NCT04447417

STATISTICAL TECHNICAL DOCUMENT

SAR231893/REGN668 - LPS15991

Open label exploratory study to evaluate the effect of dupilumab on skin barrier function in patients with moderate to severe atopic dermatitis

---

STATISTICIAN: [redacted]

DATE OF ISSUE: 06-Jul-2021

Total number of pages: 10

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD:	atopic dermatits
GISS:	global individual signs score
HV:	healthy volunteer
ISS:	individual signs score
MedDRA:	medical dictionary for regulatory activities
mITT:	modified-Intent-to-treat
SD:	standard deviation
STS:	skin tape stripping
TEAE:	treatment-emergent adverse event
TEWL:	transepidermal water loss
WHO-DD:	World Health Organization Drug Dictionnary

1 STATISTICAL AND ANALYTICAL PROCEDURES

1.1 INTRODUCTION

The purpose of this document is to provide additional technical details.

A comprehensive and detailed description of strategy and statistical technique used to perform the analysis of data was provided in Section 9 of the protocol (amendment 01, dated 28-Jul-2020).

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 24.0).

Previous and concomitant medication records will be coded according to the World Health Organization Drug Dictionary (WHO-DD version March 2021).

The definitions of potentially clinical significant abnormalities (PCSA list, BTD-009536 Version 3.0, dated 24 May 2014) used in the statistical analysis of vital signs are provided in Section 3.1 (for adult healthy volunteers), Section 3.2 (for adult atopic dermatitis patients) and Section 3.3 (for minor participants).

1.2 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

This section describes the modifications and additional statistical analyses from the protocol.

Due to unbalance between adults and adolescents atopic dermatitis (AD) patients, analyses based on age group (adult/adolescent) will only be performed for adverse event (AE) data reporting.

The study objectives are exploratory. Sample size was not based on power requirements. No multiplicity correction will be used for the tests performed as part of the statistical analyses.

Analysis population

Any participant with major deviation impacting assessment of efficacy data (except for deviations concerning AD related prohibited therapy administration) will be excluded for the modified-Intent-to-treat (mITT) population.

Demographic and medication data

Descriptive statistics for disease duration since AD diagnostic will be provided by cohort and age group (adults/adolescents).

Medications (including rescue medications) administered during the follow-up period will be summarized, in addition to previous and concomitant medications.

Efficacy analysis

Change from baseline in TEWL data is defined as change versus Day 1 TEWL data at matched number of STS samples (eg, TEWL after 5 STS at Week 16 will be compared to TEWL after 5 STS at Day 1).

Individual Signs Score (ISS) questionnaire was not done as planned per protocol. Instead, to assess lesion severity locally, Quantificare evaluation data will be used. Global Individual Signs Score (GISS) was evaluated during the study. Both Quantificare data and GISS data will be analyzed using descriptive statistics for raw data, absolute and percent by timepoints. For AD patients, on mITT population, correlation with TEWL data will be evaluated. Scatterplots will be provided to visualize the form of the relationship and Spearman's rank correlation coefficient as well as p-values at specific timepoints (Baseline, Week 8 and Week 16) will be provided.

Adverse event data

All summary of AEs will be provided by cohort and age group.

1.3 DATA HANDLING CONVENTIONS

This section describes the rules and conventions used in the presentation and analysis of data.

In the statistical appendices and in-text tables, the following cohort label and group label will be used:

- Cohort label:
  - AD patients
  - Healthy volunteers
- Group label:
  - AD patients – lesional skin
  - AD patients – non-lesional skin
  - HV – healthy skin

For parameters with evaluations before administration and in cases of rechecked value(s) for one subject, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values. After baseline, only observations planned in the protocol will be used in descriptive statistics.

If not otherwise stated in the statistical section of the protocol:

- Missing TEWL data (including data from visits excluded of the efficacy analyses after the use of prohibited medication) will be imputed using Last Observation Carried Forward (LOCF) imputation ; sensitivity analyses will be performed to assess the precision of LOCF imputation versus MMRM imputation.
- Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), minimum, maximum and median.
- Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percent (%).

Handling missing data for adverse events

In case of missing or inconsistent information on the time of onset, an AE will be counted as a treatment-emergent adverse event (TEAE) unless it can clearly be ruled out that it is not a TEAE (eg, by partial dates or other information).

2 SOFTWARE DOCUMENTATION

The analysis of clinical data will be performed under the responsibility of Sanofi Biostatistics Department, using SAS® (SAS Institute, NC USA).

3 LIST OF APPENDICES

3.1 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA – ADULT HEALTHY VOLUNTEERS

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in healthy subjects only

Parameter	PCSA	Comments
Vital signs		
HR	≤40 bpm and decrease from baseline ≥20 bpm ≥100 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥140 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥90 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SBP Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	-
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

3.2 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALISTIES CRITERIA – ADULT ATOPIC DERMATITIS PATIENTS

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	 ≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

3.3 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA – MINOR PARTICIPANTS

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Vital Signs			Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85 mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50 mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54 mHg and increase from baseline ≥10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59 mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP: St — Su ≤- 20 mmHg DBP: St — Su ≤- 10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C Axillary or skin infrared: ≥99 °F/37.2 °C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	
Sa02	All age ranges	≤95 %	
Weight	All ranges	≥5 % weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007