation in 2 hours or less. In both the initiating and loading periods one may then proceed to continue oral dosing after a preset interval (2-6 hours) to continue sotalol hydrochloride exposure to provide anti-arrhythmic action during the transition from IV to oral drug administration.

While the methods have been described in terms of what are presently considered to be practical and preferred embodiments, it is to be understood that the disclosure need not be limited to the disclosed embodiments. It is intended to cover various modifications and similar arrangements included within the spirit and scope of the claims, the scope of which should be accorded the broadest interpretation so as to encompass all such modifications and similar embodiments. This disclosure includes any and all embodiments of the following claims.

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

What is claim is:

1. A method of rapidly escalating a subject's oral sotalol hydrochloride therapy to a higher oral dose, the method comprising:

(1) identifying a subject as having symptomatic atrial fibrillation or atrial flutter, who is currently in sinus rhythm, who is under QTc monitoring, and who is receiving 120 mg oral sotalol hydrochloride therapy such that the subject has a concentration of sotalol resulting therefrom;

(2) escalating the concentration of sotalol of the subject to a higher concentration, by administering over a period of 1 hour, a single IV dosage of sotalol hydrochloride in an amount in the range of 99 mg to 105.6 mg and at a rate in the range of 1.65-1.76 mg/min; and

(3) after completion of the single IV dosage of sotalol hydrochloride, increasing the amount of the subject's oral dosing from 120 mg to 160 mg by administering at least one oral dose of 160 mg sotalol hydrochloride to the subject.

2. The method of claim **1**, further comprising repeating oral administration of the 160 mg oral dose of sotalol hydrochloride at least once at a selected interval.

3. The method of claim **2**, wherein the administering of the oral dose of 160 mg starts at about 4-12 hours after completion of the single IV dosage of sotalol hydrochloride.

4. The method of claim **3**, wherein the administering of the oral dose of 160 mg starts at about 4 hours after completion of the single IV dosage of sotalol hydrochloride.

5. The method of claim **1**, wherein:

the administering of the oral dose of 160 mg starts at about 6 hours after completion of the single IV dosage of sotalol hydrochloride.

6. The method of claim **5**, further comprising repeating oral administration of the 160 mg oral dose of sotalol hydrochloride at a selected interval, wherein the repeating of the oral administration is performed at least once.

7. The method of claim **1**, wherein:

the administering of the oral dose of 160 mg starts at about 4-12 hours after completion of the single IV dosage of sotalol.

8. The method of claim **7**, further comprising repeating oral administration of the 160 mg oral dose of sotalol hydrochloride at a selected interval, wherein the adminis-

tering of the oral dose of 160 mg and the repeating of the oral administration is performed at least once and according to a once daily or twice daily schedule.

9. The method of claim **1**, wherein the subject received a 120 mg oral dose of sotalol hydrochloride 12-24 hours before administration of the single IV dose.

10. The method of claim **2**, wherein the administering of the oral dose of 160 mg and the repeating is performed according to a once or twice daily schedule.

11. The method of claim **3**, wherein the administering of the oral dose of 160 mg and the repeating is performed according to a once or twice daily schedule.

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