A Prospective, Randomized, Multicenter, Open-Label, Pilot Study to Investigate Medication Adherence & Patient Reported Symptom Occurrence & Interference w/ Daily Life Comparing Envarsus XR® & Immediate Release Tacrolimus in Adult Renal Transplant Recipients (SIMPLE)

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CLINICAL STUDY PROTOCOL

A Prospective, Multicenter, Open-Label, Observational Pilot Study to Investigate Medication Adherence and Patient Reported Symptom Occurrence and Interference with Daily Life Comparing Once-Daily Envarsus XR® and Twice-Daily Immediate Release Tacrolimus in Adult Renal Transplant Recipients (SIMPLE)

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SYNOPSIS

Title: A Prospective, Multicenter, Open-Label, Observational Pilot Study to Investigate Medication Adherence and Patient Reported Symptom Occurrence and Interference with Daily Life Comparing Once-Daily Envarsus XR® and Twice-Daily Immediate Release Tacrolimus in Adult Renal Transplant Recipients (SIMPLE)

Name of Products Studied: Envarsus XR® and tacrolimus (twice daily formulation)

Study Center(s): Multicenter Transplant Alliance – Kidney Centers

Study Design: Prospective and observational

Study Period (years):

Estimated date of first subject enrolled: May 2019
Estimated date last subject to complete the study (12 month follow-up): May 2021

Enrollment Rationale: The Multicenter Transplant Alliance Kidney Consortium collectively transplants more than 1,500 people each year (10% of the total number of kidney transplants in the United States annually). Approximately 60% of these patients will be eligible for this study. We consider a 12 month enrollment time to be a conservative estimate.

Study Background:

Despite improvement in short-term graft outcomes in organ transplant, transplant patients still have to take on complex medication regimens to achieve current results. Adherence to these complex medications is an important problem in light of the potential risk of acute and chronic rejection and the associated burden of increased hospitalization, cost, and diminished quality of life that results from missed doses and poor overall drug taking. Part of the diminished quality of life is also tied to the bothersome symptoms patient feel after transplant. Most patients experience symptoms that relate to either the overall transplant immunosuppression or medication specific side effects. In the BENEFIT and BENEFIT-EXT trials, >60% of patients reported tiredness and lack of energy as an issue [1]. Sleep problems, mood swings, restlessness, anxiety, depression, and concentration and memory difficulties appeared in approximately 50-60% of patients. In addition to these symptoms, >38% patients also reported numerous others side effects that have been strongly associated with calcineurin-inhibitors such as tacrolimus that include dizziness, muscle cramps, trembling hands, tingling in hands and feet, and headache.

Study Rationale:

We hypothesize that the use of once-daily Envarsus XR® leads to a decrease in some transplant- and tacrolimus-related adverse symptoms and potentially leads to improvement in quality of life and medication adherence when compared to twice-daily tacrolimus. In order to assess this hypothesis, a prospective, multi-center, open-label, observational, pilot study to investigate medication adherence and patient reported symptom occurrence and interference with daily life comparing once-daily Envarsus XR® and twice-daily immediate release tacrolimus in adult renal transplant recipients (SIMPLE) is being proposed.

The primary objective of this study is to compare tacrolimus formulations (Envarsus XR® versus twice a day tacrolimus) with the hypothesis that Envarsus XR® improves transplant- and tacrolimus- associated symptoms when compared to a twice a day tacrolimus regimen. In addition, as part of this study,

adherence, additional patient reported outcomes (PROs), patient satisfaction, and health related quality of life (HRQoL) will be measured. There is currently a limited amount of data available describing the side effects/symptoms that are most important (i.e. occur most often and are poorly tolerated) to transplant patients taking tacrolimus immunosuppression. These symptoms/side effects could clearly impact medication adherence. Furthermore, no data currently exists as to how these symptoms/side effects relate to adherence, quality of life, and patient satisfaction. This study will assess the correlation between adherence, PROs, patient satisfaction, and health related quality of life (HRQoL). It is also possible that if the increase in adherence is large enough; there could be a sufficient change in long-term patient risk for antibody mediated injury and subsequent decrease in hospitalization and cost.

Study Design Rationale:

Patients will be enrolled into the study within the first 30 days post-transplant. Treatment will not be determined by this protocol, and there is no intervention. The treatment decision will be made by each patient's transplant care team, independent of the study.

For the primary objective, comparison of calcineurin inhibitor related symptoms, a standard two-group design will be used to compare treatment groups. These groups will also be compared for transplant-related symptoms, health-related quality of life, adverse events, patient satisfaction, adherence, and graft function.

Products Studied:

- Tacrolimus (twice daily immediate release (IR) oral formulation) or
- Envarsus XR® (a once daily extended-release oral tacrolimus formulation).

Envarsus XR® is an FDA approved medication and is indicated for the prevention of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants.

Primary Objective: The primary objective of the study is to determine if patients taking Envarsus XR® report fewer of the side effects that are commonly associated with calcineurin-inhibitor therapy than subjects taking tacrolimus immediate release twice daily.

Primary Endpoint: Difference in mean calcineurin inhibitor-related symptoms severity score at 12 months post- kidney transplantation in the Envarsus XR® group vs immediate-release, twice-daily tacrolimus group.

The CIRS is a questionnaire that assesses five symptoms (from PRO-CTCAE) that have been shown to be associated with calcineurin inhibitors. These symptoms include trembling hands, muscle cramps, muscle weakness, swollen gums, and increased hair growth. Each symptom is based on symptom severity in the last 7 days scaled from 0 (none) – 4 (very severe). The cumulative score ranges from 0-20. Based on internal data, we expect a mean CIRS score in the control group (immediate release tacrolimus) to be around 3.8 +/- 3.6 and hypothesize a 30% reduction in the Envarsus XR® group. This reduction is equivalent to a 1 point difference on the 0-20 scale or a standardized effect size (mean difference / standard deviation) of 0.29.

Secondary Endpoints:

1. Reduction in the population mean of any one of the five individual CIRS item including: trembling hands, muscle cramps, muscle weakness, swollen gums, and increased hair growth between the two treatment groups at 12 months
2. Total percent of patients in each treatment group with a severe or very severe score (3 or 4) on any CIRS item 12 months.
3. Total percent of patient with a reduction in a CIRS item score from a severe or very severe score (3 to 4) to a mild to moderate (1 or 2) score from 4 to 12 months.
4. Total percent of patients with a reduction in any single CIRS item by 1 point or greater from 4 to 12 months.
5. Difference in mean transplant-related symptoms (TRS) score between treatments at 12 months post-transplant.

   The TRS is a multi-item questionnaire capturing 15 symptoms (from PRO-CTCAE) that have been shown to be associated with transplant and general health-related quality of life improvement. These symptoms include change in taste, constipation, diarrhea, swelling in arms or legs, palpitations, dry skin, darkening of skin, blurry vision, headache, insomnia, anxiety, sadness, discouraged, increase in appetite, and fatigue. Each symptom is based on symptom severity in the last 7 days and scaled from 0 (none) – 4 (very severe). Some symptoms also have added questions pertaining to frequency and/or interference with daily activities. The sum of the severity score ranges from 0-60. The improvement in transplant symptoms will be measured by the difference between treatment groups in the mean TRS score.

6. Improvement in health-related quality of life (HRQoL), as measured by the PROMIS-29 health profile, will be compared between groups at 12 months post-kidney transplantation. The PROMIS-29 produces scores for depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity. Physical and mental health summary scores will also be calculated.

   Standardized effect sizes (mean difference / standard deviation) for differences in HRQOL (PROMIS-29) scores will be calculated to compare twice daily immediate release tacrolimus oral to Envarsus XR®.

7. Improvement in individual symptoms captured in the TRS questionnaire will be compared.

   The standardized effect size (mean difference / standard deviation) on TRS score will be calculated and compared between treatments. Individual TRS items will be classified as improved, worsened, unchanged and compared between treatments.

8. Improvement in overall tolerability or patient bother due to side effects, measured by item GP5 (“I am bothered by side effects of treatment”) from the FACT-G.

   Patients’ GP5 responses will be classified as improved, worsened, or unchanged and compared between treatments.

9. Improvement in mean taking adherence, defined as the percent of prescribed doses taken each day (as measured by electronic monitoring), rates between groups.

The assumption is that the mean taking adherence will 75% for the twice-daily immediate release tacrolimus and 90% for the Envarsus XR® (and standard deviations of 38% and 30%, respectively).

10. Improvements in patient medication satisfaction as assessed by Transplant Satisfaction Questionnaire for Medication (question 14) at 12 months post-transplant.

    Responses to the Transplant Satisfaction Questionnaire for Medication (question 14) will be compared between twice daily immediate release tacrolimus oral and Envarsus XR®.

11. Correlation between de novo DSA (dnDSA, collected as part of standard of care in MTA-K) and degree of taking and timing adherence.

    Proportion of patients at different adherence thresholds (>70% vs ≤70%, >80% vs ≤80%, >90% vs ≤90%, and 100% vs below 100%) of taking and timing adherences between 4 months and 12 months post-transplant will be correlated with the presence or absence of dnDSA by 12 months post-transplant.

12. Safety and tolerability of Envarsus XR, as measured by incidence of adverse events (AEs), changes in clinical safety labs, and hospitalizations.

    Difference between treatment groups in safety parameters including the incidence of adverse events (AEs), changes in clinical safety labs, and hospitalizations.

Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patient is an adult (18 years of age or older).
- Treatment with Envarsus XR® or immediate-release, twice-daily tacrolimus has been indicated by patient's transplant care team.
- Patient is a recipient of a deceased or living donor kidney transplant.
- Patient is able to comply with study procedures for the entire length of the study.
- Patient has been informed about the study survey and has signed an informed consent form.

Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- Patient is unable or unwilling to complete study patient reported outcome questionnaires.
- Patient is currently receiving azathioprine
- Patient is currently receiving an mTOR inhibitor (sirolimus, everolimus)
- Patient is currently receiving belatacept
- Patient has received investigational immunosuppression 1 month prior to transplant or post-transplant
- Patient is in a setting where a professional care taker is responsible for dispensing subject's medication.

Study Duration

Following enrollment, each patient will be maintained in the study for 12 months.

Number of Patients

A total of 240 patients will be enrolled for the study. The enrollment will occur over a 12 month period. The average monthly enrollment will be 20 patients per month.

Study Design and Methodology

This is a prospective, multi-center, open-label, observational study comparing transplant-specific patient reported outcomes and medication adherence between Envarsus XR® and immediate release tacrolimus medication in adult renal transplant recipients. The study will enroll 240 patients and survey these patients at baseline (first 30 days post-transplant), at 4 months, and at 12 months post-transplantation.

Study Method

- Adverse Events: During the entire study period, each patient will be monitored at least monthly for trough blood levels, and undergo safety and adverse event assessments as per standard of care. The patient will be followed as appropriate to maintain the tacrolimus trough drug levels of 8 to 10 ng/ml in the first month post-transplant and 6 to 8 ng/ml thereafter.
    - AEs and SAEs will be assigned based on Common Toxicity Criteria for Adverse Events (CTCAE) definitions and tabulated as incidence rates per tacrolimus formulation.
    - Regular monitoring and summaries of hematology, blood chemistries, and urine results.
    - Regular monitoring of vital signs, physical condition, and body weight measurements.
    - Clinically significant infections (confirmed by culture, biopsy, genomic, radiologic, or serologic findings) that requires hospitalization or active anti-microbial treatment will be tabulated as incidence rates per tacrolimus formulation.
    - Cytomegalovirus (CMV), BK Virus, and Epstein-Barr disease will be tabulated as incidence rates per tacrolimus formulation.
    - dnDSA and rejection events are collected as part of standard of care in MTA-K
    - Estimated glomerular filtration rate (eGFR) will be estimated using the MRDR formula.

- Patient-Reported Measures: Patients will complete surveys on their own unless they are unable to. Surveys will be administered electronically so that data will be recorded in the study's database immediately and securely. The following patient reported outcomes measures will be assessed at both study visits.
    - HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
    - Symptoms: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (15 items) – items from PRO-CTCAE or in PRO-CTCAE format.
    - Symptoms/Tolerability: FACT- G (GP5) – Single item bothersome assessment (1 question).

- Adherence/Medication Satisfaction Measures: The following adherence tools/measures will be assessed at each study visit throughout the study for those patients capable of using an adherence measurement via a digital capture system:
    - The PROMIS Self-Efficacy for Managing Medication and Treatment (26 questions) – (study visit 1 only).
    - The Transplant Satisfaction Questionnaire for Medication – question 14.

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PROTOCOL

1. STUDY BACKGROUND

Despite improvement in short-term graft outcomes in organ transplant, transplant patients still have to take on complex medication regimens to achieve current results. Adherence to these complex medications is an important problem in light of the potential risk of acute and chronic rejection and the associated burden of increased hospitalization, cost, and diminished quality of life that results from missed doses and poor overall drug taking. Part of the diminished quality of life is also tied to the bothersome symptoms patient feel after transplant. Most patients experience symptoms that relate to either the overall transplant immunosuppression or medication specific side effects. In the BENEFIT and BENEFIT-EXT trials, >60% of patients reported tiredness and lack of energy as an issue[1]. Sleep problems, mood swings, restlessness, anxiety, depression, and concentration and memory difficulties appeared in approximately 50-60% of patients. In addition to these symptoms, >38% patients also reported numerous others side effects that have been strongly associated with calcineurin-inhibitors such as tacrolimus that include dizziness, muscle cramps, trembling hands, tingling in hands and feet, and headache.

2. STUDY RATIONALE

We hypothesize that the use of once-daily Envarsus XR® decreases some transplant- and tacrolimus-related adverse symptoms and potentially leads to improvement in quality of life and medication adherence when compared to twice-daily tacrolimus. In order to assess this hypothesis, a prospective, multi-center, observational, open-label, pilot study to investigate medication adherence and patient reported symptom occurrence and interference with daily life comparing once-daily Envarsus XR® and twice-daily immediate release tacrolimus in adult renal transplant recipients (SIMPLE) is being proposed.

The primary objective of this study is to compare tacrolimus formulations (Envarsus XR® versus twice a day tacrolimus) with the hypothesis that Envarsus XR® improves transplant- and tacrolimus- associated symptoms when compared to a twice a day tacrolimus regimen. In addition, as part of this study, adherence, additional patient reported outcomes (PROs), patient satisfaction, and health related quality of life (HRQoL) will also be measured. There is currently a limited amount of data available describing the side effects/symptoms that are most important (i.e. occur most often and are poorly tolerated) to transplant patients taking tacrolimus immunosuppression. These symptoms/side effects could clearly impact medication adherence. Furthermore, no data currently exists as to how these symptoms/side effects relate to adherence, quality of life, and patient satisfaction. This study will assess the correlation between adherence, PROs, patient satisfaction, and health related quality of life (HRQoL). It is also possible that if the increase in adherence is large enough; there could be a sufficient change in long-term patient risk for antibody mediated injury and subsequent decrease in hospitalization and cost.

3. OBJECTIVE AND ENDPOINTS

Primary Objective: The primary objective of the study is to determine if treatment with Envarsus XR® reduces a group of side effects that are commonly associated with calcineurin-inhibitor therapy.

Overall Hypothesis: Treatment with Envarsus XR® leads to improved total *calcineurin inhibitor-related symptom (CIRS) score* at 1 year after kidney transplantation compared to immediate-release, twice-daily tacrolimus.

Primary Endpoint: Difference in mean calcineurin inhibitor-related symptoms severity score at 12 months post- kidney transplantation in Envarsus XR® group vs Control (immediate-release, twice-daily tacrolimus) group.

The CIRS is a questionnaire that assesses five symptoms (from PRO-CTCAE) that have been shown to be associated with calcineurin inhibitors. These symptoms include trembling hands, muscle cramps, muscle weakness, swollen gums, and increased hair growth. Each symptom is based on symptom severity in the last 7 days scaled from 0 (none) – 4 (very severe). The cumulative score ranges from 0-20. Based on internal data, we expect a mean CIRS score in the control group (immediate release tacrolimus) to be around 3.8 +/- 3.6 and hypothesize a 30% reduction in the Envarsus XR® group. This reduction is equivalent to a 1 point difference on the 0-20 scale or a standardized effect size (mean difference / standard deviation) of 0.29.

Secondary Endpoints:

1. Reduction in the population mean of any one of the five individual CIRS item including: trembling hands, muscle cramps, muscle weakness, swollen gums, and increased hair growth between the two treatment groups at 12 months

2. Total percent of patients in each treatment group with a severe or very severe score (3 or 4) on any CIRS item 12 months.

3. Difference in mean transplant-related symptoms (TRS) score between treatments at 12 months post-transplant.

   The TRS is a multi-item questionnaire capturing 15 symptoms (from PRO-CTCAE) that have been shown to be associated with transplant and general health-related quality of life improvement. These symptoms include change in taste, constipation, diarrhea, swelling in arms or legs, palpitations, dry skin, darkening of skin, blurry vision, headache, insomnia, anxiety, sadness, discouraged, increase in appetite, and fatigue. Each symptom is based on symptom severity in the last 7 days and scaled from 0 (none) – 4 (very severe). Some symptoms also have added questions pertaining to frequency and/or interference with daily activities. The sum of the severity score ranges from 0-60. The improvement in transplant symptoms will be measured by the difference between treatment groups in the mean TRS score.

4. Improvement in health-related quality of life (HRQoL), as measured by the PROMIS-29 health profile, will be compared between groups at 12 months post-kidney transplantation. The PROMIS-29 produces scores for depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity. Physical and mental health summary scores will also be calculated.

   Standardized effect sizes (mean difference / standard deviation) for differences in HRQOL (PROMIS-29) scores will be calculated to compare twice daily immediate release tacrolimus oral to Envarsus XR®.

5. Improvement in individual symptoms captured in the TRS questionnaire will be compared.

   The standardized effect size (mean difference / standard deviation) on TRS score will be calculated and compared between treatments. Individual TRS items will be classified as improved, worsened, unchanged and compared between treatments.

6. Improvement in overall tolerability or patient bother due to side effects, measured by item GP5 ("I am bothered by side effects of treatment") from the FACT-G.

   Patients' GP5 responses will be classified as improved, worsened, or unchanged and compared between treatments.

7. Improvement in mean taking adherence, defined as the percent of prescribed doses taken each day (as measured by electronic monitoring), rates between groups.

   The assumption is that the mean taking adherence will 75% for the twice-daily immediate release tacrolimus and 90% for the Envarsus XR® (and standard deviations of 38% and 30%, respectively).

8. Improved in patient medication satisfaction as assessed by Transplant Satisfaction Questionnaire for Medication (question 14) at 12 months post-transplant.

   Responses to the Transplant Satisfaction Questionnaire for Medication (question 14) will be compared between twice daily immediate release tacrolimus oral and Envarsus XR®.

9. Correlation between de novo DSA (dnDSA, collected as part of standard of care in MTA-K) and degree of taking and timing adherence.

   Proportion of patients at different adherence thresholds (>70% vs ≤70%, >80% vs ≤80%, >90% vs ≤90%, and 100% vs below 100%) of taking and timing adherences over 12 months post-transplant will be correlated with the presence or absence of dnDSA by 12 months post-transplant.

10. Safety and tolerability of Envarsus XR, as measured by incidence of adverse events (AEs), changes in clinical safety labs, and hospitalizations.

    Difference between treatment groups in safety parameters including the incidence of adverse events (AEs), changes in clinical safety labs, and hospitalizations.

4. PATIENT POPULATION

General Consideration:
The study population is composed of de novo solitary kidney transplant recipients who meet inclusion and exclusion criteria and have not been subject to investigational treatments.

Enrollment Rationale: The Multicenter Transplant Alliance Kidney Consortium collectively transplants more than 1,500 people each year (10% of the total number of kidney transplants in the United States annually). Approximately 60% of these patients will be eligible for this study. We consider a 12 month enrollment time to be a conservative estimate.

Screening Failure: Subjects who do not meet the eligibility criteria as outlined below during the screening phase of the study will be considered screening failures.

Inclusion criteria:

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patient is an adult (18 years of age or older).
- Treatment with Envarsus XR® or immediate-release, twice-daily tacrolimus has been indicated by patient's transplant care team.
- Patient is a recipient of a deceased or living donor kidney transplant.
- Patient is able to comply with study procedures for the entire length of the study.
- Patient has been informed about the study survey and has signed an informed consent form.

Exclusion criteria:

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- Patient is unable or unwilling to complete study patient reported outcome questionnaires.
- Patient is currently receiving azathioprine
- Patient is currently receiving an mTOR inhibitor (sirolimus, everolimus)
- Patient is currently receiving an belatacept
- Patient has received investigational immunosuppression 1 month prior to transplant or post-transplant
- Patient is in a setting where a professional care taker is responsible for dispensing subject's medication.

5. STUDY DURATION

Following enrollment, each patient will be maintained in the study for 12 months.

Estimated date of first subject enrolled: May 2019
Estimated date last subject to complete the study (12 month follow-up): May 2021

6. NUMBER OF PATIENTS

A total of 240 patients will be enrolled for the study. The enrollment will occur over a 12 month period.

7. STUDY DESIGN

Study Center(s): Multicenter Transplant Alliance – Kidney Centers

Study Design: This is a prospective, multi-center, observational, open-label, study comparing transplant-specific patient reported outcomes and medication adherence between Envarsus XR® and immediate release tacrolimus medication in adult renal transplant recipients. The study will enroll 240 patients and survey these same 240 patients at three time points during the study.

Study Design Rationale:

Patients will be enrolled into the study within the first 30 days post-transplant. Treatment will not be determined by this study, and there is no intervention. The treatment decision will be made by each patient's transplant care team, independent of the study.
For the primary objective, comparison of calcineurin inhibitor related symptoms, a standard two-group design will be used to compare treatment groups. These groups will also be compared for transplant-related symptoms, health-related quality of life, adverse events, patient satisfaction, adherence, dnDSA, and graft function.

8. TREATMENT ASSIGNMENT

This is an observational study, and as such, treatment will not be assigned, and there is no intervention. The treatment decision will be made by each patient's transplant care team, independent of the study.

9. STUDY METHODS AND PROCEDURES

General: Transplant recipients will be cared for according to the site's standard of care (SOC) protocols employed for post-transplant follow-up. The investigator at the site will be directly responsible for supervising the care of these recipients during the length of the study.

Products Studied:

- Tacrolimus (twice daily immediate release (IR) oral formulation) or
- Envarsus XR® (a once daily extended-release oral tacrolimus formulation).

Envarsus XR® is an FDA approved medication and is indicated for the prevention of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants

Medication Safety and Efficacy: Renal function, occurrence of biopsy proven acute rejection, development of dnDSA, and occurrence of adverse events will be assessed throughout the duration of the study as collected as part of standard of care or as part of study. Please see Criteria for Evaluation (Section 17) for detailed description of monitoring techniques.

Patient-Reported Measures:

- Patients will complete surveys on their own unless they are unable to. Surveys will be administered on tablets so that data will be recorded in the study's database immediately and securely. The following patient reported outcome measures will be assessed at both study visits.
    - HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
    - Symptoms: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (15 items) – items from PRO-CTCAE or in PRO-CTCAE format.
    - Symptoms/Tolerability: FACT- G (GP5) – Single item bothersome assessment (1 question).
    - The PROMIS Self-Efficacy for Managing Medication and Treatment (26 questions).

- The Transplant Satisfaction Questionnaire for Medication – question 14.

10. DEVIATION FROM TREATMENT REGIMEN

If deviation occurs from treatment, patient will continue study. Patient reported outcome measures will be completed as scheduled and samples will be taken as scheduled. Reason(s) for deviation will be recorded.

Criteria for Study Termination

The investigator can discontinue the study participant at any time for any reason, including development of severe adverse events, uncontrolled infection, or other clinical/administrative reasons. Allograft loss and death will be cause for automatic withdrawal from the study. If a patient unable to continue the study for any reason, an early termination visit is necessary to complete the study. If the patient needs be started on immunosuppression that is listed in the exclusion criteria of this study, an early termination visit is necessary to complete the study.

11. STUDY DRUG STORAGE, DISPENSING, AND ACCOUNTABILITY

Patient will receive open label drug through their pharmacy of choice.

12. CONCOMITANT MEDICATIONS

Subjects are required to take immunosuppressive medication to maintain allograft function. The patients will be on the following immunosuppression medications in addition to tacrolimus at the time of study entry per the inclusion criteria:

- *Mycophenolate Mofetil (CellCept®) or Mycophenolate Sodium, Enteric Coated (Myfortic®) (MMF) or generic equivalent formulations.* Target MMF doses will be between 1000 – 3000 mg/day in divided doses or the enteric coated equivalent delivered by mouth twice daily. The MMF dosage will be decreased or discontinued in the presence of adverse events as clinically warranted. Dose reduction or discontinuation will be documented. Adverse events that may warrant dosage modifications of MMF include but are not limited to gastrointestinal (gastritis, diarrhea, nausea, vomiting, dyspepsia) or hematological (leukopenia, thrombocytopenia, anemia or neutropenia). MMF may be resumed at the full dose or at a reduced dose after resolution of symptoms or the patient may receive an alternate adjunctive immunosuppression per the investigator's discretion as long as they are not those listed in the exclusion criteria.

- *Corticosteroids.* Low dose once daily oral prednisone (5-10 mg) may be administered per each site's standard of practice. Doses may be increased at the discretion of the investigator. This most commonly occurs after pulse steroid treatment for rejection.

- *Belatacept, mTOR inhibitors, azathioprine, and investigational immunosuppression* will not be allowed in this study. Patient who are deemed to require one of these medications should be removed from the study and undergo an early termination visit to complete the study.

13. TREATMENT COMPLIANCE

All subjects in the study will be adequately informed on the specific tacrolimus formulations the patients will receive throughout the study and the importance of compliance to the study protocol.

14. TIMING OF VISITS

Visit 1: Baseline/Screening
To be collected within the first 30 days post-transplant

- Informed consent
- Demographics
- Medical history
- Complete physical exam including vital signs, height, and weight
- Determination of eligibility based on inclusion/exclusion criteria
- Hematology panel
- Electrolytes including creatinine and eGFR
- Urinalysis
- Baseline Surveys:
    - HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
    - PRO-CTCAE: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (14 items)
    - FACT – G (GP5): Single item bothersome assessment (1 question)
    - The PROMIS Self-Efficacy for Managing Medication and Treatment (26 questions) – (study visit 1 only).

Visit 2: Day 120 ± 30 days
All subjects will complete the following prior to morning tacrolimus administration:

- Vital signs, height, and weight
- Hematology panel
- Electrolytes including creatinine and eGFRTacrolimus trough
- Surveys including:
    - HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
    - PRO-CTCAE: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (14 items)
    - FACT – G (GP5): Single item bothersome assessment (1 question)

Visit 3: Day 365 ± 45 days (end of study visit)
All subjects will complete the following prior to morning tacrolimus administration:

- Vital signs, height, and weight
- Hematology panel
- Electrolytes including creatinine and eGFRTacrolimus trough
- Surveys including:

- HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
- PRO-CTCAE: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (14 items)
- FACT – G (GP5): Single item bothersome assessment (1 question)
- The Transplant Satisfaction Questionnaire for Medication – question 14.

SCHEDULE OF EVENTS

	Baseline (Within the first 30 days post-transplant)	**4 Months Post-Transplant**	**12 Months Post-Transplant (End of Study)**
		(± 30 days)	**(± 45 days)**
STUDY VISIT NUMBER	**1**	**2**	**3**
Test/Procedures/Data Collection			
Informed Consent	X		
Review of Inclusion/Exclusion Criteria	X		
Demographics	X		
Medical History	X		
Adverse Event Assessment		X	X
Physical exam including vital signs and weight	X	X	X
Safety labs[1]	X	X	X
Tacolimus trough levels		X	X
Data collection from medical records pertaining to infection, immunosuppression, and graft function	X	X	X
Patient Reported Outcome Assessments			
PROMIS – Self-Efficacy for Managing Medications and Treatments v1.0 (26 items)	X		
PROMIS-29 Profile 2.1 (29 items)	X	X	X
Calcineurin Inhibitor Related Sysmptoms (CIRS) - (5 PRO-CTCAE items)	X	X	X
Transplant Specific(14 PRO-CTCAE items)	X	X	X
Patient Satisfaction: Treatment Satisfaction Questionnaire for Medication-Question 14 (1 question)			X
FACT-G (GP5)	X	X	X

1 Safety Labs (CBC with differential, Electrolytes including creatinine and eGFR)

15. DATA COLLECTION

Data will be collected at each of the MTAK sites and entered into REDCap. REDCap is a secure web application for building and managing online surveys and databases. REDcap is secure and will be managed by Mayo Clinic Rochester. REDcap is 21 CFR Part 11, FISMA, and HIPPA compliant and hosted on Mayo Clinic's secure servers.

Demographic information: Sex, race/ethnicity, transplant characteristics, and age will be collected.

Medical History: Data to be collected will include medical history and medications, pathologic and laboratory data that are in the pre and post-transplant record.

16. CRITERIA FOR EVALUATION

Safety

- AEs and SAEs will be assigned by Common Terminology Criteria for Adverse Events (CTCAE) terms and tabulated as incidence rates per tacrolimus formulation.
- Hematology parameters, blood chemistries, and urine results will be monitored regularly as part of the participating centers' standard of care.
- Vital signs, physical condition, and body weight measurements will be monitored regularly.
- Clinically significant infections (confirmed by culture, biopsy, genomic, or serologic findings) that requires hospitalization or active anti-microbial treatment will be tabulated as incidence rates per tacrolimus formulation.
- Cytomegalovirus (CMV), BK Virus, and Epstein-Barr disease will be tabulated as incidence rates per tacrolimus formulation.

Patient Reported Measures and Outcomes

- Patients will complete surveys on their own unless they are unable to. Surveys will be administered on tablets so that data will be recorded in the study's database immediately and securely. The following patient reported outcomes measures will be assessed:
    - HRQoL: PROMIS -29 profile (29 questions) measuring depression, anxiety, fatigue, pain interference, sleep disturbance, physical function, participation in social roles, and pain intensity
    - Symptoms: Calcineurin-inhibitor related symptoms (5 items) and the Transplant related symptoms (14 items) – items from PRO-CTCAE or in PRO-CTCAE format.
    - Symptoms/Tolerability: FACT- G (GP5) – Single item bothersome assessment (1 question).

- Adherence/Medication Satisfaction Measures: The following adherence tools/measures will be assessed at each study visit throughout the study for those patients capable of using an adherence measurement via a digital capture system:
    - The PROMIS Self-Efficacy for Managing Medication and Treatment (26 questions) – (study visit 1 only).
    - The Transplant Satisfaction Questionnaire for Medication – question 14.

17. STATISTICAL ANALYSES

Interpretation of scores and score differences in patient-reported measures can be a difficult task since the scales lack the clinical meaning that is inherent in measures of survival, serum concentrations, or anthropometric values. To aid in interpretation of these scores, differences are often standardized by dividing by the standard deviation in the sample to calculate an effect size. There are general guidelines for small, moderate, and large effects on this standardized scale that can be applied to any outcome measure. A standardized effect size (mean difference / standard deviation) less than 0.20 is considered clinically insignificant in the field of patient-reported outcomes research, while effect sizes of 0.30 - 0.40 are generally considered to be minimally important to moderate in magnitude.

For the CIRS, which had a standard deviation of 3.6 in a sample of patients receiving cyclosporine, an effect size of 0.30 corresponds to a difference of 1 point on the 0-20 scale. In the control group, we expect a mean CIRS score similar to or higher than that seen in a sample of patients receiving cyclosporine (3.8 +/- 3.6). A 1 point reduction in the Envarsus XR® group would be equivalent to a 30% reduction in calcineurin inhibitor-related symptoms.

A total of 240 patients will be enrolled. Estimating 15% study dropout provides 204 patients with complete data at the study endpoint, which will allow us to detect effect sizes of 0.28 or larger for the difference between treatment arms with a 2-sided 0.05 level of significance and 80% power in for individual patient reported outcome measure items. This sample size is also appropriately powered to compare adherence rates between groups. Based on assumptions of 75% and 90% mean adherence, respectively, in the 2 groups (and standard deviations of 38% and 30%, respectively), a sample size of 110 per group will yield 90% power to obtain a significant difference between the 2 groups, using a 2-sample t test at a 2-sided 0.05 level of significance.

For analyses of the CIRS, TRS, and PROMIS-29 scores, we will first calculate change within individuals from enrollment to 12 months. Analysis of covariance (ANCOVA) will be used to compare change between treatments, adjusted for baseline score. The ANCOVA model-estimated mean difference between treatments will be divided by the pooled baseline standard deviation to calculate effect size measures to aid in interpretation. Medication adherence and change in eGFR will be compared between groups using similar models.

For analyses of individual transplant-related symptoms and side effect bother (GP5), within-patient change on each item will be classified as improved, worsened or unchanged and compared between treatments using chi-square tests for ordinal data. Medication satisfaction responses at 12 months will be compared between treatments using an ordinal chi-square test.

18. RISK/BENEFIT ASSESSMENT

Risk Assessment

There is minimal risk or discomfort expected from participation in this research.

Potential Benefits

There is no direct benefit from participation in this study. Other transplant recipients may benefit in the future from what we learn in this study.

19. ADVERSE EVENT MANAGEMENT

Definition of an Adverse Event: An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- A new condition detected or diagnosed after study therapy administration even though it may have been present prior to the start of the study.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a patient's previous treatment regimen).

An AE does not include:

- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure is an AE.
- Social or convenience hospital admissions where an untoward medical occurrence did not occur.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the patient's condition.

Definition of a Serious Adverse Event: A Serious Adverse Event SAE) is any adverse experience occurring at any dose that:

1. Results in death
2. Is life-threatening (at risk of death at the time of the event)
3. Requires in inpatient hospitalization or prolongation of existing hospitalization

   NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.

4. Results in disability/incapacity
   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect.
   Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events:
Abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE ("Definition of an Adverse Event") or SAE ("Definition of a Serious Adverse Event"). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study but do not worsen, will not be reported as AEs or SAEs. The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant.

Recording of Adverse Events and Serious Adverse Events
The Investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The Investigator will then record all relevant information regarding an AE/SAE into the electronic data system. It is not accept able for the Investigator to send photocopies of the patients' medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when the medical monitor (an independent physician who is not participating in the clinical study), requests copies of medical records for certain cases. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the medical monitor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs and symptoms.

Intensity of Adverse Events and Serious Adverse Events
The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE and SAE will be assigned to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in "Definition of an SAE."

Relationship of Adverse Events and Serious Adverse Events to Study Therapy
The Investigator is obligated to assess the relationship between study therapy and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the study therapy was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study therapy will be considered and investigated. The Investigator will also consult the Clinical Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

All AE/SAE that occur during the course of the clinical study will be evaluated and a determination of relatedness to the investigational product will be defined according to one of the following categories:

- Definite - The AE/SAE is clearly related to the investigational product.
- Probable - The AE/SAE is likely related to the investigational product.
- Possible - The AE/SAE may be related to the investigational product.
- Unlikely - The AE/SAE is doubtfully related to the investigational product.
- Unrelated- The AE/SAE is clearly NOT related to the investigational product.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality.

Follow-Up of Adverse Events and Serious Adverse Events
After the initial AE/SAE report, the Investigator is required to proactively follow each patient and provide further information to the medical monitor on the patient's condition. All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

Adverse events and SAEs will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a patient experiencing a critical adverse event is treated successfully and stabilized even though they may continue to experience lingering sequelae that may never resolve), until the patient is lost to follow-up, or until it is agreed that further follow-up of the event is not warranted (e.g. non-serious, study therapy unrelated, mild or moderate adverse events ongoing at a patient's final study visit). If a patient dies during participation in the study or during a recognized follow-up period, the medical monitor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded by modifying the AE forms in the electronic data system

Timeframes for Submitting SAE Reports

Once an Investigator becomes aware that an SAE has occurred in a study patient, he/she will record the information in the electronic data record within 48 hours. Any fatal or life-threatening event must be reported within 24 hours. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before recording the event in the data system and completing as much information known at the time of the submission.

20. PROTOCOL MODIFICATION

All protocol amendments must be signed and dated by the investigator and should not be implemented without prior IRB approval.

21. REGULATORY AND ETHICAL CONSIDERATION

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

Ethics Approval

It is the Investigators' responsibility to ensure that, prior to initiating this study, this protocol is reviewed and approved by the appropriate local IRB. The IRB must also review and approve the site's informed consent form (ICF), other written information provided to the patient, and all advertisements that may be used for patient recruitment. If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB reviews and approves these amended documents. An IRB approval of the amended protocol and/or ICF must be obtained in writing before implementation of the procedures and before new patients are consented to participate in the study using the amended version of the ICF.

Informed Consent

Before being admitted to the study, all patients must consent in writing to participate. An ICF will be given to each patient which will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the patient. The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws. The Investigator or designee will review the study with each patient. The review will include the nature, scope, procedures, and possible consequences of the patient's participation in the study. The ICF and review will be in a form understandable to the patient. The Investigator or designee and the patient must both sign and date the ICF after review and before the patient can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or his/her designee will emphasize to the patient that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of health benefits to which the patient is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. The site must use the amended consent form for all new patients and, if directed by the IRB, repeat the consent process with the amended ICF for any ongoing patients.

Confidentiality

Patient's names will remain confidential and will not be included in the database. Only patient number, patient initials, and birth date will be recorded in the electronic database system. If the patient name appears on any other document collected (e.g., hospital discharge summary), the name will be obliterated before the document is transmitted. All study survey documents will be stored in a secure location such as locked office and password protected computer. The patients will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected. Patients will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA. All participants in the study will provide written authorization to disclose private health information either as a part of the written ICF or as a separate authorization form. The authorization will contain all required elements and will contain a waiver of patient access to study-related private health information until the conclusion of the clinical study. The authorization will remain valid and in full force and effect until the expiration of 5 years after the research program is discontinued. Individual patient medical information obtained during this study is confidential and its disclosure to third parties is strictly prohibited. In addition, medical information obtained during this study may be provided to the patient's personal physician or to other appropriate medical personnel when required in connection with the patient's continued health and welfare. The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

22. REFERENCE

1. Dobbels F, Wong S, Min Y, Sam J, Kalsekar A. Beneficial effect of belatacept on health-related quality of life and perceived side effects: results from the BENEFIT and BENEFIT-EXT trials. *Transplantation.* 2014;98(9):960-968.

23. INVESTIGATOR AGREEMENT

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study.

_____

Investigator's Signature* Date

_____

Name of Investigator (Typed or Printed)

_____

_____

_____

Institution, Address*

_____

Phone Number*

_____

Sponsor's Responsible Signature Date

_____

Name of Medical Officer (Typed or Printed)

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s)

24. APPENDIX 1: CALCINEURIN INHIBITOR RELATED SYMPTOM (CIRS) QUESTIONNAIRE

CALCINEURIN INHIBITOR RELATED SYMPTOMS

Version 1.0
English

As individuals go through treatment for their transplant they sometimes experience different symptoms and side effects. For each question, please check or mark an "x" in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your TREMBLING HANDS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did TREMBLING HANDS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, what was the SEVERITY of your MUSCLE CRAMPS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your MUSCLE CRAMPS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, what was the SEVERITY of your MUSCLE WEAKNESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your MUSCLE WEAKNESSS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, what was the SEVERITY of your SWOLLEN GUMS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, what was the SEVERITY of your INCREASED HAIR GROWTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

25. APPENDIX 2: TRANSPLANT RELATED SYMPTOM (CIRS) QUESTIONNAIRE

TRANSPLANT RELATED SYMPTOMS

Version 1.0
English

As individuals go through treatment for their transplant they sometimes experience different symptoms and side effects. For each question, please check or mark an "x" in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of your INCREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INCREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

5.	In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

TRANSPLANT RELATED SYMPTOMS

Version 1.0
English

6.	In the last 7 days, how OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

8.	In the last 7 days, did you have any UNUSUAL DARKENING OF THE SKIN?	
	○ Yes	○ No

9.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

TRANSPLANT RELATED SYMPTOMS

11.

In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

12.

In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.

In the last 7 days, how OFTEN did you feel ANXIETY?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.

In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.

In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

26. APPENDIX 3: PROMIS-29

PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11 1	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21 2	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23 3	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53 4	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01 5	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40 6	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41 7	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53 8	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04 9	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06 10	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29 11	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41 12	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7 13	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 14	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41 15	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 16	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109 17	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116 18	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20 19	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44 20	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS 21	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS 22	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS 23	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS 24	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9 25	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22 26	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31 27	How much did pain interfere with your ability to participate in social activities?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34 28	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Pain Intensity

In the past 7 days…

Global07 29	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

27. APPENDIX 4: FACT-G (GP5) & TRANSPLANT SATISFACTION QUESTIONNAIRE FOR MEDICATION – QUESTION 14.

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment	0	1	2	3	4

Treatment Satisfaction Questionnaire for Medication

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

28. APPENDIX 5: PROMIS SELF-EFFICACY FOR MANAGING MEDICATION AND TREATMENT

PROMIS Item Bank v1.0 - Self-Efficacy for Managing Medications and Treatments

Self-Efficacy for Managing Medications and Treatments

Please respond to each question or statement by marking one box per row.

	CURRENT level of confidence…	I am not at all confident	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
SEMMT001	I can take several medications on different schedules	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT002	I can remember to take my medication as prescribed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT003	I know when and how to take my medications	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT004	I can fit my medication schedule into my daily routine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT005	I can follow directions when my doctor changes my medications	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT006	I can manage my medication without help.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT007	I can get help when I am not sure how to take my medicine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT008	I can remember to refill my prescriptions before they run out	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT009	I can remember to take my medications when there is no one to remind me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT010	I can list my medications, including the doses and schedule	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT011	I can actively participate in decisions about my treatment	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT012	I can find information to learn more about my treatment	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT013	I can use my own judgment regarding treatment alternatives (including not having treatment)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT014	I can work with my doctor to choose the treatment that seems right for me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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	CURRENT level of confidence…	I am not at all confident	I am a little confident	I am somewhat confident	I am quite confident	I am very confident
SEMMT015	I know what to do when my medication refill looks different than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT016	I know what to do if I forget to take my medication(s)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT017	I can use technology to help me manage my medication and treatments (for example: to get information, avoid side-effects, schedule reminders)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT018	I can continue my treatment when traveling	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT019	I can take my medication when I am working or away from home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT020	I can take my medicine even if it causes mild side effects	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT021	I understand the difference between my symptoms and medication side effects	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT022	I can continue my treatment when I am not feeling well	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT023	I can take my medication when there is a change in my usual day (unexpected things happen)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT024	I can figure out what treatment I need when my symptoms change	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT026	I can follow a full treatment plan (including medication, diet, physical activity)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SEMMT027	I can travel to my local pharmacy to fill my prescriptions	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5