BMT CTN #0801: A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease

Version 6.0 dated July 2012

Outline of Analysis Plan for 6-month response

This SAP is specifically to analyze data at 6 months post randomization.

Time Line:

The database will be locked on January 15 2015. The data report will be completed and distributed to the protocol team by XX 2015.

Participants to Include

There are total of 161 participants enrolled in BMT CTN #0801. Ten of them were enrolled in ECP study who will not be included in the analyses. Twelve of them were deemed to be ineligible per Endpoint Review Committee (ERC) who will not be included in the analyses either.

Outline

Title Page with report date

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Protocol Synopsis

BMT CTN protocol # 0801 titled **"A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease"** is a combined Phase II/III, randomized, open label, multicenter, prospective comparative study. The primary objective of the study for the phase II component is to estimate the proportion of subjects with complete or partial responses after 6 months of therapy using an intention to treat analysis. Second objectives include: the percent reduction in the average daily dose of prednisone (or equivalent) by 6 and 12 months; the cumulative incidence of treatment failure at 1 year; the prevalence of active symptomatic chronic GVHD at 1 and 2 years; the cumulative incidence of discontinuation of all systemic immunosuppressive therapy at 1 and 2 years; the overall and cancer progression-free survival at 1 and 2 years; the candidate serum biomarkers of chronic GVHD at baseline, 2 months and 6 months; and, to evaluate NIH and other new response instruments in chronic GVHD.

Data Summary: Brief summary for the report being provided

Exhibit 0801-R1: Demographics and Baseline characteristics.

Demographics and baseline characteristics will be described by median and range for continuous variables and by frequencies and percents for categorical variables. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, risk status, donor age, and donor gender, conditioning intensity, donor type, peripheral blood versus marrow, time from transplant to enrollment, time from start of immunosuppressive therapy to

enrollment, percent of participants with high risk cGVHD, GVHD prophylaxis, maximum grade of acute GVHD and acute GVHD treatment, chronic GVHD organ involvement at baseline.

Exhibit 0801-R2: Treatment Success by treatment arms
The proportion of treatment success at 6 months will be summarized by treatment arms

Exhibit 0801-R3: Overall survival by treatment arms
Kaplan-Meier plot and estimator at 6-month post randomization with a 95% confidence interval will be provided. Survival curves will be compared across treatment using the Log-rank Test.

Exhibit 0801-R4: Progression-free survival by treatment arms
Kaplan-Meier plot and estimator at 6-month post randomization with 95% confidence interval will be provided. Survival curves will be compared across treatment using the Log-rank Test. Estimator at 6-month post randomization with a 95% confidence interval will be provided.

Exhibit 0801-R5: Primary cause of death

Exhibit 0801-R6: Cumulative incidence of relapse
Time to relapse will be estimated using cumulative incidence function with death prior to relapse as the competing risk. Cumulative incidence curves will be compared between groups using Gray's Test. Estimator at 6-month post randomization with a 95% confidence interval will be provided.

Exhibit 0801-R7: Use of secondary immunosuppressive therapy
The proportion of participants who received secondary therapy at month 6 will be computed and compared using a Chi-Square test.

Exhibit 0801-R8: Prednisone sparing

The median percent reduction in average daily dose among survivors will be estimated for each treatment with a 95% confidence interval by 6 months post randomization. These will be compared between treatments using the Kruskal-Wallis Test.

Exhibit 0801-R9: Patient-Reported Symptomatic Chronic GVHD Symptoms

The proportion of participants with symptomatic chronic GVHD will be estimated for each treatment with a 95% confidence interval at 6 months. These proportions will be compared between groups using the Chi-Square Test**.**

Exhibit 0801-R10: NIH Consensus Clinically Relevant Adjudicated CR and PR Rates
The proportion of participants experiencing a CR or PR according to the NIH consensus definition will be estimated for each treatment with a 95% confidence interval. Agreement between the NIH consensus guidelines CR/PR evaluation and the CR/PR outcome based on the primary endpoint will be computed using the Kappa statistic.

Exhibit 0801-R11: Health Quality of life by treatment arm
The HQL assessments will be performed at baseline, months two and six after randomization. Pairwise t-tests at each time point will be used as a descriptive analysis.

Exhibit 0801-R12: Unexpected grades 3-5 adverse events by treatment arm

Exhibit 0801-R13: Core and protocol-specific toxicities (Grade>2) by visit

Exhibit 0801-R14: Infections
Table of infections incidence per patient, severity, organisms. Only infections within 6 months post randomization will be summarized.

Exhibit 0801-R15: Significant protocol deviations

BMT CTN #0801 2-year Statistical Analysis Plan (SAP)

Drafted by Jessica Zhu on 5/4/2016
Reviewed by Maggie Wu
Finalized after the team call on 5/20/2016

Protocol:

BMT CTN #0801: A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease

Protocol Synopsis:

BMT CTN protocol # 0801 titled "A Phase II/III Randomized, Multicenter Trial Comparing Sirolimus plus Prednisone and Sirolimus/Calcineurin Inhibitor plus Prednisone for the Treatment of Chronic Graft-versus-Host Disease" is a combined Phase II/III, randomized, open label, multicenter, prospective comparative study. The primary objective in Phase II is to estimate the proportion of participants with complete or partial responses after 6 months of therapy in both study arms using an intention to treat analysis. The Phase II study will proceed into the Phase III component of the protocol if the experimental arm is observed to have a higher response rate. The primary objective in Phase III is to compare the proportion of participants with complete resolution of all manifestations at 24 months after starting therapy in both study arms. Secondary objectives include evaluating prednisone dose reduction, treatment failure, overall survival and progression-free survival. The target sample size was 100 participants for Phase II (50/arm) with an additional 200 (100 per arm) participants added for Phase III.

Study Status and Publication Plan:

The study opened to accrual in April 2010. Due to inadequate accrual from Extracorporeal Photophoresis (ECP) centers, the study made major changes to the original design and the accrual from ECP centers was closed in September 2011. Ten participants who were enrolled in the ECP study are excluded from the primary analyses. On the November 7, 2013 DSMB meeting, DSMB suggested to suspend phase III accrual due to reaching the futility endpoint at 6 month. As the result of the meeting, the accrual for the study was closed in December 2013. At Phase II of the study, 50 participants from each treatment arm were evaluated for Complete Response/Partial Response (CR/PR) at 6 months post randomization and the results did not provide evidence to proceed to Phase III. As a result, all enrolled patients continue to be followed for the Phase III outcomes.

The BMT 0801 Endpoint Review Committee was formed and reviewed the 6-month data of the study in 2014. The 6-month analysis report was provided to the protocol team and the results were presented at the 2016 BMT Tandem meeting. In preparation for the manuscript, the protocol team agreed to include the 2-year data into the manuscript. Additional ERC process including data QC of the 2-year data is being initiated and will be completed in the summer of 2016. Data freeze will be done after the completion of 2-year

data and analysis will be conducted within 2 weeks of the data freeze. Note that since the baseline and 6-month data have already been provided in the 6-month analysis report, this SAP is limited to the 2-year analysis and all data at (and before) 6 month are not included in this SAP.

Participants to Include:

A total of 161 participants were enrolled in BMT CTN #0801. Ten of them were enrolled in ECP study that will not be included in the analyses. Out of the 151, 13 participants were deemed to be ineligible per previous ERC adjudication. These 13 participants were excluded from the 6-month analysis report and will also be excluded from the 2-year analysis report to be consistent.

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Details of Exhibits

Exhibit 0801-R1: Treatment Success by Treatment Arm

The proportion of treatment success at 2 years post randomization will be summarized by treatment arms. Treatment success is defined as a participant who is alive and achieved a complete response without receiving secondary systemic immunosuppressive therapy and had no subsequent progression added through 2 years after randomization.

(A) Treatment Success by Treatment Arm

	Control (N=)	Siro/Pred (N=)	Chi-Square p-value
Treatment Success[1]			
Yes[1]			
Off Immunosuppressive Therapy			
On Immunosuppressive Therapy			
No[2]			
VGPR			
Yes			
Off Immunosuppressive Therapy			
On Immunosuppressive Therapy			
No			
Death			
Yes			
No			
Relapse of Disease			
Yes			
No			
Secondary Therapy			

Yes			
No			

Notes: [1] Treatment success is defined as a study participant who is alive and who achieved a complete response and the participant did not receive secondary systemic immunosuppressive therapy and had no subsequent progression or additional secondary immunosuppressive therapy added through 2 years after randomization.
[2] Events in treatment failure (death or relapse or secondary therapy) are not mutually exclusive.

Exhibit 0801-R2: Overall survival by Treatment Arm
Kaplan-Meier plot and estimator at 2-year post randomization with 95% confidence interval will be provided. Patients are considered a failure if they die from any cause. The time to this event is the time from randomization to death, loss to follow up or end of study whichever comes first. Survival curves will be compared across treatment using the Log-rank test.

Exhibit 0801-R3: Progression-free Survival by Treatment Arm
Kaplan-Meier plot and estimator at 2-year post randomization with 95% confidence interval will be provided. Progression of a cancer is defined as any clinical evidence of progression or relapsed disease, or any therapy used to treat persistent, progressive, or relapsed disease including withdrawal of immunosuppressive therapy or cellular lymphocyte infusion (DLI). The time to this event is the time from randomization to death, loss to follow up, disease progression or end of study whichever comes first. Survival curves will be compared across treatment using the Log-rank test.

Exhibit 0801-R4: Primary Cause of Death
Primary causes of deaths for patients expired within 2 years post randomization will be described by treatment arm.

	Control		**Siro/Pred**		**Total**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Recurrence/Persistence						
Acute GVHD						
Chronic GVHD						

	Control		Siro/Pred		Total	
	N	Percent	N	Percent	N	Percent
Organ Failure						
Interstitial Pneumonia						
Vascular						
Infection						
Bacterial Infection						
Fungal Infection						
Viral Infection						
Other						
Total						
Total Enrolled						
Total Death						

Exhibit 0801-R5: Cumulative Incidence of Relapse
Time to relapse of disease will be estimated using cumulative incidence function with death prior to relapse as the competing risk. Cumulative incidence curves will be compared between groups using Gray's Test. Estimator at 2-year post randomization with a 95% confidence interval will be provided.

Exhibit 0801-R6: Use of Secondary Immunosuppressive Therapy
Secondary immunosuppressive therapy is defined as the time any secondary systemic therapy is added to control manifestations of chronic GVHD. Cumulative incidence curves will be compared between groups using Gray's Test.

Exhibit 0801-R7: Discontinuation of all Systemic Immunosuppressive Therapy

The cumulative incidence of discontinuation of all systemic immunosuppressive therapy will be estimated by treatment with a 95% confidence interval at 2 years. Death will be considered as competing risk and Gray's test will be used to compare cumulative incidence curves between groups.

Exhibit 0801-R8: Prednisone Sparing

The summary statistics of prednisone dose at baseline and at 2 years and the dose reduction at Year 2 from baseline will be described for each treatment with a 95% confidence interval. Since laboratory assessment form is only collected up to 1 year post-randomization, patient's weight at Year 1 will be used to calculate average daily dose of prednisone at 2 years. These will be compared between treatments using the Kruskal-Wallis Test. The box plots of prednisone dose at baseline, Day 30, Day 60, Day 90, Month 6, Month 12, and Month 24 will be provided.

	Treatment Arm											
	Control						Siro/Pred					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Steroids Dose at baseline, mg/kg												
Steroids Dose at 24 Month, mg/kg												
Dose Reduction, mg/kg												

Exhibit 0801-R9: Serum Creatinine

The summary statistics of serum creatinine at baseline and at 2 years and the mean change from baseline to 2-year will be described for each treatment with a 95% confidence interval. These will be compared between treatments using the Kruskal-Wallis Test.

	Treatment Arm											
	Control						Siro/Pred					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Creatinine at baseline, mg/dL												
Creatinine at 24 Month, mg/dL												

	Treatment Arm											
	Control						Siro/Pred					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Change from baseline to 24 months, mg/dL												

Exhibit 0801-R10: Patient-Reported Symptomatic Chronic GVHD Symptoms

The severity of symptomatic chronic GVHD at baseline and at 2 years will be estimated for each treatment based on patient-reported survey and NIH Consensus guidelines. The proportions of participants will be compared between groups using the Chi-Square Test.

	Treatment Arm		
	Control (N=) N (%)	Siro/Pred (N=) N (%)	p-value
At baseline			
None			
Mild			
Moderate			
Severe			
Not Evaluable*			
At 2 years			
None			
Mild			
Moderate			
Severe			
Died within 2 years			
Not Evaluable*			

Note: *Patients either did not complete the forms or the field.

Exhibit 0801-R11: NIH Consensus Clinically Relevant Adjudicated CR and PR Rates

The proportion of participants experiencing a CR or PR at 2 year post-randomization according to the NIH consensus definition will be estimated for each treatment with a 95% confidence interval. Agreement between the NIH consensus guidelines CR/PR evaluation and the CR/PR outcome based on the primary endpoint will be computed using the Kappa statistic.

A) Provider-Reported Chronic GVHD Severity

	Treatment Arm		
	Control (N=) N (%)	Siro/Pred (N=) N (%)	p-value
At Baseline			
None			
Mild			
Moderate			
Severe			
Not Evaluable**			
At 2 Years*			
None			
Mild			
Moderate			
Severe			
Died within 2 years			
Not Evaluable**			

Notes: *If the severity was adjudicated by ERC, the adjudicated results are used.
**Patients either did not complete the forms or the field.

B) Calculated NIH Consensus Chronic GVHD Severity

	Treatment Arm		
	Control (N=) N (%)	Siro/Pred (N=) N (%)	p-value
At baseline			
None			
Mild			
Moderate			
Severe			
Not Evaluable*			
At 2 years			
None			
Mild			
Moderate			
Severe			
Died within 2 years			
Not Evaluable*			

Note: *Sites either did not complete the forms or the fields.

Exhibit 0801-R12: Health Quality of Life (FACT-BMT) by Treatment Arm

The HQL assessments from FACT-BMT instruments will be performed at baseline, 1 and 2 years after randomization. FACT-BMT scores of four subscales for completed interviews – physical well-being, social/family well-being, emotional well-being and functional well-being will be provided. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the

FACT-BMT data. Exhibits (B) to (I) graphically illustrates results of interviewed subjects within mean ± 1 SE at each time point will be presented graphically.

(A) Summary Table

		Treatment Arm								
		Control			Siro/Pred			Total		
		N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr
Physical Well-Being (7 Items)	**Baseline**									
	12 Months									
	24 Months									
Social / Family Well-Being (7 Items)	**Baseline**									
	12 Months									
	24 Months									
Emotional Well-Being (6 Items)	**Baseline**									
	12 Months									
	24 Months									
Functional Well-Being (7 Items)	**Baseline**									
	12 Months									
	24 Months									
FACT BMT Concerns (10 Items)	**Baseline**									
	12 Months									
	24 Months									
FACT-G Total (27 Items)	**Baseline**									
	12 Months									
	24 Months									
FACT-BMT Total (37 Items)	**Baseline**									
	12 Months									
	24 Months									

		Treatment Arm						Total		
		Control			Siro/Pred					
		N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr
FACT-BMT Trial Outcome Index (24 Items)	Baseline									
	12 Months									
	24 Months									

(B) FACT-Physical Well-Being (7 items)

(C) FACT-Social/Family Well-Being (7 items)

(D) FACT-Emotional Well-Being (6 items)

(E) FACT-Functional Well-Being (7 items)

(F) FACT-G Total Score (27 items)

(G) FACT-BMT Symptoms (10 items)

(H) FACT-Total Score (37 items)

(I) FACT-Trial Outcome Index (24 items)

Exhibit 0801-R13: Health Quality of Life (SF-36) by Treatment Arm

The HQL assessments from SF-36 will be summarized at baseline, 1 and 2 years after randomization. The SF-36 is an instrument that assesses the health quality of life with eight components. Each domain is positively scored, indicating that higher scores are associated with positive outcome. SF-36 physical and components will be summarized graphically in exhibits (B) and (C) at baseline, 1 and 2 years post-randomization. Pairwise t-tests at each time point will be used as a descriptive analysis.

(A) Summary Table

		Treatment Arm								
		Control			Siro/Pred			Total		
		N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr
SF-36 PAIN INDEX (0-100)	Baseline									
	12 Months									
	24 Months									
SF-36 GENERAL HEALTH PERCEPTIONS (0-100)	Baseline									
	12 Months									
	24 Months									
RAW SF-36 HEALTH TRANSITION ITEM	Baseline									
	12 Months									
	24 Months									
SF-36 MENTAL HEALTH INDEX (0-100)	Baseline									
	12 Months									
	24 Months									
SF-36 PHYSICAL FUNCTIONING (0-100)	Baseline									
	12 Months									
	24 Months									
SF-36 ROLE-EMOTIONAL (0-100)	Baseline									
	12 Months									
	24 Months									

(B) Physical Component Scale

(C) Mental Component Scale

Exhibit 0801-R14: Biomarkers by Treatment Arm

T regulatory cell numbers and BAFF to B cell ratios will be summarized at baseline, 2 month, and 6 month. The comparison will be conducted within groups using the Paired T Test, or between groups using the Two Sample T-Test. The biomarker data will be also correlated with CP+PR status at 6 months using logistic regression.

(A) Summary of T Regulatory Cell Numbers

	Treatment Arm											
	Control						Siro/Pred					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
T regulatory cell numbers at baseline												
T regulatory cell numbers at 2 months												
T regulatory cell numbers at 6 months												

(B) Summary of BAFF to B Cell Ratios

	Treatment Arm											
	Control						Siro/Pred					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
BAFF to B Cell Ratios at baseline												
BAFF to B Cell Ratios at 2 months												
BAFF to B Cell Ratios at 6 months												

(C) Correlation between Biomarker Data and CP+PR at 6 Months

Exhibit 0801-R15: Unexpected Grades 3-5 Adverse Events by Treatment Arm
Details for unexpected grade 3 to 5 adverse events reported within 2 years post randomization will be listed.

Exhibit 0801-R16: Core and Protocol-specific Toxicities (Grade>2) by Treatment Arm

Use bar graphs and scatter plot to show toxicities frequencies within 12 months post randomization for overall from transplant through 12 months. The maximum core and protocol-specific toxicities across time points through Year 1 for each arm will be summarized graphically.

Exhibit 0801-R17: Infections

Table to summarize infections incidence per patient, severity, organisms. Only infections within 2 year post randomization will be summarized.

	Control (N=)	Siro/Pred (N=)	All (N=)
# Patients randomized			
# Patients with Infections			
# Patients with Infection Reports **1** **2** **3** **4** **5** **6-10** **>=10**			
Total Infection Events			
Maximum Severity **None** **Moderate** **Severe** **Life-Threatening/Fatal**			
Infection Type **Bacterial** **Viral** **Fungal**			

	Control (N=)	Siro/Pred (N=)	All (N=)
Protozoal			
Other			