

Office of Clinical Pharmacology Review

NDA Number	204141/ S-009
Submission Date(s)	12/15/2020 (SDN 119) – resubmission after a refuse to file 4/29/2020 (SDN 113) – original submission
Submission Type	Efficacy Supplement (S-009)
Brand Name	TOPICORT
Generic Name	Desoximetasone
Dosage Form and Strength(s)	Spray, 0.25% (w/w)
Route of Administration	Topical
Proposed Indication	Treatment of plaque psoriasis in patients 18 years of age and older
Applicant	Taro Pharmaceuticals
Associated IND	101789
Primary Reviewer	Soo Hyeon Shin, Pharm.D., Ph.D.
Secondary Reviewer	Chinmay Shukla, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology
OND Division	Division of Dermatology and Dentistry

Table of Contents

1. EXECUTIVE SUMMARY	2
1.1 Recommendations	2
1.2 Post-Marketing Requirements/Commitments	2
2. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS	2
2.1 Overall study design (Study DSXS-1303)	2
2.2 BSA Assessment	5
2.3 HPA Axis Suppression Assessment.....	5
2.4 Pharmacokinetics.....	6
2.5 Bioanalytical methods.....	9

1. EXECUTIVE SUMMARY

TOPICORT (desoximetasone) Topical Spray, 0.25% is currently approved for the treatment of plaque psoriasis in patients 18 years of age or older. Desoximetasone is a corticosteroid and it is considered as a high to super-high potency topical corticosteroid.

The current efficacy supplement is a re-submission after a refusal-to-file letter (RTF) was sent to the Applicant on 06/25/2020. The reason for the RTF letter for the initial submission (SDN 113) was because the original submission was missing labelling and bioanalytical method validation and bioanalysis reports for cortisol, in addition to other deficiencies identified from other disciplines.

The purpose of this supplement is to fulfill the post-marketing requirement (PMR) 2029-1.

2029-1 Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis ages 2 to 16 years and 11 months. Evaluate the safety and effect of Topicort (desoximetasone) Topical Spray, 0.25% on the hypothalamic-pituitary-adrenal (HPA) axis and pharmacokinetics (PK) of desoximetasone under maximal use conditions after 4 weeks of treatment. Conduct the trial in sequential cohorts, for example:

Cohort 1: age 12 years to 16 years and 11 months

Cohort 2: age 6 years to 11 years and 11 months

Cohort 3: age 2 years to 5 years and 11 months

To fulfill the PMR, the Applicant conducted Study DSXS-1303. The HPA axis suppression data was obtained from an adequate number of subjects as planned. The PK data was collected from Cohorts 1 and 2 only with less than 12 completers in each cohort. In Cohort 3, the Applicant did not get any PK samples citing difficulty in getting plasma samples and recruiting subjects.

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 204141/S-009 acceptable and finds the PMR 2029-1 fulfilled.

1.2 Post-Marketing Requirements/Commitments

None.

2. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

2.1 Overall study design (Study DSXS-1303)

Study DSXS-1303 was an open-label, post marketing safety study to assess the potential of a TOPICORT (desoximetasone) Topical Spray, 0.25% to suppress HPA axis function following twice daily dosing for 28 days.

Objectives of the study

The primary objective was to evaluate the potential for HPA axis suppression in pediatrics, aged 2 to 17 years of age. The secondary objectives were to evaluate the efficacy parameters, PK and adverse event profile.

Study subjects

A total of 129 subjects were enrolled to obtain 100 evaluable subjects. Eligible subjects were required to have a confirmed diagnosis of plaque psoriasis with body surface area (BSA) involvement of at least 10% (excluding the face and scalp). The participants were serially enrolled into 3 cohorts, based on their age as follows:

Cohort 1: age 12 years to 16 years and 11 months

Cohort 2: age 6 years to 11 years and 11 months

Cohort 3: age 2 years to 5 years and 11 months

The planned, enrolled, and completed subject disposition by study cohort is summarized below:

Cohort	Planned	Overall Study Completed/Enrolled (%)	HPA Subgroup Evaluable ^b /Completed (%)	PK Subgroup Completed/Enrolled (%)
1	10-60, including 12 for PK	66/84 (79%)	60/66 (91%)	11/17 (65%)
2	5-20, including 12 for PK ^a	30/35 (86%)	30/30 (100%)	8/8 (100%)
3	5-20, including 12 for PK ^a	10/10 (100%)	10/10 (100%)	0/0 (NA)

^a To minimize blood collection in young subjects, sparse PK samplings were planned in Cohorts 2 and 3.

^b Evaluable subjects are those with both baseline and end-of-study (Week 4) cortisol data.

Reviewer's comment: *The HPA axis suppression data was obtained from an adequate number of subjects as planned. However, the PK data was collected from Cohorts 1 and 2 only with less than 12 completers in each cohort. The Applicant has requested a partial waiver for PK evaluation in Cohort 3 due to difficulty recruiting subjects. Since the primary objective of this study was to evaluate the HPA axis suppression potential and that the decision was made to not approve this product in pediatrics due to high incidence of HPA axis suppression, the insufficient PK data obtained from this study does not affect the overall conclusion of this efficacy supplement.*

The demographic data for the PK subgroup and HPA subgroup are summarized in Table 1 and Table 2, respectively.

Table 1. Summary of Demographic Data (Evaluable PK Subgroup)

Demographic Category	Parameter	Cohort 1 (12 - <18 years)	Cohort 2 (6 - < 12 years)	Cohort 3 (2 - < 6 years)
Age (years)	Number of subjects (N)	17	8	0
	Mean (range)	14.9 (12-17)	9.3 (7-11)	-

	Median	15.0	9.0	-
Sex	Male	3 (17.6%)	5 (62.5%)	-
	Female	14 (82.4%)	3 (37.5%)	-
Ethnicity	Hispanic or Latino	17 (100.0%)	8 (100.0%)	-
	Not Hispanic or Latino	0 (0.0%)	0 (0.0%)	-
Race	White	12 (70.6%)	8 (100.0%)	-
	Other	5 (29.4%)	0 (0.0%)	-
Weight (kg)	Mean \pm SD	54.3 \pm 14.6	34.9 \pm 8.6	-
	Median	54.0	33.8	-
	Range	33 – 83.5	23 – 46.5	-
Height (cm)	Mean \pm SD	159.1 \pm 9.4	134.4 \pm 8.5	-
	Median	159.0	135.0	-
	Range	142 – 177	126 – 153	-

Source: Table 8, Integrated Summary of Safety

Table 2. Summary of Demographic Data (Evaluable HPA Subgroup)

Demographic Category	Parameter	Cohort 1 (12 - <18 years)	Cohort 2 (6 - < 12 years)	Cohort 3 (2 - < 6 years)
Age (years)	Number of subjects (N)	60	30	10
	Mean (range)	14.2 (12-17)	9.3 (7-11)	3.4 (2-5)
	Median	14.0	9.5	3.0
Sex	Male	25 (41.7%)	19 (63.3%)	4 (40.0%)
	Female	35 (58.3%)	11 (36.7%)	6 (60.0%)
Ethnicity	Hispanic or Latino	58 (96.7%)	30 (100.0%)	10 (100.0%)
	Not Hispanic or Latino	2 (3.3%)	0 (0.0%)	0 (0.0%)
Race	White	54 (90.0%)	21 (70.0%)	10 (100.0%)
	Other	6 (10.0%)	9 (30.0%)	0 (0.0%)
Weight (kg)	Mean \pm SD	60.9 \pm 14.2	38.4 \pm 9.9	17.0 \pm 4.8
	Median	58.0	40.3	16.0
	Range	35 – 103.5	22.5 – 61	13 – 29.5
Height (cm)	Mean \pm SD	164.9 \pm 37.1	136.3 \pm 8.7	102.7 \pm 10.5
	Median	160.0	135.0	99.0
	Range	130 – 439	121 – 153	88 – 125

Source: Table 7, Integrated Summary of Safety

Dosing regimen

The subject or parent/legal guardian were instructed to spray and rub in gently and completely the study drug to the affected areas twice daily (morning and evening) for 28 days. The mean amount of study product used per cohort is as below:

Parameter	Cohort 1 (12 - <18 years)	Cohort 2 (6 - < 12 years)	Cohort 3 (2 - < 6 years)
Evaluable Population (N = 100)			
Number of subjects (n)	60	30	10
Mean \pm SD (g)	95.5 \pm 38.5	77.2 \pm 40.7	85.5 \pm 27.2
PK Subgroup (N=25)			
Number of subjects (n)	16	8	0
Mean \pm SD (g)	76.1 \pm 45.3	97.4 \pm 54.5	--

Source: Table 11, Integrated Summary of Safety

2.2 BSA Assessment

At each visit, subjects were evaluated % BSA covered with plaque psoriasis. The results are summarized below in Table 3.

Table 3. Summary of % BSA Assessments Per Visit

Visit	Statistic	Cohort 1 (n=84)	Cohort 2 (n=35)	Cohort 3 (n=10)
Day 1	Mean ± SD	16.2 ± 8.3	18.8 ± 8.5	16.3 ± 6.0
	Median	12.0	16.0	15.0
	Range	10 - 50	11 - 38	12 - 32
	n	84	35	10
Day 8	Mean ± SD	21.9 ± 11.2	17.1 ± 7.9	0.0 ± 0.0
	Median	20.0	16.0	0.0
	Range	8 - 45	8 - 28	0 - 0
	n	17	8	0
Day 15	Mean ± SD	12.0 ± 7.8	11.5 ± 6.1	9.6 ± 4.5
	Median	9.0	8.5	7.0
	Range	0 - 50	5 - 25	6 - 18
	n	77	34	10
Day 22	Mean ± SD	8.9 ± 4.6	6.9 ± 3.8	0.0 ± 0.0
	Median	9.0	5.0	0.0
	Range	3 - 18	3 - 12	0 - 0
	n	12	8	0
Day 29	Mean ± SD	7.1 ± 7.5	4.6 ± 4.0	2.4 ± 2.4
	Median	5.0	3.0	2.5
	Range	0 - 52	0 - 14	0 - 6
	N	79	35	10

Source: Table 14.1.5, CSR DSXS-1303

Reviewer's comment: *The baseline disease severity in terms of % BSA affected was generally comparable across study cohorts. The enrolled subjects met the minimum requirement of at least 10% BSA involvement at baseline.* (b) (4)

2.3 HPA Axis Suppression Assessment

The cortisol response (ACTH stimulation) test was performed at baseline and at the end of treatment (non-PK sampling group) or post-treatment (PK sampling group) visit. Subjects with abnormal results were asked to return to the site for reassessment(s). HPA axis suppression in this study was defined as a cortisol level of ≤ 18 $\mu\text{g/dL}$ 30 minutes poststimulation at the end of the treatment. The HPA axis suppression assessment data is summarized by cohort and by geographic region (if applicable) in Table 4.

Table 4. Number of Subjects with HPA Axis Suppression

	Cohort 1 (12 - <18 years)		Cohort 2 (6 - <12 years)		Cohort 3 (2 - <6 years)
Number of subjects (N)	60		30		10
HPA Axis Suppression	21 (35.0%)		13 (43.3%)		2 (20.0%)
	Central America	United States	Central America	United States	(All Central America)
Number of subjects (N)	13	47	17	13	

HPA Axis Suppression	6 (46.2%)	15 (31.9%)	7 (41.2%)	6 (46.2%)	
----------------------	-----------	------------	-----------	-----------	--

Source: Table 13, Integrated Summary of Safety

A total of 36 subjects (36%) showed HPA axis suppression. Among these subjects, the suppression was reversible in 29 subjects after treatment cessation. Seven subjects were lost to follow up or refused follow up testing, of which 2 agreed to referral to an endocrinologist.

Reviewer's comments: *The observed HPA axis suppression rate in this study was higher than the rate observed in adults (36% vs. 14%). In addition, the high HPA axis suppression rate in Cohort 1 of 35% makes it not possible to carve out a population of pediatric subjects based on age where the treatment benefit could be justified. Therefore, this product should not be recommended for use in pediatric subjects.*

The Applicant defined HPA axis suppression as a cortisol level of ≤ 18 $\mu\text{g/dL}$ 30 minutes post-stimulation which is used by the Agency. A consultation review from Dr. Shivangi Vachhani, Clinical Reviewer, Division of General Endocrinology (DGE), stated that the criteria for HPA axis suppression commonly used in clinical practice is < 18 $\mu\text{g/dL}$ and not ≤ 18 $\mu\text{g/dL}$. According to Dr. Vachhani, if the cutoff criteria of < 18 $\mu\text{g/dL}$ is used, then a total of 31 (31%) subjects, including 19 (32%) subjects in Cohort 1, 10 (33%) subjects in Cohort 2 and 2 (20%) subjects in Cohort 3, would have been classified as having HPA axis suppression.

It is noted that using either criteria for HPA axis suppression, the rate of HPA axis suppression observed in this study is considered as high, and thus the overall conclusion that this product should not be recommended in pediatrics would remain the same.

2.4 Pharmacokinetics

The plasma concentrations of desoximetasone following twice-daily applications of desoximetasone 0.25% topical spray over 28 days. The PK samples were collected at the following time points:

Cohort 1:

- Days 1, 8, 15 and 22: morning pre-dose
- Day 29: morning pre-dose, and 15 min, 30 min, 40 min, 50 min, 60 min, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 12 h following the morning dose.

Cohort 2:

- Days 1, 8, 15, 22: morning pre-dose
- Day 29: morning pre-dose and at 1 h and 3 h following the morning dose.

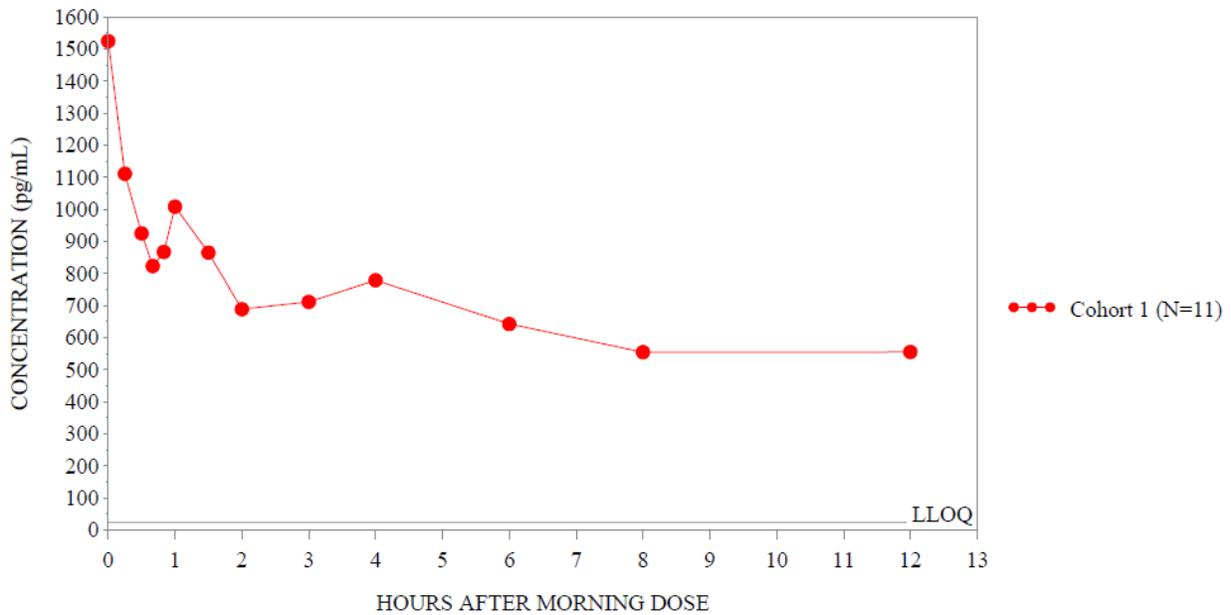
In Cohort 1, 16 subjects provided at least one post-dose PK blood sample from Day 8 onwards and 11 subjects completed the full PK sampling on Day 29. In Cohort 2, 8 subjects completed the PK sampling as planned from Day 8 to Day 29. The PK parameters by cohort is summarized in Table 5. The mean desoximetasone plasma concentrations on Day 29 from Cohorts 1 and 2 can be seen in Figures 1 and 2, respectively.

Table 5. Summary of PK Parameters for Desoximetasone from PK Subgroup

Cohort	Parameter	Mean	SD	CV (%)	Min	Median	Max	Geometric Mean	Geometric CV (%)	n
1	AUC _{ss} (h·pg/mL)	8141.86	10527.98	129.31	22.60	3417.26	34308.46	2400.43	1033.35	11
1	C _{12-ss} (pg/mL)	555.70	780.34	140.43	0.00	196.30	2619.50	366.51	185.02	11
1	C _{max-ss} (pg/mL)	1881.36	2396.01	127.35	51.10	552.40	7303.70	614.48	479.78	11
1	C _{pre-ss} (pg/mL)	1525.10	2242.21	147.02	0.00	535.00	7303.70	527.64	574.47	11
1	T _{max-ss} (h)	1.61	2.37	147.93	0.00	0.83	8.00	NA	NA	11
2	C _{max-ss} (pg/mL)	1116.36	998.66	89.46	94.20	1084.35	2386.30	589.20	239.35	8
2	C _{pre-ss} (pg/mL)	881.25	831.73	94.38	81.00	631.85	2116.50	475.41	215.66	8
2	T _{max-ss} (h)	1.38	1.41	102.39	0.00	1.00	3.00	NA	NA	8

Source: Table 11.3.1.1, CSR DSXS-1303

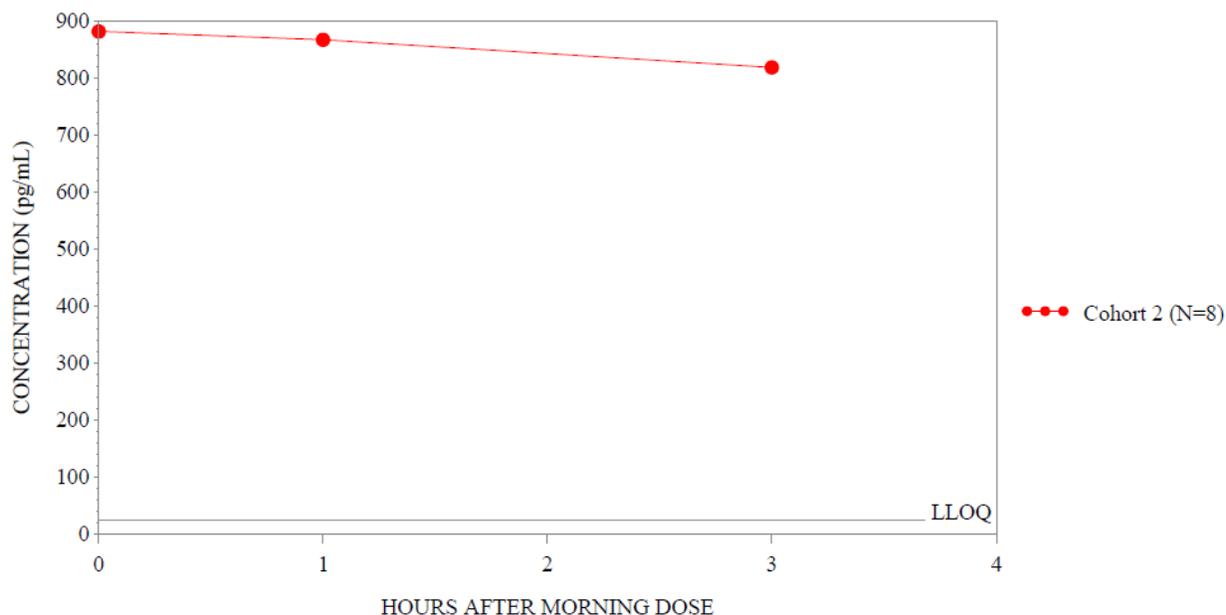
Figure 1. Mean Desoximetasone Plasma Concentrations on Day 29 from Cohort 1



Source: Figure 11.3.1.2, CSR DSXS-1303

Figure 2. Mean Desoximetasone Plasma Concentrations on Day 29 from Cohort 2

F16.1.9.1.3 Mean Desoximetasone Plasma Concentrations on Day 29 (± 2)



Mean concentration values below LLOQ (<25.0) in the terminal phase are not plotted

Source: Figure 11.3.1.4, CSR DSXS-1303

Reviewer’s comments: A high inter-subject variability in PK values was observed. While the mean PK parameter values (C_{max} and C_{trough}) are higher in Cohort 1 compared to Cohort 2, the geometric mean values are somewhat comparable between the two cohorts. High inter-subject variability and small sample size makes it difficult to interpret and compare the PK data; however, the overall extent of systemic exposure in these two age groups appear to be similar. Although a direct comparison with the available adult PK data is not possible since the PK sampling timepoints were different, the mean concentration of desoximetasone determined from two randomly collected samples in 24 adult subjects was lower (449 pg/mL on Day 14 and 678 pg/mL on Day 28), which is consistent with the lower HPA axis suppression observed in adults compared to pediatrics.

The PK parameters for desoximetasone by HPA axis suppression results and by cohort is summarized in Table 6.

Table 6. Summary of PK Parameters for Desoximetasone by HPA Axis Suppression Results

	Cohort 1 (12 - <18 years)		Cohort 2 (6 - < 12 years)	
	Suppressed	Non-Suppressed	Suppressed	Non-Suppressed
Number of subjects	5	11	4	4
Mean amount used	74.5 g	76.8 g	124.4 g	70.4 g
C_{pre-ss} (pg/mL)				

Mean (range)	2440.80 (1475.00 – 3743.00)	1181.71 (0.00 – 7303.70)	1112.98 (150.80 – 1751.60)	649.53 (81.00 – 2116.50)
CV (%)	47.97	212.34	64.12	150.98
C_{max-ss} (pg/mL)				
Mean (range)	3544.63 (2346.40 – 4544.50)	1257.64 (51.10 – 7303.70)	1538.65 (150.80 – 2386.30)	694.08 (94.20 – 2116.50)
CV (%)	31.38	198.27	62.76	138.13
AUC_{ss} (h·pg/mL)				
Mean (range)	20520.18 (12309.88 – 34308.46)	3499.99 (22.60 – 15805.63)	--	
CV (%)	58.54	147.95		

Source: Table 14, Integrated Summary of Safety

Reviewer's comments: Subjects with HPA axis suppression had higher systemic exposure compared to those without suppression. In Cohort 1, mean C_{pre-ss}, C_{max-ss}, and AUC_{ss} on Day 29 were 2.1-, 2.8- and 5.9-fold higher in the suppressed group compared to the non-suppressed group. In Cohort 2, mean C_{pre-ss} and C_{max-ss} on Day 29 were 1.7- and 2.2--fold higher in the suppressed group compared to the non-suppressed group.

2.5 Bioanalytical methods

To determine desoximetasone in plasma from samples collected in Study DSXS-1303, a validated HPLC method using MS/MS detection was employed. The method validation results are summarized in Table 7. The bioanalysis performance results are summarized in Table 8.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis for plasma samples were acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ±20% of the original sample concentrations). All samples were analyzed within the established long-term stability window.

The Applicant did not submit bioanalysis report for determination of cortisol levels and the Agency sent an information request asking for this report at the time of filing this application. The Applicant responded that the requested report was not available. Since the Applicant is not seeking a pediatric indication, the missing report does not prohibit the conclusion of this PMR fulfillment from a Clinical Pharmacology perspective.

Table 7. Summary of HPLC-MS/MS Bioanalytical Method Validation

Analytical Validation	TOU-W5-359(R2)
Short description of method	Solid-phase/Supported Liquid Extraction with 96-well plates Reversed-phase HPLC with MS/MS detection
Biological matrix	Human plasma
Anticoagulant	K2 EDTA
Analyte	Desoximetasone
Internal standard (IS)	Desoximetasone-D5
Calibration concentrations	25.0 pg/mL to 2500.0 pg/mL.
QC concentrations	25.0 pg/mL, 75.0 pg/mL, 500.0 pg/mL, 1250.0 pg/mL and 1875.0 pg/mL.

Specificity	No significant interference observed in the 10 regular blank matrix lots screened, as well as in lipemic and hemolyzed matrix lots.
Specificity in presence of concomitantly	No significant interference observed.
Carryover	No significant carryover observed.
Lower limit of quantification (LLOQ)	25.0 pg/mL Between-run accuracy: 104.7% Between-run precision: 11.3% Within-run accuracy: 97.8% - 100.3% Within-run precision: 3.7% - 5.0%
Between-run accuracy	99.0% - 104.7%
Between-run precision	2.8% - 11.3%
Within-run accuracy	97.7% - 103.4%
Within-run precision	1.6% - 6.4%
Recovery of analyte	64.5% - 76.3%
Recovery of IS	76.1%
Freeze and thaw stability	4 cycles
Short-term stability	Confirmed up to 27.0 hours at 22°C nominal
Autosampler storage	Confirmed up to 110.3 hours at 4°C nominal
Long-term stability	Confirmed up to 1419 days at -20°C nominal

Table 8. Summary of Bioanalysis Performance

Relevant Clinical Trial	DSXS-1303
Report	TOU-P6-124
Associated Validation Report	TOU-W5-359(R2)
Analyte	Desoximetasone
Internal standard (IS)	Desoximetasone-D5
Calibration concentrations	25.0 pg/mL to 2500.0 pg/mL.
Precision of QCs (%CV)	2.5 to 7.4, including LLOQ
Accuracy of QCs (% Nominal)	97.4 to 102.0, including LLOQ
Incurred Sample Reanalysis	
Total no. of incurred sample reanalysis	36 out of 256 samples (14% of samples)
Total no. of sample whose % differences are within 20%	34
% of total no. of samples whose % differences are within 20 %	94.4
Duration from time sample was first drawn to date of last sample analysis including ISR	1034 days (within the established stability window of 1419 days)
Actual sample storage temperature	-20 °C

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SOO HYEON SHIN
08/18/2021 07:26:43 PM

CHINMAY SHUKLA
08/18/2021 09:33:30 PM