Statistical Analysis Plan

SCR-005: Assessment of the Human Systemic Absorption of Sunscreen Ingredients

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Contents

1 Study Objectives

The primary objective of this study is:

1. To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of sunscreen products are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

1.1 Primary Objective (Part 1)

Part 1 is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective:

- To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

1.2 Primary Objective (Part 2)

Part 2 is an open-label, 4-arm study in 48 healthy adult subjects with the following primary objective:

- To assess, where applicable, the pharmacokinetics and systemic absorption of the active components (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, of 4 sunscreen products (1 sunscreen product in each arm) under maximal-use conditions.

Part 2 will include the sunscreen product with maximal avobenzone exposure from Part 1 and 3 additional new sunscreen formulations. More detailed information about the study (inclusion/exclusion criteria and schedule of events) can be found in the study protocol.

2 Sample Size

Approximately 72 healthy subjects are planned for enrollment, of which 24 will be assigned to Part 1 (randomized to 4 arms of 6 participants each) and 48 will be assigned to Part 2 (randomized to 4 arms of 12 participants each). Subjects are considered enrolled after determination by the Principal Investigator on Day 0 that they meet all eligibility criteria and are subsequently assigned a randomization/study identification number. The sample size was determined empirically and is typical for exploratory investigations of this type.

3 Analysis Populations

The analysis population will include all subjects who receive at least 1 dose of any of the study drugs and have PK sample data for the treatment period collected before dosing and at 1 or more time points after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

4 General Statistical Considerations, Subject Disposition and Demographics and Baseline Characteristics

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Continuous demographic and baseline characteristic variables (age, height, weight, body mass index) will be summarized overall and by treatment using descriptive statistics (number of subjects, mean, standard deviation [SD], median, interquartile range [IQR], and minimum and maximum). The number and percentage of subjects in each class of categorical demographic and baseline characteristic variables will also be summarized.

5 Pharmacokinetic (PK) Analyses and Primary/Secondary Outcomes

The PK sampling schedule for this study is summarized in Appendix A. The following PK parameters will be determined for each subject in Part 1 and Part 2:

Across all study days

- Maximum concentration (observed peak drug concentration) (C_{max})

Day 1

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- AUC from time 0 to the 23 hour time point (C_{last}) (AUC_{0-23})

Days 2 and 3

- Residual drug concentration (predose level) (C_{trough})
- Concentration 3 hours after the last dose of the day

Day 4

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- Elimination rate constant (K_{el}) and terminal half-life ($t_{1/2}$); calculated after final dose using all the available data up to last study sample (144 hours for Part 1; 432 hours for Part 2)
- AUC from time 71 to the 95 hour time point (AUC_{73-95})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}) and/or last observed time point

Day 5, 6, 7, 10 (Part 2 only), 14 (Part 2 only) and 21 (Part 2 only)

- Residual drug concentration (C_{trough})

The primary and secondary outcomes of this study are as follows:

Primary Outcome:

1. Maximum* Avobenzone concentration (C_{max})

Secondary Outcomes:

1. Maximum* Oxybenzone concentration (C_{max})
2. Maximum* Octocrylene concentration (C_{max})
3. Maximum* Ecamsule concentration (C_{max})
4. Maximum* Homosalate concentration (C_{max})
5. Maximum* Octisalate concentration (C_{max})

6. Maximum* Octinoxate concentration (C_{max}) (Part 2 Only)

* observed maximum;

Note that Cmax could occur on any of the days of the study. PK parameters C_{max}, C_{last}, C_{trough}, T_{max}, AUC_{0-t}, K_{el}, $t_{1/2}$ and AUC_{0-inf}, will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum) for the days above for avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and/or octinoxate (depending on whether the specific sunscreen formulation contains each of the active ingredients; see Attachment B) in Part 1 and 2. The PK parameters will be analyzed using non-compartmental methods based on actual sampling times. Mean and individual concentration-time profiles will be presented in graphs.

6 Safety Analyses

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs), organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

Vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and changes from Baseline for these parameters will be summarized by treatment and time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

7 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in

the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

8 Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark remote electronic data capture (EDC) system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Attachment A. Pharmacokinetic Sample Collection Schedule

Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate plasma concentrations (where applicable to the different sunscreen formulations), at the following time points (the time limit for PK sample draws can be +/- 5 minutes from the nominal time):

- Day 1: 0 and 0.5, 1, 1.5, 2, 3 (Part 2 only), 4, 6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, 28, 33 h
- Day 3: 47, 52, 57 h
- Day 4: 71, 73, 74, 76, 78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours
- Day 10: 216 hours (Part 2 only)
- Day 14: 312 hours (Part 2 only)
- Day 21: 480 hours (Part 2 only)

NOTE: when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

Attachment B. Randomization Schedule

Randomization in this study is unblinded.

After screening, subjects will be randomized to one of 4 treatment sequences in either Part 1 (24 subjects) or Part 2 (48 subjects). Example of treatment codes from the study protocol:

- Treatment sequences of Part 1:
  - A: La Roche Posay (Cream), Anthelios SX Daily Moisturizing Cream with Sunscreen, SPF 15 with Mexoryl SX (6 subjects): Avobenzone (2%), Ecamsule (2%) and Octocrylene (10%)
  - B: Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (4%) and Octocrylene (6%)
  - C: Neutrogena (Spray), Ultra Sheer Body Mist SPF 45 (6 subjects): Avobenzone (3%), Oxybenzone (6%), Octocrylene (2.35%), Homosalate (15%) and Octisalate (5%)
  - D: Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (5%) and Octocrylene (10%)

- Treatment sequences of Part 2:
  - E: Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 (12 subjects): Avobenzone (3%), Oxybenzone (4%) and Octocrylene (6%)
  - F: Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100 (12 subjects): Avobenzone (3%), Oxybenzone (6%), Octocrylene (10%), Homosalate (15%) and Octisalate (5%)
  - G: Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50 (12 subjects): Avobenzone (3%), Octocrylene (10%), Homosalate (10%), Octisalate (5%) and Octinoxate (7.5%)
  - H: Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50 (12 subjects): Avobenzone (3%), Homosalate (10%),Octisalate (5%) and Octinoxate (7.5%)

The script performs randomization across treatment groups; all subjects in Part 1 will be studied in 1 cohort (cohort 1) and subjects in part 2 will be studied in 2 cohorts (cohorts 2 and 3).

Treatment schedule

RANDID	PART	COHORT	SEQ
1001	1	1	D
1002	1	1	A
1003	1	1	C
1004	1	1	B

1005	1	1	D
1006	1	1	B
1007	1	1	A
1008	1	1	C
1009	1	1	C
1010	1	1	B
1011	1	1	A
1012	1	1	D
1013	1	1	B
1014	1	1	A
1015	1	1	D
1016	1	1	C
1017	1	1	B
1018	1	1	A
1019	1	1	C
1020	1	1	D
1021	1	1	A
1022	1	1	D
1023	1	1	C
1024	1	1	B
2001	2	2	G
2002	2	2	E
2003	2	2	F
2004	2	2	H
2005	2	2	E
2006	2	2	G
2007	2	2	F
2008	2	2	H
2009	2	2	G
2010	2	2	E
2011	2	2	H
2012	2	2	F
2013	2	2	F
2014	2	2	G

2015	2	2	E
2016	2	2	H
2017	2	2	H
2018	2	2	E
2019	2	2	G
2020	2	2	F
2021	2	2	E
2022	2	2	F
2023	2	2	G
2024	2	2	H
2025	2	3	F
2026	2	3	H
2027	2	3	G
2028	2	3	E
2029	2	3	G
2030	2	3	H
2031	2	3	E
2032	2	3	F
2033	2	3	G
2034	2	3	E
2035	2	3	H
2036	2	3	F
2037	2	3	H
2038	2	3	E
2039	2	3	F
2040	2	3	G
2041	2	3	G
2042	2	3	E
2043	2	3	F
2044	2	3	H
2045	2	3	G
2046	2	3	E
2047	2	3	H
2048	2	3	F