Safety, Pharmacokinetics and Proof-of-Mechanism of an Oral Bruton’s Tyrosine Kinase Inhibitor HM71224 in Healthy Adult Volunteers

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Introduction

- Bruton’s Tyrosine Kinase (BTK) plays key roles in B-cell receptor (BCR) and Fc receptor (FcR) signaling cascades and B cell development and activation1-8
- HM71224 is an orally available, irreversible and highly selective small molecule inhibiting BTK protein
- HM71224 may provide therapeutic opportunities in autoimmune diseases

Objectives

- Primary Objective: To evaluate the safety and tolerability and if possible to determine the maximum tolerated dose of HM71224 after single and multiple ascending dose administration in healthy subjects
- Secondary Objective:
  a. To determine the pharmacokinetics(PK) of HM71224 and selected metabolites (M1 and M10) following single and multiple oral dose administration of HM71224
  b. To assess whether the PK of HM71224 is affected by food
  c. To assess the occupancy by HM71224 after multiple oral administration of HM71224 (Multiple Ascending Dose Part only)

Methods

- Phase 1 study is consisted of 3 parts: a single ascending dose (SAD) part, a single food effect (FE) part and a multiple ascending dose (MAD) part.
- The SAD, FE and a part of MAD part results were revealed previously
- In the MAD part, once daily dosing and twice daily dosing were evaluated in placebo controlled manner under fasted conditions

Results

1. Subject Demography

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAD Part (n=18)</th>
<th>FE Part (n=6)</th>
<th>MAD Part (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% BTK occupancy at Ctrough</td>
<td>80mg</td>
<td>20mg</td>
<td>40mg</td>
</tr>
</tbody>
</table>

2. Adverse Events in Multiple Ascending Dose Part

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Dose (mg)</th>
<th>SAD Part (n=18)</th>
<th>FE Part (n=6)</th>
<th>MAD Part (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Pharmacokinetic Profiles

- HM71224 showed increasing PK profiles as ascending dose levels in QD dosing
- HM71224 indicated slight accumulation after multiple dosing for 14 days
- Inter subject variability in exposure was relatively large
- Excretion of HM71224 and metabolites in urine was limited (data not shown)

4. BTK Occupancy

<table>
<thead>
<tr>
<th>Study Drug Administration</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3-5</th>
<th>Day 6-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>On</td>
<td>O</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

5. PK-PD Modeling

- A PK-PD model for HM71224 showed a steep dose response relationship with BTK occupancy
- According to the PK-PD model above 10mg BID dosing or 20mg QD dosing shows 90% of BTK occupancy with HM71224

Conclusions

- HM71224 demonstrated well-tolerated safety profile in healthy volunteers and desirable PK and PD properties
- The data support the potential for HM71224 to be evaluated for treatment of autoimmune diseases such as rheumatoid arthritis

Reference


Acknowledgement

- We would like to thank all of the participating patients and their families, as well as study coordinators of the all study sites
- This study was sponsored by Hanmi Pharmaceutical Co., Ltd. ClinicalTrial.gov identifier: NCT01905478

The 16th European League Against Rheumatism (EULAR) Annual European Congress, Rome, Italy; June 10-13, 2015
HM71224, a Selective BTK Inhibitor, Ameliorates Murine Lupus Development

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Introduction
• Systemic lupus erythematosus (SLE) is known to be associated with the formation of autoantibodies by B cell hyperactivity.
• Bruton’s tyrosine kinase (BTK) is a member of TEC family tyrosine kinases important in B cell activation, proliferation, survival and differentiation.

MM71224 is an orally irreversible BTK inhibitor with IC50 of 2.6 nM in kinase inhibition assay and IC50 of 1 nM in phosphorylation inhibition assay.

• Commonly used model for SLE drug discovery is the spontaneous lupus mouse model. MRL/lpr with the lymphoproliferation mutation (Fas−/−) and New Zealand Black and White F1 hybrid (NZB/W F1) strain with co-expression of several SLE susceptibility genes.

The aim of this study is to evaluate the impacts of therapeutic intervention on the development of SLE like disease features by MM71224 in MRL/lpr and NZB/W F1 mice lupus models.

Methods
1. Animals and Administration

<table>
<thead>
<tr>
<th>Mice</th>
<th>NBL/lpr</th>
<th>NZB/W F1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

- 28 weeks old
- 40 weeks old

No.12 group once a day

- Dosing start
- Disease onset
- End of the study

2. Observations

• The measurements of urine protein with urine strip, blood urea nitrogen and creatinine with chemical analyzer and anti-dsDNA IgG with ELISA were conducted.
• Relative organ weights of spleen, cervical lymph nodes and kidney were measured.
• Phenotyping of splenic B cells were performed by flow cytometry.
• Renal histopathology was scored in H&E and PAS stain.
• Survival rates were calculated with the Kaplan-Meier method.
• Statistical significance between groups was evaluated by one-way ANOVA with Dunnett’s test or Kruskal-Wallis with Dunn’s test.

Results
1. In vitro Cellular Activity

- MM71224 is a potent and selective BTK inhibitor

<table>
<thead>
<tr>
<th>Cell</th>
<th>Inhibition of phospho-kinase (IC50, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramos ¹</td>
<td>anti-IgM p-RTK223 1.0</td>
</tr>
<tr>
<td>IL-4</td>
<td>p-FLIP 1.0</td>
</tr>
<tr>
<td>CD23</td>
<td>p-STAT6 445</td>
</tr>
<tr>
<td>A21 ²</td>
<td>p-EGRF 800</td>
</tr>
</tbody>
</table>

- MM71224 inhibits the B cell activation, autoantibody production and enlargement of lymphatic organs

a. Splenic Activated B cells
b. Splenic Germinal Center B cells
c. Autoantibody
d. Organ weights

2. Results in MRL/lpr Mice

- MM71224 prevents the development of skin lesions

- MM71224 inhibits the B cell activation, autoantibody production and enlargement of lymphatic organs

a. Serum BUN
b. GN score
c. B score

3. Results in NZB/W F1 Mice

- MM71224 inhibits the activation of B lymphocytes

a. Splenic Activated B cells
b. Splenic Plasma B cells
c. Urine Protein
d. Survival Rates

CONCLUSION

- BTK inhibition by HM71224 in MRL/lpr and NZB/W F1 mice
- Effectively dampened splenic B cells and autoantibody.
- Significantly decreased the development of SLE like manifestations such as skin lesions, enlargement of lymph node, splenomegaly, urine protein and renal injury.
- Markedly decreased mortality from SLE in NZB/W F1 mice model.

- HM71224 can efficaciously ameliorate lupus developments in murine disease model that resembles human SLE.

References
• Current Protocol in Pharmacology 2011; 5: 5.60.1-5.60.48.
• BioDrugs 2013; 27(2), 85-95.
• Arthritis Research & Therapy 2012; 14, R243.