HIVTR-CCR5

IMPACT OF CCR5 BLOCKADE IN HIV+ KIDNEY TRANSPLANT RECIPIENTS
DAIDS-ES 20730 (HIVTR-CCR5)
Summary of Changes to Study Protocol and Consent Templates
February 28, 2019

PROTOCOL VERSION 4.0		
Location in Redline Version	**Amended Protocol Text Version 4.0**	**Rationale**
Protocol Team Roster (p.1)	Rockville, MD 20852-9829	Updated city/zip code
Protocol Signature Page (p. 2)	New signature page added to protocol	Added a protocol signature page, as indicated in LOA #1, and per DAIDS requirement as the IND-holder for this protocol.
Protocol Synopsis Study Objectives (p. 3) AND 1.2 Objectives 1.2.2 The secondary clinical objectives are to evaluate the: (p. 19)	The secondary clinical objectives are to evaluate the: 1. Impact of CCR5 blockade (maraviroc, MVC) on inflammation in the graft at week 26 and week 52 post-transplant. ~~1.~~2. Impact of CCR5 blockade on long term kidney function in the HIV positive kidney transplant recipient at months 3, 6, 9 and years 1, 2, 3. ~~2.~~3. Impact of the addition of CCR5 blockade to cART and immunosuppression on HIV persistence following kidney transplantation ~~3.~~4. Impact of CCR5 blockade on the incidence and severity of rejection ~~4.~~5. Incidence of HIV infection/HIV nephropathy (HIVAN) in the kidney allograft ~~5.~~6. Safety profiles with use of CCR5 blockade ~~6.~~7. Pharmacokinetics and impact of CCR5 blockade exposure to CNIs	Added a new secondary clinical objective to look at the impact of CCR5 blockade on inflammation in the graft at week 26 and week 52 to address the possibility of not reaching power for the primary objective looking at renal function at 52 weeks post-transplant if 130 subjects are not randomized, and to take advantage of new technologies in the field that were previously unavailable when the protocol was first written. This does not involve any changes to sample collection from subjects. It utilizes samples already outlined in the protocol

Protocol Synopsis Secondary Clinical Endpoints (p. 3-4) AND 3.3 Secondary Clinical Endpoints (p. 27)	1. Inflammation in the graft a. CD45 gene expression (PTPRC) on the FFPE kidney biopsy sample at 26 weeks post-transplant b. CD45 quantitative IHC on the FFPE sample at 26 weeks post-transplant c. Gene expression profiling using the 11-gene tCRM module on FFPE biopsy shaves at 26 weeks and the 11-gene uCRM module on urine cell pellets at 26 weeks and 52 weeks post-transplant.	Added a new secondary clinical endpoint to look at inflammation in the graft, to correlate with the new secondary clinical objective. This capatilizes on new technology not available when the protocol was first written. Does not require any additional samples to be collected.
Protocol Synopsis Treatment Description (p. 6) 6.2.2 Modified Dosage Regimen (p. 38)	Once GFR >= 30, the dose should be returned to the non-renal dosage. If GFR is consistently fluctuating (especially immediately post-transplant), the site investigator may choose when to resume normal dosing of study products based on clinical assessment of stability.	Per Letter of Amendment 1 to protocol version 3.0.
Protocol Synopsis Inclusion Criteria (p. 6) AND 4.2 Inclusion Criteria (p. 30)	4) CD4+ T-cell count >/= 200/µL at any time in the ~~16~~ 26 weeks prior to enrollment. 5) Most recent HIV-1 RNA < 50 copies RNA/mL. Eligibility at the time of enrollment will be determined based on the most recent HIV-1 RNA, not more than ~~16~~ 26 weeks prior to enrollment. Subjects who require a switch in cART regimen to become study eligible must also have an eligible HIV-1 RNA result post change in cART.	Per Letter of Amendment 1 to protocol version 3.0.
Protocol Synopsis Participant Stopping Rules Treatment discontinuation (p. 8) AND 6.5 Premature Discontinuation of Study Drug (p. 39) AND 12.2.1 Treatment Discontinuation (p. 64)	4. Treatment is held or discontinued for clinical reasons for greater than 60 days.	To provide protocol guidelines on when treatment must be discontinued permanently if study drug is held for clinical reasons.

Protocol Synopsis Study Stopping Rules (p. 9 AND 12.4.1 Continuous Monitoring of Specific Events (p. 64)	3. During year 1 of follow-up, site-reported treated acute rejection above 35%	This change was requested by the DSMB on December 19, 2017 and is now being incorporated in the new protocol version 4.0. The DSMB requested the study team to develop stopping rule(s) for acute rejection.
Study Definition Page (p. 17)	HIV Breakthrough: 2 consecutive plasma HIV viral load > 200 copies/mL or one HIV viral load > 1000 copies/mL after a period of virologic control post-transplant. HIV persistent virologic failure: HIV Viral load > 1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment.	This change was requested by the DSMB on December 19, 2017 and is now being incorporated in the new protocol version 4.0. The DSMB requested the study team to develop a protocol definition for virologic failures and to report virologic failures in future DSMB reports.
Description of Study Design (p. 27)	Major study endpoints will be determined for each participant 26 and 52 weeks after transplantation.	Added week 26 since the protocol added two new secondary endpoints using the 26 week kidney biopsy.
Section 6.2.1 Initial dosage Regimen, Decision to use maraviroc 300 mg bid (p. 37)	https://rsc.niaid.nih.gov/sites/default/files/Maraviroc%20%28Selzentry%29%20PI%20dated%20July%202018.pdf ~~http://rsc.tech-res.com/docs/default-source/pi-list-doc/selzentry-pi-mg-ifu_nov-2016.pdf?Status=Master&sfvrsn=0~~	Updated link to the package insert for maraviroc.
6.2.2 Modified Dosage Regimen (p. 38)	**For up to date lists of CYP3A4 inhibitors and inducers, we recommend checking* ***https://~~medicine.iupui.edu/clinpharm/ddis/main-table~~39T~~drug-interactions.medicine.iu.edu/Main-Table.aspx.~~***	Updated web address
7.1 Toxicity Management (p. 40)	The grading system is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, located at the DAIDS RSC Web Site: 39TUhttps://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables~~http39TUhttp://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables~~	Provided new link to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
Section 7.1.9 HIV Persistent Virologic Failure (P. 42)	**7.1.9 HIV Persistent Virologic Failure** HIV persistent virologic failure defined as a HIV viral load > 1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment should also be recorded as an adverse event in the EMMES IDES, regardless of grades.	Added a new section 7.1.9 for "HIV Persistent Virologic Failure". This change was requested by the DSMB on December 19, 2017 and is now

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<tr><td></td><td></td><td>being incorporated in the new protocol version 4.0. The DSMB requested the study team to develop a protocol definition for virologic failures and to report virologic failures in future DSMB reports so these will be reported as an adverse event in the EMMMES data system.</td></tr>
<tr><td>12.4 Study Stopping Rules (p. 64)</td><td>the pharmaceutical supporter(s) or designee</td><td>Correction to reconcile language with the protocol synopsis to accurately indicate entities who can stop the study.</td></tr>
<tr><td>Table 5: Thresholds for Meeting the Stopping Rule for Treated Acute Rejection (p. 66)</td><td>Table 5: Thresholds for Meeting the Stopping Rule for Treated Acute Rejection
<table><tr><th>Number of Subjects with Event (n)</th><th>Number of Subjects Randomized (N)</th><th>Observed Incidence Rate (%)</th><th>Lower 95% Confidence Limit (%)</th></tr><tr><td>7</td><td>10</td><td>70.0</td><td>39.3</td></tr><tr><td>12</td><td>20</td><td>60.0</td><td>39.4</td></tr><tr><td>16</td><td>30</td><td>53.3</td><td>37.0</td></tr><tr><td>20</td><td>40</td><td>50.0</td><td>36.1</td></tr><tr><td>24</td><td>50</td><td>48.0</td><td>35.7</td></tr><tr><td>28</td><td>60</td><td>46.7</td><td>35.6</td></tr><tr><td>32</td><td>70</td><td>45.7</td><td>35.5</td></tr><tr><td>37</td><td>80</td><td>46.3</td><td>36.7</td></tr><tr><td>40</td><td>90</td><td>44.4</td><td>35.6</td></tr><tr><td>44</td><td>100</td><td>44.0</td><td>35.6</td></tr><tr><td>48</td><td>110</td><td>43.6</td><td>35.6</td></tr><tr><td>52</td><td>120</td><td>43.3</td><td>35.7</td></tr><tr><td>5</td><td>130</td><td>42.3</td><td>35.0</td></tr></table></td><td>This change was requested by the DSMB on December 19, 2017 and is now being incorporated in the new protocol version 4.0. The DSMB requested the study team to develop stopping rule(s) for acute rejection. Table 5 provides the thresholds.</td></tr>
<tr><td>13 Safety and Monitoring Plan
13.1 Overview (p. 67)</td><td>In addition, adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per section 13.5 Expedited Adverse Event Reporting to DAIDS) to the sponsor following Version 2.0 of the DAIDS EAE manual which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables~~http://rsc.tech-res.com/clinical-research-~~</td><td>Updated link to the DAIDS EAE manual</td></tr>
</table>

	~~sites/safety-reporting/manual~~.	
13.2.1 Adverse Event (AE) (p. 67)	Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/~~policy/adveventguid.html#Q2T~~sites/default/files/ohrp/policy/adveventguid.pdf~~)~~	Updated web address
13.4.5 Special Adverse Events requiring reporting (p. 70)	• HIV persistent virologic failure defined as an HIV viral load >1000 copies/mL for more than 90 days that is not the result of an investigator/physician approved interruption in antiretroviral treatment.	This change was requested by the DSMB on December 19, 2017 and is now being incorporated in the new protocol version 4.0. The DSMB requested the study team to develop a protocol definition for virologic failures and to report virologic failures in future DSMB reports.
13.5 Expedited Adverse Event Reporting to DAIDS (p. 70)	Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at 39T~~Uhttp://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual~~https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids39T. The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting ~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting~~.	Updated link to the DAIDS EAE form.
16.2 Measures to Minimize Bias (p. 74)	**16.2 Measures to Minimize Bias** Donor type (deceased versus live) is an important confounding factor known to impact graft function, inflammation and survival outcomes post kidney transplantation, and recent approval regarding the use of HIV+ donors, although not observed in the South Africa experience, could yield differences in outcomes compared to use of HIV- donors.	To address the new secondary clinical endpoints looking at inflammation in the 26 week kidney biopsy.

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<td>16.3.2 Supportive Analysis of Primary Efficacy Endpoint (p74)</td>
<td>16.3.2 Supportive Analyses of Primary Efficacy Endpoints
We will conduct 2 sensitivity analyses for the primary efficacy endpoint: (1) include only the completers in the analysis (i.e., exclude all dropouts and treatment discontinuations prior to week 52); (2) impute the worst GFR value observed at that time point in the study or a value of 10 ml/min/1.73m^2, whichever is lower, for deaths with graft function that occur prior to week 52. The sensitivity analyses will be included as additional secondary analyses.</td>
<td>To provide provide more detail that treatment discontinuations prior to week 52 will be excluded from the sensitivity analysis for the primary efficacy endpoint.</td>
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<td>16.3.4 Secondary Clinical Endpoints (pp. 75-76)</td>
<td>Table 65: Summary of Proposed Analyses for Primary and Secondary Clinical Response Variables
<table>
<tr><th>Response type</th><th>Response</th><th>Measurement Scale</th><th>Summary Statistics</th><th>Models to test for treatment effects</th></tr>
<tr><td>Secondary/sensitivity analyses for primary efficacy endpoint</td><td>Mean GFR at week 52, with dropouts deleted removed</td><td>continuous</td><td>Mean and/or geometric mean + 95% CI, and median [IQR]</td><td>Wilcoxon rank-sum test</td></tr>
<tr><td></td><td>Mean GFR at week 52, with a GFR imputation for deaths with function as well. and graft failures</td><td>continuous</td><td>Mean and/or geometric mean + 95% CI, and median [IQR]</td><td>Wilcoxon rank-sum test</td></tr>
<tr><td>Primary Safety Endpoint</td><td>Cumulative incidence of graft loss, toxicities ≥ Grade 3 per the DAIDS toxicity table and/or permanent treatment discontinuation</td><td>continuous</td><td>Kaplan Meier estimates by treatment group</td><td>Logrank test for a treatment group difference</td></tr>
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<td>To address the new p secondary endpoints looking at inflammation in the graft.</td>
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	Inflammation Endpoints	Mean CD45 gene expression count (PTPRC) at week 26	continuous	Mean and/or geometric mean + 95% CI, and median [IQR]	Wilcoxon rank-sum test	
		Mean CD45 quantitative IHC at week 26	continuous	Mean and/or geometric mean + 95% CI, and median [IQR]	Wilcoxon rank-sum test	
		Mean tCRM score at week 26	continuous	Mean and/or geometric mean + 95% CI, and median [IQR]	Wilcoxon rank-sum test	
		Mean uCRM score at weeks 26 and 52	continuous	Mean and/or geometric mean + 95% CI, and median [IQR]	Wilcoxon rank-sum test	
16.5 Sample Size Considerations (p. 77-78)	Based on expected rates of normal, borderline changes and acute cellular rejection in the HIV+ kidney transplant recipients at 26 weeks from previous studies, the expected mean ± SD CD45 gene expression count (PTPRC mRNA in log2 scale) for the control group (Arm 2) was assumed to be 7.9 ± 1.0. Using the same SD for the maraviroc group (Arm 1) and group sample sizes of 30 (assuming enrollment of 60 HIV+ cases in the study with follow-up to week 26 or further), we would achieve about 80% power to detect a difference of 0.8 or more in mean CD45 gene expression count between the two groups (with a significance level of 0.05 using a two-sided Wilcoxon rank-sum test with normal actual distribution assumption). ~~One of the~~Another secondary endpoint of interest is the incidence of treated acute					To address the new secondary endpoint looking at inflammation in the graft.

	rejection at 52 weeks post-transplant. We expect 1-year cumulative incidence of rejection for the placebo group to be around 0.30, based on the rate observed in the HIVTR study. By assuming a loss-to-follow-up rate of 0.13 and proportional hazard rates, a two-sided log rank test achieves at least 80% power at a 0.05 significance level to detect a reduction of 0.21 or more in the rejection rate in the maraviroc group. Sample size calculations were performed using PASS 2008 software.	
17 Identification and Access to Source Data (p. 79)	As part of participating in a NIAID (DAIDS)-supported and/or –sponsored clinical trial, the site investigators and site staff will permit authorized representatives of the sponsor(s), DAIDS, ~~and regulatory agencies~~the FDA, the OHRP, and other local, US, and international regulatory entities, other state and local health authorities, and pharmaceutical or device companies and their commercial partners, and the local Institutional Review Board to examine (and when required by applicable law, to copy) clinical research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.	Per Letter of Amendment 1 to protocol version 3.0.
Schedule of Events, footnote (p 89)	4. Recommend collecting every 12 weeks from primary provider if not done locally since the protocol requires a result no more than ~~16~~ 26 weeks prior to transplant, although not required. Only pre-transplant results used for study eligibility/enrollment into segment B are required.	Per Letter of Amendment 1 to protocol version 3.0.
Schedule of Events, footnote (p 89)	5. Baseline samples must be drawn not more than 13 weeks prior to day of transplant (day 0). Urine is not required in subjects with anuria.	Per Letter of Amendment 1 to protocol version 3.0.
Appendix 4: Reduced Follow-up Schedule for Participants who Prematurely Discontinue Study Treatments (p. 92)	• At time of study drug discontinuation. • If study treatment discontinued due to drug toxicity, should have follow-up safety evaluations as deemed necessary by local investigators. • Every 6 Months Post Discontinuation if available as standard of care.	Clarified in the schedule of events that safety labs should be recorded every 6 months post premature discontinuation of study drug if available as standard of care.

RECIPIENT CONSENT TEMPLATE VERSION 4.0		
Location in Redline Version	**Amended Protocol Text Version 4.0**	**Rationale**
"Can you stop being in the study) (p. 9)	• The study is stopped by the Institution, the IRB (a committee that watches over the safety and rights of research participants), the Sponsor(s), pharmaceutical supporter(s) or designee, or by the Food and Drug Administration (FDA) or other health authorities.	Reconciled language with protocol section 12.4
How will information about you be kept confidential? (p. 10)	• the OHRP, • other local, US and international regulatory entities,	Per Letter of Amendment 1 to protocol version 3.0

DONOR CONSENT TEMPLATE VERSION 4.0		
Location in Redline Version	**Amended Protocol Text Version 4.0**	**Rationale**
How will information about you be kept confidential? (p. 4)	• the OHRP, • other local, US and international regulatory entities,	Per Letter of Amendment 1 to protocol version 3.0