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Amendment No. 01

Description: Pooled analyses of elderly subjects (aged ≥ 65 years) who participated in select belimumab clinical trials.

Subject: SLE, systemic lupus erythematosus, belimumab, aggregated analysis, pooled analysis, SRI, flares, SELENA SLEDAI, BILAG, steroid use, safety, vasculitis, lupus nephritis.

Amendment Author:

PPD
Biostatistics

Date 01-MAY-2019

Approved via email by:

PPD
Biostatistics

Date 01-MAY-2019

PPD
M.D.
Clinical Development

Date 01-MAY-2019

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
ANCA	Anti-neutrophil cytoplasmic antibodies
ANCOVA	Analysis of covariance
Anti-dsDNA	Anti-double-stranded DNA
Anti-MPO	Anti- myeloperoxidase
BILAG	British Isles Lupus Assessment Group of SLE Clinics
DMID	Division of Microbiology & Infectious Diseases
DNA	deoxyribonucleic acid
DO/TF=NR	Dropout/Treatment Failure = Non-Responder
HGS	Human Genome Sciences, Inc.
Ig	Immunoglobulin
ITT	Intention to treat
IV	Intravenous
LOCF	last observation carried forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
PBO	Placebo
PGA	Physician's Global Disease Assessment
PR3	Proteinase 3
PSAP	Program Safety Analysis Plan
RAP	Reporting and Analysis Plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDAP	Summary Document Analysis Plan
SELENA	Safety of Estrogen in Lupus National Assessment
SFI	SLE Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SOC	System Organ Class
SRI	SLE Responder Index

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SDAP AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (Global)	01-MAY-2019
Original	*09-MAR-2016*

Amendment 01: 01-MAY-2019

Overall Rationale for the Amendment: To update the SDAP regarding Analysis 4.

Section # and Name	Description of Change	Brief Rationale
1, Introduction	Update regarding C1113/BEL115467 study. Update pooling when number of elderly subjects in a study is <3.	Clarification regarding data presentation for this study. Allow flexibility on a case by case basis.
Table 1	Updates made to Trials for Analysis	Provide current status of trials
Table 2	Update made to Planned Analyses of Efficacy Data	Provide plan based on actual enrollment
Table 3	Updates made to Planned Analyses of Safety Data	Provide plan based on actual enrollment
Table 4	Updates made to Estimated Subject Numbers for Pooled SLE Studies	Add “Elderly” to table title for clarification. Provide plan based on actual enrollment
4.2, Aggregated Analysis	Added text regarding overall displays (elderly + non-elderly combined) for the SLE continuation trials.	Provide all subjects data for comparative purposes
6, General Considerations for Data Analyses	Added text regarding elderly + non-elderly displays	Provide all subjects data for comparative purposes
Table 5	Updates made to Stratification Factors for Pooled SLE Studies	Correction made for a missing BEL113750 stratification factor

1. INTRODUCTION

This analysis plan documents planned analyses for the pooled data from the elderly (age ≥ 65 years) subpopulation treated in the following belimumab studies: LBSL02 (Phase 2, IV), BEL110751/HGS1006-C1056 (BLISS-76, Phase 3, IV), BEL110752/HGS1006-C1057 (BLISS-52, Phase 3, IV), BEL113750 (NE Asia, IV), BEL112341/HGS1006-C1115 (BLISS-SC, Subcutaneous Phase 3), and BEL115471/HGS1006-C1112 (EMBRACE, Black Race, IV).

LBSL02 efficacy data cannot be pooled with other SLE studies due to differences in the medication rules, efficacy endpoints, and differences in gating techniques for the biomarker assays.

Elderly data from the safety study BEL115467/HGS1006-C1113 (BASE, Safety, IV) will be reported in a side-by-side presentation. Relevant collected safety data from the prospective observational registry (BEL116543/ HGS1006-C1124, SABLE) will be reported for subjects ≥65 with each analysis set once the study has been enrolling for at least 1 year. This data will not be pooled with any other study given it is an observational study. Additionally, safety and efficacy data from elderly subjects in the belimumab vasculitis study (BEL115466/HGS1006-C1100, BREVAS) and the lupus nephritis study (BEL114054/HGS1006-C1121, BLISS-LN) will be described separately from the pooled SLE studies. Safety data from the three open-label, single arm continuation studies (BEL112626/LBSL99, BEL112233/HGS1006-C1066, and BEL112234/HGS1006-C1074) will be pooled and reported first as interim report and after all of the three continuation studies have completed.

The analyses will be conducted sequentially as ongoing and new studies complete until all the studies identified for inclusion have completed. In general, in order to pool subjects for analysis, there should be at least three elderly subjects in the study, but this may be evaluated on a case-by-case basis. These analyses will be performed to provide descriptive information on safety and efficacy of belimumab in elderly SLE subjects. For analyses performed in subgroups and in individual studies, the results should be interpreted with caution due to small sample sizes.

2. OBJECTIVE

The primary objective is to evaluate the safety of belimumab treatment on elderly subjects with SLE. A secondary objective is to evaluate the efficacy of belimumab treatment in elderly SLE subjects. Additionally, the safety and efficacy of subjects with vasculitis and lupus nephritis will be assessed.

3. STUDIES TO BE INCLUDED

The analysis will be based on the pooled data from elderly SLE subjects who were treated in one of the following belimumab studies. Data marked with an * will not form part of the pooled SLE data analysis but will be summarised separately.

Table 1 Trials for Analysis

Trial	Safety	Efficacy	N randomized (N elderly) *Ns shown in italics are planned (estimates[1])*	Status/ Completion Date
SLE studies				
LBSL02	Yes	Yes*	449 (8)	Complete
C1056 *BLISS-76*	Yes	Yes	819 (16)	Complete
C1057 *BLISS-52*	Yes	Yes	865 (11)	Complete
BEL113750 *North East Asia Phase 3*	Yes^	Yes^	705 (1)	Complete
C1115 *Subcutaneous Phase 3*	Yes	Yes	839 (19)	Complete
C1112 *EMBRACE Study*	Yes	Yes	503 (8)	Complete
C1113 *BASE safety trial*	Yes*	No	4018 (156)	Complete
Open-label Continuation SLE studies				
LBSL99	Yes *	No†	298 (8)	Complete
C1066			268 (8)	Complete
C1074			736 (9)	Complete
Observational SLE studies				
SABLE *Safety Registry*	Yes *	No	*3000[3] (210)*	Aug 2025
Non-SLE studies				
C1100 *Vasculitis*	Yes*	Yes *	100 (26)	Complete
Other SLE studies				
C1121 *Lupus Nephritis*	Yes*	Yes *	428 (2)[2]	Apr 2020

[1]For SLE studies and lupus nephritis: it is estimated 1.6% of the randomized subject population would be elderly; this percentage was derived from the pooled LBSL02, C1056, and C1057 studies. For vasculitis it is estimated that as many as 30% to 50% of the subjects in this study will be elderly. For SABLE, it is estimated 7% of the final enrolled population would be elderly based on actual enrolment as of August 2017.

[2]Enrolment is completed. The number of randomized and elderly subjects is based on actual not planned enrolment. However, the final number may change during final data review/cleaning processes.

[3]Subjects are not randomized in this observational registry.

* = data that would not form part of pooled SLE analyses but would be summarised separately.

^=For report 2 data was not pooled due to only 1 elderly subject in the study, but as BEL113750 all subjects data will be pooled for comparative purposes, the elderly subject will be pooled for report 4.

†=Efficacy data was collected in C1066 only but will not be summarized due to the caveats around data collection differences and interpretation in a single-arm, open-label setting.

4. PLANNED ANALYSES

The analysis will be based on data from belimumab SLE, vasculitis, and lupus nephritis studies. Data from the SLE observational safety registry (SABLE), SLE Phase 2 LBSL02 efficacy data, vasculitis, and lupus nephritis studies (representing different subject populations to SLE) will not be pooled with the SLE study data, but each will be reported separately. Additionally, data from the three open-label continuation trials will be pooled and summarized but they will not be pooled with any other studies.

4.1. Sequence of planned Analyses

The following table details the planned sequence and pooling strategy for the series of aggregated analyses. The timing of these analyses is based on projections for study completion and thus may change. As these analyses are descriptive, no alpha-spending functions will be employed to adjust for multiple looks at the data over time.

Table 2 Sequence of Planned Analyses of Efficacy Data[1]

Studies	Analysis				
	1	**2**	**3**	**4**	**5[2]**
LBSL02 *(Phase 2)*	E1A				
C1056 *(Phase 3)*	E1B	E2C		E4F	
C1057 *(Phase 3)*	E1B	E2C		E4F	
BEL113750 *(NE Asia)*		E2D[3]		E4F[4]	
C1115 (*SC)*		E2C		E4F	
C1112 (*Black)*				E4F	
C1100 (*Vasculitis)*			E3E		
C1121 *(Lupus Nephritis)*				E4G[5]	

[1]The three-character values in the table represent the following: 1st character is 'E' for Efficacy data; the 2nd character represents the analysis (1, 2, 3, 4, or 5); the 3rd character represents a unique pooling of studies for the analysis. Note: LBSL02, the vasculitis study, and the lupus nephritis study will not be pooled with any other studies due to differences in the subject population, blinding, and/or length of follow-up

[2]There is no new efficacy data for this analysis.

[3]BEL113750 enrolled only one elderly subject, for Analysis #2 this study was not pooled with the SLE trials; a narrative for the subject will be submitted instead.

[4]The BEL113750 one elderly subject will be pooled for Analysis #4 analysis.

[5]Narratives for the 2 elderly subjects will be provided within the C1121 study CSR which will be delivered separately from Elderly Analysis Report #4.

Table 3 Sequence of Planned Analyses of Safety Data[1]

Studies	Analysis				
	1	2	3	4	5
LBSL02 *(Phase 2)*	S1A	S2B		S4I	
C1056 *(Phase 3)*	S1A	S2B		S4I	
C1057 *(Phase 3)*	S1A	S2B		S4I	
BEL113750 *(NE Asia)*		S2C[2]		S4I[5]	
C1115 (*SC)*		S2B		S4I	
C1112 (*Black)*				S4I	
C1113 Final (*Safety)*				S4L	
SLE Continuation Trials *(LBSL99, C1066, C1074) Interim*		S2D			
SLE Continuation Trials *(LBSL99, C1066, C1074) Final*			S3F		
SABLE *(Registry)*		S2E[3]	S3G[3]	S4J[3]	S5M[3,4]
C1100 (*Vasculitis)*			S3H		
C1121 *(Lupus Nephritis)*				S4K[6]	

[1]The two-character values in the table represent the following: 1st character is 'S' for Safety data; the 2nd character represents the analysis (1, 2, 3, 4, or 5); the 3rd character represents a unique pooling of studies for the analysis. Note: The SABLE safety registry, vasculitis, and lupus nephritis studies will not be pooled with any SLE studies due to differences in the subject population, blinding, and/or length of follow-up. BASE safety data will no longer be pooled because of the potential imbalance in the analysis due to the large number of elderly subjects who enrolled in this study. Elderly results from this study will be provided in a side-by-side presentation.

[2]BEL113750 enrolled only one elderly subject and therefore this study will not be pooled with the SLE trials; a narrative will be submitted instead.

[3]The elderly data from most recent annual report datacut will be submitted.

[4]Final SABLE report will be submitted.

[5]BEL113750 one elderly subject will be pooled for Analysis #4 analysis.

[6]Narratives for the 2 elderly subjects will be provided within the C1121 study CSR which will be delivered separately from Elderly Analysis Report #4.

Table 4 Estimated Elderly Subject Numbers by Treatment Arm for Pooled SLE Studies

Trial (*estimated elderly*)	**IV Pbo**	**SC Pbo**	**1**	**4**	**10**	**SC 200mg**	**All Placebo**	**All Belimumab**
LBSL02 *Phase 2*	2	-	3	2	1	-	2	6
C1056/C1057 *Phase 3*	14	-	8	-	5	-	14	13
C1115 *SC Phase 3* *(n=19, 2:1 ratio b:p)*	-	7	-	-	-	12	7	12
C1112 *Black Race* *(n=11, 2:1 ratio b:p)*	4	-	-	-	4	-	4	4
BEL113750 (*n=1 2:1 ratio b:p)*	0				1		0	1
Efficacy Total[1]	18	7	8	0	10	12	22	31
Safety Total	20	7	11	2	11	12	24	36

[1]Efficacy total does not include LBSL02 data.

4.2. Aggregated Analyses

The analyses defined in this document represent a series of aggregated analyses performed by pooling subject-level data from studies of interest, and conducting the analyses on the pooled data. Since subject-level data is available for all studies, meta-analyses methods in which only summary statistics are combined across the individual studies in order to integrate the findings are not necessary.

In addition to the pooled aggregated final analysis for the elderly subjects in the SLE Continuation Trials (LBSL99, C1066, C1074), a similar pooled aggregated analysis will be performed for all subjects in order to perform a side by side comparison of the elderly subjects to all subjects.

If any derivations defined in this SDAP do not match the individual study derivations defined in the study RAP, then the individual study derivation will be used.

5. ANALYSIS POPULATIONS

5.1. Primary Population

The primary population for these proposed analyses is defined as the subpopulation of elderly subjects (aged ≥ 65 years at baseline) who were randomized and received at least 1 dose of study agent from the studies identified in Section 3. This population will be referred to as the elderly Intent-to-Treat (ITT) population. The ITT analysis will be based on the planned treatment group rather than the actual treatment received in the event a subject received a treatment different than the randomized treatment.

Additionally, the subpopulation of very elderly, defined as subjects ≥ 75 years of age at baseline who were randomized and received at least 1 dose of study agent, will also be summarized. If the numbers are very small, these subjects may be summarized using narratives and/or data listings.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES

For efficacy analysis, descriptive statistics will be presented for the elderly population using point estimates, treatment differences, and 2-sided, 95% confidence intervals. The data will be presented by treatment group and all belimumab doses combined (see Section 8).

For comparative purposes, displays across the pooled intent to treat populations (elderly + non-elderly) for the double-blind placebo controlled studies (C1056, C1057, C1115, C1112 and BEL113750) as well as separate displays for C1113 will be produced to enable a side by side comparison to the subset of pooled elderly patients.

Similar displays across the pooled LTC (elderly + non-elderly) population will be produced for comparison to the pooled LTC elderly subset.

6.1. Estimated Power

Due to the small expected numbers of elderly subjects to be evaluated, no power calculations were performed. The data will be presented using descriptive statistics.

6.2. Multicentre Studies

Individual centers will not be considered in the analyses due to low expected numbers of subjects at any given center which will result in difficulties estimating a center effect. Individual studies will not be considered in the analyses due to low numbers of elderly subjects in any given study which will result in difficulties estimating a study effect.

6.3. Multiple Comparisons and Multiplicity

No adjustments will be made for multiplicity. Analyses should be considered in the context of other supportive analyses with trends being observed across several endpoints in a clinically meaningful manner.

7. DATA HANDLING CONVENTIONS

This section describes data handling conventions for the pooled efficacy data and reflects the methods used in the Phase 3 trials. This includes the handling of premature withdrawal and missing data for the SRI endpoint, each of the three components that make up the SRI endpoint, and for all analyses of SLE flares measured by a modified SLE Flare Index. Missing data for analyses at time points other than Week 52 will be managed in a similar manner. For other endpoints, handling of withdrawals and missing data will be described in Section 10.

Data handling conventions for efficacy data that is not to be pooled (LBSL02, vasculitis, and lupus nephritis) will be managed per the conventions defined in the study-specific analysis plan.

The following treatment descriptors will be used on all data tabulations:

- Placebo (IV + SC)
- Belimumab IV
    1. 1 mg/kg
    2. 4 mg/kg
    3. 10 mg/kg
- Bel 200mg SC
- All Belimumab

7.1. Premature Withdrawal and Missing Data

Individual studies will be managed according to their respective Reporting and Analysis Plan (RAP).

7.2. Concomitant Medications

Individual studies will be managed according to their respective RAP.

Concomitant medications will be coded according to drug name as defined in the GSK drug dictionary and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

7.3. Stratification Factors

The SLE studies identified for the pooled analyses were stratified by a variety factors as indicated in Table 5 below.

Table 5 Stratification Factors for Pooled SLE Studies

Studies	SELENA SLEDAI[1]	Proteinuria[2]	AIA [3]	Complement [4]	Country [5]	Black Race	Region [6]	Steroid Dose[7]
LBSL02 *Ph 2*	X[a]							
C1056/ C1057 *Ph 3*	X	X	X					
BEL113750 *NE Asia*	X			X	X		X[a]	
C1115 *SC*	X			X		X		
C1112 *EMBRACE*	X			X			X[b]	
C1113 *Safety*	X						X[c]	X

[1]SELENA SLEDAI score (≤ 9 vs. ≥ 10), [a]LBSL02 used (≤ 7 vs. ≥ 8).
[2]Proteinuria level (< 2 g/24 hour vs. ≥ 2 g/24 hour equivalent)
[3]Race (African descent or indigenous-American descent vs. other)
[4]Complement (C3 and/or C4 low vs. other)
[5]Country (China, Japan, Korea)
[6]Region:[a] Country of Origin [b] (US/Canada vs. rest of the world); [c] (US/Canada vs. Central America/South America/Mexico vs. Europe/Australia/Israel vs. Asia)
[7]Steroid dose (< 7.5 mg/day vs.≥ 7.5 mg/day prednisone or equivalent)

Due to differences among the studies in stratification factors, the pooled efficacy analyses will be stratified for baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10). However, the adjustment will not occur if there are < 5 events (e.g., responders or non-responders) in either stratum (i.e., score ≤ 9 or ≥ 10).

Stratification factors for the vasculitis study include ANCA type (anti-PR3 vs. anti-MPO), disease stage (initial diagnosis vs. relapsing disease) and induction regimen (cyclophosphamide vs. rituximab). For the lupus nephritis study, the randomization will be stratified by the induction regimen (high dose corticosteroids [HDCS] plus CYC vs HDCS plus MMF) and race (black race vs other).

8. POPULATION SUMMARY

For the pooled SLE studies, the elderly population (see Section 5) will be summarized according to baseline demography, disease characteristics, and concomitant SLE therapy.

For non-pooled studies, baseline characteristics will be managed per the conventions defined in the study-specific analysis plan.

8.1. Subject Completion Status

The subject's completion status will be assessed to evaluate percentages of dropouts by treatment arm as well as the reasons for dropout. For the pooled SLE studies, the number and percentage of subjects who completed through Week 52 and who withdrew, including reasons for withdrawal, will be displayed by treatment arm. Additionally, a table for time to withdrawal and corresponding graph will be generated to evaluate the pattern of dropouts over time.

8.2. Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the demographic and baseline characteristics for the elderly population (as defined in Section 5) by treatment group.

The following data will be summarized for SLE studies:

- Demographics and baseline characteristics
- Baseline disease activity
- SELENA SLEDAI category by organ domain and item at baseline
- BILAG category by organ domain at baseline

- Baseline autoantibody levels
- Baseline immunoglobulin levels
- Baseline levels of complement and anti-dsDNA
- Allowable SLE medication usage at baseline

Baseline characteristics specific to the vasculitis and lupus nephritis studies will be reported per the study-specific analysis plans.

9. SAFETY ANALYSES

9.1. Extent of Exposure

For both pooled and the SLE continuation trials, the extent of exposure to study agent will be assessed according to Program Safety Analysis Plan (PSAP) Version 2 or later, if a more recent version is available [PSAP, 2015].

The extent of exposure in weeks and the total number of infusions will be summarized by mean, standard deviation, median, and minimum and maximum value. The total number of infusions will be summarized using counts and percentages.

9.2. Adverse Events

Subjects will be followed for safety according to individual study protocols. Individual studies will be managed according to their respective Reporting and Analysis Plan (RAP).

Only treatment-emergent AEs will be summarized. A treatment-emergent AE is an AE that emerges during treatment, having been absent pre-treatment, or that worsens relative to the pre-treatment state.

All AEs will be classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. The investigator will evaluate all AEs with respect to seriousness, severity, and causality. The severity of an AE is to be evaluated according to the Adverse Event and Laboratory Value Severity Grading Tables in Appendix 1 of this analysis plan.

The incidence of treatment-emergent AEs will be summarized for each of the following AE categories:

- AEs
- Study agent-related AEs
- Severe AEs
- Serious AEs
- Serious, study agent-related AEs
- AEs resulting in discontinuation of study agent

- Deaths

The tabular summary for each category of AE listed above will include the number of events, number of subjects who reported at least one event, and percentage of subjects who reported at least one AE (incidence) for each SOC, each preferred term category, and by treatment group. A listing for all AEs will also be produced.

9.2.1. Deaths and Serious Adverse Events

In addition to the tabular summaries of AEs described in Section 10.2, listings for all SAEs and all deaths will be produced.

9.2.2. Adverse Events Leading to Discontinuation of Investigational Product

In addition to the tabular summary described in Section 10.2, a listing of all AEs leading to discontinuation of study agent will be produced.

9.2.3. Adverse Events of Special Interest

AEs of special interest include infusion reactions/hypersensitivity, psychiatric events, malignancies, opportunistic infections, and serious infections. These analyses will be performed using the current definition at the time of the planned analysis as defined by the Section 10.3 of the PSAP Version 2 or later, if a more recent version is available [PSAP, 2015].

9.3. Immunogenicity

For the immunogenicity assessment, two types of antibody assays will be performed, i.e. a binding assay and neutralizing assay. For the binding assay, there are 2-testing steps. A screening assessment is performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay is then carried out, which also produces a result of positive or negative. Patients will be viewed as positive for the binding assay if the confirmation assay was positive. Subjects, who tested positive for the binding assay, will be tested for the neutralizing assay, which again produces a result of positive or negative.

For the incidence of patients with positive binding antibody, a table will be produced summarizing results for the binding antibody assay by treatment group and visit. The table will include the number and proportion of subjects in each results category for each visit (including early withdrawal visit). Binding confirmatory assay results will be categorized as negative, persistent positive (defined as a positive immunogenic response at least 2 consecutive assessments or a single result at the final assessment) or transient positive (defined as a single positive immunogenic response that does not occur at the final assessment).

10. EFFICACY ANALYSES

The pooled analyses will be performed for the elderly ITT population as defined in Section 5 unless otherwise stated. The data will be presented by treatment group and all belimumab doses combined.

For the analysis of steroid use, all steroid dosages are converted to a prednisone equivalent in milligrams; therefore analyses refer to daily prednisone dose instead of daily steroid dose.

Section 10.1 - Section 10.3 define the efficacy analyses to be conducted for the pooled SLE studies. Key analyses for the Phase 2 SLE study (LBSL02), vasculitis, and lupus nephritis studies will be presented per their study-specific analysis plans.

10.1. Primary Efficacy Analysis

The primary endpoint is the SLE Responder Index (SRI) response rate at Week 52, consistent with the primary efficacy endpoint for the phase 3 clinical studies.

An SRI response is defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score,

  AND

- No worsening (increase of < 0.30 points from baseline) in PGA,

  AND

- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (ie, at Week 52).

The percent of subjects achieving an SRI response at Week 52 will be presented for belimumab and placebo. A logistic regression model will be used to estimate the odds of an SRI response for belimumab vs. placebo. The independent variables in the model will include treatment group and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum.

Handling of missing data will be managed as described in Section 7.1 and treatment failures due to concomitant medications will be handled as described in Section 7.2. The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% confidence interval.

10.1.1. Supportive Analyses of the Primary Efficacy Endpoint

10.1.1.1. SRI Response Rate by Visit

An analysis of the SRI response endpoint defined in Section 10.1 will be performed by visit. The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95%

confidence interval vs. placebo. A line graph of the percent of responders by treatment group will also be generated.

Subgroup analyses of this endpoint will be performed for subjects with baseline SELENA SLEDAI ≥ 10 and subjects with low complement who are positive for anti-dsDNA (C3 and/or C4 low AND anti-dsDNA ≥ 30).

10.1.1.2. SRI 5-7 at Week 52

The SRI5, SRI6, and SRI7 are defined as the SRI in Section 10.2, except for requiring higher thresholds of improvement (5, 6, and 7 point improvements, respectively) for SELENA SLEDAI in order for a subject to be declared a responder. Since the minimum SELENA SLEDAI score for inclusion varies among the studies (minimum of 4, 6, or 8), these analyses will be conducted among subjects whose baseline SELENA SLEDAI score is greater than or equal to the minimum threshold required to be a responder (e.g., SRI5 will be evaluated among subjects with a baseline SELENA SLEDAI score ≥ 5).

For each SRI5-7, the proportion of responders at Week 52 will be compared between the belimumab treatment group and placebo using a logistic regression model. The independent variables in the model will include treatment group (belimumab vs. placebo) and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10). However, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum.

10.1.1.3. Percent of Subjects with >= 4 Point Reduction from Baseline in SELENA SLEDAI Score at Week 52

The percent of subjects with ≥ 4 point reduction from baseline in SELENA SLEDAI score at Week 52 will be compared between each of the belimumab groups and placebo group. The independent variables in the model will include treatment group and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum. A responder is defined as achieving a ≥ 4 point reduction from baseline in SELENA SLEDAI score. As this endpoint is a component of the primary SRI endpoint, handling of missing data, including concomitant medication changes resulting in treatment failure designation, will be the same as described for the SRI analysis (Section 7.1 and Section 7.2).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% confidence interval vs. placebo.

10.1.1.4. Percent of Subjects with No New BILAG A Organ Domain Score or 2 New BILAG B Organ Domain Scores Compared With Baseline at Week 52

The percent of subjects with no new BILAG A organ domain score or 2 new BILAG B organ domain scores at Week 52 will be compared between each of the belimumab groups and placebo. A logistic regression model will be used to estimate the odds of no new BILAG A organ domain score or 2 new BILAG B organ domain scores for each belimumab group vs. placebo. The independent variables in the model will include

treatment group and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10). However, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum. A responder is defined as having no new BILAG A organ domain score or 2 new BILAG B organ domain scores. As this endpoint is a component of the SRI endpoint, handling of missing data, including concomitant medication changes resulting in treatment failure designation, will be the same as described for the SRI endpoint analysis (Section 7.1 and Section 7.2).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% confidence interval vs. placebo.

10.1.1.5. Percent of Subjects with No Worsening (Increase of < 0.30 points From Baseline) in PGA at Week 52

The percent of subjects with no worsening in PGA will be compared at Week 52 between each of the belimumab groups and placebo. A logistic regression model will be used to estimate the odds of no worsening in PGA. The independent variables will include treatment group, baseline PGA score, and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum. A responder is defined as no worsening in PGA. As this endpoint is a component of the SRI endpoint, handling of missing data, including concomitant medication changes resulting in treatment failure designation, will be the same as described for the SRI endpoint analysis (Section 7.1 and Section 7.2).

The table will display the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% confidence interval vs. placebo.

10.2. Secondary efficacy Analyses

10.2.1. Time to 1st SEVERE SLE flare over 52 weeks by modified SLE Flare Index

Severe flares are defined by the modified SELENA SLEDAI SLE flare index (SFI) (Appendix 3 to the BLISS-52 and BLISS-76 protocols) in which the modification excludes severe flares that were triggered only by an increase in SELENA SLEDAI score to < 12 (since this may only represent a modest increase in disease activity.

The time to the 1st severe SLE flare over 52 weeks will be compared between the treatment groups using a Cox proportional hazard model. Independent variables in the model will include treatment group and baseline SELENA SLEDAI score (≤ 9 vs.≥ 10); however, the SELENA SLEDAI adjustment will not occur if there are < 5 events in either stratum.

If a subject withdraws from the study or completes week 52 without a severe SLE flare, time to the 1st severe SLE flare will be censored at the time of the last observation (last visit measuring flare). However, if a subject receives a protocol-prohibited medication or a dose of allowable (but protocol restricted) medication that results in treatment failure

designation during the time period being analyzed, the subject will be considered as having a severe SLE flare at the time the medication is started. Data observed at or prior to the baseline visit will not be included in this analysis. Handling of missing data in the SELENA SLEDAI component of SLE Flare Index will be managed according to their respective RAP.

The table will display the number and percentage of subjects with a severe flare in the interval, the median days to severe flare, the 25th and 75th percentile of days to first severe flare, and the hazard ratio and 95% confidence interval vs. placebo. A Kaplan-Meier curve for time to 1st severe SLE flare over 52 weeks will also be produced.

10.2.2. Percent of Subjects Whose Average Prednisone Dose has been reduced by >= 25% from > 7.5 mg/day at Baseline to=< 7.5 mg/day During Weeks 40 through 52

The percent of subjects with average prednisone dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 will be compared between each belimumab treatment and placebo using a logistic regression model. Independent variables in the model will include treatment, baseline prednisone dose level, and baseline SELENA SLEDAI score (≤ 9 vs.≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or non-responders exist in either stratification level. A responder is defined as having a prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52. The analysis will be performed on subjects who used prednisone > 7.5 mg/day at baseline.

The average prednisone dose will be the total prednisone dose during Weeks 40 through 52 divided by the number of days during Weeks 40 through 52.

Any subject who withdraws from the study prior to the Day 364 (Week 52) visit, misses the Day 364 (Week 52) visit, and/or receives a dose of protocol prohibited/restricted medication that results in treatment failure designation prior to the Day 364 (Week 52) visit will be managed per individual study RAP.

10.3. Other efficacy analyses

10.3.1. SELENA SLEDAI Score Percent Change from Baseline at Weeks 24 and 52

The percent change from baseline in SELENA SLEDAI score at Weeks 24 and 52 will be compared between each belimumab treatment and placebo using an ANCOVA model adjusted for baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10). The last observation carried forward (LOCF) method will be employed for subjects with missing data for SELENA SLEDAI score at the visit being evaluated. Specifically, if a subject misses a regularly scheduled visit or if partial data are missing from a subject's visit, the missing data will be handled by using the last observation (or item) carried forward method. See individual study RAPs for further details. For example, if the data on 1 or more items of the 24 SELENA SLEDAI questions are missing, the last available answer(s) to the corresponding question(s) from the previous visit will be assigned to the missing item(s) in order to obtain a total score. If a subject misses an entire visit, the missing data on

SELENA SLEDAI will be handled by using the last score from the previous visit. If a subject takes a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that results in treatment failure designation prior to the study visit being evaluated, the data on percent change from baseline on SELENA SLEDAI will be handled by using the score from the last visit on or prior to the date that the medication was started.

The table will display the mean, standard error of the mean, median, minimum value, maximum value, least squares mean, standard error of the least square mean by treatment group and the treatment difference in least square means and 95% confidence interval vs. placebo.

10.3.2. PGA Percent Change from Baseline at Week 52

Percent changes from baseline in PGA will be summarized at Week 52. An analysis of covariance (ANCOVA) model will be used to compare the effect of each belimumab treatment group vs. placebo adjusted for baseline PGA score and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10). The LOCF method will be employed for subjects with missing data for PGA score. Specifically, if a subject misses the visit being evaluated, the missing data will be handled by using the last observation available. See individual study RAPs for further details. If a subject takes a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that results in treatment failure designation prior to the visit, change from baseline will be calculated using the score from the last visit on or prior to the date of treatment failure

The table will display the mean, standard error of the mean, median, minimum value, maximum value, least squares mean, standard error of the least square mean by treatment group and the treatment difference in least square means and 95% confidence interval vs. placebo.

10.3.3. Daily prednisone dose reduced to =< 7.5 mg/day at Week 52 from >7.5 mg/day at baseline

For the analysis of steroid use, all steroid dosages are converted to a prednisone equivalent in milligrams; therefore tables refer to daily prednisone dose instead of daily steroid dose.

The percent of subjects with daily prednisone dose reduced to ≤ 7.5 mg/day at Week 52 from > 7.5 mg/day at baseline will be compared between each belimumab treatment and placebo using a logistic regression model. The analysis will be performed adjusting for baseline prednisone dose level and baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum. A responder is defined as subject who decreased their daily prednisone dose to ≤ 7.5 mg/day from a baseline dose > 7.5 mg/day. This analysis will be performed on subjects who used prednisone > 7.5 mg/day at baseline. If a subject withdraws from the study and/or receives a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that results in treatment failure

designation prior to a scheduled visit, the subject will be considered a non-responder (i.e., no reduction in prednisone) for that and subsequent visits.

The table will display the number and percentage of subjects achieving a response by treatment arm, the treatment difference versus placebo, and the odds ratio and 95% confidence interval vs. placebo.

10.3.4. Daily prednisone dose increased to > 7.5 mg/day at Week 52 from =< 7.5 mg/day at baseline (LOCF)

The percent of subjects with average daily prednisone dose increased to > 7.5 mg/day at Week 52 from ≤ 7.5 mg/day at baseline will be compared between the treatment groups using a logistic regression model. The analysis will be performed adjusting for baseline prednisone dose level and baseline SELENA SLEDAI score (≤ 9 vs.≥ 10); however, the SELENA SLEDAI adjustment will not occur if < 5 responders or < 5 non-responders exist in either stratum. A non-responder is defined as subject who must increase dose to > 7.5 mg/day from a baseline dose ≤ 7.5 mg/day. This analysis will be performed on subjects who used prednisone ≤ 7.5 mg/day at baseline. The LOCF method will be employed for subjects with missing data at the visit being evaluated. Specifically, if a subject misses the visit being evaluated, the missing data will be handled by using the last observation available. However, if a subject receives a protocol-prohibited medication or a dose of allowable (but protocol restricted) medication that results in treatment failure designation prior to the study visit being evaluated, the data on the average daily dose will be handled by using the score from the last visit on or of treatment failure date .See individual study RAPs for further details.

The table will display the number and percentage of non-responders by treatment arm, the treatment difference versus placebo, and the odds ratio and 95% confidence interval vs. placebo.

10.3.5. Biomarkers

The following biomarkers will be summarized by treatment group for baseline, Weeks 8, 24 and 52. The analysis will be performed on observed data with no imputation for missing data. The analysis will be summarized in table and figure formats. If the effect of dropouts makes interpretation of the results questionable, the analysis may also be performed on completers if the sample size is sufficient.

- Percent change from baseline at Weeks 8, 24 and 52 in absolute B cell subsets
  - $CD20^{+}$,
  - memory ($CD20^{+}/27^{+}$),
  - naïve ($CD20^{+}/27^{-}$), and
  - plasma cells ($CD20^{-}/138^{+}$).
- Percent change from baseline and the percent that normalized at Weeks 8, 24 and 52 for:

  Total serum immunoglobulin (IgG, IgM and IgA).

Autoantibodies (anti-dsDNA).

Complement (C3, C4) levels.

For anti-dsDNA, analyses will be performed on subjects who were positive at baseline. For complement, analyses will be performed on subjects with low complement at baseline.

10.3.6. Time to 1st SLE flare over 52 weeks by modified SLE Flare Index

Flares are defined by the modified SELENA SLEDAI SLE flare index (SFI) (as defined by the individual study reporting and analysis plans) in which the modification excludes severe flares that were triggered only by an increase in SELENA SLEDAI score to > 12 (since this may only represent a modest increase in disease activity). Data censored at last available visit by week 52 visit. For subjects who died, data are censored at death if no flares occurred before death. Time to first flare is defined as (event date - treatment start date +1)

The time to the 1st SLE flare over 52 weeks will be compared between the treatment groups using a Cox proportional hazard model. Independent variables in the model will include treatment group and baseline SELENA SLEDAI score (≤ 9 vs.≥ 10); however, the SELENA SLEDAI adjustment will not occur if there are < 5 events in either stratum.

If a subject withdraws from the study or completes week 52 without a SLE flare, time to the 1st SLE flare will be censored at the time of the last observation (last visit measuring flare). However, if a subject receives a protocol-prohibited medication or a dose of allowable (but protocol restricted) medication that results in treatment failure designation during the time period being analyzed, the subject will be considered as having a SLE flare at the time the of treatment failure occurred. Data observed at or prior to the baseline visit will not be included in this analysis. Handling of missing data in the SELENA SLEDAI component of SLE Flare Index will be as described in Section 7.1 and Section 7.2

The table will display the number and percentage of subjects with a flare in the interval, the median days to severe flare, the 25th and 75th percentile of days to first flare, and the hazard ratio and 95% confidence interval vs. placebo. A Kaplan-Meier curve for time to 1st SLE flare over 52 weeks will also be produced.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables

HEMATOLOGY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin	> 9.5 - 11.0 g/dL	> 8.0 – 9.5 g/dL	6.5 - 8.0 g/dL	< 6.5 g/dL
Leukocytes	3000-3999/mm3	2000-2999/mm3	1000-1999/mm3	< 1000/mm3
Absolute Neutrophil Count	1500-1999/mm3	1000-1499/mm3	500-999/mm3	< 500/mm3
Platelets	75,000 - 99,999/mm3	50,000 – 74,999/mm3	25,000 - 49,999/mm3	< 25,000/mm3
Prothrombin Time (PT)	> 1.0-1.25 x ULN*	> 1.25-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0 x ULN
Partial Thromboplastin Time (PTT)	> 1.0-1.66 x ULN	> 1.66-2.33 x ULN	> 2.33-3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0-10.0 %	10.1-15.0 %	15.1-20.0 %	> 20%
				(continued)

*ULN = Upper Limit of Normal.
Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

CARDIOVASCULAR	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac Arrhythmia	-	Asymptomatic/transient; dysrhythmia; no treatment req	Recurrent/persistent dysrhythmia. Symptomatic; treatment req	Unstable dysrhythmia hospitalization and treatment required
Hypotension	Transient orthostatic hypotension, no treatment	Symptoms correctable with oral fluid treatment	IV fluid req, no hospitalization req	Hospitalization req
Hypertension	Transient, increase > 20 mm/Hg; no treatment	Recurrent; chronic increase > 20 mm/Hg, treatment req	Acute treatment req; out patient hospitalization possible	Hospitalization req
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion, pain, ECG changes	Tamponade OR pericardiocentesis OR surgery req
Hemorrhage, Blood Loss	-	Mildly symptomatic; no treatment required	Gross blood loss OR 1-2 units transfused	Massive blood loss OR > 2 units transfused

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium				
Hyponatremia	130-135 meq/L	123-129 meq/L	116-122 meq/L	< 116 meq/L
Hypernatremia	146-150 meq/L	151-157 meq/L	158-165 meq/L	> 165 meq/L
Potassium				
Hypokalemia	3.0-3.4 meq/L	2.5-2.9 meq/L	2.0-2.4 meq/L	< 2.0 meq/L
Hyperkalemia	5.6-6.0 meq/L	6.1-6.5 meq/L	6.6-7.0 meq/L	> 7.0 meq/L
Phosphate				
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL	1.0-1.4 mg/dL	< 1.0 mg/dL
Calcium- (Corrected For Albumin)				
Hypocalcemia	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL
Magnesium				
Hypomagnesemia	1.2-1.4 meq/L	0.9-1.1 meq/L	0.6-0.8 meq/L	< 0.6 meq/L
Albumin				
Hypoalbuminemia	3.00-3.49 g/dL	2.50-2.99 g/dL	2.00-2.49 g/dL	< 2.00 g/dL
Bilirubin (Total)				
Hyperbilirubinemia (Total)	> 1.0-1.5 x ULN	> 1.5-2.5 x ULN	> 2.5-5 x ULN	> 5 x ULN
Glucose				
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL
Hyperglycemia (nonfasting & no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL
Triglycerides	151-399 mg/dL	400-750 mg/dL	751-1200 mg/dL	> 1200 mg/dL
Creatinine	> 1.0-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

CHEMISTRIES (continued)	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uric Acid				
Hyperuricemia	7.5-10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	> 15.0 mg/dL
Liver Transferases (AST, ALT, and GGT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Alkaline Phosphatase	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10.0 x ULN	> 10.0 x ULN
Pancreatic Enzymes				
Amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Pancreatic amylase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
*Hypoglobulinemia (IgG)**	550-700 mg/dL	400-549 mg/dL	250-399 mg/dL	< 250 mg/dL

(continued)

*[Eibl, 1995; Goldfarb, 2001; Yamani, 2001].

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

GASTROINTESTINAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Nausea	Mild OR transient; reasonable intake maintained	Mod discomfort OR intake decreased for < 3 days	Severe discomfort OR minimal intake for ≥ 3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes/day OR mild vomiting lasting < 1 week	Mod OR persistent; 4-5 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR IV treatment req	Hypotensive shock OR hospitalization required for IV treatment req
Diarrhea	Mild or transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; OR orthostatic hypotension OR > 7 loose stools/day OR IV treatment req	Hypotensive shock OR hospitalization req
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req
Constipation	Mild	Moderate	Severe	Distention with vomiting

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

RESPIRATORY	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cough (for aerosol studies)	Transient; no treatment	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic treatment req	
Bronchospasm Acute	Transient; no treatment; FEV1 70% to < 80% (or peak flow)	treatment req; normalizes with bronchodilator; FEV1 50% to < 70% (or peak flow)	No Normalization with bronchodilator; FEV 25% to < 50% (or peak flow), retractions	Cyanosis; FEV1 < 25% (or peak flow) OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O2 therapy

URINALYSIS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proteinuria				
Dispstick Protein	1 +	2-3 +	4 +	Nephrotic syndrome
Spot Urine: Protein:Creatinine Ratio mg/mg	0.2-1.0	> 1.0-2.0	> 2.0-3.5	> 3.5
24 Hour Urine: Protein	200 mg - 1g loss/day	> 1-2 g loss/day	> 2-3.5 g loss/day	Nephrotic syndrome OR > 3.5 g loss/day
Hematuria	Microscopic only > 3 to < 10 RBC/hpf	Gross, No clots ≥ 10 RBC/hpf	Gross plus clots OR RBC casts	Obstructive OR transfusion required

(continued)

RBC = red blood cell; hpf = high power field.

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

MISCELLANEOUS	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fever (oral > 12 hours)	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C OR 101.6-102.9°F	39.6-40.5°C OR 103-105°F	> 40.5°C OR > 105°F
Headache	Mild; No treatment req	Mod; or non-narcotic analgesia treatment	Severe; OR responds to initial narcotic treatment	Intractable; OR requiring repeated narcotic treatment
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria angioedema	Anaphylaxis
Cutaneous/Rash/ Dermatitis	Erythema, pruritus rash OR dry desquamation	Diffuse maculopapular OR dry desquamation	Vesiculation OR moist desquamation ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction (secondary to parenteral treatment- not vaccination or skin test)	Erythema	Induration < 10 mm OR inflammation OR phlebitis	Induration > 10 mm OR ulceration	Necrosis of skin
Fatigue	Normal activity Reduced < 25%	Normal activity Reduced 25-50%	Normal activity reduced > 50%; cannot work	Unable to care for self

(continued)

Modified from DMID Adult Toxicity Tables, 2001

Appendix 1: Adverse Event and Laboratory Value Severity Grade Tables (continued)

NEUROLOGIC	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuro-cerebellar	Slight incoordination OR dysdiadochokinesia	Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/ mood		none	Severe mood changes requires medical intervention	Acute psychosis requiring hospitalization
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment needed	Mod discomfort non-narcotic analgesia req	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop), and mod proximal weakness ie, in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheelchair because of muscle weakness
Neuro-sensory	Mild impairment sensations, (ie, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment mod de-sensation, (ie, of vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical.	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (ie, upper and lower extremities)	Sensory loss involves limbs and trunk

(concluded)

Modified from DMID Adult Toxicity Tables, 2001