PHARMACOKINETIC REPORT

Pharmacokinetics of OCT-598 Following Oral Administration to Male Cynomolgus Monkeys

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Sponsor:	Oscotec Inc.
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1 SIGNATURE PAGE

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2 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
API	Active pharmaceutical ingredient
ASD	Amorphous solid dispersion
$AUC_{(0-t)}$	Area under the time-concentration curve from zero to the last time point
$AUC_{(0-\infty)}$	Area under the time-concentration curve from zero to infinity
BLOQ	Below the limit of quantification
CE	Collision energy
CL	Clearance
C_{max}	Maximum concentration
CV	Coefficient of variation
CXP	Collision cell exit potential
DP	Declustering potential
EP	Entrance potential
ESI	Electrospray ionization
g	Acceleration of gravity
HPLC	High performance liquid chromatography
h	Hour
IS	Internal Standard
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantification
mg	Milligram
min	Minute
MRM	Multiple reaction monitoring
m/z	Ratio of mass to charge
NA	Not available
ng/mL	Nanogram per milliliter
PO	Oral
QC	Quality control
R	Correlation coefficient
RPM	Revolutions per minute
RS	Reference Standard
SD	Standard deviation
sec	Second
$t_{1/2}$	Terminal half life

Abbreviation	Definition
T_{max}	Time of occurrence for maximum (peak) drug concentration following oral administration
µL	Microliter
ULOQ	Upper limit of quantification
v/v	Volume/volume

3 SUMMARY

The purpose of this study is to evaluate the pharmacokinetic profiles of OCT-598 following single oral gavage administration of three OCT-598 formulations to Cynomolgus Monkeys.

PK parameters of OCT-598 in plasma were determined following oral administration of three different formulations (ASD C2, C10B and C12B) of OCT-598 to male Cynomolgus Monkeys according to the design in Table 3-1.

Table 3-1 Study Design

Group No.	Treatment	API Dose Level (mg/kg)	API Conc.	TA Dose Level (mg/kg)	Dose Volume (mL/kg)	TA (mg/mL)	Dilution factor	Route	No. of Animals
1[a]	ASD C2	20	500 mg/g	40	5 mL/kg	8	-	Oral Gavage	3 Males
2[b]	C10B (Nanosuspension)	20	100 mg/g	200	2 g/kg	-	10	Oral Gavage	3 Males
3[b]	C12B (Nanosuspension)	20	100 mg/g	200	2 g/kg	-	10	Oral Gavage	3 Males

1) a: For G1, the content of API in ASD powder is 50%.

2) b: For G2 and G3, the content of API in Nano suspension stock is 10%

Plasma samples were collected at 0.5, 1, 2, 4, 8, and 24 h post-dose. Clinical chemistry samples were collected at prior to dose and 24 h post dose. The concentrations of OCT-598 were determined in plasma and the mean PK parameters of OCT-598 are summarized in Table 3-2.

Table 3-2 Mean Plasma Pharmacokinetic Parameters of OCT-598 Following Oral Administration of Three OCT-598 Formulations to Male Cynomolgus Monkeys

Treatment	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0-24h)}$ (h.ng/mL)	$AUC_{(0-\infty)}$ (h.ng/mL)	$t_{1/2}$ (h)
ASD C2	20	1169	2.67	7646	NA	NA
C10B (Nanosuspension)	20	5537	1.00	13708	14025	5.08
C12B (Nanosuspension)	20	3553	1.33	10848	10971	3.98

NA: Not applicable

Oral administration of all dose groups was performed without incident. Some abnormal clinical symptoms were observed during the entire experiment. Loose feces and Emesis were observed from 1/3 (20C04047) of Group 3 at 2 h post-dose, and loose feces was observed from 1/3 (20C04047) of Group 3 at approximately 21 h post-dose.

The pharmacokinetics of OCT-598 were evaluated in male Cynomolgus Monkeys (N = 3/Group). The vehicle for group 1 formulation was "1% SLS (Sodium Lauryl Sulfate) in water", vehicles for group 2 and group 3 formulations were "PVP K30 4% w/w, Kolliphor P188 5% w/w liquid" and "Kolliphor P188 5% w/w liquid", respectively.

Group 1, following ASD C2 dose, the C_{max} and $AUC_{(0-24h)}$ were 1169 ng/mL and 7646 h*ng/mL in plasma, respectively.

Group 2, following C10B (Nanosuspension) dose, the C_{max} and $AUC_{(0-24h)}$ were 5537 ng/mL and 13708 h*ng/mL in plasma, respectively.

Group 3, following C12B (Nanosuspension) dose, the C_{max} and $AUC_{(0-24h)}$ were 3553 ng/mL and 10848 h*ng/mL in plasma, respectively.

Overall, among the three different formulations, Nanosuspensions (C10B and C12B) showed better absorption and exposure compared to ASD suspension (ASD C2).

4 OBJECTIVE

The purpose of this study is to evaluate the pharmacokinetic profiles of OCT-598 following single oral gavage administration of three different OCT-598 formulations to Cynomolgus Monkeys.

5 MATERIALS AND METHODS

5.1 Test article information

OCT-598 provided by the Sponsor was used for the dose formulation and standard stock solution preparation as listed in Table 5-1:

Table 5-1 Test materials information

Formulation Identification	Lot No	MW	Salt Factor	Correction Factor	Storage Condition
ASD C2	OSCO-SDP/C2:50:50-Soluplus-23K16	507.62	1	NA	15-25℃
C10B (Nano suspension)	OSCO-NS/C10B-100 mg/g-24B26	507.62	1	NA	15-25℃
C12B (Nano suspension)	OSCO-NS/C12B-100 mg/g-24B26	507.62	1	NA	15-25℃
OCT-598[a]	EW40829-43-P1	507.62	1	NA	2-8℃
OCT-598-D3[b]	P-0003800-002	510.64	1	NA	2-8℃

a Reference standard

b Internal standard

5.2 Animals

Male Cynomolgus Monkeys were purchased from AniKeeper (Zhanjiang) Biotech Co., Ltd. The animals were 2~3 years old with body weights of 3.9-4.4 kg on the dosing date. This study was approved by the Pharmaron Institutional Animal Care and Use Committee (IACUC).

5.3 Study design

Total of 9 male Cynomolgus Monkeys were dosed via a design as shown in Table 5-2.

Table 5-2 Dosing information

Group No.	Treatment	API Dose Level (mg/kg)	API Conc.	TA Dose Level (mg/kg)	Dose Volume (mL/kg)	TA (mg/mL)	Dilution factor	Route	No. of Animals

1[a]	ASD C2	20	500 mg/g	40	5 mL/kg	8	-	Oral Gavage	3 Males
2[b]	C10B (Nanosuspension)	20	100 mg/g	200	2g/kg	-	10	Oral Gavage	3 Males
3[b]	C12B (Nanosuspension)	20	100 mg/g	200	2g/kg	-	10	Oral Gavage	3 Males

1) a: For G1, the content of API in ASD powder is 50%.

2) b: For G2 and G3, the content of API in Nano suspension stock is 10%

Feeding condition: All animals for PO will be fasted overnight prior to dosing and will be fed approximately 4 hours after dosing.

All the animals have free access to water.

5.4 Formulation preparation

Preparation of dosing formulation for G1 to G3 (ASD C2, C10B and C12B) administration:

Group 1, dissolved 698.14 mg of ASD C2 in 87.268 mL of 1% SLS in water with vortexing and stirring to obtain a homogeneous suspension.

Group 2, added 3.094 g of C10B (Nanosuspension) in a suitable sized bottle, then transferred 27.036 g of the corresponding nanosuspension vehicle to the bottle using a pipette, closed the bottle and homogenize manually by inverting the bottle (30 sec) to obtain a homogeneous suspension of 10 mg/g.

Group 3, added 3.094 g of C12B (Nanosuspension) in a suitable sized bottle, then transferred 27.034 g of the corresponding nanosuspension vehicle to the bottle using a pipette, closed the bottle and homogenize manually by inverting the bottle (30 sec) to obtain a homogeneous suspension of 10 mg/g.

Animal No.	Route	Dosing Volume (mL)/(g)	Total Dosed API Weight (mg)	Animal Weight (kg)	Actual Dose Level (mg/kg)
20C05039	POA_1	21.0	70.7	4.10	17.2
19C09031	POA_2	21.0	70.7	4.10	17.2
19C11071	POA_3	22.0	74.1	4.30	17.2
20C02037	POB_4	7.69	66.5	3.90	17.0
20C04031	POB_5	6.37	55.0	4.10	13.4

20C04045	POB_6	7.52	65.0	4.00	16.2
20C04047	POC_7	7.73	72.2	4.00	18.0
20C05093	POC_8	8.18	76.4	4.40	17.4
20C05099	POC_9	7.89	73.7	4.25	17.3

The concentration of each dose formulation was measured by LC-MS, and the results shown in Appendix III.

5.5 Dosing procedure

A syringe was filled with the required amount of the formulation. A gavage tube was placed in the animals' stomach and the formulation was administered by oral gavage. After administration of the dose, the gavage tube was flushed with 5 mL of water.

5.6 Sample collection

Blood samples (0.3 mL) were collected from each animal via cephalic vein on the following time points: 0.5, 1, 2, 4, 8, and 24 h post-dose. Blood samples were placed into tubes containing EDTA-K2, and then centrifuged at 2000 g for 10 minutes at 20-25 ℃ to prepare plasma. All samples were stored at -75±15 ℃ until analysis.

5.7 Preparation of standard solutions and internal standard solution for LC-MS/MS Analysis

OCT-598 was prepared in DMSO with vortexing at 1 mg/mL (free form) to make the standard stock solution.

Calibration standard working solutions were prepared at concentrations of 5, 10, 20, 50, 100, 500, 1000, 5000, and 10000 ng/mL by serial dilution of the standard stock solution by 50% acetonitrile in water. Quality control working solutions at concentrations of 10, 20, 50, 500, and 8000 ng/mL were prepared by serial dilution of the standard stock solution by 50% acetonitrile in water. These QC samples were prepared on the day of analysis in the same way as calibration standards.

OCT-598-D3 was prepared in DMSO with vortexing at 1 mg/mL (free form) to make the internal standard stock solution.

The internal standard working solutions were prepared at concentrations of 20 ng/mL by dilution of the internal standard stock solution by 100% acetonitrile for precipitating protein respectively.

5.8 Sample treatment

5 μL of each calibration standard working solution (5, 10, 20, 50, 100, 500, 1000, 5000, and 10000 ng/mL) was added to 50 μL of blank monkeys plasma to achieve calibration standards of 0.5-1000 ng/mL (0.5, 1, 2, 5, 10, 50, 100, 500, and 1000 ng/mL) in a total volume of 55 μL. Quality Control (QC) samples at 1 ng/mL (low-1), 2 ng/mL (low-2), 5 ng/mL (low-3), 50 ng/mL (mid) and 800 ng/mL (high) in blank plasma were prepared independently from those used for the calibration curves. These QC samples were prepared on the day of analysis in the same way as calibration standards.

55 μL of standards, 55 μL of QC samples or 55 μL of unknown samples (50 μL of plasma sample with 5 μL 50% acetonitrile in water) were mixed with 200 μL of acetonitrile containing IS (OCT-598-D3 with concentration at 20 ng/mL) to precipitate proteins. Then the samples were vortexed for 30 sec. After centrifugation at 4 ℃, 3900 rpm for 15 min, the supernatant was diluted at a ratio of 1:2 with water (v/v: 1/2). 10 μL of diluted supernatant was injected into the LC-MS/MS system for quantitative analysis.

5.9 LC-MS/MS conditions

The LC-MS/MS system consisted of Degasser DGU-20A5R, S, Liquid Chromatograph LC-30AD, Communications Bus Module CBM-20A, Auto Sampler SIL-30AC, Rack changer II and an AB API 5500 LC/MS/MS instrument (Serial No. EF20361804).

Chromatographic separation was performed on a Raptor Biphenyl 2.7 μm (50*2.1 mm) at room temperature. The mobile phase was composed of A: 5% acetonitrile (0.1% formic acid) in water; B: 95% acetonitrile (0.1% formic acid) in water. The flow rate was 0.6 mL/min. The injection volume was 10 μL.

Positive mode electrospray ionization (ESI) was performed on a Turbo V® ion source to obtain a protonated ion of OCT-598 (RS) and OCT-598-D3 (IS). A multiple reaction monitoring (MRM) method was selected for quantitative analysis. The optimized transitions were 508.102/306.00 and 511.081/168.00 for OCT-598 and OCT-598-D3, respectively. The instrument parameters were set as follows: ion spray voltage: 5500 V; curtain gas: 40 psi; nebulizer gas: 50 psi; turbo gas: 50 psi; collision gas: 9 psi; temperature: 500 ℃. The compound dependent parameters are listed in Table 5-3.

Table 5-3 Compound-dependent parameters on MS

Compound ID	OCT-598 (RS)	OCT-598-D3 (IS)
Transition	508.102/306.00	511.081/168.00
DP	256	256
CE	31	49
CXP	12	16

5.10 Data acceptance criteria

Acceptance criteria of standard calibration samples:

At least 6 samples should be analyzed to obtain a calibration curve. Acceptance of calibration standards requires calculated concentration within 80%-120% of the nominal concentration. 75% of the calibration standards should be within the acceptable range.

Acceptance criteria of quality control samples:

At least 3 concentrations of quality control samples (QCs) should be analyzed in a run. Each concentration should include at least 2 individual samples. Acceptance of QCs requires calculated concentration within 80%-120% of the nominal concentration. QCs should be analyzed amongst all unknown samples and 2/3 of the QCs should be within the acceptable range, including at least 1 sample at each concentration level in an analytical run.

Acceptance criteria of unknown samples:

Unknown samples with normal peak shape of analytic and calculated concentration within the calibration range should be accepted. Samples with calculated concentration below LLOQ should be recorded as BLOQ. Samples with calculated concentration above 100% of ULOQ should be diluted with blank matrix and re-assayed. The re-assayed concentration should be multiplied by the dilution factor to obtain the final data. In cases of abnormality, such as equipment malfunction, power outage, sample treatment failure and/or sample injection failure, re-assay should be done in an individual analytical run.

5.11 Statistical analysis

Data acquisition was performed by Sciex Analyst 1.7.2 software (AB Sciex, Forster City, CA). All concentration data and Pharmacokinetic parameters were reported with 3 significant figures. BLOQ was set to zero in calculation. Data statistics were performed using Excel 2010 software.

5.12 Quality standard

This study has been performed in compliance with Pharmaron standard operating procedures. This report represents a true and accurate record of the results obtained.

This report has been reviewed for scientific content and consistency against the Working Practice.

5.13 Study plan and working practice deviations

There were no deviations from the study plan or working practice.

5.14 Data Storage

All raw data, the study plan, and the final report will be retained at Pharmaron for five years after issue of the final report. After this period, the Sponsor will be contacted to determine whether further storage of the data is required, whether the data should be sent to the Sponsor, or if it should be destroyed.

6 RESULTS

6.1 Clinical observations

Oral administration of all dose groups was performed without incident. Some abnormal clinical symptoms were observed during the entire experiment. Loose feces and Emesis were observed from 1/3 (20C04047) of Group 3 at 2 h post-dose and loose feces was observed from 1/3 (20C04047) of Group 3 at approximately 21 h post-dose.

6.2 Linearity

In this study, a calibration standard was used for the regression of a $1/x^2$ weighted calibration curve. The curve was plotted using peak area ratio of OCT-598 (RS) and OCT-598-D3 (IS) versus the nominal concentration. The back-calculated concentrations of the calibration standards and calibration curve parameters are shown in Appendix II for plasma samples. The accuracy of the accepted standard samples was 93.3%-106% for male Cynomolgus Monkeys plasma samples. The accuracy of calibration standard samples was within acceptance criteria (80-120%).

6.3 Quality control samples

The results of QC samples for plasma are shown in Appendix II. The accuracy of the accepted QC samples was 93.9%-107% for male Cynomolgus Monkeys plasma. The accuracy of quality control samples was within acceptance criteria (80-120%).

6.4 Bioanalytical sample analysis

OCT-598 plasma concentration in monkeys is shown in Table 8-1 to Table 8-3. The OCT-598 plasma concentrations vs. time profiles are shown in Figure 9-1 and Appendix I.

6.5 Pharmacokinetic analysis

OCT-598 plasma concentrations for each animal following oral administration were used to calculate pharmacokinetic parameters by employing a non-compartmental analysis (Phoenix TM WinNonlin® 8.3). The linear trapezoidal algorithm was used for AUC calculation. Plasma pharmacokinetic parameters are shown in Table 8-4 to Table 8-6.

The pharmacokinetics of OCT-598 were evaluated in male Cynomolgus Monkeys (N = 3/Group). The vehicle for group 1 formulation was “1% SLS in water”, vehicles for group 2 and group 3

formulations were “PVP K30 4% w/w, Kolliphor P188 5% w/w liquid” and “Kolliphor P188 5% w/w liquid”, respectively.

Group 1, following ASD C2 dose, the C_{max} and $AUC_{(0\text{-}24h)}$ were 1169 ng/mL and 7646 h*ng/mL in plasma, respectively.

Group 2, following C10B (Nanosuspension) dose, the C_{max} and $AUC_{(0\text{-}24h)}$ were 5537 ng/mL and 13708 h*ng/mL in plasma, respectively.

Group 3, following C12B (Nanosuspension) dose, the C_{max} and $AUC_{(0\text{-}24h)}$ were 3553 ng/mL and 10848 h*ng/mL in plasma, respectively.

7 CONCLUSIONS

Oral administration of all dose groups was performed without incident. Some abnormal clinical symptoms were observed during the entire experiment. Loose feces and Emesis were observed from 1/3 (20C04047) of Group 3 at 2 h time point. Loose feces were observed from 1/3 (20C04047) of Group 3 at approximately 21 h post-dose.

Overall, among the three different formulations, nanosuspensions (C10B and C12B) showed better absorption and exposure compared to ASD suspension (ASD C2).

8 TABLES

Table 8-1: OCT-598 Plasma Concentrations Following Oral gavage Administration of ASD C2 to Male Cynomolgus Monkeys at 40 mg/kg

Time	Concentration (ng/mL)			Mean	SD
(h)	20C05039	19C09031	19C11071	(ng/mL)	(ng/mL)
0.5	13.4	104	576	231	302
1	16.9	377	383	259	210
2	656	1990	435	1027	841
4	267	989	861	706	385
8	163	204	586	318	233
24	14.0	113	61.4	63	50

BLOQ = below quantifiable limit of 0.5 ng/mL.

Table 8-2: OCT-598 Plasma Concentrations Following Oral gavage Administration of C10B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg

Time	Concentration (ng/mL)			Mean	SD
(h)	20C02037	20C04031	20C04045	(ng/mL)	(ng/mL)
0.5	870	4850	8440	4720	3787
1	980	4430	4250	3220	1942
2	3320	1050	1860	2077	1150
4	725	518	876	706	180
8	315	286	405	335	62
24	45.5	31.5	52.6	43.2	10.7

BLOQ = below quantifiable limit of 0.5 ng/mL.

Table 8-3: OCT-598 Plasma Concentrations Following Oral gavage Administration of C12B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg

Time	Concentration (ng/mL)			Mean	SD
(h)	20C04047	20C05093	20C05099	(ng/mL)	(ng/mL)
0.5	234	427	4710	1790	2530
1	418	1620	7100	3046	3562
2	1940	541	2020	1500	832

4	636	608	536	593	52
8	243	160	640	348	257
24	22.9	6.99	30.5	20.1	12.0

BLOQ = below quantifiable limit of 0.5 ng/mL.

Table 8-4: Plasma Pharmacokinetic Parameters of OCT-598 Following Oral gavage Administration of ASD C2 to Male Cynomolgus Monkeys at 40 mg/kg

Animal	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (h*ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	MRT_{inf} (h)	$AUC_{(0-24h)}/D$ (h*mg/mL)
20C05039	4.65	2.00	656	3546	3640	6.54	177
19C09031	NA	2.00	1990	9231	NA	NA	462
19C11071	NA	4.00	861	10162	NA	NA	508
Mean	NA	2.67	1169	7646	NA	NA	382
SD	NA	1.15	718	3581	NA	NA	179

NA: Not applicable

Table 8-5: Plasma Pharmacokinetic Parameters of OCT-598 Following Oral gavage Administration of C10B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg

Animal	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (h*ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	MRT_{inf} (h)	$AUC_{(0-24h)}/D$ (h*mg/mL)
20C02037	5.20	2.00	3320	11839	12180	5.28	592
20C04031	4.97	0.500	4850	11989	12214	4.08	599
20C04045	5.06	0.500	8440	17296	17681	4.29	865
Mean	5.08	1.00	5537	13708	14025	4.55	685
SD	0.11	0.87	2628	3109	3166	0.64	155

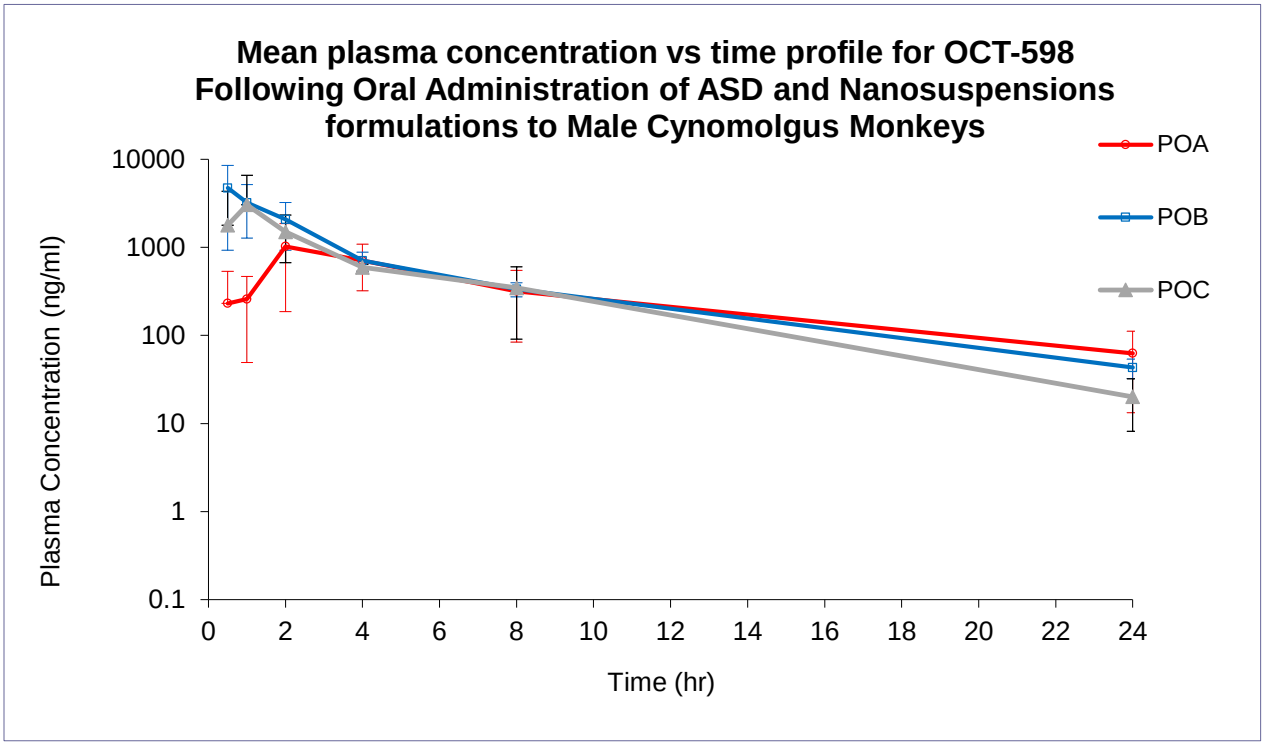
Table 8-6: Plasma Pharmacokinetic Parameters of OCT-598 Following Oral gavage Administration of C12B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg

Animal	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (h*ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	MRT_{inf} (h)	$AUC_{(0-24h)}/D$ (h*mg/mL)
20C04047	4.31	2.00	1940	7862	8004	5.24	393
20C05093	3.22	1.00	1620	5720	5752	4.40	286
20C05099	4.42	1.00	7100	18962	19157	4.28	948

Mean	3.98	1.33	3553	10848	10971	4.64	542
SD	0.66	0.58	3076	7108	7178	0.52	355

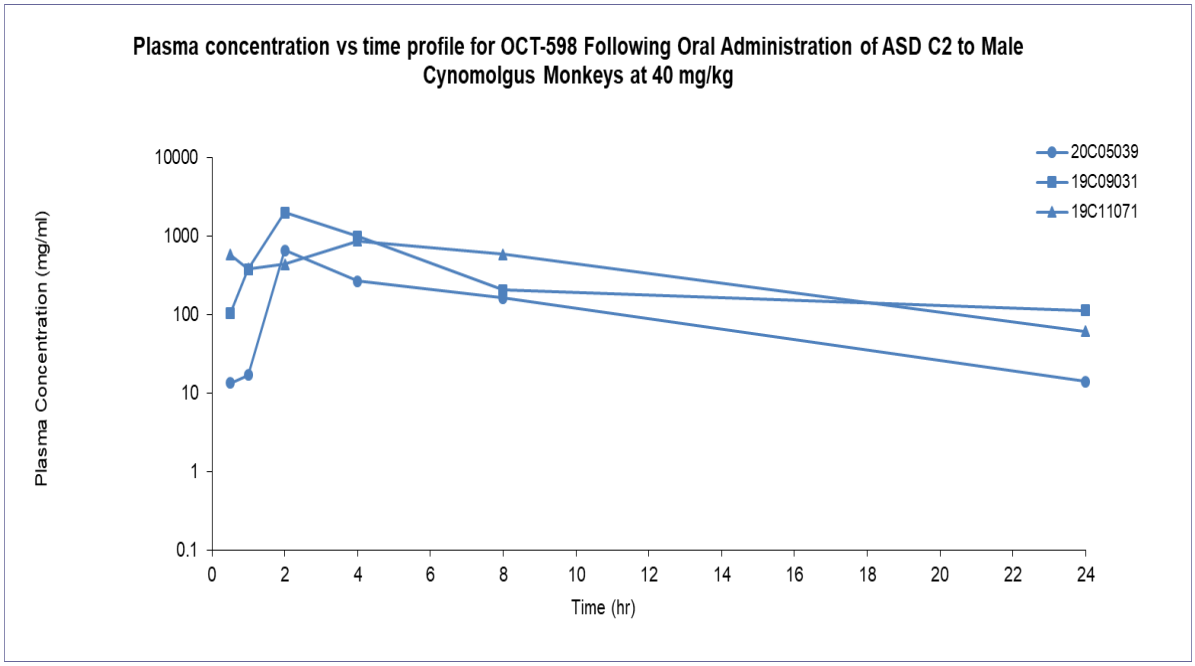
9 FIGURES

Figure 9-1: Mean (± SD, n = 3) Plasma Concentration Vs Time Curves of OCT-598 Following Oral Administration of ASD and Nanosuspensions formulations to Male Cynomolgus Monkeys

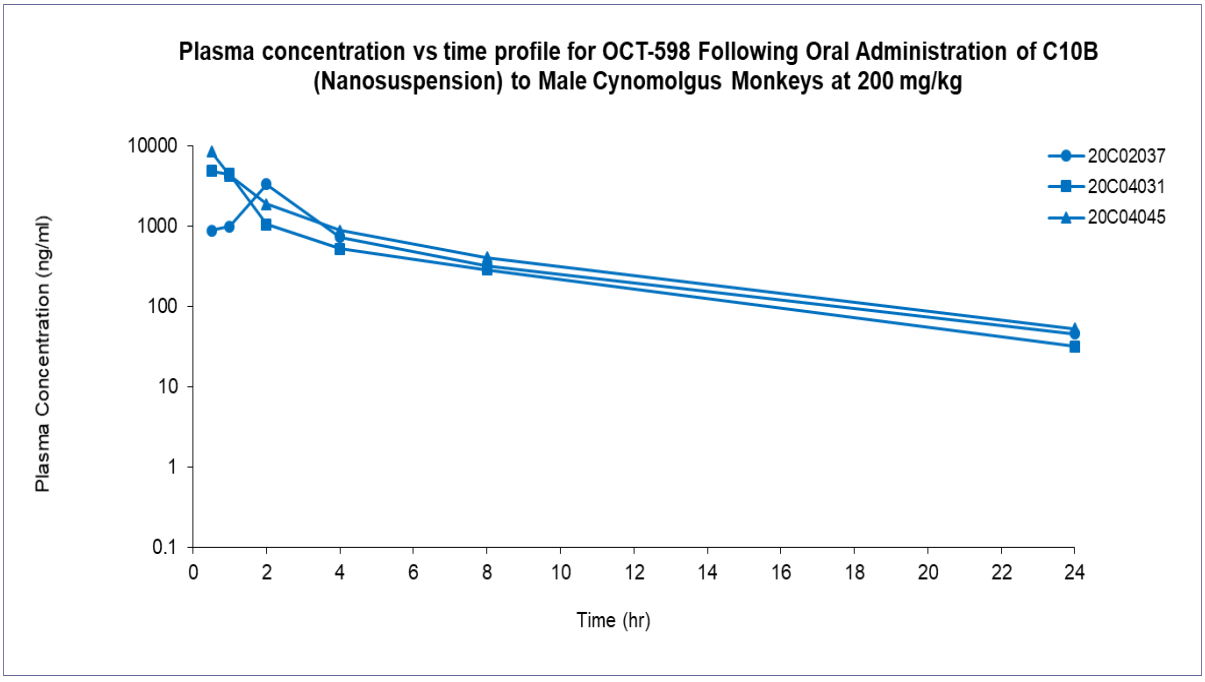


Appendix I: Plasma vs Time-Concentration Curves

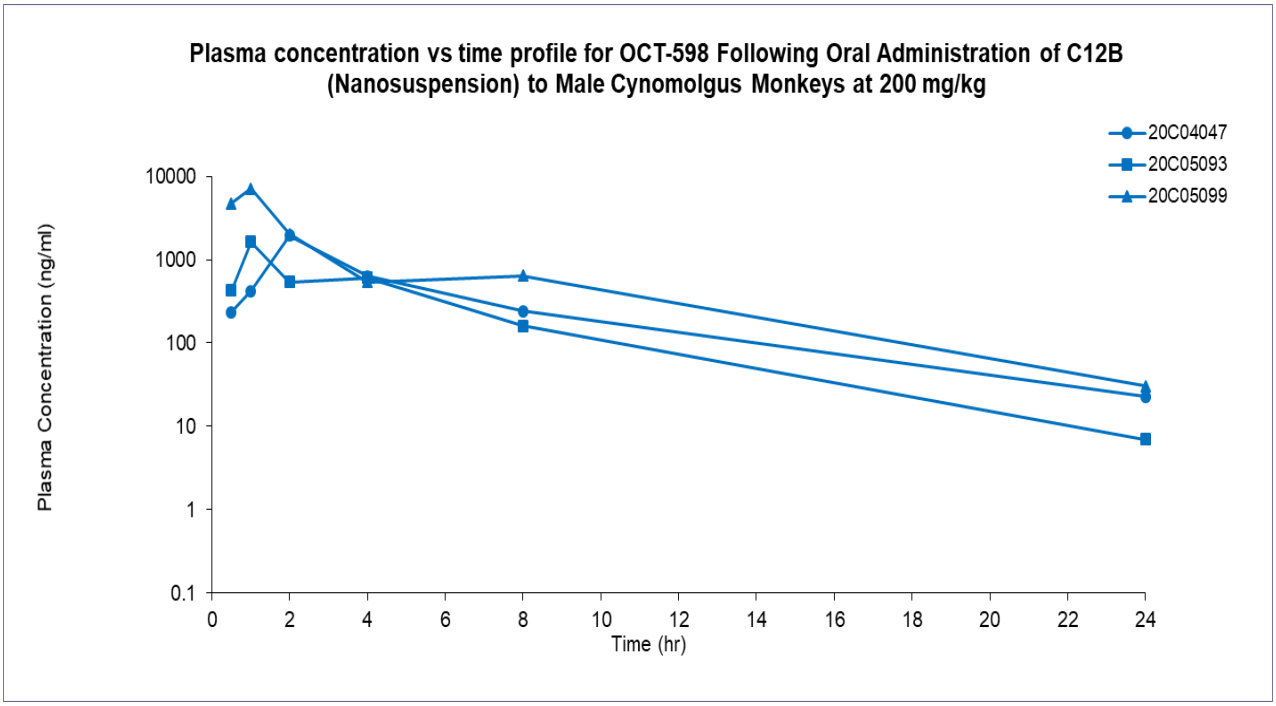
Plasma Semi-log Time-Concentration Curves of OCT-598 Following Oral Administration of ASD C2 to Male Cynomolgus Monkeys at 40 mg/kg



Plasma Semi-log Time-Concentration Curves of OCT-598 Following Oral Administration of C10B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg



Plasma Semi-log Time-Concentration Curves of OCT-598 Following Oral Administration of C12B (Nanosuspension) to Male Cynomolgus Monkeys at 200 mg/kg



Appendix II: LC-MS/MS Validation Data

Back-Calculated Concentration of Calibration Standards of OCT-598 to Male Cynomolgus Monkeys Plasma

Expected Concentration (ng/mL)	Number of Values	Calculated Concentration (ng/mL)	% Accuracy
0.5	2	0.509	102
1	2	0.951	95.1
2	2	2.02	101
5	2	5.26	105
10	2	9.8	98.0
50	2	52.9	106
100	2	102	102
500	2	491	98.2
1000	2	933	93.3

$y = 0.0136 x + 0.00071$ ($r = 0.9987$)

Precision and Accuracy of QC Samples PO of OCT-598 to Male Cynomolgus Monkeys Plasma

Nominal Concentration (ng/mL)	Number of Values	Calculated Concentration (ng/mL)	% Accuracy
1	2	0.940	94.0
2	2	2.02	101
5	2	5.35	107
50	2	51.5	103
800	2	751	93.9

Appendix III: Dose Solution Concentration

Group	Sample Name	Dilution Factor	Nominal (mg/mL)	Measured (mg/mL)	Mean (mg/mL)	Accuracy (%)	SD (mg/mL)
1	DOSE_POA_1	100000	4	3.25	3.37	84.2	0.126
	DOSE_POA_2	100000		3.50			
	DOSE_POA _3	100000		3.35			
2	DOSE_POB_1	100000	10	8.85	8.75	86.4	0.194
	DOSE_POB_2	100000		8.88			
	DOSE_POB_3	100000		8.53			
3	DOSE_POC_1	100000	10	9.19	9.35	93.4	0.144
	DOSE_POC_2	100000		9.47			
	DOSE_POC_3	100000		9.39			

Appendix IV: CoA

ARDENA

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Mariakerke, 1st March 2024

Subject: Oscotec PK Dog study

Dear Hainan,

Following up on the correspondence with Mr. Jason Jung from Oscotec, we have the pleasure to send you the new, remanufactured nanosuspensions and lipid formulations for the PK Dog study:

- Nanosuspension concept 10B (active 100 mg/ml):
  OSCO-NS/C10b-100 mg/g-24B26 → 20 g
- Nanosuspension concept 10B (Placebo):
  OSCO-PLACEBO/C10b-24B23 → 2x 75 g
- Nanosuspension concept 12B (active 100 mg/ml):
  OSCO-NS/C12b-100 mg/g-24B26 → 20 g
- Nanosuspension concept 12B (Placebo):
  OSCO-PLACEBO/C12b-24B23 → 2x 75 g
- Lipid formulation concept:
  OSCO-LIP/C8-79 mg/mL-24B23 → 26 mL

Storage conditions: room temperature (15°C-25°C)

Attached you will find the new Certificate of Analysis and the Safety Data Sheet of the active ingredient.

Do not hesitate to contact us (luis.guerzoni@ardena.com) should you have any questions.

Kind regards,

Vera Vermaut
Sr. Facility Material Logistics Officer

Ardena Gent NV
Kleimoer 4
B-9030 Mariakerke
Belgium

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pm.gent@ardena.com

CERTIFICATE OF ANALYSIS

Information	
Report Number	OSCO-CoA-003
Version	1
GMP	☐ YES / ☒ NO
ID Name	OCT-598 100 mg/g (nanosuspension), 79 mg/ml (lipids)
Contract Giver	Oscotec
Manufacturer	Ardena Gent NV
Batch Number concepts	OSCO-SOL/C8-24B23 OSCO-NS/C10b-24B26 OSCO-NS/C12b-24B26
Storage Conditions	15 °C – 25 °C
Assignment	SoW OSCO-P23-112
Date of Analysis	Started on 26 Feb 2024
Lab Notebook Reference	2024-ZVDB-02 p. 38

REVISION HISTORY

Version	Reference	Description / Reason of Revision	Effective Date
1	NA	New document based on SOP-0408_T7 v1	See last signature date

Parameter	Test Method Reference	Acceptance Criteria	Concept	Results	Unit
Assay active substance (n = 1)	OSCO-MDes-001 v1.2	Determine and report	C8	93.9	%, l.c.
			C10b	102.1	
			C12b	103.0	
Purity (n = 1):	OSCO-MDes-001 v1.2	Determine and report	C8	RRt 0.83: 0.21 RRt 0.87: 1.1 RRt 0.88: 0.52 RRt 1.01: 0.23 RRt 1.38: 0.12 RRt 1.46: 0.16	%, l.c.
a. Any unspecified degradant/impurity			C10b	RRt 0.97: 0.12 RRt 1.01: 0.11	
			C12b	RRt 0.97: 0.12	
b. Total degradants/impurities		Determine and report	C8	2.3	%, l.c.
			C10b	0.23	
			C12b	0.12	

%, l.c.: %, label claim; RRt: Relative Retention time.

SIGNATURES

I have read this report and confirm that, to the best of my knowledge, the information is accurate.

Action	Function	Name	Signature and Date
Author	Associate Scientist - Analytical Development	Zenobie Van den Broek	**Signature:** *Electronically signed by: Zenobie Van den Broek Reason: I approve the document Date: Feb 28, 2024 11:54 GMT+1* **Email:** zenobie.vandenbroek@ardena.com
Approver	Director - Analytical Development	Romain Mailhot	**Signature:** *Electronically signed by: Romain Mailhot Reason: I approve the document Date: Feb 28, 2024 12:01 GMT+1* **Email:** romain.mailhot@ardena.com

ARDENA

PRO FORMA INVOICE	**N° OSCO-P23-112_24C01** **Date: 01 March 2024**
World Courier HWB#: 7151232559	Incoterms: DDP
SHIPPER/EXPORTER: Ardena Gent NV Kleimoer 4 9030 Mariakerke Belgium Contact: Vera Vermaut FacilityMaterialLogisticsGent@ardena.com ☎ +32 9 267 65 00 VAT/EORI: BE0453881707	CONSIGNEE/IMPORTER: Pharmaron Ningbo Technology Development, Co., Ltd No. 800 Bin-Hai 4th Road Hangzhou Bay New Zone Ningbo, 315336 P.R. China Contact: Hongshu Jin/Hainan Gao/Yifa Zhang nbshipping@pharmaron-bj.com ☎ +86 574 56330275

Intended use: Free samples for use in analytical investigation only (nanosuspension for dog PK Study). Not intended for any human or animal therapeutic or diagnostic use.
The material does not contain any animal or cell culture derived products or additives such as albumin or serum. Non-hazardous material. Non-infectious.

Country of origin: Belgium — Country of ultimate destination: China

Manufacturer: Ardena Gent NV, Kleimoer 4, 9030 Mariakerke, Belgium
Storage conditions: Room Temperature (15 °C – 25 °C)

N° of Units	Net Content	Description of Goods	HS code	Unit Value	Sub Total
2 glass vials	2 x 75 g	OSCO-NS/PLACEBO/C10b-24B23	2853009010	5 EUR	10 EUR
2 glass vials	2 x 75 g	OSCO-NS/PLACEBO/C12b-24B23	2853009010	5 EUR	10 EUR
1 glass vial	20 g	OSCO-NS/C10b-100 mg/g-24B26	29420000	5 EUR	5 EUR
1 glass vial	20 g	OSCO-NS/C12b-100 mg/g-24B26	29420000	5 EUR	5 EUR
1 glass vial	26 mL	OSCO-LIP/C8-79 mg/mL-24B23	29420000	5 EUR	5 EUR

Total n° of boxes: 1 **Total Weight: 945 g** **Total Value: 35 EURO**

Value is for customs purposes only. No commercial value. Not for payment.
Not for (re)sale.

I declare all the information contained in this invoice to be true and correct.

Signature of Shipper/Exporter
Vera Vermaut, Sr. Facility Material Logistics Officer — Date: 01/March/2024

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B-9030 Mariakerke
Belgium

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ARDENA

END USE STATEMENT

Mariakerke, 1st March 2024

To whom it may concern,

World Courier shipment, HWB# 7115123259, contains

7 free samples of investigational medicinal product for lab testing:

- 4 glass vials containing a placebo suspension and
- 3 glass vials of different formulations containing the active substance OCT-598

Active substance formula: 6-(4-((3'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-2,5-dimethylthiophene-3-carboxamido)spiro[3.3]heptane-2-carboxylic acid).

The samples will be used for lab investigation (PK study) at Pharmaron Ningbo Technology Development, Co., Ltd, No. 800 Bin-Hai 4th Road, Hangzhou Bay New Zone, Ningbo, 315336, P.R. China.

Product list:

Samples of lipid formulation and Nanosuspensions for dog PK:

1. OSCO-NS/C10b-100 mg/g-24B26 → 20 g
2. OSCO-NS/PLACEBO/C10b-24B23 → 2x 75 g
3. OSCO-NS/C12b-100 mg/g-24B26 → 20 g
4. OSCO-NS/PLACEBO/C12b-24B23 → 2x 75 g
5. OSCO-LIP/C8-79 mg/mL-24B23 → 26 mL

The samples are manufactured by Ardena Gent NV, Kleimoer 4, 9030 Mariakerke, Belgium.

The samples are not for sale, nor are they intended for human consumption.

HEKA HERMAUT

on behalf of

Luis Guerzoni,
Project Manager
luis.guerzoni@ardena.com

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