# Administration of BPX-501 Cells Following α/β T-cell and B-cell-Depleted HLA-Haploidentical HSCT (haplo-HSCT) in Children with Primary Immunodeficiencies

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# Disclosures

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**Franco Locatelli**
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# Background

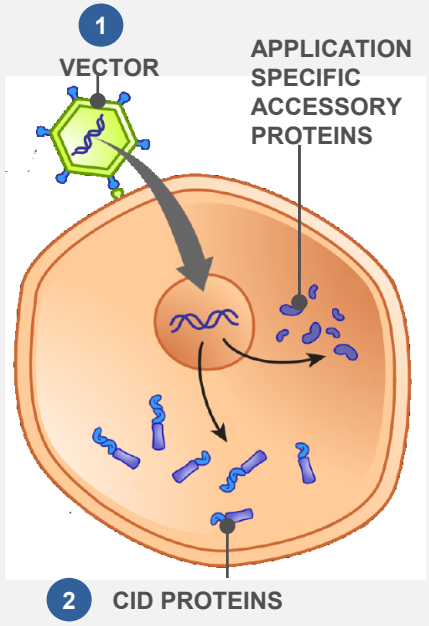
BPX-501 T-cells in children with primary immunodeficiencies

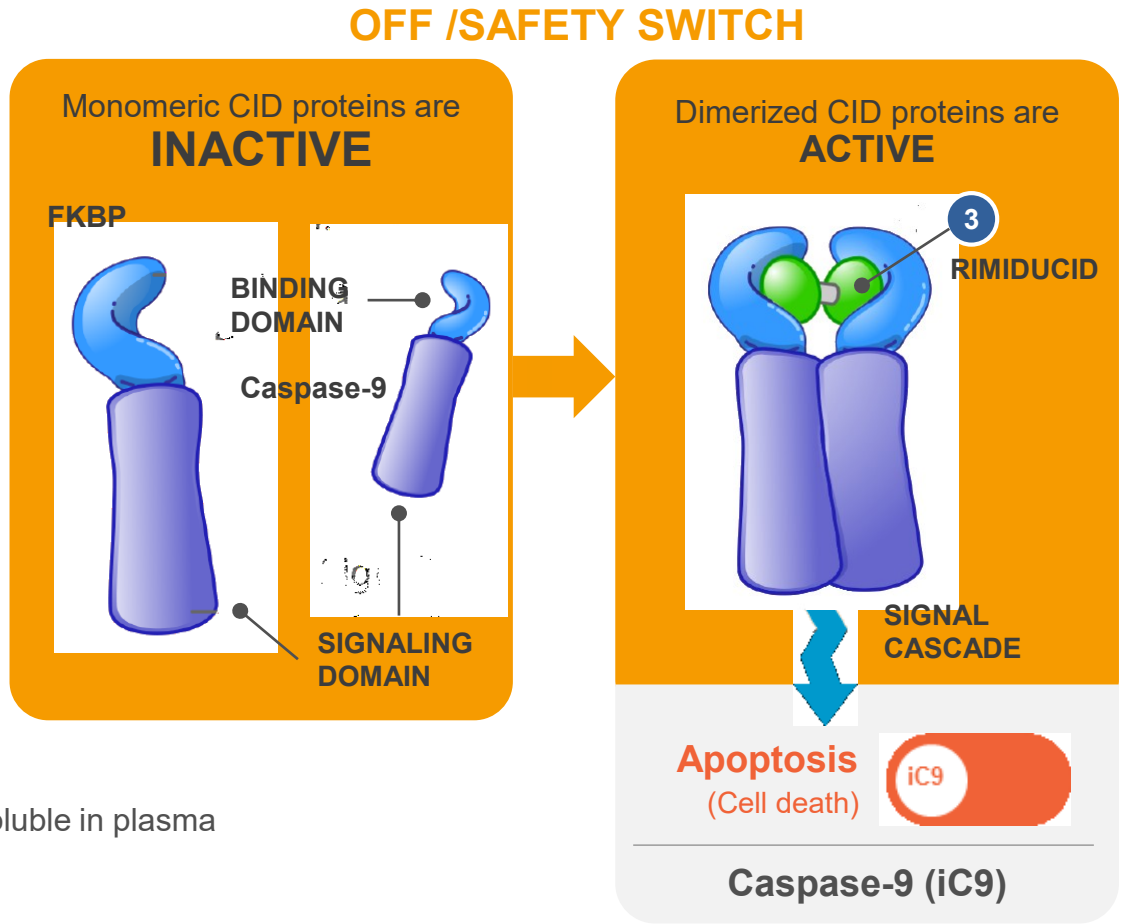
- Allogeneic HSCT is a well-established treatment for children with a wide range of primary immunodeficiencies (PIDs)
- Approximately 25% of patients have a HLA-matched sibling and ~50% have a suitable matched unrelated donor, leaving ~25% of patients who require an alternative donor.
- HLA-partially matched (haploidentical, haplo) donors represent a suitable alternative option for children who lack a matched donor
  - However, extensive T-cell depletion of the graft is required to minimize the risk of graft-vs-host disease (GvHD)
- BPX-501 is a polyclonal donor T cell product derived from haplo-donors engineered to include an inducible 'Safety Switch', offering the benefits of T cells in facilitating engraftment and preventing infections, with the unique ability to promptly and durably resolve GvHD symptoms
- The objectives of this Phase 1/2 study are to evaluate the safety and efficacy of BPX-501 T-cells administered after a T-cell receptor $\alpha\beta$ and B-cell depleted haplo-HSCT in pediatric patients with PIDs

# Bellicum's iCaspase-9 safety switch controls GvHD

The chemical induction dimerization (CID) switch controls GvHD through infusion of a selective dimerizing ligand (rimiducid) which activates cell signalling that leads to apoptosis

1. Viral transduction transfers the DNA from a **vector** into the target cell.
2. Vector-derived DNA directs expression of **CID** and **accessory proteins.**
3. **Rimiducid** dimerizes the CID proteins, thus turning on the signal cascade.



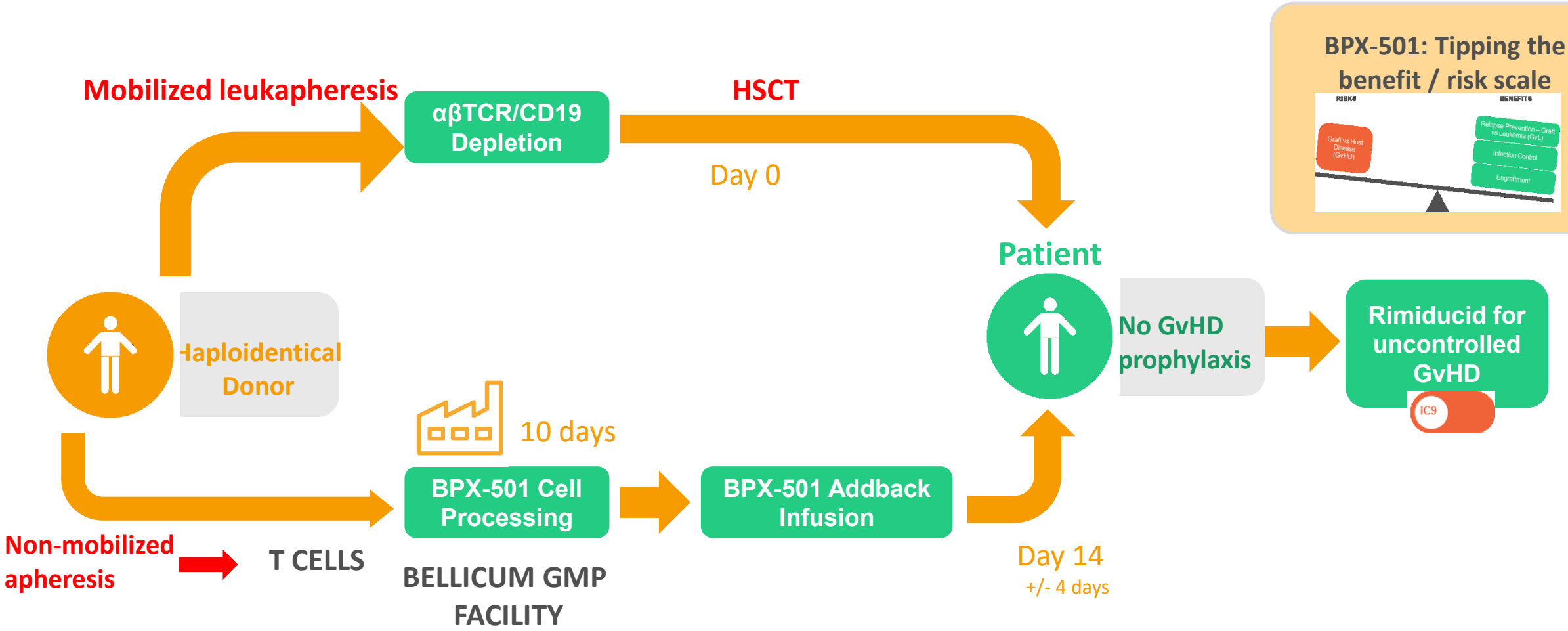




## Rimiducid is a selective CID ligand dimerizer

- Small (12 kDa, 107aa), bio-inert "activator" that is membrane-permeable, soluble in plasma
- Non-immunogenic
- <2 hour half-life
- No known side-effects

# BPX-501 addresses the “T-cell dilemma” in Haplo-HSCT

Study Schema



# Pediatric Ph1/2 trial design

Multicenter study of gene modified donor T-cells following TCR $\alpha\beta$ depleted stem cell transplant

**Pediatric high-risk malignancies and non-malignant disorders**

**No matched donor or urgent need of an allograft**

**Haploidentical donor available**

**αβ T-cell and B-cell depleted Haplo-HSCT**
**+**
**BPX-501[1]**
**(NO post-HSCT GvHD prophylaxis)**

**Rimiducid** for patients who develop GvHD or are refractory to SOC treatment

**Phase I: 3+3 design (no MTD reached)**
$2.5x10^5$, $5x10^5$, $1x10^6$ BPX-501 T-cells/kg (no DLTs observed)

**Phase II:**
$1x10^6$ BPX-501 T-cells/kg (chosen for further evaluation)

## Outcomes

- Event-free survival
- Transplant related mortality (non-malignant)
- Non relapse mortality (malignant)
- Incidence and severity of GvHD
- Time to resolution of GvHD after administration of rimiducid
- Immune reconstitution

## KEY INCLUSION CRITERIA

- Life-threatening acute leukemia or myelodysplastic syndrome
- **Non-malignant disorder deemed curable by HSCT**
- Life expectancy > 10 weeks
- Age < 18 years and > 1 month

## KEY EXCLUSION CRITERIA

- Active GvHD or immunosuppressive treatment from a previous allograft
- Renal or liver dysfunction
- Active infection
- Pregnant or breast feeding

# Baseline clinical characteristics

**PATIENT POPULATION**

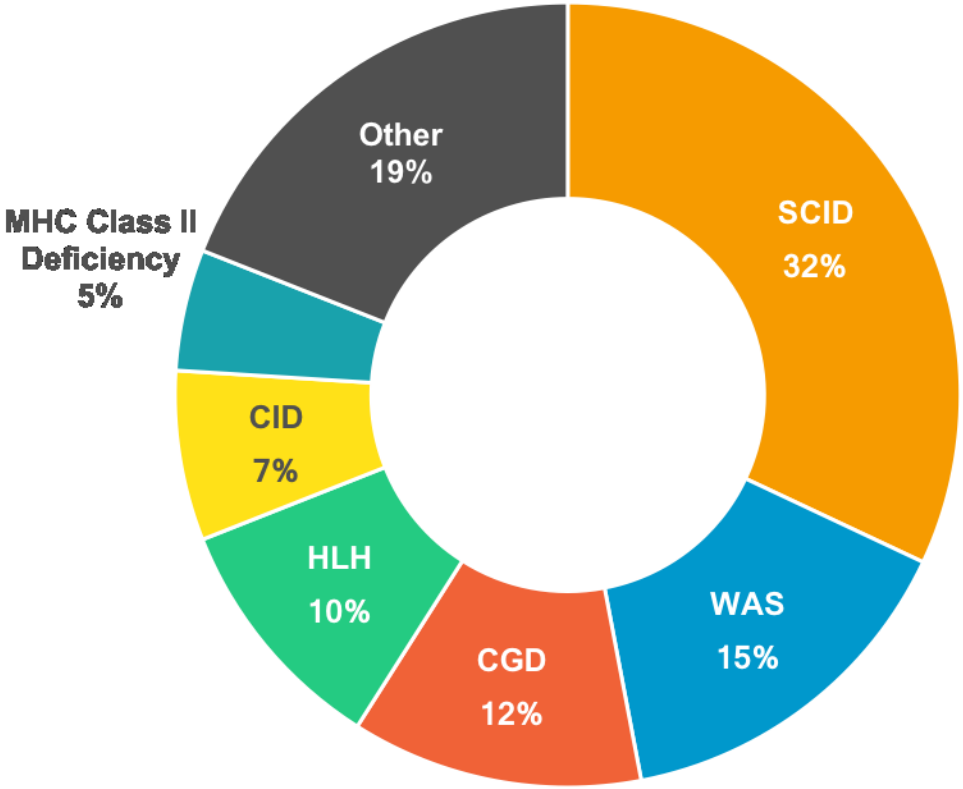
**n=59**

**AGE, MEDIAN (RANGE)**

**1.85 (0.21-17.55)**

**MALE (%)**

**57.6%**




**Other diagnoses** (N=1 each): XIAP-deficiency; IL-2 Receptor Deficiency; IFNgamma-receptor 1 deficiency; IL-10 RB deficiency; Partial complement C4 deficiency with multiple autoimmune manifestations; CD40 Ligand deficiency; IKBetaAlfa gain of function mutation; Dock 8 deficiency; Severe congenital neutropenia; Hyper IgM syndrome, Hyper IgD syndrome

# Transplant characteristics

| CHARACTERISTIC | N=59 |
|---|---|
| **Conditioning regimen** | |
| Treosulfan-based | 29 (49.2%) |
| Busulfan-based | 23 (39.0%) |
| Other | 7 (11.9%) |
| **Median CD34 dose x $10^6$/kg (range)** | 22.0 (3.0-57.0) |
| **Median $\alpha\beta$ T-cell dose x $10^5$/kg (range)** | 0.4 (0.01-1.0) |
| **Donor age in years (range)** | 34 (21-52) |
| **Type of donor** | |
| Parent | 56 (94.9%) |
| Sibling | 3 (5.1%) |
| **Time to BPX-501 infusion in days (range)** | 15 (11-56) |
| **Time to discharge in days (range)** | 40 (18-204) |
| **Median follow-up in days (range)** | 536 (32-1252) |

# Safety

**15.2%**
(9 patients) experienced ≥1 adverse event (AE)

**AEs occurring after BPX-501 cells were limited to Grade 1-2**

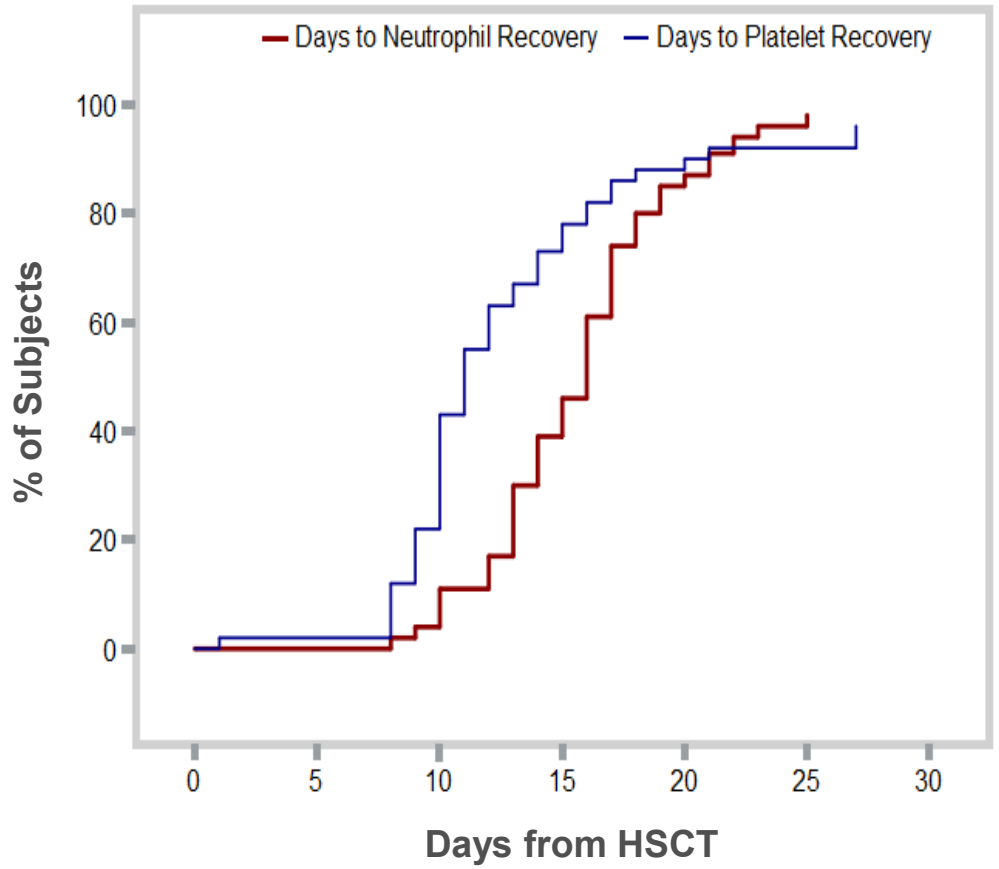
Preferred terms included: Diarrhoea, Vomiting, Pyrexia, Cytomegalovirus viraemia (2), Rhinovirus infection, Hypokalaemia, Pruritus, Rash

**No SAEs attributed to BPX-501 were reported in this cohort**

**BPX-501 T-cells were well tolerated**

# Neutrophil and platelet recovery

Rapid neutrophil and platelet recovery




**Neutrophil & platelet recovery were rapid**

**Median neutrophil engraftment: 16 days (95% CI, 14-17)**

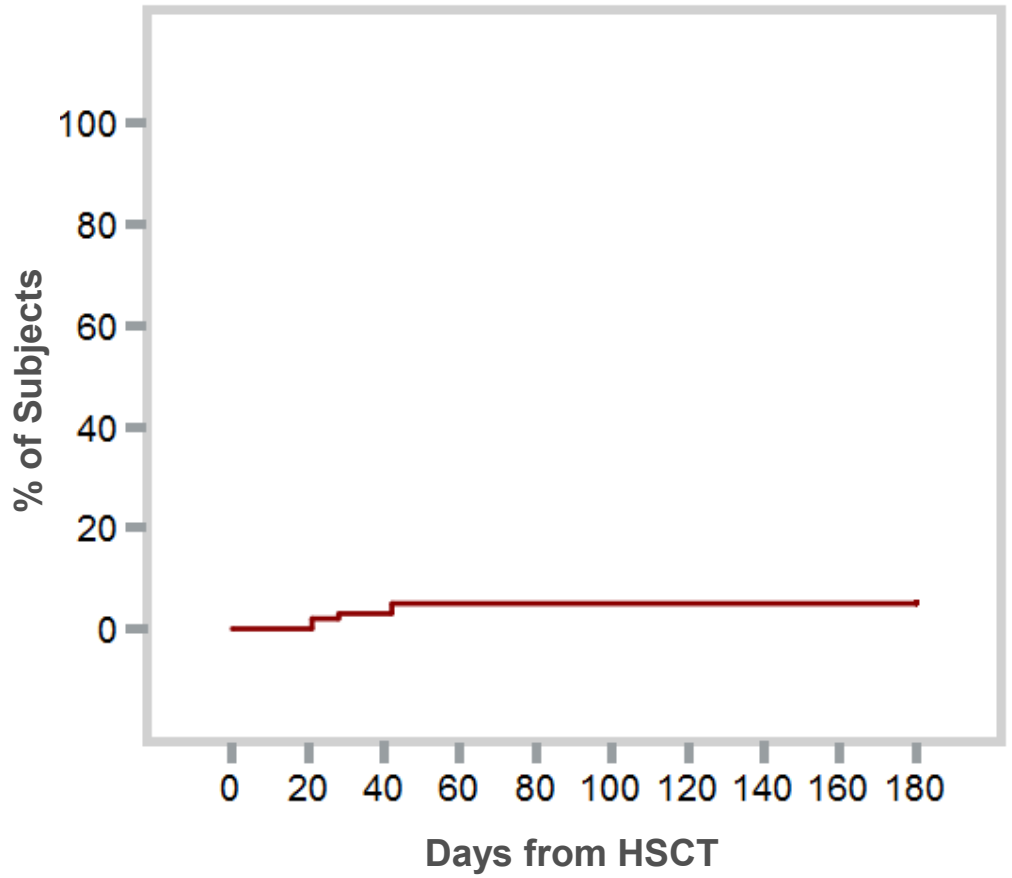
**Median platelet engraftment: 11 days (95% CI, 10-12)**

Only 1 subject received G-CSF

Median follow-up:
536 days (32-1252 days)

# Graft failure

Low graft failure rate at 5.1%

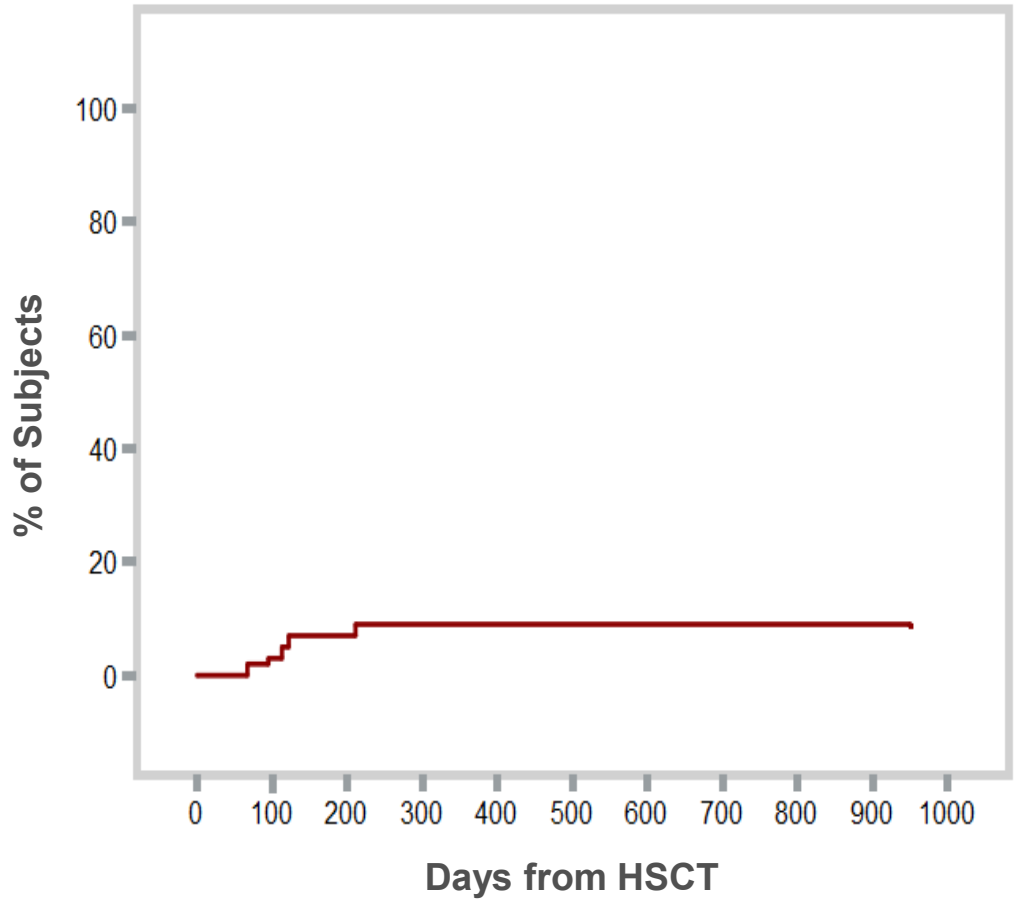



**Graft failure rate: 5.1% (95% CI, 0.0-10.7)**

1 of 3 patients were successfully re-transplanted

# Cumulative incidence of transplant-related mortality (TRM)

Low TRM incidence of 8.7%

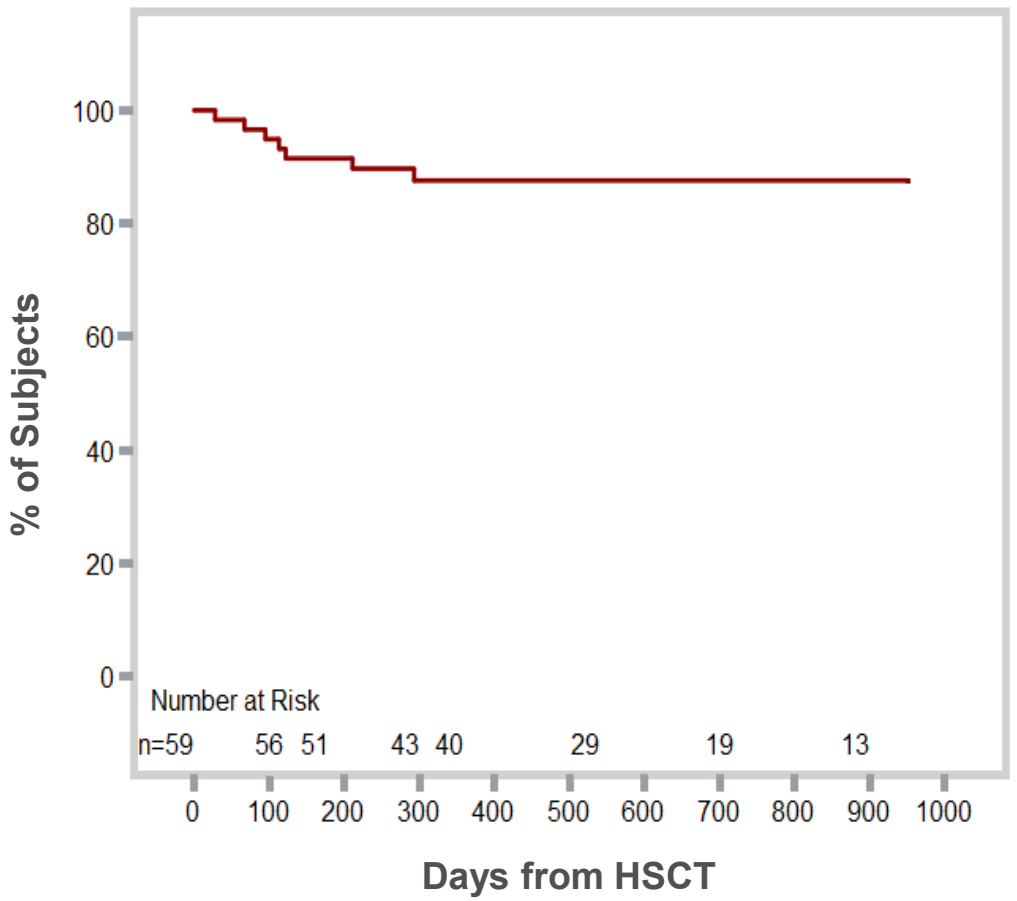



**Transplant-related mortality: 8.7% (95% CI, 1.4-16.0)**

5 cases of TRM:

- Graft failure/disseminated fungal infection
- CMV encephalitis
- Worsening juvenile dermatomyositis/macrophage activation syndrome
- Bronchopulmonary hemorrhage
- CMV and adenovirus infection/respiratory failure

# Disease-free survival (DFS)




## Disease-free survival: 87.6% (95% CI, 79.0-96.3)

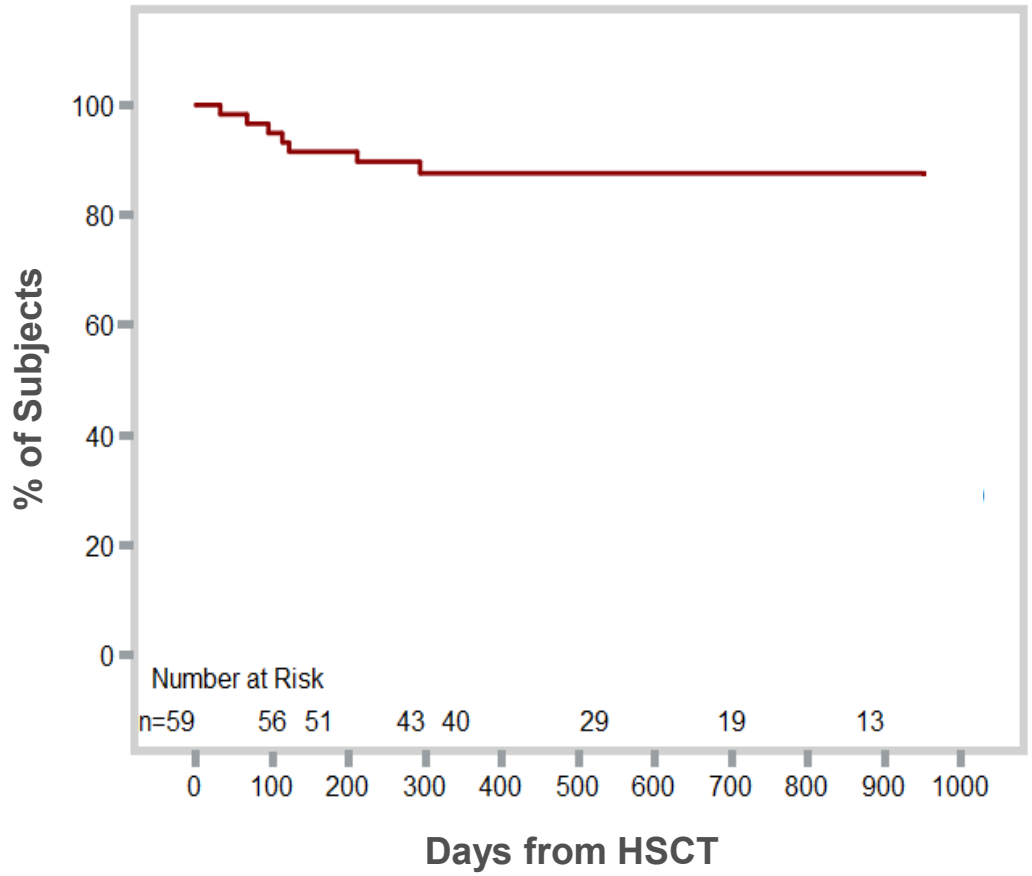
Events:

- Graft failure without successful re-transplantation (1)
- Graft failure with death due to disseminated fungal infection (1)
- Other grade 5 events (1 each):
  - CMV encephalitis
  - Worsening juvenile dermatomyositis/macrophage activation syndrome
  - Refractory HLH
  - Bronchopulmonary hemorrhage
  - Respiratory failure

1 time from treatment until graft failure or death from any cause.

# Overall survival (OS)

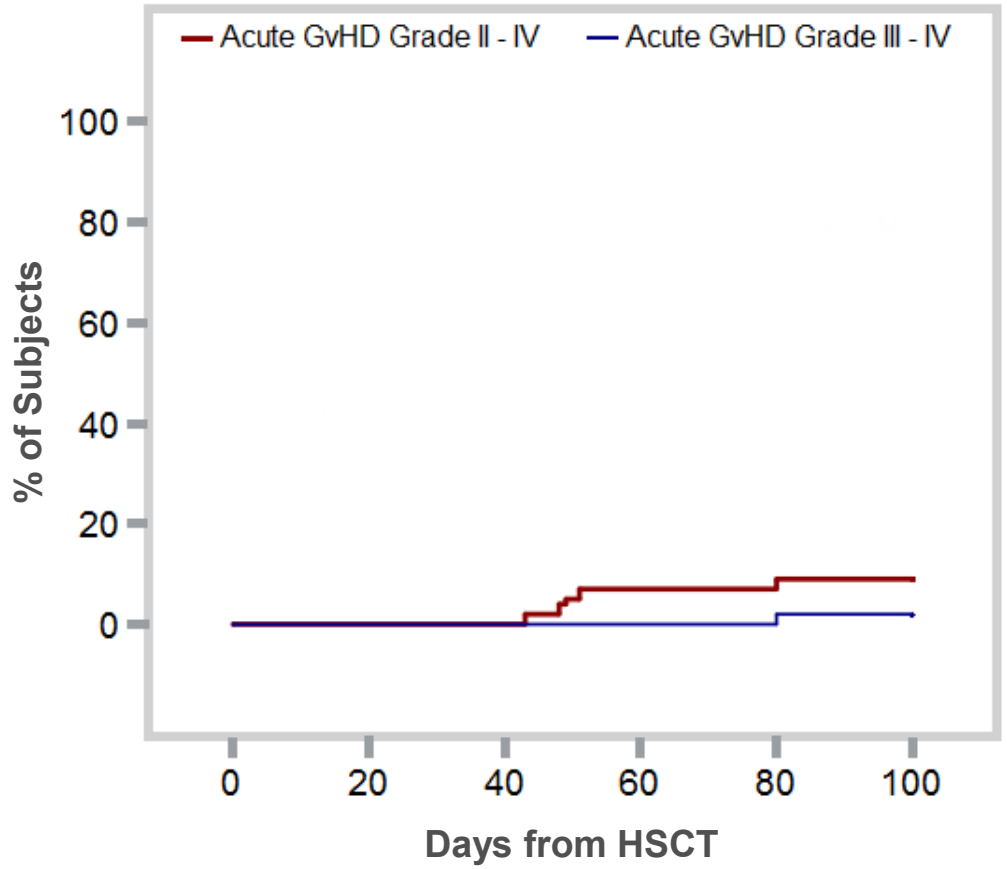
Median follow-up: 536 days (Range, 32 – 1252 days)




**Overall survival:**
**87.6% (95% CI, 79.0-96.3)**

# Acute GvHD

Low rates of acute GvHD Grade II-IV and Grade III-IV (first 100 days)




**Grade II-IV:**
**8.9% (95% CI, 1.5-16.4)**

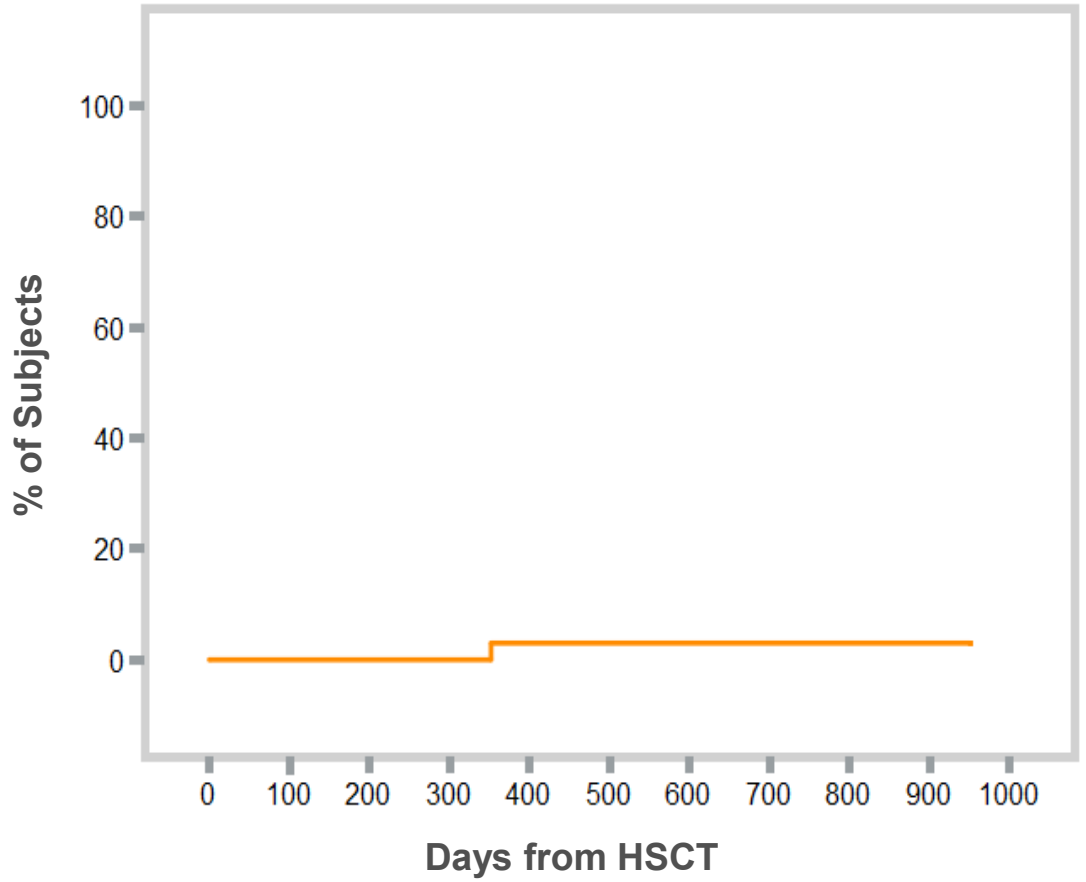
**Grade III-IV:**
**1.8% (95% CI, 0.0-5.3)**

Cases of acute GvHD within 100 days included:

- Grade II (n=4)
  - Stage 3 skin (n=3)
  - Stage 1 upper GI (n=1)
- Grade III (n=1)
  - Stage 3 liver

# Cumulative incidence of chronic GvHD

Low rates of chronic GvHD were observed




**cGvHD rate:**
**3.0% (95% CI, 0.0-8.9)**

1 case of moderate skin cGvHD; rimiducid was not administered

# Response to rimiducid

**Of the 19 patients who developed aGvHD, 7 received ≥ 1 dose of rimiducid for aGvHD not responsive to standard of care treatment or for visceral involvement**

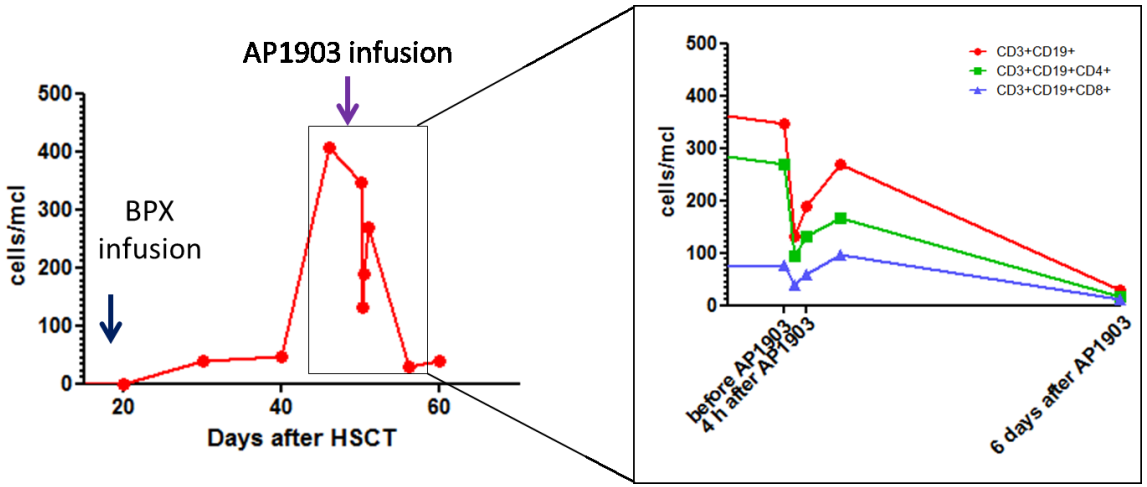
**>80% response rate in evaluable PID patients (5 of 6)**

| OVERALL | STAGE | RESPONSE |
|---|---|---|
| Grade I | Stage 1 skin | CR |
| Grade I | Stage 2 skin | PR |
| Grade II | Stage 3 skin | CR |
| Grade II | Stage 1 upper GI | CR |
| Grade II | Stage 3 skin | NE* |
| Grade III | Stage 3 liver | CR |
| Grade III | Stage 3 liver | NR |

*NE: Patient on corticosteroids and cyclosporine with controlled GvHD but failure to wean corticosteroids. Rimiducid given in an attempt to wean corticosteroids

# Rimiducid (AP1903) use

| | aGVHD, grade | Response |
|---|---|---|
| **Patient 1** | Skin, II | Complete |



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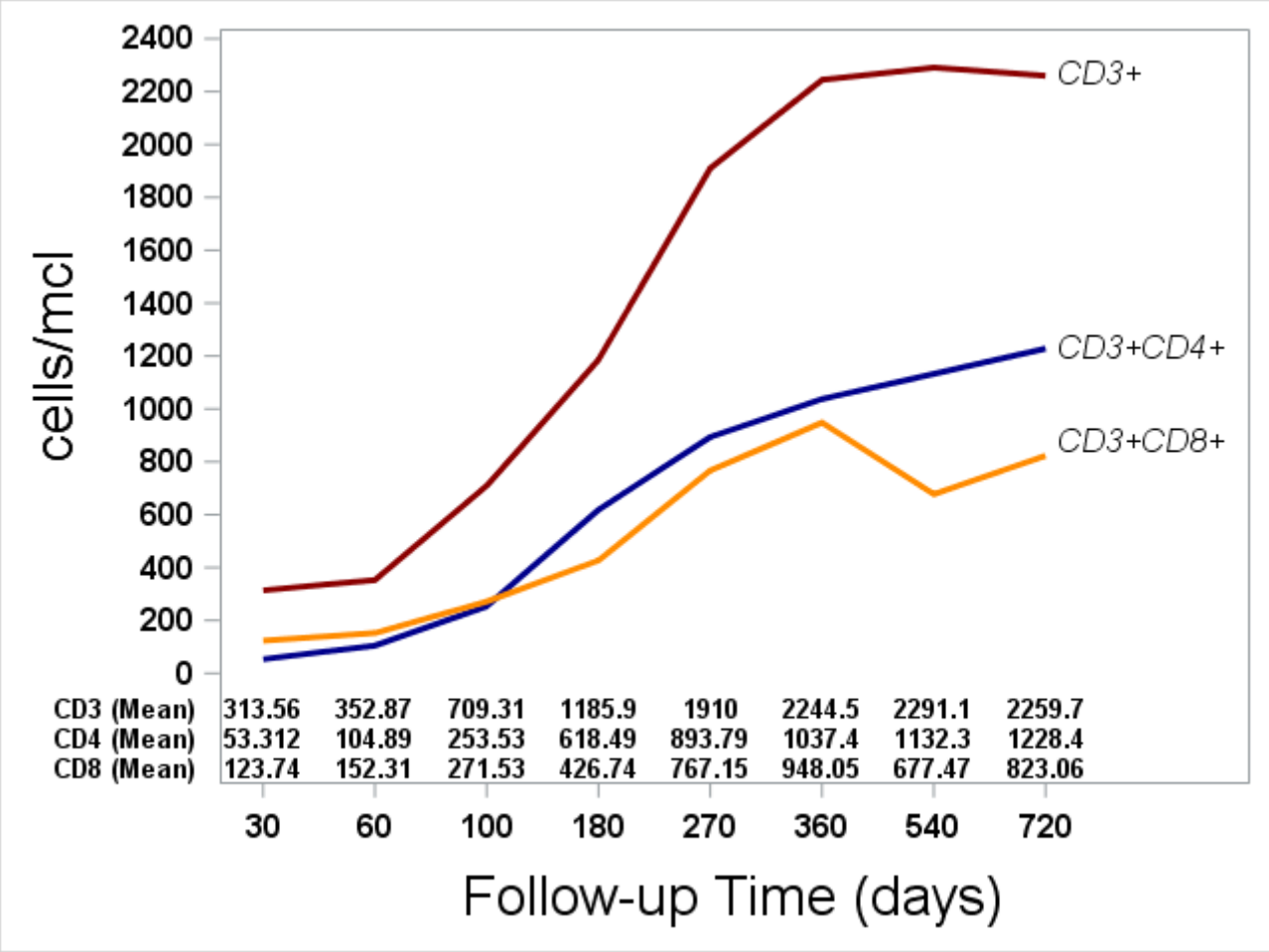
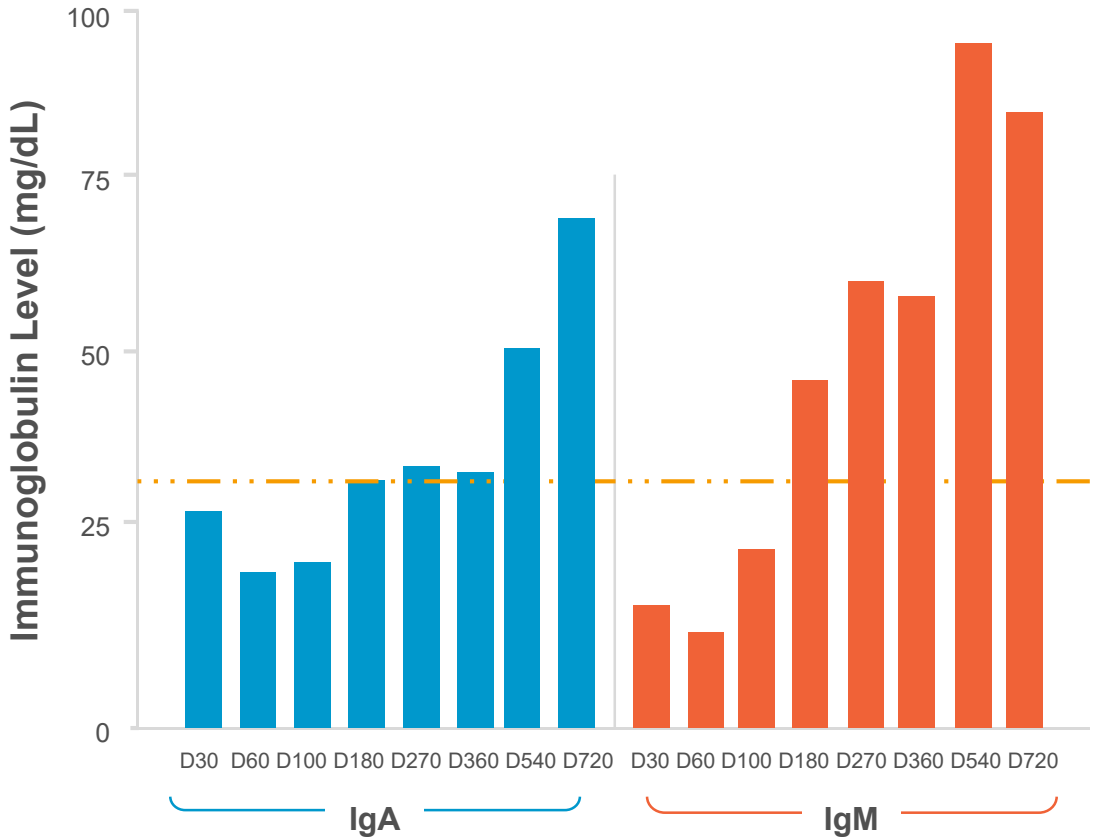
# Immune recovery

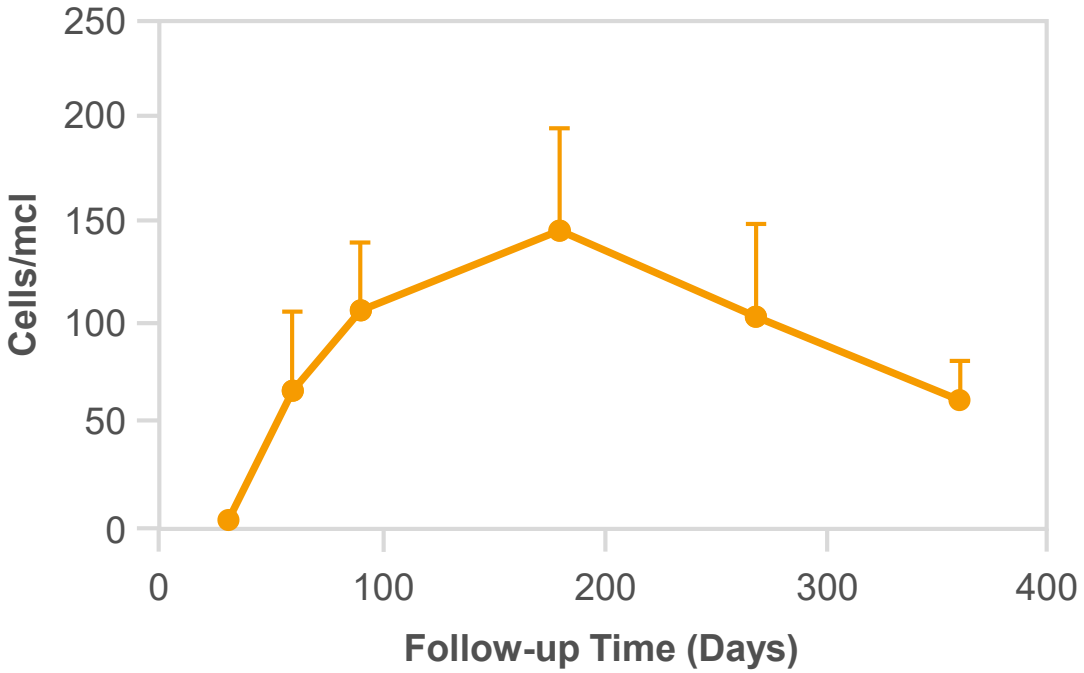
Immune recovery: CD3 T-cell count > 500 cells/μl achieved by 100 days and normal levels of IgA and IgM was achieved by 180 days

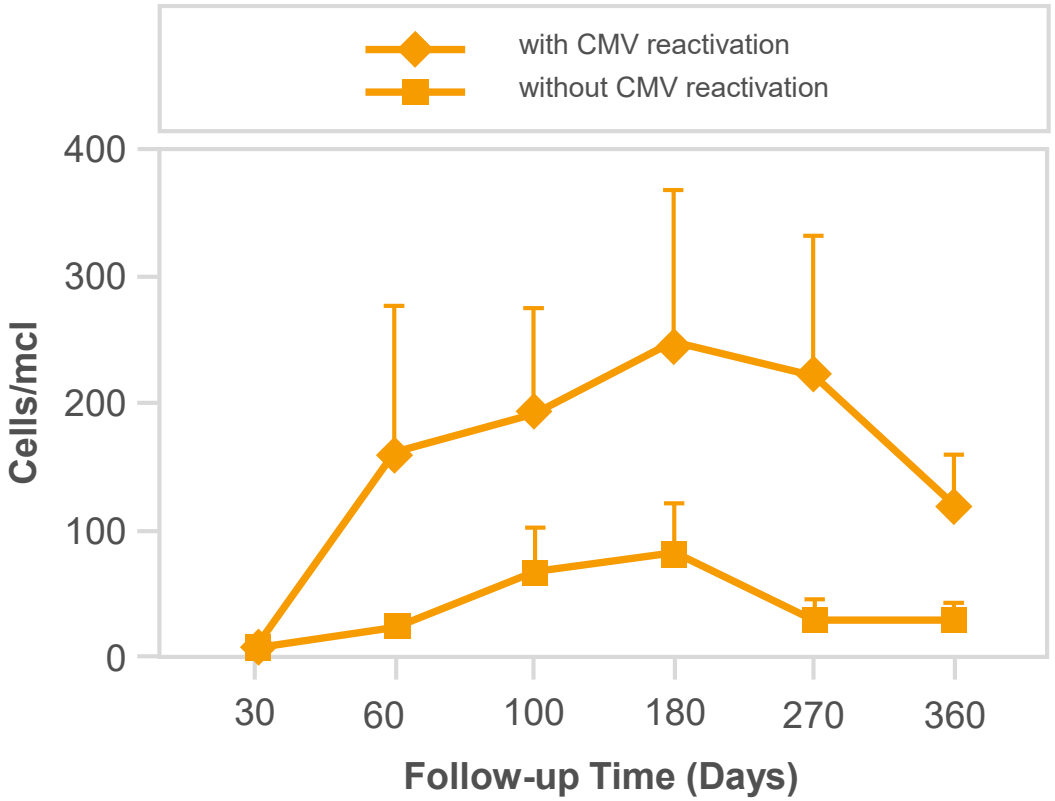


# Immune recovery

BPX-501 engraftment after HSCT




**Mean BPX-501 cell counts exceed 100 cells/mcl by day 100**

**Increased number of BPX-501 cells observed in patients that experienced CMV reactivation**

# Summary

**α/β T-cell and B-cell depleted haploidentical HSCT followed by infusion of BPX-501 cells is a novel and highly effective transplantation strategy for children with a wide range of primary immunodeficiencies lacking a suitable HLA-compatible donor**

- Disease-free survival and overall survival (87.6% and 87.6%, respectively) compare favourably with data reported using matched unrelated donors
- The cumulative incidence of severe acute (grade III-IV) (1.8%) in the first 100 days and chronic GvHD (3.0%) was low compared to other transplant methods
- >80% of patients with treatment resistant acute GvHD responded after administration of rimiducid
- CD3+ T-cells, IgA and IgM achieved normal levels by 180 days post HSCT
- BPX-501 T-cells expand over-time and persist post infusion through all timepoints, the main driver for BPX-501 T-cell expansion being represented by CMV infection

# Acknowledgements

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