A two-part, single- and two-arm randomized, open-label study to evaluate the safety, tolerability and pharmacokinetics of KRP203 in subjects with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation

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Background

The success of allogeneic hematopoietic stem cell transplantation (HSCT) is limited by disease relapse. Alloreactive donor T cells have the potential to prevent relapse by the graft-versus-leukemia (GVL) response. The GVL response is essential, however, the same allo-T cells cause acute graft-versus-host disease (aGVHD). T cell trafficking out of lymphoid organs is a major step in raising peripheral immune responses and is regulated by sphingosine-1-phosphate (S1P) gradients. Pre-clinical data showed that pharmacological modulation of S1P receptor (S1PR) signalling by KRP203 sequesters T cells in lymphoid organs and prevents their egress to aGVHD target sites. In murine models, KRP203 efficiently reduced aGVHD. Because T cell function is not suppressed by KRP203, GVL was maintained, resulting in improved survival. Here, we show data of the first clinical trial investigating the safety and tolerability of KRP203 in patients with hematological malignancies undergoing HSCT.

Methods

This multicentric, phase Ib, prospective, open label, two-part study evaluated safety, tolerability and pharmacokinetics of KRP203 in intermediate to high-risk patients undergoing HSCT for hematological malignancies. Three treatment arms were investigated: 3mg KRP203+CsA/MTX, 1mg KRP203+CsA/MTX and 3mg KRP203+Tac/MTX. KRP203 was administered from day 1 until day 111 and HSCT was performed on day 11.

Results

KRP203 was safe and well-tolerated in these fragile patients. Upon conditioning and KRP203 treatment absolute lymphocyte counts (ALC) were reduced to about $0.2x10^9$/L and during

KRP203 exposure stabilized at <0.7x10^9/L in all three treatment arms, well below pre-HSCT levels. The treatment effect on ALC counts resolved when KRP203 was stopped on day 111, resulting in blood ALC to pre-HSCT levels. $CD4^+$ and $CD8^+$ T cells, were reduced in peripheral blood in response to KRP203 treatment. $CD4^+$ T cells remained below pre-HSCT level (<100 cells/µl) during the treatment period. CD8+ T cell counts recovered more rapidly, also during treatment. Overall survival probability was highest for subjects in the 3mdg KRP203+CsA arm with the first death reported on day 532. Overall survival at 1 year was 100% in the 3mg KRP203+CsA, 67% in the 1mg KRP203+CsA and 36% in the 3mg KRP203+Tac arm. The median time to relapse was 749 days. 2/6 subjects in 1mg KRP203+CsA, 4/10 subjects in 3mg KRP203+CsA and 4/7 subjects in 3mg KRP203+Tac arm relapsed. The median time to any aGVHD was 55 days. 21.7% of subjects presented with grade III-IV aGVHD. The median time to any chronic GVHD was 174 days. 56.5% of subjects presented with moderate and 8.7% with severe chronic GVHD. 52.2% of subjects did not experience a GRFS event and were alive at 6 months.

Conclusions

KRP203 is safe and well tolerated and shows promising early clinical outcomes with a limited number of relapses, acute and chronic GVHD. These data support the initiation of a phase 2b trial investigating KRP203 as an adjunctive and maintenance treatment to HSCT to maintain GVL.