# CLINICAL STUDY REPORT

## Cardiovascular (CV) risk prediction and CV biomarkers in renal transplant recipients treated with belatacept compared to calcineurin inhibitors (CNI)

## Open randomized 12 month study

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| **Protocol codes/references:** | • SMERUD: SMR-2729<br>• BMS: IM103-307<br>• EudraCT no: 2013-001178-20 |
| **Investigational Products:** | • Belatacept (test drug)<br>• Calcineurin inhibitors: tacrolimus, cyclosporine A (comparator) |
| **Indication:** | Renal transplant recipients |
| **Development Phase:** | IV |
| **Study Initiation Date:** | FPFV: 18Sep2014 |
| **Study Completion Date:** | LPLV: 13Sep2018 |
| **Report Completion Date:** | 29 June 2020 (Final version) |
| **Name and Address of Co-ordinating Investigator:** | Professor Bengt Fellström MD, PhD<br>Department of Medical Science, Renal Unit, University Hospital, Uppsala, Sweden |
| **Name and Address of Sponsor:** | University Hospital, MHT, Department of Nephrology, Uppsala, Sweden |
| **Responsible for Sponsor:** | Professor Bengt Fellström MD, PhD<br>Department of Medical Science, Renal Unit, University Hospital, Uppsala, Sweden |
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**GCP STATEMENT**
This study was conducted in compliance with Good Clinical Practices, according to the ICH Harmonised Tripartite Guideline.

# 2 SYNOPSIS

**Title of Study:**
Cardiovascular (CV) risk prediction and CV biomarkers in renal transplant recipients treated with belatacept compared to calcineurin inhibitiors (CNI)

**Co-ordinating Investigator:**
Bengt Fellström MD, PhD
Department of Medical Science, Renal Unit, University Hospital, Uppsala, Sweden

**Study Centre(s):**
- DK01: Aarhus University Hoospital, Aarhus, Denmark
- DK02: Rigshospitalet, Copenhagen, Denmark
- SE01: Uppsala University Hospital, Uppsala, Sweden
- SE02: Karolinska University Hospital, Huddinge, Sweden
- SE03: Karolinska University Hospital, Solna, Sweden
- SE04: Sahlgrenska University Hospital, Gothenburg, Sweden
- SE05: Örebro University Hospital, Örebro, Sweden
- SE06: Central County Hosital of Eskilstuna, Eskilstuna, Sweden:
- NO02: Drammen Hospital, Drammen, Norway
- NO03: A-hus Akershus University Hospital, Nordbyhagen, Norway
- NL01: Leiden University Medical Center, Leiden, The Netherlands

**Publication (reference):**
N/A

| **Studied Period (years):** | **Clinical Phase:** |
|---|---|
| First patient enrolled - last patient completed:<br>18 Sep 2014 – 13 Sep 2018 | Phase IV |

**Objectives:**
The primary objective was to compare belatacept to CNI-based immunosuppression in terms of CV risk estimated by a renal transplant specific CV risk calculator in renal transplant recipients (RTR).

**Secondary:**
To compare belatacept to CNI-based immunosuppression in RTR for
- individual components of CV risk: blood pressure, lipids and eGFR
- differences in vascular function measured by EndoPAT
- changes in biomarkers of bio-ageing (such as peripheral markers (leukocyte telomere length, CDKN2A) and RNA expression profiling in peripheral blood leukocytes)
- changes in biomarkers associated with CV risk factors (such as Proximity Ligation Assay, ELISA, multi-coloured FACS analyses (Dutch sites only), SDF Imaging (Dutch sites only) and miRNA measurements)
- transplant biopsy specimens (histology, RNA expression) targeting chronic allograft nephropathy
- safety variables such as adverse events, mortality, rejection episodes and graft losses

**Methodology:**
This was a 12-months, open-label, multi-center, randomized, controlled study with two parallel groups in maintenance renal transplant patients. At the enrolment visit written informed consent was obtained and baseline data collected to determine each patient's eligibility for study participation. Patients who fulfilled all of the inclusion criteria and none of the exclusion criteria were randomized, stratified by center, in a 1:1 ratio to one of two treatment arms:
- Group A: To continue current CNI-based immunosuppressive regimen.
- Group B: To switch to belatacept treatment

Clinic visits for patients in group B (belatacept) were performed at Day 1 (day of randomization), Days 15, 29, 43, 57 and thereafter once a month until month 12. Previous CNI therapy should be down-titrated during the first 4 weeks. For group A (CNI), clinic visits were fewer, and scheduled for Day 1, week 6, Month 3, 6, 9 and 12.

**Number of Patients (total and for each dosage):**
According to the study protocol, n=110 (n=55 per group) was planned; whereas n=111 (58 in belatacept group (4 withdrawn prior to study intake) vs. 53 in CNI group (2 withdrawn) were randomised. Thus n=54 patients received belatacept, whilst n=51 continued CNI treatment.

**Diagnosis and Criteria for Inclusion:**
1. Signed written informed consent.

2.a Renal transplant recipients of living donor or deceased donor kidney transplant.
2.b Stable renal graft (eGFR > 20 ml/min) with no need for exploratory examination.
2.c Tacrolimus or cyclosporine A (CsA) standard treatment since transplantation.
2.d 3-60 months post-transplantation at randomization.
3.a Men and women, aged 18 to 80 years, both inclusive.
3.b Women of childbearing potential (WOCBP) must be using adequate method of contraception.

**Exclusion Criteria**

1.a Women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the last dose of study drug.
1.b Women who are pregnant or breastfeeding.
1.c Women with a positive pregnancy test.
2. Patient who are Epstein-Barr virus (EBV) IgG negative or have unknown IgG status for EBV.
3.a De novo or recurrent renal disease that, in the Investigator's opinion, could adversely influence the current allograft.
3.b History of vascular or antibody-mediated rejection in the present transplant.
3.c Ongoing serious infections as per Investigator's opinion.
3.d Signs of post-transplant lymphoproliferative disorder.
3.e History of tuberculosis (TB): If the patient has a history of active TB or a history of latent but untreated TB, the patient had to be excluded from the study. If the patient has a history of latent and treated TB, the patient can be included.
3.f Signs of malignancy. Exceptions are BCC/SCC or non-malignant melanoma.
3.g History of malignancy, unless patient has been considered to have fully recovered from malignancy since >1 year, without any signs of relapse.
3.h Life expectancy < 3 years at randomization.
4.a Known hypersensitivity to belatacept.
4.b Previous/ongoing use of rituximab in connection with the current transplant.
5.a Prisoners or patient who are involuntarily incarcerated.
5.b Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness.

**Test Product, Dose, Mode of Administration, Batch No.:**

Belatacept was dosed at 5 mg/kg IV, with previous CNI to be tapered as follows: 100% on day 1, to 70-80% on day 7, to 40-60% on day 15, 20-30% on day 23 and none on day 29 and beyond. It was recommended that patients should take mycophenolate mofetil and corticosteroids as a supplement to belatacept.

**Duration of Treatment:**

Belatacept arm: Last dose was to be given on Month 11, and then a follow-up visit on Month 12.

**Reference Therapy, Dose, Mode of Administration, Batch No.:**

The current standard treatment with calcineurin inhibitors was to be continued for 12 Months

- Calcineurin inhibitor (cyclosporine or tacrolimus)
- +/- Mycophenolic acid (Mycophenolate Mofetil or Enteric-coated-Mycophenolate sodium)
- +/- Corticosteroid

**Criteria for Evaluation:**

Efficacy:

- Calculated CV risk (MACE and mortality) using the method developed by Soveri et al. (2012, 2013) from baseline to 12 months. Variables included for prediction of Major Adverse Cardiac Events (MACE) risk:
    - Age (per 10 years)
    - Previous coronary heart disease
    - Previous smoker
    - Current smoker
    - Creatinine (per 20µmol/L)
    - Diabetes mellitus
    - Low-density lipoprotein (LDL) (per 1mmol/L)
    - Number of transplants

Safety:

Safety assessments were performed by means of AE recording, vital signs, physical examination according to local practice and laboratory evaluations.

**Statistical Methods:**

Due to a skewed distribution, the primary variable (estimated CV risk for MACE) was log-transformed (natural logarithm). The primary endpoint was the comparison of the log of the HR between treatment groups (belatacept vs. CNI-based immunosuppression) at one year. The primary analysis on the primary endpoint was performed in the intention-to-treat population using analysis of covariance (ANCOVA) with treatment as a group variable and baseline log CV risk for MACE and centre as covariates.

All other comparisons on primary and secondary endpoints were based on intention-to-treat or per-protocol comparisons of treatment groups using parametric or non-parametric comparisons, or analysis of covariance (ANCOVA) with correction for baseline variables and/or centre as appropriate.

**SUMMARY – CONCLUSIONS**

**Efficacy Results:**
There was no difference between the treatment groups in terms of change in predicted risk, neither for MACE nor for mortality. For *MACE* the risk (mean±SD) at baseline was estimated to 0.15±0.13 which had in effect not changed at all after 1 year of belatacept treatment: 0.15±0.15. Similar figures for the CNI continuation group was 0.14±0.14 at baseline, changing to 0.15±0.15 after 1 year.

For individual, traditional CVD risk factors, the mean changes of most of them from visit 1 to visit 15 were similar in both treatment groups. However, there were differences in the effects on blood pressures, and for diastolic blood pressure, there was a significant lowering of 5.4 mmHg (95%CI: 1.33, 9.50) after belatacept treatment compared with CNI.

For arterial stiffness, we found no differences in the pulse wave velocity or Augmentation Index, but there was a significant difference on central diastolic pressure from visit 1 to visit 15. Compared with the CNI group, central diastolic pressure in patients of the belatacept group decreased by 6.55 mmHg (95%CI: 1.83, 11.27; p = 0.007) after one year of treatment.

When analysing the population in subgroups related to time since their last transplantation (more than 36 months vs less than 36 months) we found no significant difference between such subgroups, neither on MACE nor on mortality risk outcome.

During the 12 months study period, there were no cardiovascular events and no deaths.

**Safety Results:**
All patients in either study group reported at least one adverse event during the duration of the study. More patients in the belatacept group (53.7% vs 21.6%) reported adverse events that were considered possibly or probably related to the intervention. Likewise, 3 patients in the belatacept group versus 1 patient in the CNI continuation group reported adverse events that led to withdrawal from the study. In terms of Serious Adverse Events, such events were reported by 29.6% of the patients in the belatacept group as compared with 15.7% in the CNI group.

For the most frequent adverse events, patients allocated to the belatacept group appeared to experience more adverse events, although the way of capturing, reporting, categorising/coding and (lack of any) formal adjudication of such events does not allow for robust comparison between the treatment groups in this study. The data do however suggest that there were more any-grade infections contracted in the belatacept group: urinary tract infections (experienced by 35.3% of patients in the belatacept group vs 7.8% in the CNI group), fever (31.5% vs 2.0%), upper respiratory tract infections incl. pneumonia (14.9% vs 9.8%) and coughing (14.8% vs 2.0%). For gastro-intestinal AEs, abdominal discomfort or pain was reported by 18.2% of belatacept patients compared with 2.0% among CNI patients, whereas gastroenteritis was reported by 1.0% vs 5.9%, respectively.

There were no deaths during the course of the study. In the belatacept arm 16 patients (29.6%) experienced a total of 27 SAEs, of which 4 had more than one event. In the CNI arm there were 8 patients (15.7%) with a total of 12 SAEs. Three of these had more than one event. Among those SAEs that were considered related to treatment, there were 4 such events, all in the belatacept group: 2 pneumonia episodes (in the same patient), 1 anemia and 1 case of lung cancer. All SAEs with causality of “related to study drug” were all expected as similar events had been seen in previous clinical experience with study drug.

During the study, a total of 8 acute rejection episodes were suspected and kidney biopsy obtained for further diagnosing; 7 in the belatacept group and 1 in the CNI group. Two of these, both in the belatacept group, were considered severe rejections: 1 led to graft loss (vascular rejection), and the patient had to start with hemodialysis; whereas the other severe

rejection scored Banff grade III, but recovered after anti-rejection treatment. All other suspected rejection episodes recovered upon treatment with corticosteroids or ATG and Solu-Medrol, as per local practices.

For safety laboratory tests, there were no obvious treatment differences for any of the variables, except that there was a slightly higher proportion of patients in the belatacept group with positive finding of protein in urine dipstick tests compared to the CNI group.

For the vital signs (systolic blood pressure, diastolic blood pressure, heart rate and body weight) there were no findings that gave rise to any specific safety concern in any of the two study groups.

**Conclusion:**
Overall, we conclude that 1 year after switching immunosuppressive regimen from CNI (mainly tacrolimus) to belatacept did not result in any detectable effect of cardiovascular risk reduction. Except for a significant improvement in diastolic blood pressures (peripheral and central), we found no effects on any cardiovascular risk factors for kidney transplant recipients. We observed an inferior safety profile of belatacept in terms of adverse events, also serious, and the frequency of acute rejections. One emergent lung cancer as well as one graft loss suggests that further studies on long-term toxicities of belatacept may be warranted.