CIS2022

Update: Single-Agent Conditioning with Anti-CD117 Antibody JSP191 Shows Donor Engraftment, Naïve Lymphocyte Production, and Clinical Benefit in Patients with Severe Combined Immunodeficiency (SCID)

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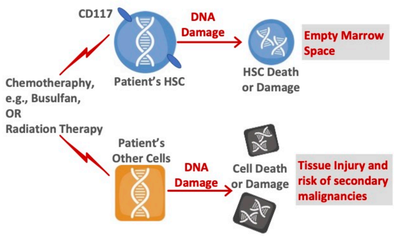
Background

Hematopoietic cell transplantation (HCT) is the definitive life-saving treatment for SCID. However, limitations related to pre-transplant conditioning can result in poor outcomes, either due to the adverse events caused by genotoxic agents used to augment hematopoietic stem cell (HSC) engraftment and/or because the choice is made to perform HCT without genotoxic conditioning, which results in a higher risk of graft failure. We are developing a non-toxic approach to target and deplete HSC using a humanized monoclonal antibody JSP191. JSP191 acts by inhibiting stem cell factor (SCF) binding to CD117 (c-Kit) present on HSC. SCF-CD117 signaling provides an essential survival and maintenance signal to HSC. Here, we present an update of an ongoing clinical trial in which JSP191 is used as single-agent conditioning for SCID patients in whom an initial HCT failed to engraft (NCT#02963064). Study subjects are required to lack donor HSC engraftment, evidenced by 0% donor CD15+ granulocyte chimerism. In the dose-finding portion of this study, JSP191 was infused as a single IV dose (0.1, 0.3, 0.6 and 1.0 mg/kg JSP191) followed by infusion of $CD34^+$-selected cells from original donors. Study endpoints include 1) safety and tolerability of JSP191, 2) donor chimerism of stringently flow-sorted CD15+ blood granulocytes, 3) lymphocyte reconstitution, and 4) improved clinical outcomes.

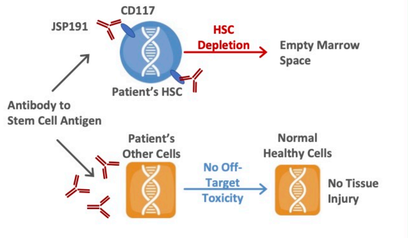
Toxic Conditioning Regimens is an Obstacle for Transplant: JSP191 can be a Safer Alternative

Current Transplant Conditioning Removes HSCs Through Highly Toxic Regimens



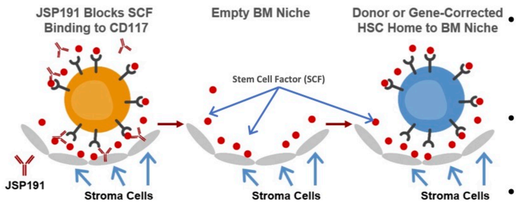
Marrow ablation by chemotherapy or radiation therapy causes cell damage or death to other patient cells

JSP191 Selectively Targets HSCs: An Alternative to Toxic Conditioning Regimens



Using an antibody that targets a stem cell antigen limits off-target tissue damage seen with conventional conditioning

JSP191 Binds to CD117 on HSCs and Depletes HSCs



- 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

Clinical Study Design:
Evaluation of SCID patients in a re-transplant and first transplant settings

Key Inclusion Criteria

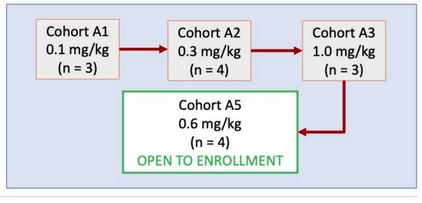
GROUP A: SCID Re-Transplant Population

- SCID defined by PIDTC
- Prior donor must be available
- Prior transplant ≥ 6 months
- Inadequate B cell engraftment
- Incomplete T cell reconstitution
- Clinical symptoms due to poor immune function

GROUP B: SCID First-Transplant Population

- SCID defined by PIDTC
- No prior history of HCT
- Haploidentical or HLA matched donor

Dose Finding Cohorts



Subject Demographics

T-B-NK+ SCID Re-Transplant Subjects:

JSP191 Dose	ID	Genotype	Age (years) at JSP191 HCT	Donor	Conditioning used in 1st HCT	Follow-up post-JSP191 HCT
0.1 mg/kg	0001	Artemis	3	Haplo maternal	Flu/ATG	Wk 208
	0002	Artemis	21	HLA-matched sibling	ATG	Wk 208
0.3 mg/kg	0004	PRKDC	12	Haplo maternal	Bu/Cy/ATG	Wk 156
	0008	RAG1	11	HLA-matched sibling	None	Wk 156
	0014	RAG1	38	HLA-matched sibling	None	Wk 104
0.6 mg/kg	0012	RAG1	11	HLA-matched parent	None	Wk 78
	0016	RAG1	4	HLA-matched parent	None	Wk 52
	0022	Artemis	2	HLA-matched sibling	None	Wk 12
1.0 mg/kg	0009	Artemis	32	Haplo sibling	Cy/ATG	Wk 104
	0010	Artemis	24	Haplo sibling	Cy/ATG	Wk 104

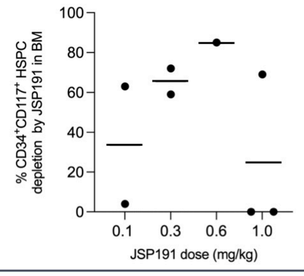
T-B+NK+ and T-B+NK- SCID Re-Transplant Subjects:

JSP191 Dose	ID	Genotype	Age (years) at JSP191 HCT	Donor	Conditioning used in 1st HCT	Follow-up post-JSP191 HCT
0.1 mg/kg	0003	IL2RG	13	Haplo maternal	None	Wk 156
0.3 mg/kg	0006	IL2RG	12	Haplo paternal	None	Wk 156
0.6 mg/kg	0021	IL7R	21	HLA-matched unrelated	ATG	Wk 12
1.0 mg/kg	0007	IL2RG	15	Haplo maternal	None	Wk 156

JSP191 is a well-tolerated conditioning regimen in patients to date

- No JSP191-related serious adverse events
- No significant infusion reactions
- No myelosuppression
- Protocol allows for outpatient conditioning for group A re-transplant subjects
- Protocol open to and enrolling subjects ≥3 months of age

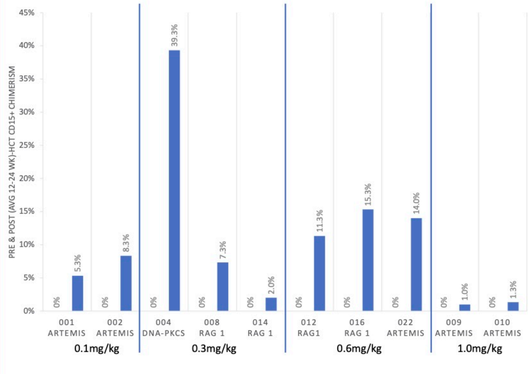
JSP191 as a single agent depletes CD34+CD117+ hematopoietic stem and progenitor cells (HSPCs) in SCID re-transplant subjects



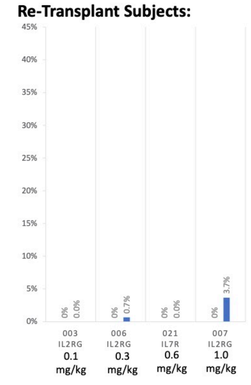
CD34+CD117+ HSPC depletion in the marrow on the day of HCT prior to donor cell infusion, relative to screening marrow. 0.6 mg/kg JSP191 has been proposed as recommended phase 2 dose (RP2D), as it provides consistent pharmacokinetic clearance across subjects, as well as a period of sustained inhibition of SCF that allows for optimal HSC depletion. 1.0 mg/kg JSP191 exhibited more variable pharmacokinetic clearance compared to lower JSP191 doses, leading to a prolonged period of time between JSP191 dosing and donor cell infusion, potentially allowing for endogenous HSPC recovery. Marrow samples were obtained from subjects who consented to the procedure. Marrow samples with low specimen quality were excluded from analysis.

JSP191 conditioning leads to engraftment of HSCs in T-B-NK+ SCID re-transplant

T-B-NK+ SCID Re-Transplant Subjects:



T-B+NK+ and T-B+NK- SCID Re-Transplant Subjects:

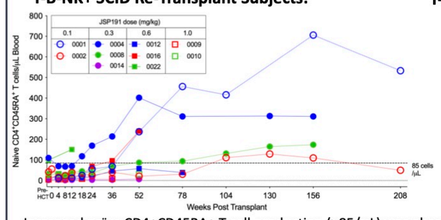


HSC engraftment was observed in 7 of 8 T-B-NK+ SCID re-transplant subjects conditioned with 0.1-0.6 mg/kg JSP191, as evidenced by stringently flow-sorted blood CD15+ donor chimerism of >5% averaged from 12-24 weeks post-HCT. 0.6 mg/kg JSP191 is the RP2D. SCID subjects conditioned with 1.0 mg/kg JSP191 and T-B+ SCID did not achieve stringent CD15+ chimerism of >5%. 1.0 mg/kg JSP191 exhibited more variable clearance compared to lower JSP191 doses. T-B+ SCID may have higher immune-mediated resistance in the re-transplant setting, which may necessitate additional immune ablation to enable successful donor HSC engraftment. All subjects pre-HCT had 0% CD15+ donor chimerism.

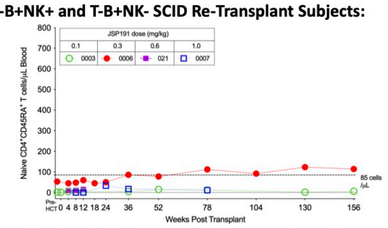
JSP191 single-agent conditioning leads to immune cell production in T-B-NK+ SCID re-transplant subjects

Naïve CD4+ T cells

T-B-NK+ SCID Re-Transplant Subjects:

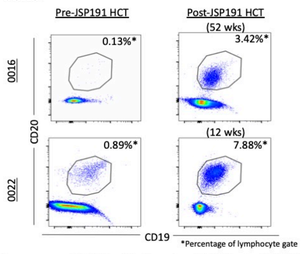


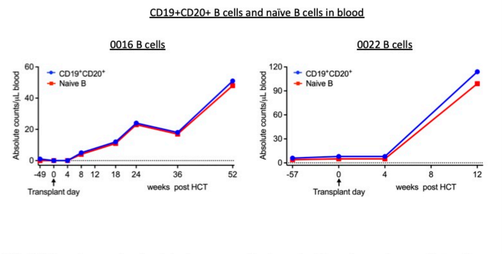
T-B+NK+ and T-B+NK- SCID Re-Transplant Subjects:



Increased naïve CD4+CD45RA+ T cell production (>85/µL) was observed in the majority of T-B-NK+ SCID re-transplant subjects conditioned with 0.1-0.6 mg/kg JSP191, versus T-B-NK+ SCID subjects conditioned with 1.0 mg/kg JSP191 and T-B+ SCID subjects.

B cells





At proposed RP2D of 0.6mg/kg JSP191, 2 of 3 T-B-NK+ SCID re-transplant subjects are producing significant numbers of blood CD19+CD20+ and naïve CD19+CD20+IgD+CD27- B cells at last follow up.

Clinical Benefit

T-B-NK+ SCID Re-Transplant Subjects:

JSP191 Dose	ID	Genotype	Clinical Status	Follow-up post-JSP191 HCT
0.1 mg/kg	0001	Artemis	**IVIG reduced, Chronic norovirus enteritis resolved, Chronic URI resolved**	Wk 208
	0002	Artemis	**Off IVIG, Ab response to vaccination**	Wk 208
0.3 mg/kg	0004	PRKDC	Continues on IVIG, **Chronic URI resolved**	Wk 156
	0008	RAG1	**Off IVIG, Ab response to vaccination**	Wk 156
	0014	RAG1	Continues on IVIG, **Improvement in chronic URI**	Wk 104
0.6 mg/kg	0012	RAG1	Continues on IVIG, **Improvement in chronic URI**	Wk 78
	0016	RAG1	IVIG/SCIG dependent, **Generating naïve B cells**	Wk 52
	0022	Artemis	IVIG dependent, **Generating naïve B cells**	Wk 12
1.0 mg/kg	0009	Artemis	Off Study at 140 weeks – Deceased	Wk 104
	0010	Artemis	Continues on IVIG, Persistent chronic URI, **Improvement in chronic diarrhea**	Wk 104

T-B+NK+ and T-B+NK- SCID Re-Transplant Subjects:

JSP191 Dose	ID	Genotype	Clinical Status	Follow-up post-JSP191 HCT
0.1 mg/kg	0003	IL2RG	Off study at 156 weeks – Continues on IVIG, Persistent chronic norovirus enteritis	Wk 156
0.3 mg/kg	0006	IL2RG	Continues on IVIG	Wk 156
0.6 mg/kg	0021	IL7R	Continues on IVIG	Wk 12
1.0 mg/kg	0007	IL2RG	Continues on IVIG, Persistent chronic URI	Wk 156

Summary (NCT#02963064)

- JSP191 demonstrates safety and tolerability as single-agent conditioning for SCID patients to date.
- 0.6 mg/kg JSP191 is the RP2D, based on pharmacokinetics and pharmacodynamics.
- JSP191 can create HSC niche space and has the potential to replace genotoxic conditioning.
- HSC engraftment in SCID patients is possible without myeloid suppression.
- Clinically meaningful production of naïve donor T and/or B cells has been achieved in T-B-NK+ SCID
- JSP191 can provide durable engraftment, chimerism, and clinical benefit (resolution of chronic infections, independence from IVIG, or antibody response to vaccine challenge) in SCID patients undergoing re-transplantation.
- Based on safety and successful HSC engraftment in re-transplant SCID subjects, the study of JSP191 has been expanded to include newly diagnosed infants with SCID.
- This trial remains open to enrollment for both first-transplant and re-transplant patients with SCID.

Acknowledgements

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- Jasper Therapeutics and the Investigators thank the patients and families for participating in this trial

Jasper THERAPEUTICS INC.

JSP191 is an investigative drug and not approved for any indication.