M118, A NOVEL, RATIONALLY ENGINEERED LOW MOLECULAR WEIGHT HEPARIN, WITH POTENT ANTI-XA AND ANTI-IIA ACTIVITIES IS REVERSIBLE BY PROTAMINE SULFATE, AND MONITORABLE WITH ACT FOLLOWING MULTIPLE IV INJECTIONS

ABSTRACT

BACKGROUND: M118, a rationally engineered LMWH, is being developed for IV and subcutaneous use under development for the treatment of ACS with or without PCI. It is a novel, potent anti-Factor Xa and IIa (aXa) LMWH, with a predictable anti-Xa:IIa ratio (X:IIa ~1:1), and superior antithrombotic efficacy compared to currently approved heparins. The aim was to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of multiple ascending IV doses of M118, and reversibility by protamine sulfate (PS).

METHODS: This randomized, double-blind, placebo-controlled (PBO), 4-period, 7-day washout, ascending IV doses of M118, 0, 30, 150, 210 and 260 mg/kg, and effects were determined by ACT values, following intravenous injection of M118.

SUBJECT POPULATION: healthy male volunteers between 18 and 50 years of age participated in the study and were randomized to 2 cohorts.

RESULTS: Blood samples were collected for 24h to assess PK, coagulation parameters and safety. ACT and APTT returned to normal within 12h post injection of M118.

CONCLUSION: M118 total dose of up to 5g/kg did not reach the 1.5dose, and multiple M118 bolus injections maintained the anti-coagulation effect. M118 activity can be monitored by ACT and is reversible by PS. These results support further development of M118 in PCI and ACS.

INTRODUCTION

• Hepatic derivatives, including unfractionated heparin (UFH) and low-molecular weight heparins (LMWH), play a central role in treatment paradigms for acute coronary syndromes (ACS), including adjunctive therapy during percutaneous coronary intervention (PCI).

• Both classes of agents have potent antithrombotic effects, but also limitations. UFH has unpredictable parenterally-dependent pharmacokinetics, limited biodegradability, variability, and the potential for serious adverse bleeding events or thrombocytopenia. LMWH has reduced inhibition of Factor Xa, limited reversibility with protamine sulfate, and is not mountable by parenteral reuse assays. Activated clotting time (ACT) assays remain.

• M118 (Figure 1) is a novel rationally engineered LMWH under development for the treatment of ACS with or without PCI.

• The design of the study involved 5 dose escalation periods, with an IV bolus injection of M118 at low, medium and high dose levels, and six randomized doses of M118 with or without PS, to evaluate the safety and tolerability of M118, and to evaluate M118 as a prototype of LMWH, with a predictable antithrombotic efficacy.

OBJECTIVES

PRINCIPAL OBJECTIVE

The primary objective of this study was to evaluate the safety and tolerability of M118 given as multiple IV doses in a rising dose cohort regime in healthy subjects.

SECONDARY OBJECTIVES

The secondary objective of this study was to gain information about the pharmacokinetics and pharmacodynamics of an rationally engineered LMWH. In addition the reversibility of anticoagulation effect of M118 was assessed following an intravenous infusion of protamine sulfate.

METHODS

TRIAL

A Phase I, Randomized, Double-Blind, Placebo Controlled, Multiple Ascending Dose Study to Evaluate Safety, Pharmacodynamics and Pharmacokinetics of M118 in Healthy Volunteers, Including a Protamine Sulfate Arm.

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