Phase 1 Study of JSP191, an Anti-CD117 Monoclonal Antibody, with Low Dose Irradiation and Fludarabine in Older Adults with MRD-Positive AML/MDS Undergoing Allogeneic HCT

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**Background**

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are hematologic malignancies primarily affecting older adults. Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for MDS/AML, but intensive conditioning limits its application in older or frail patients. Non-myeloablative (NMA) or reduced intensity conditioning (RIC) achieves tolerability at the expense of heightened disease relapse; thus, innovative strategies to reduce relapse while maintaining low toxicity are needed. We are developing a first-in-class monoclonal antibody (mAb), JSP191, which targets and depletes normal and MDS/AML disease-initiating hematopoietic stem cells (HSC). JSP191 acts by inhibiting stem cell factor (SCF) binding to CD117 (c-Kit) present on HSC. We and others showed in pre-clinical models that HSC depletion donor cell engraftment can be enhanced by combining anti-CD117 mAb with low dose total body radiation (TBI). Based on these data, we hypothesized that the addition of JSP191 prior to NMA conditioning of 200 cGy TBI and fludarabine (Flu) would result in clearance of disease, lower toxicity, and reduced relapse in older patients with MDS/AML and measurable residual disease (MRD). This Phase 1 trial evaluated this clinical hypothesis (NCT#04429191).

**Treatment Schema**

- **JSP191**
  - Day -10 to -14
  - Fludarabine 30 mg/m²/day
  - TBI 2 Gy/day
  - HCT

- **Primary endpoints:**
  - Safety and tolerability of JSP191/TBI/Flu
  - Engraftment and donor chimerism
  - MRD clearance, Non-relapse mortality, Event-free Survival and Overall Survival

- **Secondary endpoints:**
  - Safety of JSP191/TBI/Flu
  - Pharmacokinetics (PK)

- **JSP191 Conditioning Leads to Successful Transplant and Conversion to MRD-Negative/ MRD Reduction in First Five Evaluable Subjects**

### Table

**Table**

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Prior Therapy for MDS or AML</th>
<th>Donor</th>
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<tr>
<td>011</td>
<td>69M</td>
<td>AML</td>
<td>Cytarabine/ Daunorubicin (73)</td>
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**Subject Demographics**

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<td>010</td>
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<tr>
<td>011</td>
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**JSP191 Conditioning Leads to Successful Transplant and Conversion to MRD-Negative/ MRD Reduction in First Five Evaluable Subjects**

<table>
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<tr>
<th>Subject Number</th>
<th>MTD at Screening</th>
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<th>MTD at TDI</th>
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<th>MTD at TDI</th>
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<td>KMT2A duplication</td>
<td>KMT2A duplication</td>
<td>KMT2A duplication</td>
<td>Subject still on study – assessments TBD</td>
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<td>KMT2A duplication</td>
<td>KMT2A duplication</td>
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<td>QNS</td>
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<td>KMT2A duplication</td>
<td>KMT2A duplication</td>
<td>Subject still on study – assessments TBD</td>
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<tr>
<td>011</td>
<td>JSP2 (14%)</td>
<td>JSP2 (14%)</td>
<td>JSP2 (14%)</td>
<td>JSP2 (14%)</td>
<td>Subject still on study – assessments TBD</td>
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**Chimerism observed**

- Total blood chimerism
- Myeloid cell chimerism
- T cell chimerism
- NK cell chimerism

**Summary**

- This study is the first to evaluate JSP191 given in combination with non-myeloablative conditioning (NMA) Flu/TBI 2 Gy for older MDS/AML patients.
- JSP191 added to TBI/Flu was well tolerated in the first 6 subjects; protocol allows for subjects to receive conditioning regimen in an outpatient setting.
- JSP191 PK (at 0.6 mg/kg) was observed to be consistent among subjects (n = 6).
- This trial is currently enrolling (NCT#04429191).

**Acknowledgements**

- We wish to thank Kevin N. Heller, Janet Hurt, Joe Laver, Susan Prohaska, Beverly Smith, and Bin Yao for their tireless effort to generate data and support this clinical trial.
- Jasper Therapeutics and the investigators thank the patients and families for participating in this clinical trial.

**Key Inclusion Criteria**

- Patients with AML or MDS
- ≥ 60 years or with HCT CI ≥3
- Minimal Identifiable Disease (MID) or Measurable Residual Disease (MRD) detected by cytogenetics (cyto), difference from normal flow cytometry (flow), or next-generation sequencing (NGS)
- HLA matched related or unrelated donor
- Patients with prior HCT were excluded

**Toxic Conditioning Regimens is an Obstacle for Transplant: JSP191 is a targeted approach**

**Current Myeloablative Conditioning Removes HSCs Through Highly Toxic Regimens**

- Patients with prior HCT were excluded
- HLA matched related or unrelated donor

**JSP191 Selectively Targets HSCs: An Alternative to Toxic Conditioning Regimens**

- Stem Cell Factor (SCF) / Stem Cell Factor Receptor (CD117) interaction required for stem cell survival
- JSP191 blocks SCF signaling leading to patient stem cell depletion from the bone marrow
- Allows for healthy donor stem cell engraftment

**JSP191 when added to TBI/Flu appears to be a safe and tolerable**

- No infusion reactions
- No treatment related toxicities
- Protocol allows for outpatient conditioning
- All subjects are still on study

**JSP191 PK at 0.6 mg/kg was observed to be consistent among subjects (n = 6)**

**JSP191 Conditioning observed**

- Days post JSP191 infusion

**Table data reflected in graphs:**

- A: Total blood chimerism
- B: CD15+ Myeloid cell chimerism
- C: CD3+ T cell chimerism
- D: CD56+ NK cell chimerism

**Subject Number**

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Donor Chimerism</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
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<tr>
<td>004</td>
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<tr>
<td>005</td>
<td>81% 100% 33% 94% 96% 100% 40% 99% 96% 100% 52% 99%</td>
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<td>006</td>
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<tr>
<td>009</td>
<td>92% 94% 60% 90%</td>
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**Mutation clearance after transplantation for MDS is associated with an improved Progression-Free Survival (Duncavage et al, NEJM 2018; 379:1028-41).**

**Primary endpoints:**

- Safety and tolerability of JSP191/TBI/Flu
- Engraftment and donor chimerism
- MRD clearance, Non-relapse mortality, Event-free Survival and Overall Survival

**Second primary endpoints:**

- DFS
- DFS-R
- OS
- OS-R
- OS-T
- DFS-T
- MRD-Negative/ MRD Reduction in First Five Evaluable Subjects

**Secondary endpoints:**

- Safety of JSP191/TBI/Flu
- Pharmacokinetics (PK)

**Drug doses and preparative regimens**

- Myeloablative therapy with busulfan, cyclophosphamide, and total body irradiation
- Non-myeloablative therapy with busulfan and fludarabine

**JSP191 Binds to CD117 on HSCs and Depletes HSCs**

- Using an antibody to stem cell antigens will limit extramedullary tissue damage and may enhance NMA conditioning