A Randomized, Double-Blind Study to Assess Serum Transaminase Elevations and Antibody Formation Following Repeat Subcutaneous Dosing of LMWH, UFH or the Novel Anticoagulant M118 in Healthy Volunteer

INTRODUCTION

MT 118 is a novel anticoagulant in the human clinical development stage, recently engineered to reduce molecular weight (MW) from 5000 to 1500 Da, with controlled-directed administration. The study investigated initial toxicokinetic properties in patients diagnosed with acute coronary syndrome (ACS) in a previous study (Moore et al., 2009). M118 is intended for s.c. administration. Platelet (PLT) activation (M118) was also detected by electrophoretic-thermal shift assay (ETSA). In this study, the effects of M118 on transaminases were evaluated in subjects that developed AEs, as measured by ELISA assay, with a confirmed positive serological response absence (SHA).

METHODOLGY

Study Population

A total of 48 healthy male subjects between the ages of 18 and 50 years were enrolled. Subjects added the inclusion and exclusion criteria, with verification at check-in. All subjects completed the clinical phase of the study and there were no subjects who withdrew/discontinued from the study.

RESULTS

Primary Objectives

- To characterize the time course/kinetics of the development of heparin/PF4 Ab formation and function.
- To evaluate the occurrence of heparin/PF4 Ab formation and function.

Main outcomes were:
- AST and ALT greater than 3 x upper limit of normal (ULN) were seen in 4.7% and 4.2% of patients during treatment.
- Asymptomatic increases in AST and ALT greater than 3 x ULN were seen in up to 6.1% and 5.9% of patients treated with enoxaparin.

Figure 1: Mean ALT and AST Results

Mean ALT and AST concentrations were measured before dosing on Day 1, prior to each morning dose on Days 2 to 5, at 24 and 48 hours after the last dose, and on Days 7, 12, and 33. The results are presented in Figure 1. In total, 4 subjects (8%) were found to have either borderline or weak positive heparin-platel Ab responses for at least one time point, as measured by ELISA as shown in Table 2. These subjects had transaminasemia values at baseline and in relation to treatment that were asymptomatic and without clinical relevance. The biological interpretation was that the response for high test values was not strong enough to activate platelets and generate a positive result in the assay.

Figure 2: Mean Alkaline Phosphatase and Total Bilirubin Results

Mean alkaline phosphatase (ALP) and total bilirubin were measured at baseline, before dosing on Day 1, prior to each morning dose on Days 2 to 5, at 24 and 48 hours after the last dose (Day 5) and at the follow-up visit on Day 13. Bilirubin levels were assessed at 7 days after the last dose and at Day 13. The results are presented in Figure 2.

Figure 3: Heparin-induced PLT Ab (GTH-EIA) Results by Treatment

The incidence rates of heparin-induced PLT Ab results by treatment are presented in Figure 3. In total, 166 subjects added the incidence and exclusion criteria, with verification at check-in. All subjects completed the clinical phase of the study and there were no subjects who withdrew/discontinued from the study.

Figure 4: Mean Serum Bilirubin Concentrations (mg/dL)

Mean serum bilirubin concentrations were measured before dosing on Day 1, prior to each morning dose on Days 2 to 5, at 24 and 48 hours after the last dose, and on Days 7, 12, and 33. The results are presented in Figure 4. In total, 4 subjects (8%) were found to have either borderline or weak positive heparin-platel Ab responses for at least one time point, as measured by ELISA as shown in Table 2. These subjects had transaminasemia values at baseline and in relation to treatment that were asymptomatic and without clinical relevance. The biological interpretation was that the response for high test values was not strong enough to activate platelets and generate a positive result in the assay.

Table 1: Triage Toxicity Grade for ALT and AST Results by Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>0.405</td>
<td>0.646</td>
<td>0.740</td>
<td>0.590</td>
<td>0.28</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>0.224</td>
<td>0.646</td>
<td>0.471</td>
<td>0.393</td>
<td>0.211</td>
</tr>
<tr>
<td>UFH</td>
<td>0.394</td>
<td>0.457</td>
<td>0.412</td>
<td>0.211</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Table 2: Number (%) of Subjects With Adverse Events by System Organ Class

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Consistent with both literature reports and data from previous clinical trials conducted by Menarini Pharmaceuticals, Inc. (MAH 02181 and EBM 02181), elevations in ALT and AST were observed, especially heparin-induced thrombocytopenia (HIT). In particular, the M118 and dalteparin data sets were comparable.

The data obtained in the comparative study and conclusion with both the known side effect of heparin and LMWH in causing transaminase elevations (HIT) in patients to receive an increased rate of drug-related toxicity.

- Anti-heparin/PF4 Ab generation was low in all groups. There were no adverse events of clinical importance in the current study, consistent with the known side effect of heparin-induced thrombocytopenia (HIT).

- No meaningful differences were seen when compared to dalteparin for M118 at present. M118 HIT causes severity (HI/PT and UFH LMWH) prophylactic dosing. Therefore, there appears to be an increased risk of HIT or HIT-related events in other heparin-based treatments evaluated in this study.

- Safety profile of all products utilized in this study were comparable or superior to literature.

REFERENCES

- are required to determine the potential for adverse effects in subjects treated with M118.
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