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BRIEF COMMUNICATION

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Phase I study of single-dose pharmacokinetics and pharmacodynamics of belatacept in adolescent kidney transplant recipients

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Belatacept is an intravenously infused selective T cell costimulation blocker approved for preventing organ rejection in renal transplant recipients aged ≥18 years. This phase I trial examined the pharmacokinetics and pharmacodynamics (percentage CD86 receptor occupancy [%CD86RO]) of a single dose of belatacept (7.5 mg/kg) administered to kidney transplant recipients aged 12-17 years receiving a stable calcineurin inhibitor–based immunosuppressive regimen. Nine adolescents (mean age 15.1 years) who were seropositive for Epstein-Barr virus were enrolled; all completed the 6-month study. Pharmacokinetics suggested relatively low variability of exposure (coefficients of variation for maximum observed serum concentration [C_{max}] and area under the serum concentration-time curve from time zero extrapolated to infinity [$AUC_{0\text{-}INF}$] were 20% and 25%, respectively). Mean half-life ($T_{1/2}$) occurred 7.2 days postinfusion. Belatacept total body clearance was 0.48 mL/h/kg, and volume of distribution at steady-state (V_{ss}) was low at 0.09 L/kg. Compared with historical data from healthy adult volunteers administered a single dose of belatacept 10 mg/kg and adult kidney transplant recipients administered multiple doses of belatacept 5 mg/kg, pharmacokinetic values for adolescents were similar, indicating consistency across adolescent and adult populations. Mean %CD86RO increased with increasing belatacept concentration, indicating a direct relationship between pharmacokinetics and pharmacodynamics. Four patients reported 7 serious adverse events; none was considered related to belatacept. These data will inform belatacept dose selection in future studies of adolescent kidney transplant recipients.

KEYWORDS
belatacept, clinical research/practice, immunosuppressant - fusion proteins and monoclonal antibodies, kidney transplantation, kidney transplantation/nephrology, living donor, pharmacokinetics/pharmacodynamics, simulation

Abbreviations: %CD86RO, percentage CD86 receptor occupancy; AE, adverse event; $AUC_{0\text{-}INF}$, area under the serum concentration-time curve from time zero extrapolated to infinity; $AUC_{0\text{-}T}$, area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration; CLT, total body clearance; C_{max}, maximum observed serum concentration; C_{min}, minimum observed serum concentration; CNI, calcineurin inhibitor; E_0, baseline effect; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; E_{max}, maximum effect; ESRD, end-stage renal disease; MRT, mean residence time; PRA, panel reactive antibody; RO, receptor occupancy; SD, standard deviation; $T_{1/2}$, half-life; V_{ss}, volume of distribution at steady-state.

1 | INTRODUCTION

Adolescent renal transplant recipients aged 13-17 years have the poorest long-term graft-survival rates (5-year) of any age group ≤65 years,[1] irrespective of whether they have been transplanted with a kidney from a living or deceased donor.[1,2] Regardless of the age at which transplantation has occurred, pediatric renal transplant recipients are most vulnerable to graft loss during adolescence/young adulthood.[3,4] Nonadherence with oral immunosuppression has been identified as a major contributor to graft loss among adolescents.[5,6] In addition, chronic use of calcineurin inhibitors (CNIs) is associated with chronic allograft injury, including tubulointerstitial fibrosis and chronic allograft dysfunction,[7-12] and cardiovascular and metabolic adverse events (AEs).[13]

Belatacept is an intravenously infused soluble fusion protein that selectively blocks CD86-CD28 costimulation between antigen-presenting cells and T cells (Figure S1).[14] Ligation of CD28 with CD86 is an important stimulatory signal for CD28-bearing T cells; belatacept blocks ligation of CD28 by CD86, resulting in T cell quiescence.[14] Belatacept is approved in the United States, the European Union, and other countries, for preventing renal transplant rejection in adults who are seropositive for the Epstein-Barr virus. As a result of belatacept being intravenously infused under medical supervision and the lack of nephrotoxicity,[15,16] belatacept may improve adherence and clinical outcomes in adolescent kidney transplant recipients. However, belatacept is currently indicated for use only in adults. Because the pharmacokinetics of numerous immunosuppressive agents have been shown to differ between pediatric and adult patients,[17,18] the present phase I study was undertaken to assess the pharmacokinetics and pharmacodynamics of a single intravenous infusion of belatacept administered to renal transplant recipients aged 12-17 years.

2 | MATERIALS AND METHODS

2.1 | Study design

In this multicenter (5 sites), open-label, phase I study (NCT01791491), kidney transplant recipients aged 12-17 years, seropositive for Epstein-Barr virus, received a single intravenous infusion of belatacept of 7.5 mg/kg over 30 minutes. Eligible patients had been transplanted with a living or deceased donor kidney ≥6 months before enrollment and were receiving a stable regimen of CNI-based immunosuppression. Patients continued maintenance immunosuppression per local practice without change following belatacept infusion. Under the original protocol, patients were to continue to receive mycophenolate mofetil or mycophenolic acid with concomitant corticosteroids. However, following a protocol amendment, maintenance immunosuppression with corticosteroids became optional (thus, only 8 of the 9 adolescents treated in this study were receiving maintenance corticosteroids). Study participants also had an estimated GFR (eGFR) ≥45 mL/min/1.73 m^2 per the updated Schwartz formula[19] and urine albumin-to-creatinine ratio <56.5 mg/mmol (<0.5 mg albumin/mg creatinine). Individuals with a history of any treated or biopsy-proven acute rejection in the 3 months before enrollment were excluded, as were individuals with any active infection. The study conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. The protocol was approved by the institutional review board/ethics committee at the participating centers.

2.2 | Dose selection

Because belatacept had not been previously studied in adolescents, initial dose selection for this age group was based on simulations that extrapolated data from an adult population pharmacokinetic model[20] to adolescents.[21] The dose selected for use in adolescents was that necessary to achieve steady-state trough (C_{min}) concentrations comparable to those observed in stable adult renal transplant recipients participating in a phase II study.[22,23] Based on the assumption that belatacept exposure at C_{min} is highly correlated with receptor occupancy, which then drives pharmacologic activity,[20] and because it was expected that belatacept clearance would increase with decreasing age (due to generally higher metabolic rates in children), we reasoned that a higher belatacept dose was likely needed for adolescents to achieve C_{min} similar to that observed in adults. Thus, belatacept 7.5 mg/kg was selected as the dose to be administered to adolescents.

2.3 | Endpoints

The primary endpoint was evaluation of single-dose pharmacokinetics (maximum observed serum concentration [C_{max}], time of maximum observed serum concentration [T_{max}], area under the serum concentration-time curve from time zero extrapolated to infinity [$AUC_{0\text{-}INF}$], area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration [$AUC_{0\text{-}T}$], half-life [$T_{1/2}$], total body clearance [CLT], and volume of distribution at steady-state [V_{ss}]). C_{min} can only be evaluated under multiple-dose, steady-state conditions (and IM103-144 was a single-dose study). Thus, C_{min} was assessed through model-based simulations and not measured directly. Blood was collected for the evaluation of pharmacokinetics on day 1 (predose, 0.5, and 2 hours after the start of the infusion) and on days 8, 15, 29, and 57; samples were then analyzed at a central facility (Pharmaceutical Product Development, Richmond, VA) using a previously validated enzyme-linked immunosorbent assay (ELISA).

Secondary endpoints included the percentage of CD86 receptor occupancy (%CD86RO; pharmacodynamics) under belatacept administration and the relationship between pharmacokinetics and pharmacodynamics. Blood was collected for the evaluation of the %CD86RO on days 1, 29, and 57 and centrally assessed (Q^2 Solutions, Morrisville, NC) using a flow cytometry–based CD86 receptor competition assay. AEs were recorded up to day 57, and serious AEs were recorded up to month 6 (final visit). AEs were mapped

to terms from the Medical Dictionary for Regulatory Affairs version 19.0.

2.4 | Pharmacokinetics

Pharmacokinetic data were calculated via Phoenix version 1.4, with individual patient pharmacokinetic parameter values derived by noncompartmental methods. Serum concentration-time data and nominal times were used for the generation of mean serum concentration-time plots and summary statistics.

C_{max} and T_{max} were recorded directly from experimental observations. The terminal log-linear phase of the concentration-time curve (without a weighting factor) was identified by least-squares linear regression of ≥3 data points (excluding T_{max}) that yielded an adjusted R^2 value. $T_{1/2}$ was calculated as ln2/λ, where λ was the absolute value of the slope of the terminal log-linear phase. $AUC_{0\text{-}T}$ was calculated by mixed log-linear trapezoidal summations. $AUC_{0\text{-}INF}$ was estimated by summing $AUC_{0\text{-}T}$ and the extrapolated area, which was computed by the quotient of the last observable concentration and λ. CLT was calculated by dividing the total dose administered by $AUC_{0\text{-}INF}$. V_{ss} after intravenous dosing was calculated by dividing the product of dose × mean residence time (MRT) by $AUC_{0\text{-}INF}$, where MRT was derived by dividing the area under the moment curve by the corresponding $AUC_{0\text{-}INF}$ value. We then compared numerically the pharmacokinetic data derived from adolescents administered a single dose of belatacept of 7.5 mg/kg with historical data derived from healthy adult volunteers administered a single dose of

TABLE 1 Baseline demographics and disease characteristics

	Patients (N = 9)
Mean age (range), y	15.1 (13-17)
Female, n (%)	4 (44.4)
Race, n (%)	
Caucasian	5 (55.6)
Black/African American	4 (44.4)
Mean weight (range), kg	59.1 (37.6-103.5)
Mean BMI (range), kg/m^2	23.8 (16.4-39.0)
Prior number of kidney transplants, n (%)	
0	5 (55.6)
1	4 (44.4)
Categorized highest PRA, n (%)	
<20%	9 (100.0)
≥20%	0 (0)
Reported cause of ESRD, n (%)	
Congenital renal hypodysplasia	2 (22.2)
Glomerular disease	2 (22.2)
Congenital obstructive uropathy	1 (11.1)
Chronic tubulointerstitial disease with glomerulosclerosis	1 (11.1)
Nephronophthisis	1 (11.1)
Renal artery stenosis	1 (11.1)
Unknown	1 (11.1)
HLA mismatches, n (%)	
1	1 (11.1)
2	0 (0)
3	2 (22.2)
4	2 (22.2)
5	3 (33.3)
6	1 (11.1)
EBV seropositive, n (%)	9 (100.0)
CMV seropositive, n (%)	4 (44.4)
Recipient of a living donor kidney, n (%)	6 (66.7)
Mean estimated GFR,[a] mL/min/1.73 m^2 (range)	73.1 (55.3-106.8)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; ESRD, end-stage renal disease; PRA, panel reactive antibody.

[a]Per the updated Schwartz formula.

TABLE 2 Pharmacokinetic parameters derived from adolescent kidney recipients administered a single dose of belatacept 7.5 mg/kg, healthy adult volunteers administered a single dose of belatacept 10 mg/kg, and adult kidney transplant recipients administered multiple doses of belatacept 5 mg/kg

	Adolescent kidney transplant recipients N = 9	Healthy adult volunteers[a] N = 15	Adult kidney transplant recipients[a] N = 14
Belatacept			
Dose	7.5 mg/kg	10 mg/kg	5 mg/kg
Dosing frequency	Single	Single	Multiple
C_{max}, μg/mL	151 (20)	300 (26)	139 (20)
$T_{1/2}$, h	173 (47)	235 (29)	197 (29)
CLT, mL/h/kg	0.48 (27)	0.39 (18)	0.51 (27)
V_{ss}, L/kg	0.09 (30)	0.09 (22)	0.12 (25)
AUC, μg·h/mL	15 407 (25)[b]	26 398 (20)[b]	14 090 (27)[c]

$AUC_{0\text{-}INF}$, area under the serum concentration-time curve from time zero extrapolated to infinity; $AUC_{0\text{-}T}$, area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration; CLT, total body clearance; C_{max}, maximum observed serum concentration; $T_{1/2}$, half-life; V_{ss}, volume of distribution at steady-state.
Data are mean (coefficient of variation expressed as a percentage).
[a]Data derive from the Nulojix package insert, 2017.
[b]$AUC_{0\text{-}INF}$ after a single dose.
[c]$AUC_{0\text{-}T}$ after multiple doses, where "*T*" is equivalent to 4 weeks.

belatacept of 10 mg/kg and adult kidney transplant recipients administered multiple doses of belatacept of 5 mg/kg.[24]

2.5 | Pharmacodynamics

As previously described,[20] the %CD86RO was calculated at baseline and at each postinfusion time point. The relationship between pharmacokinetics and pharmacodynamics was assessed using Phoenix version 1.4, with simultaneous assessment of belatacept concentration and CD86RO. The maximal CD86RO by belatacept was calculated by multiplying the quotient of E_{max}/E_0 by 100%, where E_{max} is the maximal decrease in free CD86 receptor level and E_0 is the baseline free CD86 receptor level when drug concentration is 0. A maximum effect (E_{max}) model was used to describe the relationship between the percentage of CD86 receptor occupancy and belatacept concentration.

2.6 | Statistical analysis

Data from nine adolescents would provide 97% confidence that the point estimate of the geometric mean would be within 20% of the true value for C_{max} and within 20% of the true value for $AUC_{0\text{-}INF}$, assuming that C_{max} and $AUC_{0\text{-}INF}$ values were log-normally distributed with coefficients of variation of 27% and 28%, respectively.

3 | RESULTS

3.1 | Patients

Nine adolescent kidney transplant recipients received a single intravenous infusion of belatacept 7.5 mg/kg, and all continued in the study to day 57 and completed the follow-up visit at month 6. Baseline demographics and disease characteristics are summarized in Table 1. The actual mean (standard deviation [SD]) dose of belatacept administered was 7.4 (0.3) mg/kg over a mean (SD) duration of infusion of 29.9 (1.3) minutes.

3.2 | Pharmacokinetics

Pharmacokinetic data were available for all 9 study participants and are summarized in Table 2. The single-dose pharmacokinetics of belatacept in adolescent renal transplant recipients demonstrated low variability in the exposure parameters C_{max} and $AUC_{0\text{-}INF}$, with coefficients of variation of 20% and 25%, respectively. Median T_{max} was 0.73 (range 0.45-2.05) hours, and mean $T_{1/2}$ was 7.2 days after single-dose intravenous infusion. The V_{ss} of belatacept was 5.26 L (0.09 L/kg when adjusted for weight)—consistent with previous observations in adults that the distribution of belatacept is restricted to the extracellular fluid volume.[20] Pharmacokinetic values from adolescent kidney transplant recipients who received a single belatacept intravenous infusion (7.5 mg/kg) were similar to historical values derived from healthy adult volunteers who received a single belatacept intravenous infusion (10 mg/kg) and adult kidney transplant recipients who received multiple intravenous doses of belatacept (5 mg/kg) (Table 2).[24]

3.3 | Pharmacodynamics

Pharmacodynamic data were available for 7 study participants on day 1 (0.5 hours) and day 29, and for 5 study participants on day 57. Mean CD86RO was highest at hour 0.5 of day 1, with mean (SD) CD86RO of 94.7% (4.0) at hour 0.5 of day 1, 78.0% (11.0) at day 29, and 51.5% (43.3) at day 57.

3.4 | Relationship between pharmacokinetics and pharmacodynamics

The highest CD86RO was observed at high belatacept concentrations and decreased as belatacept concentrations declined (Figure 1).

3.5 | Safety

During the protocol-specified, 57-day postdose safety monitoring period, 3 patients reported 7 AEs. Only headache occurred in more than one patient (n = 2). One patient experienced 3 AEs that were considered related to belatacept (asthenia [day 2], vomiting [day 6], upper abdominal pain [day 6]); all 3 events were graded as mild. During the protocol-specified monitoring period through month 6, 4 patients reported 7 serious AEs, all of which were considered by the investigator to be unrelated to belatacept. There were no reports of biopsy-proven acute rejection, graft loss, or death during the protocol-specified 6-month follow-up period. Episodes of renal function deterioration were reported for 3 patients between 191 and 663 days following a single intravenous dose of belatacept. Each was associated with an AE (acute gastroenteritis or acute pyelonephritis/urinary tract infection), and all were considered by the investigator to be unrelated to belatacept.

4 | DISCUSSION

The pharmacokinetic data derived from this phase I study of adolescent renal transplant recipients demonstrate relatively low variability of exposure to intravenously infused belatacept (percentage coefficients of variations for C_{max} and $AUC_{0\text{-}INF}$ were 20% and 25%, respectively). In addition, mean values for $T_{1/2}$, CLT, and V_{ss} in adolescent kidney transplant recipients were comparable to historical values from healthy adult volunteers and adult kidney transplant recipients, indicating consistency across adolescent and adult populations. To identify a dosing regimen that matches the belatacept exposures in adult kidney transplant patients, a population pharmacokinetic model was developed using data from the 9 adolescent patients in this study. Utilizing this model and the pharmacokinetic parameters and variability generated, simulations were performed to assess various belatacept dosing regimens in a virtual population of adolescent kidney transplant recipients. This virtual population was varied based on the distributions of body weight by age and gender derived from the National Health and Nutrition Examination Survey database (unpublished data). The simulations from this modeling work indicate that in adolescent renal allograft recipients, a belatacept dose of 7.5 mg/kg will provide a level of exposure comparable to adult kidney transplant recipients receiving belatacept 5 mg/kg.[25]

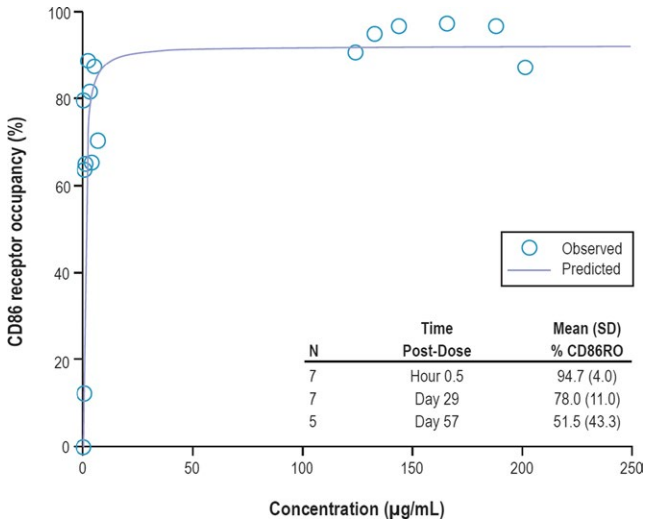

FIGURE 1 Relationship between pharmacokinetics (belatacept concentration) and pharmacodynamics (percentage CD86 receptor occupancy [%CD86RO]) in adolescent kidney transplant recipients. RO, receptor occupancy; SD, standard deviation [Color figure can be viewed at wileyonlinelibrary.com]

Saturation of the CD86 receptor has been shown to correlate with inhibition of the alloimmune response[14] and presumably a reduced risk of acute rejection episodes. High levels of CD86RO were observed in this study (94.7% on day 1). In adults, 94% occupancy of CD86 was observed on day 5.[14,20] Thus, the extent of CD86RO measured in adolescent kidney transplant recipients was comparable to that observed in adult renal transplant recipients. We observed a pharmacologic relationship between pharmacokinetics (drug concentration) and pharmacodynamics (%CD86RO), such that saturation of the CD86 receptor increased with increasing concentrations of belatacept. This relationship was also observed in adults and was best described using an E_{max} model.[20] No new belatacept-related safety events were reported in any patient during the protocol-specified 6-month follow-up period. The data from this phase I study will be used to inform belatacept dose selection in future studies of adolescent kidney transplant recipients.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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