STATISTICAL ANALYSIS PLAN

Study Title: A Randomized, Double-Blind, Placebo-Controlled Phase 1b Study to Assess the Safety and Effect of Repeated Administration of Granulocyte Colony-Stimulating Factor (G-CSF; filgrastim) on Hot Flashes and Other Vasomotor Symptoms of Menopause in Postmenopausal Women

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Protocol ID: MNGX-102

Statistician: [redacted]

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Approval Signatures	Date
[redacted]	08Aug2022
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1 INTRODUCTION

Human granulocyte colony-stimulating factor (G-CSF) is currently indicated to stimulate the proliferation and differentiation of granulocytes. G-CSF is available in the US as Neupogen®, TevaGrastim® and Zarxio®. Neupogen® is the Amgen Inc. trade name for filgrastim, recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF), synthesized in bacteria. TevaGrastim® is the Teva Pharmaceuticals trade name for filgrastim. Zarxio® is the Sandoz, a Novartis company, trade name for filgrastim. Both TevaGrastim® and Zarxio® are approved as Neupogen® biosimilars. Since filgrastim is produced in bacteria, it differs slightly from that of the naturally produced human G-CSF.

The purpose of this study is to describe the effect of repeated administration of G-CSF on the frequency and severity of hot flashes in postmenopausal women.

This statistical analysis plan is based on the MNGX-102 version 4 of the study protocol, dated 20OCT2020. Refer to the protocol for further details regarding the study plan.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this pilot study is to describe the safety of three single (repeated) subcutaneous injections of G-CSF in post-menopausal women as well as to describe the efficacy of three repeated injections of G-CSF on reducing the frequency and severity of hot flashes in postmenopausal women from baseline.

2.2 Secondary Objectives

The secondary objectives of this pilot study are to assess additional measures of hot flash burden, circulating hormone and inflammatory cytokine concentrations, and safety.

3 STUDY DESIGN

This is a 12-week, multicenter, double-blind, placebo-controlled study. Eligible subjects will be stratified by natural or surgical menopause and randomized (1:1) to receive three injections, 28-days apart, of either 300 mcg G-CSF or placebo.

Subjects enrolled will be given three single 1.0 mL SC injections (repeated 28-days apart), in the outer area of either upper arm, of either G-CSF or placebo (sterile physiological saline) at

Baseline, Day 28 and Day 56. Subjects will be followed for 12 weeks and will complete hot flash diary entries every day for the duration of treatment. Safety will be assessed by adverse events, clinical laboratory tests (clinical chemistry and CBC with differential) and vital signs. The study will have an independent Data Safety Reviewer assigned by the NIH to review safety data at regular intervals.

4 SAMPLE SIZE JUSTIFICATION

In total, approximately 65 subjects were planned, however due to the COVID-19 pandemic situation, only 61 subjects will be enrolled in this study. Subjects will be stratified by natural menopause or surgical menopause groups, and randomized 1:1 to either 300 mcg G-CSF or placebo.

The sample size of 61 subjects is based on clinical feasibility. This is a phase 1b study to determine feasibility of the treatment and the ability to conduct a larger powered study.

5 ENDPOINTS

5.1 Safety Endpoints

The primary safety of three single subcutaneous injections of G-CSF at 28-day intervals in a postmenopausal healthy subpopulation. Safety endpoints will include the incidence of serious adverse events and related adverse events over the duration of the study.

5.2 Efficacy Endpoints

Changes from baseline throughout the entire 12 weeks will be evaluated in the:

Primary Endpoints:

Safety and pharmacodynamics.

- Pharmacodynamic Endpoints: Assessment of changes from baseline in circulating white blood cells, hormone and inflammatory cytokine concentrations.

Secondary Endpoints:

Efficacy Endpoints

The effect of repeated administration of G-CSF in the following indicators of vasomotor symptoms in women with naturally occurring or surgically induced menopause at weeks 2, 4, 6, 8, 10 and 12 weeks post-administration:

Hot flashes – change from baseline in:

- Number of total daily hot flashes (mild + moderate + severe hot flashes)
- Number of total daily moderate + severe hot flashes combined
- Daily composite hot flash severity score (1 x mild + 2 x moderate + 3 x severe hot flashes)
- Hot flash severity score per total hot flashes ((1 x mild + 2 x moderate + 3 x severe hot flashes)/total hot flashes)

Hot flashes:

- percent of subjects achieving 50 percent reduction from baseline in total number of hot flashes

Quality of life Endpoints:

Change from baseline in:

- Hot Flash Related Daily Interference Scale (HFRDIS)
- Fatigue Severity Scale (FSS)
- Insomnia Severity Index (ISI)
- Menopause-specific Quality of Life Questionnaire (MENQOL)
- Arthritis Impact Measurement Scale (AIMS)

Exploratory Endpoints:

Changes from baseline throughout the entire 12 weeks and will be evaluated in the:

- Circulating hormone levels as a result of three injections of G-CSF or placebo; and
- Circulating pharmacodynamics and inflammatory cytokine levels as a result of three injections of G-CSF or placebo.

6 ANALYSIS POPULATION SUBSETS

6.1 All Randomized Analysis Set

All subjects who are enrolled in the study and randomized. This analysis set will be used for subject listings.

6.2 Full Analysis Set

All subjects who are randomized and receive at least one dose of study drug will be included in this subset. This analysis subset will be used for efficacy analyses. Subjects will be analysed according to the randomized treatment group regardless of treatment received.

6.3 Safety Analysis Set

All subjects who enroll who receive a single injection of G-CSF or placebo will be considered evaluable for all safety analyses. Subjects will be analyzed according to the treatment received.

6.4 Per Protocol Analysis Set

If significant deviations from the protocol occur, secondary efficacy analyses may be conducted for those patients who were protocol compliant, the Per Protocol (PP) population.

7 STATISTICAL METHODS OF ANALYSIS

7.1 Data Analysis

All analyses will be performed using the FAS population. Additional analyses may be performed on the per protocol population if significant protocol deviations occur. These analyses will employ descriptive statistics (means, medians, etc.) and post-hoc hypothesis testing.

This is an exploratory, pilot study intended to gather descriptive information on safety and effect. No *a priori* assumptions are made regarding estimated treatment effects or statistical power.

7.2 General Principles

The frequency of hot flashes per day will be calculated for each week by calculating the weekly mean, providing that within a week at least 4 days' worth of information were gathered. Descriptive statistics will be used to describe changes from baseline in average frequency and severity of hot flashes.

Descriptive statistical analyses will be performed to compare pre-treatment to all post-treatment points using analysis of variance (ANCOVA), with appropriate *post hoc* testing, to determine statistical significance of the observed effects.

Analyses of Primary Efficacy Data

Descriptive statistics will be used to summarize changes from baseline throughout the entire 12 weeks in frequency and severity of hot flashes (at weeks 2,4,6,8,10,12). The frequency and severity of hot flashes will be examined separately by analyzing changes from Baseline hot flash frequency and severity at each of weeks 2, 6, 10, and 12.

Average frequency of hot flashes per week for each subject will be determined from diary entries and calculated as total number of recorded hot flashes from day 1 through day 7 divided by the number of days for which entries were made. Data are entered as numbers of mild, moderate, and severe hot flashes per day. Calculations to be considered:

1) Mean daily Total Hot Flashes per week (THF)
2) Score in 1) presented as % of Baseline
3) Percent subjects achieving 50% reduction in THF per week
4) Mean daily (moderate + severe) hot flashes per week (M+S)
5) Mean Composite Daily Hot Flash Severity score per week (CDS): per Stearns/Sloan. Mean Composite Score = [1 x (# of mild) + 2 x (# of moderate) + 3 x (# of severe)]

6) Mean Composite Individual Daily Hot Flash Severity Score per week (HFSS): Composite Individual Hot flash severity = [(1 x (# of mild) + 2 x (# of moderate) + 3 x (# of severe)] / (Total # hot flashes on that day)

Plots of these data versus time will be constructed so that visual trends may be readily observed.

Analyses of Secondary Efficacy Data

Analyses of Secondary End Points (HFRDIS, ISI, MENQOL, FSS, and AIMS) will include evaluation of changes in scores of each of the above scales from baseline. Descriptive statistics and graphical methods will be used to characterize the changes as well as to compare the G-CSF and Placebo groups.

Descriptive statistics will be used to summarize changes from baseline throughout the entire 12 weeks in Hot Flash Related Daily Interference Scale (HFRDIS); Insomnia Severity Index (ISI); Menopause Specific Quality of Life Questionnaire (MENQOL); Fatigue Severity Scale (FSS), and Arthritis Impact Measurement Scale (AIMS). The HFRDIS, ISI, MENQOL, FSS, and AIMS will also be scored at all relevant study weeks (Baseline, Days 28, 56, and 84).

Analyses of Safety Data

Safety data will be presented using the Safety Analysis Set. Summary statistics for demographic data will be presented in tabular form for subject characteristics (age, menopause type, etc.).

Descriptive statistics will be used to summarize safety data, and summary tables for all AEs will be generated. Additional summary tables may be generated for subjects with related AEs, subjects with SAEs, subject deaths, and subjects who discontinue due to AEs.

Analyses of Exploratory Data

Descriptive exploratory analyses will be performed to determine whether or not G-CSF or placebo administration affects endogenous circulating hormone levels (FSH, LH, TSH, DHEA, DHEAS, testosterone, and estradiol) and proinflammatory cytokine effects (including but not limited to IL-1, IL-6, IL-8, and TNF-alpha) at every visit. ANOVA will be performed as described above.

7.3 Data Review and Acceptance

Clinical data will be entered by the clinical site coordinators into REDCap.

REDCap (Research Electronic Data Capture) is a HIPAA compliant, secure, web-based application designed exclusively to support data capture for research studies. REDCap provides:

1) An intuitive interface for data entry (with data validation)
2) Procedures for importing data from external sources
3) Automated export procedures for seamless data downloads to common statistical packages
4) Audit trails for tracking data manipulation and export procedures

REDCap use is underwritten by Colorado Clinical Translational Sciences Institute (CCTSI) for all studies approved by an investigational review board (IRB).

After entry of the clinical data is verified by the Project Monitor/Manager (PM), the PM and the Medical Monitor or designee will review the eCRF data/data listings. Review of the data will be according to the Data Management Plan (DMP). Queries will be created, sent to the site for resolution, and updated into the clinical database, all by the Project Manager.

If adverse event coding is deemed necessary, it will be conducted by the PM or designee. All coding will be reviewed by the Medical Monitor for correctness and consistency.

After all data have been entered and reviewed, reconciliation has been performed, all discrepancies have been resolved, and the clinical database accurately reflects the eCRF data and query resolution, the database will be audited and locked.

7.4 Missing or Incomplete Data and Methods of Handling Missing Data

Data will be reported as they are collected. No imputation will be used. A weekly hot flash score will be computed based on available data if at least 4 daily scores are reported for a subject foe a given week.

7.5 Outliers

No adjustments for outliers will be made.

7.6 Characteristics of the Distribution

Binary outcome variables, such as rates of adverse events, will be assumed to follow binomial distributions. Laboratory data such as biochemistry and hematology parameters will be assumed to follow Normal distributions. Change from baseline in self-report data will be assumed to follow a normal distribution. If deviations from Normality are apparent, nonparametric (rank-based) methods may be employed.

7.7 Subject Disposition Analysis

The number of enrolled subjects will be tabulated for the placebo or G-CSF group in the study.

Summary tables showing the distribution of subjects (number and percent) in each group will be generated for all randomized subjects.

7.8 Description of Baseline Characteristics and Baseline Comparisons

Demographic and baseline characteristics including age, race, BMI, menopause status, and smoking history will be tabulated for each group. The distribution of subjects, including number and percentage of total subjects, will be shown for the categorical variables. The univariate summary statistics N, median, minimum, and maximum will be calculated for all continuous variables. Mean, standard deviation, and standard error may also be reported when appropriate.

7.9 Concomitant Medications

All concomitant medications, indications, start dates, and stop dates will be listed. Medications will be coded using the generic name.

7.10 Safety Analyses

Safety will be analyzed as the Safety Analysis Set. All subjects who receive an injection of G-CSF or placebo will be considered evaluable for all safety analyses.

Descriptive statistics will be used to summarize safety data, and summary tables for all AEs will be generated. Additional summary tables may be generated for the following population subsets: subjects with related AEs, subjects with SAEs, subjects with related SAEs, subject deaths, and subjects who discontinue due to AEs.

7.10.1 Adverse Events

Incidence of AEs will be summarized by seriousness, deaths, and discontinuation due to adverse events. Severity, Investigator-attributed relationship to study drug, duration, and outcome of the events will also be recorded. These AEs will be reported verbatim. The number and percent of each event will be calculated and summarized. Signs and symptoms reported at baseline will be coded and mapped in the same manner as AEs. Summary tabulations of all AEs, SAEs, related AEs, and related SAEs will be generated for the placebo and G-CSF groups. Summary tabulations and data listings will be generated to support each of these summary tables.

7.10.2 Clinical Laboratory Data

Descriptive statistics will be used to summarize lab data. Chemistry and CBC data will be displayed in tabular form, with values outside of normal ranges noted.

Data listings will be generated for all laboratory parameters for each Subject. These laboratory parameters will include CBC with differential (including RBC, WBC, platelets, hemoglobin, hematocrit, RDW, MCV, MCH, MCHC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils [absolute], lymphocytes [absolute], monocytes [absolute], eosinophils [absolute], basophils [absolute]) and chemistry (including sodium, potassium, calcium, ALT, AST, bilirubin, creatinine, BUN, alkaline phosphatase, and albumin). Values outside of normal

ranges will be flagged. Normal ranges from the central clinical laboratory will be used to determine whether or not a value is out of range.

8 TESTING, VALIDATION, AND SOFTWARE

Initial data summaries will be written in Microsoft Excel 2112. All tables, listings and figures will be validated against original data in REDCap.

Statistical analyses will be run using SAS (Statistical Analysis Software Package) v 9.4 (SAS Institute, Cary, North Carolina). Data summaries written using Microsoft Excel will be used to validate descriptive statistics in SAS tables and figures.

9 APPENDICES

9.1 Glossary of Abbreviations

AE	Adverse event	ISI	Insomnia Severity Index
ALT	alanine aminotransferase (SGPT)	ITT	Intent-to-treat
AST	aspartate aminotransferase (SGOT)	LH	luteinizing hormone
BMI	Body mass index	MCH	Mean corpuscular hemoglobin
BUN	blood urea nitrogen	MCHC	Mean corpuscular hemoglobin concentration
Ca	calcium	MCV	Mean corpuscular volume
Cl	chlorine	N (n)	Sample size
CCTSI	Colorado Clinical Translational Sciences Institute	PM	Project manager
CRA	Clinical Research Associate	PP	Per Protocol
DMP	Data Monitoring Plan	PSQI	Pittsburgh Sleep Quality Index
eCRF	electronic case report form	RBC	Red blood cell
DHEA	dehydroepiandrosterone	RDW	Red cell distribution width
DHEAS	dehydroepiandrosterone-sulfate	REDCap	Research Electronic Data Capture
FSH	follicle-stimulating hormone	rmANOVA	Repeated measures analysis of variance
FSS	Fatigue Severity Scale	SAE	Serious adverse event
G-CSF	Granulocyte Colony-Stimulating Factor	SC	Subcutaneous
GGT	gamma-glutamyltransferase	SEM	Standard error of the mean
HFRDIS	Hot Flash Related Daily Interference Scale	SC	Subcutaneous
IL-1	Interleukin-1	TNF-α	Tumor necrosis factor alpha
IL-6	Interleukin-6	TSH	Thyroid stimulating hormone
IL-8	Interleukin-8	US	United States
IRB	Institutional Review Board	WBC	White blood cell

9.2 Table, Figure, and Listing Shells

Table 1: Disposition of Subjects

	G-CSF (n=X)		Placebo (n=X)		Total (N=X)	
	n	(%)	n	(%)	n	(%)
All Randomized						
Full Analysis Set	X	(XX)	X	(XX)	X	(XX)
Safety Analysis Set	X	(XX)	X	(XX)		
Per Protocol Analysis Set						
Completed Study	X	(XX)	X	(XX)	X	(XX)

Table 2: Summary of Demographic Characteristics and Baseline Assessments

	G-CSF (N=X)		Placebo N=X)		Total (n=X)	
Characteristic	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Race n (%)						
White	X	(XX)	X	(XX)	X	(XX)
Black	X	(XX)	X	(XX)	X	(XX)
Asian	X	(XX)	X	(XX)	X	(XX)
Hispanic	X	(XX)	X	(XX)	X	(XX)
Other	X	(XX)	X	(XX)	X	(XX)
Age at Baseline (Years)						
< 50	X	(XX)	X	(XX)	X	(XX)
50-55	X	(XX)	X	(XX)	X	(XX)
55-60	X	(XX)	X	(XX)	X	(XX)
60-65	X	(XX)	X	(XX)	X	(XX)
Surgical or Natural Menopause						
Surgical	X	(XX)	X	(XX)	X	(XX)
Natural	X	(XX)	X	(XX)	X	(XX)

Table 3: Summary of Continuous Demographic Characteristics and Baseline Assessments

Parameter	Value	G-CSF (N=X)	Placebo (N=X)	Total (N=X)
Age (Years)	Mean (SD)	XX (xx.x)	XX (xx.x)	XX (xx.x)
	Median	XX	XX	XX
	Min-Max	XX-XX	XX-XX	XX-XX
Weight (kg)	Mean (SD)			
	Median	XX	XX	XX
	Min-Max	XX-XX	XX-XX	XX-XX
Height (cm)	Mean (SD)			
	Median	XX	XX	XX
	Min-Max	XX-XX	XX-XX	XX-XX
BMI	Mean (SD)			
	Median	XX	XX	XX
	Min-Max	XX-XX	XX-XX	XX-XX
Baseline Daily Hot Flash THF (Weekly Mean)	Mean (SD) Median (Range)			
Baseline Daily Hot Flash Moderate Plus Severe (M+S) **(Weekly Mean)**	Mean (SD) Median (Range)			

Table 4: Baseline Visit Signs and Symptoms

	G-CSF (n=X)		Placebo (n=X)		Total (N=X)	
Verbatim Baseline Signs and Symptoms	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Total Subjects with Any Baseline Sign or Symptom						

Table 5: Menopause-related and Other Concomitant Medications

Therapeutic Class	G-CSF (n=X)		Placebo (n=X)		Total (N=X)	
	n	(%)	n	(%)	n	(%)

Table 6: Overall Summary of Safety

	G-CSF (n=X)		Placebo (n=X)		Total (N=X)	
	n	(%)	N	(%)	n	(%)
Subjects with at least 1 AE						
Subjects with at least 1 study-treatment-related AE						
AEs regardless of causality by worst severity						
Mild						
Moderate						
Severe						
Life-threatening						
Study-treatment-related AEs by worst severity						
Mild						
Moderate						
Severe						
Life-threatening						
Subjects with at least 1 SAE						
Subjects with at least 1 study-treatment-related SAE						
Subject with study discontinuation due to AE						

Table 7: Incidence of Subjects with Adverse Events Regardless of Causality

	G-CSF (n=X)						Placebo (n=X)						Total (n=X)					
	Any Severity		Mild	Moderate	Severe	Life-threatening	Any Severity		Mild	Moderate	Severe	Life-threatening	Any Severity		Mild	Moderate	Severe	Life-threatening
Verbatim AE	**n**	**(%)**	**n**	**n**	**n**	**n**	**n**	**(%)**	**n**	**n**	**n**	**n**	**n**	**(%)**	**n**	**n**	**n**	**n**
Total Subjects with Any AE																		
Headache																		
Etc.																		

Note: This table classifies Subjects/events using initial Placebo or G-CSF assignments
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
The "Any Severity" column will include number of incidences and percentages; others will include only the number of incidences.

Figure 1: Mean (SE) of Composite Daily Score (CDS) vs. Time

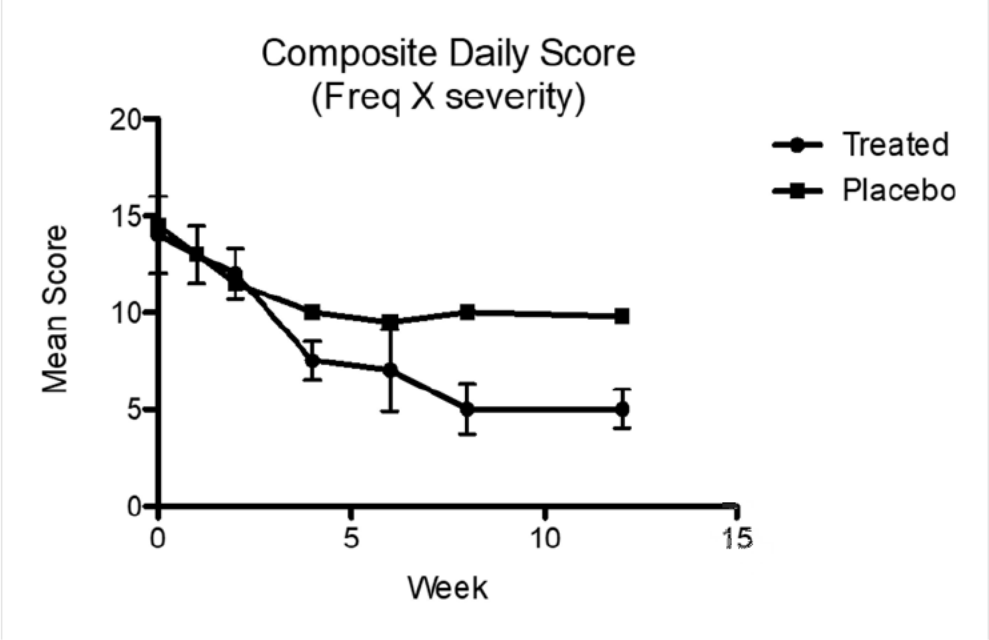


Figure 1b: Change from Baseline (SE) of Composite Daily Score (CDS) vs. Time

Table 7 and 7b: data to accompany Figure 1 and 1b

Figure 2: Mean (SE) Number of Hot Flashes of Any Severity (THF) vs. Time

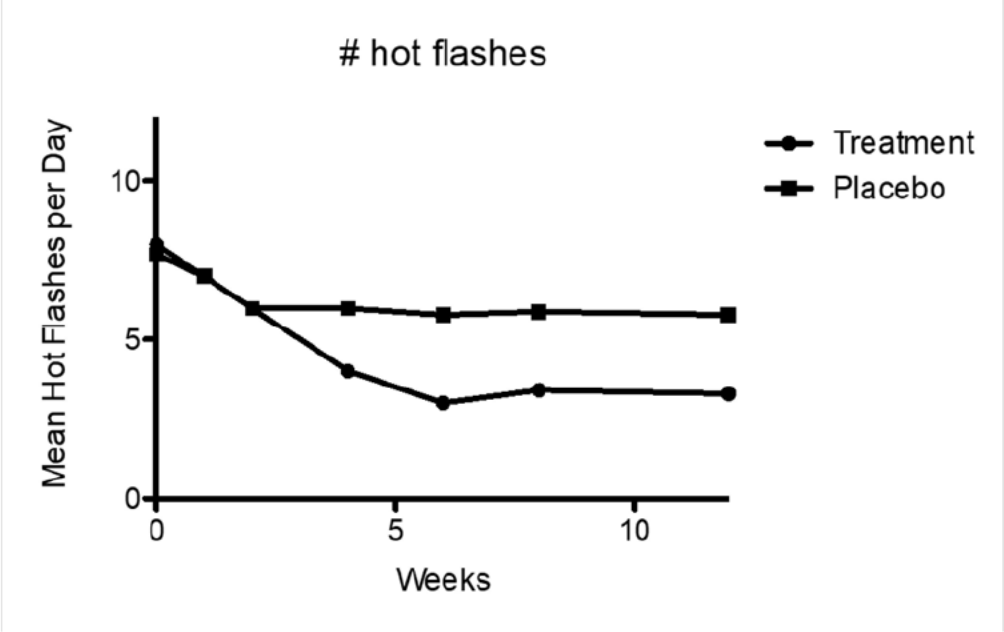


Figure 2b: Change from Baseline (SE) in Number of Hot Flashes of Any Severity (THF) vs. Time
Table 8 and 8b: data to accompany Figure 2 and 2b

Figure 3: Mean (SE) Number of Moderate+Severe Hot Flashes (M+S) vs. Time

Figure 3b: Change from Baseline in Number of Moderate+Severe Hot Flashes (M+S) vs. Time

Table 9 and 9b: data to accompany Figure 3 and 3b

Use format for Figure 2, including only moderate and severe hot flashes.

Figure 4: Mean (SE) Daily Hot Flash Severity Score

Figure 4b: Reduction from Baseline in Daily Hot Flash Severity Score (HFSS)

Table 10 and 10b: data to accompany Figure 4 and 4b

Figure 5: Percent Reduction in Total Number of Hot Flashes vs. Time

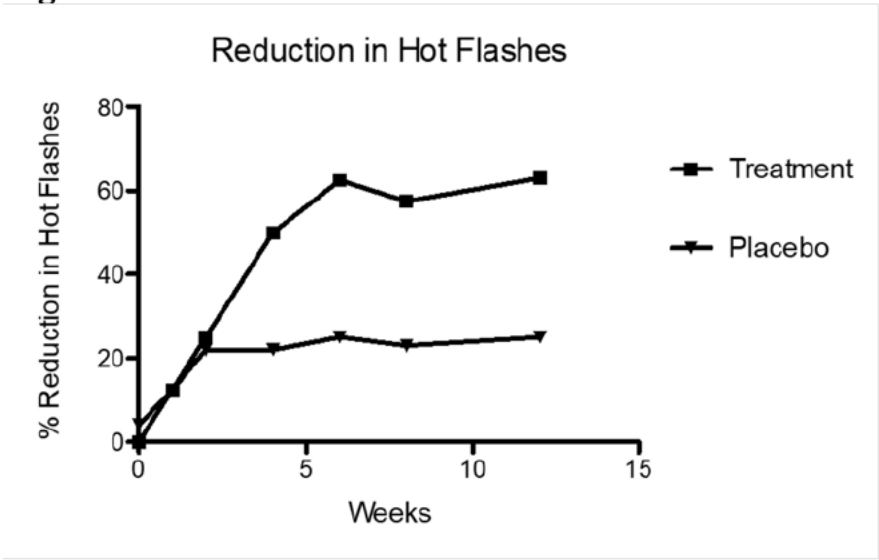
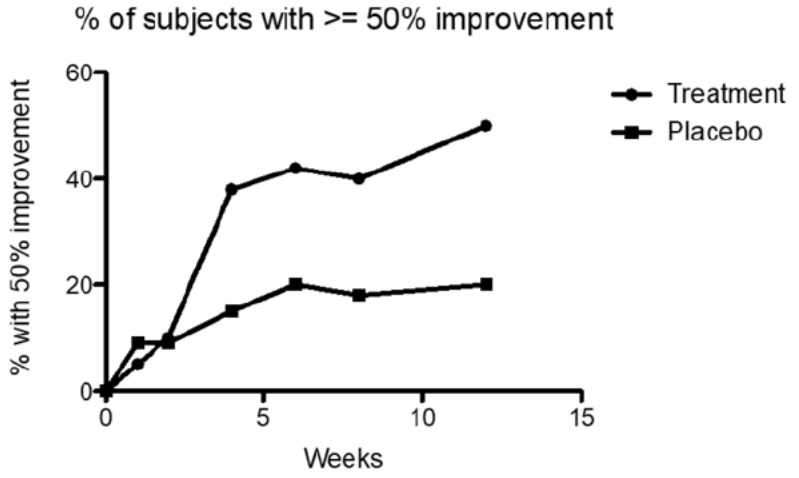


Table 11: data to accompany Figure 5

Figure 6: Percentage of Subjects Showing at least 50% Reduction in Total Hot Flashes



Note: Consider bar chart over time instead of line graph if feasible.

Table 12: data to accompany Figure 6

Listing 1: Subject Disposition

Subject	Surgical or Natural Menopause	Treatment	1st Dose Start Date	2nd Dose Date	3rd Dose Date	Date off Study	Days hot flash diary completed
101-1101		G-CSF	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	
102-1102		Placebo	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	
103-1203			ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	ddMMMyyyy	
Etc.							

"Start Date" should be the day of first dose.

Listing 2: Demographics and Baseline Assessments

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Age	Race	Ethnicity	Consent Date	First Date of Last Period	Date of Surgically Induced Menopause
101-1101		G-CSF		White	Hispanic/Latino	ddMMMyyyy	ddMMMyyyy	(blank)
102-1102		Placebo		Black	Not Hispanic/Latino			ddMMMyyyy
103-1203				Asian	Unknown			
Etc.				Hispanic				
				Other				

Listing 3: Baseline Assessments

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Subject Met All Inclusion Criteria	Inclusion Criteria Not Met	Subject Met Any Exclusion Criteria	Exclusion Criteria Met	Pregnancy Test	BMI
101-1101		G-CSF						
102-1102		Placebo						
103-1203								
Etc.								

Inclusion/Exclusion should be recorded as "Yes" or "No".
"Pregnancy Test" should be reported as "Positive" or "Negative".

Listing 4: Medical and Surgical History

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Medical History Diagnosis/ Surgical Procedure
101-1101		G-CSF	
102-1102		Placebo	
103-1203			
Etc.			

Start date should be "Unknown" when unknown.
Date should be in the ddMMMyyyy format when available. If only year is available, list only the year.

Listing 5: Prior Hot Flash Treatments

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Prior Treatment	Start Date	Stop Date
101-1101		G-CSF		ddMMMyyyy	ddMMMyyyy
102-1102		Placebo			MMMyyyy
103-1203					yyyy
Etc.					

Dates should be reported in the ddMMMyyyy format when available. If only year is available, list only the year (list as much of date as available).

Listing 6: Baseline Physical Examination Abnormalities

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Date of Exam	Body System	Result	Abnormalities
101-1101		G-CSF	ddMMMyyyy	General Appearance	Abnormal	(text)
		Placebo		Dermatologic	Abnormal	(text)
				HEENT		
				Lymphatic		
				Breast Exam		
				Pelvic Exam		
				Cardiovascular		
				Gastrointestinal		
				Neurological		
				Other		
Etc.						

Only PE abnormalities will be listed. Body systems will be assumed to be Normal unless otherwise noted.

Listing 7: Vital Assessments

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Date of Exam	Study Week	Pulse (/min)	Blood Pressure (Sys/Dia)	Weight (kg)
101-1101		G-CSF	ddMMMyyyy	Baseline	XXX	XXX/XXX	XX.X
			ddMMMyyyy	Week 4			
				Week 8			
				Week 12			
102-1102		Placebo	ddMMMyyyy	Baseline			
			ddMMMyyyy	Week 4			
				Week 8			
				Week 12			
Etc.							

Listing 2: Concomitant and Prestudy Medications

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Medication	Indication	Prophylactic Use	Pre-study	Date Started	Date Stopped
101-1101							ddMMMyyyy	ddMMMyyyy
102-1102							ddMMMyyyy	ddMMMyyyy
Etc.							ddMMMyyyy	Ongoing

Listing 8: Average Weekly Hot Flash Severity Count (mild, moderate, severe) by Week (add 2nd and 3rd dose dates)

Subject	Placebo or G-CSF	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
		Screening/ Baseline			Week 1			Week 2			Week 3			Week 4			Week 5			Week 6			Week 7			Week 8			Week 9			Week 10			Week 11			Week 12		
101-1101	G-CSR																																							
	Placebo																																							
Etc.																																								

These data can be included in an appendix rather than an in-text table unless they are relevant to the interpretation.

Listing 9: Adverse Events Regardless of Causality

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Adverse Event (Verbatim)	AE Onset Date	AE Stop Date	Severity	Related to Study Treatment	Serious	Action Taken
101-1101				ddMMMyyyy	ddMMMyyyy	Mild	Yes	Yes	
						Moderate	No	No	
						Severe			
						Life-threatening			
Etc.									

Listing 10: Hematology

Subject	Placebo or G-CSF	Lab Date	Study Day	Hgb (Units)	WBC (Units)	Neuts (units)	Lymph (units	etc											
101-1101		ddMMMyyyy																	

All measured hematology parameters will be reported. Data will be listed out directly from REDCap. These data can be included in an appendix rather than an in-text table unless they are relevant to the interpretation.

Listing 11: Chemistry

- Use the same format as Listing 11, with chemistry lab tests.
- Please order the biochemistry parameters as Creatinine, Total Bilirubin, AST (SGOT), ALT (SGPT), Albumin, Alkaline Phosphatase, Gamma-GT (GGT), and Triglycerides. Further parameters may be added on a data-driven basis. If lab parameters which are not graded are chosen to be in the table, the column for grade will be empty for those parameters for the entire listing.
- HbA1c, TSH and FSH lab tests will be included for the screening visit only.
- *All measured chemistry parameters will be reported, also directly from REDCap.*

Listing 32: Protocol Deviations

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Visit Name	Type of Deviation	Description of Protocol Deviation
101-1101					

10 HFRDIS, ISI MENQOL, FSS, AND AIMS2-SFSCORING CRITERIA AND INSTRUCTIONS

Hot Flash Related Daily Interference Scale (HFRDIS)

The Hot Flash Related Daily Interference Scale (HFRDIS) measures (as a score of 0 to 10) the effect of hot flashes on overall quality of life and on nine specific activities: work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, and enjoyment of life. The 10 answers are added up to get a total score.

Insomnia Severity Index (ISS)

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score.

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = Total score

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Menopause-specific Quality of Life (MENQOL) Questionnaire

The MENQOL is self-administered and consists of a total of 29 items in a Likert-scale format. Each item assesses the impact of one of four domains of menopausal symptoms, as experienced over the last month: vasomotor (items 1–3), psychosocial (items 4–10), physical (items 11–26), and sexual (items 27–29).

Items pertaining to a specific symptom are rated as present or not present, and if present, how bothersome on a zero (not bothersome) to six (extremely bothersome) scale. Means are computed for each subscale by dividing the sum of the domain's items by the number of items within that domain. Non-endorsement of an item is scored a "1" and

endorsement a “2,” plus the number of the particular rating, so that the possible score on any item ranges from one to eight.

Fatigue Severity Scale (FSS) of Sleep Disorders

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue. The FSS is a short questionnaire that requires the subject to rate level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of fatigue symptoms.

Each statement is read and the corresponding number from 1 to 7 is circled, based on how accurately it reflects the condition during the past week and the extent to which you agree or disagree that the statement applies to you.

A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value
(e.g., 7) indicates strong agreement.

Total Score:

Scoring your results
Now that you have completed the questionnaire, it is time to score your results and evaluate your
level of fatigue. It's simple: Add all the numbers you circled to get your total score.

The Fatigue Severity Scale Key
A total score of less than 36 suggests that you may not be suffering from fatigue.

Arthritis Impact Measurement Scales 2 (AIMS2-SF)

In AIMS2, the response format has been standardized across sections to 5-point scales. For scoring, the Guttman scaling is ignored and each item is scored separately without weights. Higher scores indicate greater disability. The score for each section is standardized to a 0–10 scale using a standardization formula.

Scale:

Guttman.

Score range:

Range is 0 –10 for each section. Total health score 0 – 60.

Interpretation of scores:

Zero represents good health status, 10 and 60 represent poor health status.

Method of scoring:

Each section contains a Guttman Scale (a series of questions/statements that are graded so that endorsement of one level of disability automatically indicates disability on all levels below it). In AIMS the number of response options within the Guttman scales varies across sections. In AIMS2, the response format has been standardized across sections to 5-point scales. For scoring, the Guttman scaling is ignored, and each item is scored separately without weights. Higher scores indicate greater disability. The score for each section is standardized to a 0 –10 scale using a standardization formula. The total health score is calculated by summing the standardized scores for mobility, physical and household activities, dexterity, pain, and depression.

11 APPENDIX

Total Daily Hot Flash Count for Individual Subject

Subject	Surgical or Natural Menopause	Placebo or G-CSF	Date	StudyWeek	Study Day	#Mild	# Moderate	#Severe	Daily Total
101-1101		G-CSF	ddMMMyyyy	1	1				
		Placebo		1	2				
				1	3				
				1	4				
				1	5				
				1	6				
				1	7				
				2	8				
				2	9				
				2	10				
				2	11				
				2	12				
				2	13				
				2	14				

These data will be included in an appendix, reported directly from REDCap.