Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT/IND Number:	2010-022899-32
Study Number:	TH0918
Protocol Title:	An open-label, randomised, single dose, 5-way crossover pilot study to compare the rate and extent of absorption of a 8.75 mg flurbiprofen lozenge with flavour and excipient base variants of an 8.75 mg flurbiprofen spray
Study Phase:	I
Date First Subject Enrolled:	02 February 2011
Date Last Subject Completed:	10 March 2011
Report Date:	09 November 2011
Principal Investigator:	Dr. Stephen Patrick Smith, MB, BCh, BAO, 22-24 Lisburn Road, Belfast, BT9 6AD, Northern Ireland, United Kingdom
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (Seoul, 2008), as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as “essential documents” will be archived in the RB company archive in Hull, UK.

Reviewed and Agreed by:

This clinical study report was reviewed and agreed upon by the following Scientists at Celerion:

Statistician: Christine Erskine, MSc

Pharmacokineticists: Mary Lor, BSc, GrDip: Helen Manthos, MScA

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Reviewed and Approved by:

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Mr. G. Smith, BSc, MSc — 21 Nov 11 — Date

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Dr. P. Berry MB, ChB, MPH — 23 November 2011 — Date

Director, Clinical Pharmacology Sciences at Celerion:

Anthea Cromie, PhD
Director,
Clinical Pharmacology Sciences
Celerion

24-Nov. 2011
Date

Study Sponsor: Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7D8, UK

2 SYNOPSIS

Name of Sponsor/Company: Reckitt Benckiser	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: TBD	**Volume:**	
Name of Active Ingredient(s): Flurbiprofen	**Page:**	
Title of Trial: An open-label, randomised, single dose, 5-way crossover pilot study to compare the rate and extent of absorption of a 8.75 mg flurbiprofen lozenge with flavour and excipient base variants of a 8.75 mg flurbiprofen spray		
Investigator(s): Dr. Stephen Patrick Smith, MB, BCh, BAO		
Trial Site(s): Celerion, Belfast, United Kingdom		
Publication (reference): None		
Studied Period: 5 weeks **Date first subject enrolled:** 02 February 2011 **Date last subject completed:** 10 March 2011		**Phase of Development:** I
Objectives: The objective of this pilot study was to compare the rate and extent of absorption of 4 different flavour variants of a flurbiprofen spray format (each of the 4 variants delivered as a single dose via 3 sprays) to an 8.75 mg honey and lemon Strefen flurbiprofen lozenge.		
Methodology: The physician assessed subjects for eligibility according to the stated inclusion and exclusion criteria and conducted a physical examination. On the day before dosing, subjects reported to the unit at 1800 hours (hr). Following baseline assessments, eligible subjects were randomised into the study and assigned a randomisation number. On treatment days, each subject received the formulation for that treatment visit according to the randomisation schedule. Subjects remained in the unit for 12 hr postdose. Following dosing, blood was collected for analysis. Subsequent dosing was between 4 and 7 days after the previous treatment. Subjects returned to Celerion for a post study follow-up visit between 2 and 7 days after Day 2 of Treatment Visit 5.		
Number of Subjects: **Planned:** 12 **Analysed:** 12		
Diagnosis and Main Criteria for Inclusion: Only subjects to whom all of the following conditions applied were included: voluntarily consented healthy male or female subjects aged between > 18 to < 55 years with a body mass index (BMI) of > 20 and < 27 kg/m^2 with an absence of relevant abnormalities in safety assessments.		
Test Product: Subjects were randomised to the following treatments (Treatments B through E were 4 flavour variants of flurbiprofen 8.75 mg/540 µL spray): Treatment B: 15 mL of 8.75 mg/540 µL flurbiprofen spray (Lot No.: 02143/093) Treatment C: 15 mL of 8.75 mg/540 µL flurbiprofen spray (Lot No.: 02143/099) Treatment D: 15 mL of 8.75 mg/540 µL flurbiprofen spray (Lot No.: 02143/105) Treatment E: 15 mL of 8.75 mg/540 µL flurbiprofen spray (Lot No.: 02143/111) Each subject received the treatment as a 15 mL spray of 8.75 mg/540 µL flurbiprofen, administered as a single dose of 3 sprays (each 180 µL) with a total volume of 540 µL.		
Duration of Treatment: Each subject visited the centre on a maximum of 8 occasions (1 screening visit [could have been conducted over 1 or 2 visits], 5 treatment visits, and 1 post study visit) over a 5-week period. Each treatment visit required an overnight stay before dosing the following morning and subjects remained in the centre for at least 12 hr postdose.		

Name of Sponsor/Company: Reckitt Benckiser	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
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Reference Therapy: Subjects randomised to Treatment A received 8.75 mg flurbiprofen (Lot No.: 3EE), administered orally as a 1 x 8.75 mg flurbiprofen honey and lemon lozenge.

Criteria for Evaluation:

Pharmacokinetics:

The following pharmacokinetic (PK) parameters were calculated for flurbiprofen in plasma: AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{\%extrap}$, partial AUCs, C_{max}, t_{max}, $t_{1/2}$, and k_{el}.

Safety:

Safety was evaluated by the assessment of physical examination, adverse events (AEs), haematology, serum chemistry, urinalysis, vital signs, and electrocardiograms (ECGs).

Statistical Methods:

Pharmacokinetics:

Descriptive statistics were calculated for flurbiprofen plasma concentrations and the PK parameters. Analyses of variance (ANOVAs) were performed on the ln-transformed PK parameters AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. The statistical analyses were performed using the SAS® PROC MIXED procedure.

The 90% confidence intervals (CIs) for the ratios were derived by exponentiation of the CIs for the difference between formulation least-squares mean (LSM) resulting from the analyses on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. The CIs were expressed as a percentage relative to the reference formulation.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 13.1 and were summarised by treatment for number of subjects reporting the AE and the number of AEs reported. Summary tables were also produced for severity and relationship to the study treatment. Concomitant medications were coded using the World Health Organisation (WHO) drug dictionary, Version 01 September 2010. Laboratory summarisations were computed at screening, post study, and the change from screening to post study results. Shift tables comparing results at screening to post study were also produced for clinical laboratory data. For ECGs and vital signs, mean measurements and change from screening to post study were summarised by time point. Descriptive statistics were calculated for quantitative safety data and frequency counts were compiled for qualitative safety data. All safety data for the above safety assessments were presented in by-subject listings.

SUMMARY & CONCLUSIONS

PHARMACOKINETIC RESULTS:

This was a bioavailability study and no efficacy parameters were assessed. The results of the bioavailability data are summarised in the figures and tables below.

The mean plasma flurbiprofen concentration-time profiles following Treatments A, B, C, D, and E are presented in the figures below.

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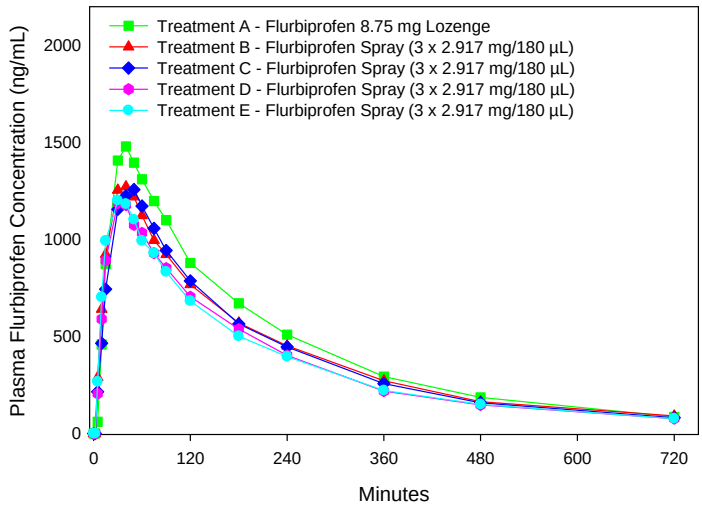
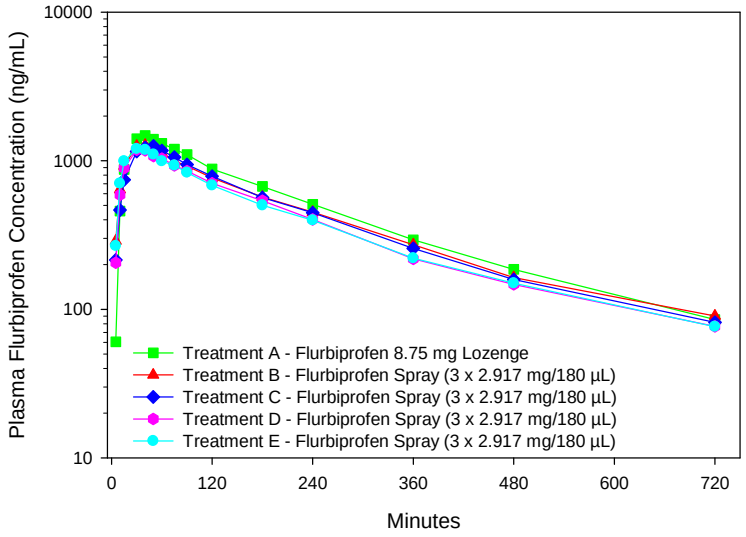
Mean Plasma Concentrations Versus Time Following Administration of Flurbiprofen (Linear and Semi-Log Scales)





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Overall, mean peak and extent of exposure for plasma concentrations of flurbiprofen appeared to be lower for all 4 of the test spray formulations (15 mL of 8.75 mg/540 µL flurbiprofen administered as 3 sprays [180 µL each]) when compared to the reference formulation, flurbiprofen 8.75 mg lozenge. However, all 4 spray formulations appeared to have comparable mean peak plasma concentrations and extent of exposure for flurbiprofen relative to each other.

The mean peak plasma concentrations occurred approximately 30 – 50 minutes postdose, based on observed concentrations, for the test and reference formulations. Mean flurbiprofen concentrations declined in a multi-exponential manner and remained above the lower limit of quantitation (LLOQ) for up to 720 minutes postdose for most subjects.

The main PK parameters for flurbiprofen for each treatment are summarised in the table below.

Summary of the Main Pharmacokinetic Parameters of Plasma Flurbiprofen

PK Parameters	Treatment A (N = 12)	Treatment B (N = 12)	Treatment C (N = 12)	Treatment D (N = 12)	Treatment E (N = 12)
Geometric Mean [Coefficient of Variation (CV%)]					
C_{max} (ng/mL)	1535 (13.6)	1344 (24.4)	1354 (22.4)	1205 (27.3)	1256 (31.0)
AUC_{0-t} (ng·hr/mL)	5315 (12.1)	4651 (21.5)	4512 (22.7)	4132 (25.0)	4072 (27.1)
$AUC_{0-\infty}$ (ng·hr/mL)	5732 (12.6)	5097 (22.2)	4897 (22.6)	4527 (24.1)	4446 (27.8)
Median (Min - Max)					
t_{max} (hr)	0.667 (0.501 – 1.50)	0.666 (0.248 – 2.00)	0.665 (0.499 – 0.835)	0.501 (0.255 – 1.01)	0.500 (0.249 – 0.833)
Arithmetic Mean ± SD					
$t_{1/2}$ (hr)	3.34 ± 0.477	3.57 ± 0.732	3.28 ± 0.738	3.52 ± 0.879	3.43 ± 0.692

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108

The results above show that the C_{max} and extent of exposure (AUC_{0-t} and $AUC_{0-\infty}$) to flurbiprofen was greater for the lozenge than for the spray formulations.

The mean apparent elimination half-life ($t_{1/2}$) of flurbiprofen was comparable across all studied formulations and ranged between 3.28 and 3.57 hr.

The results of the statistical comparisons of the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of flurbiprofen are presented in the tables below.

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Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}: Treatment B Versus Treatment A and Treatment C Versus Treatment A

Parameters	% Geometric Mean Ratio B versus A	CIs (90% Confidence) B versus A	% Geometric Mean Ratio C versus A	CIs (90% Confidence) C versus A
C_{max}	86.59	77.20 – 97.13	87.03	77.59 – 97.62
AUC_{0-t}	85.74	77.37 – 95.02	83.28	75.15 – 92.29
$AUC_{0-\infty}$	87.06	78.45 – 96.61	83.71	75.43 – 92.89

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096

The geometric mean ratios (GMRs) for Treatment B compared to Treatment A were 86.59%, 85.74%, and 87.06% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; however, the 90% CIs were not within the 80 – 125% range.

The GMRs for Treatment C compared to Treatment A were 87.03%, 83.28%, and 83.71% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; however, the 90% CIs were not within the 80 – 125% range.

Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}: Treatment D Versus Treatment A and Treatment E Versus Treatment A

Parameters	% Geometric Mean Ratio D versus A	CIs (90% Confidence) D versus A	% Geometric Mean Ratio E versus A	CIs (90% Confidence) E versus A
C_{max}	78.35	69.88 – 87.85	81.60	72.78 – 91.49
AUC_{0-t}	77.54	70.00 – 85.90	76.25	68.82 – 84.47
$AUC_{0-\infty}$	78.71	70.95 – 87.32	77.26	69.65 – 85.71

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108

The GMRs for Treatment D compared to Treatment A were 78.35%, 77.54%, and 78.71% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were not within the 80 – 125% range.

The GMRs for Treatment E compared to Treatment A were 81.60%, 76.25%, and 77.26% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. The 90% CIs for all 3 PK parameters were not within the 80 – 125% range.

Following a non-parametric evaluation using the Wilcoxon Matched Pair Test, there was no statistically significant difference in t_{max} between the flurbiprofen lozenge and any of the spray formulations ($p > 0.05$), there was, however, a small delay ranging between 0.0011 – 0.1682 hr with the administration of spray formulations relative to the lozenge.

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SAFETY RESULTS:

Treatment-emergent adverse event (TEAE) reporting was minimal during the course of this study and comparable across treatments. Adverse event incidence is presented in the table below.

Treatment-Emergent Adverse Event Incidence

	Treatments					**Total**
	A (N = 12)	**B (N = 12)**	**C (N = 12)**	**D (N = 12)**	**E (N = 12)**	**(N = 12)**
Subject Incidence (%)	2 (17%)	4 (33%)	1 (8%)	4 (33%)	3 (25%)	8 (67%)
Number of AEs	2	4	2	5	5	18

Treatment A = Flurbiprofen 8.75 mg lozenge

Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090

Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096

Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102

Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108

There were 2 vital sign events of postural dizziness reported during the study, 1 each following Treatments A (lozenge) and D (spray). Both events for these 2 subjects were considered by the Investigator to be mild in intensity and unlikely related to the study treatment.

Overall, there were no clinically significant observations in the AE, clinical laboratory, ECG, or physical examination assessments in this study.

CONCLUSION:

Pharmacokinetic

- The peak and overall extent of exposure of the flurbiprofen spray test formulations were lower than that of the flurbiprofen 8.75 mg lozenge. The 90% CIs for the geometric mean ratios for C_{max} and AUCs of the flurbiprofen spray test formulations to the flurbiprofen 8.75 mg lozenge fell outside the 80% – 125% range.
- The peak and overall extent of exposure for all 4 flurbiprofen spray formulations were comparable to each other, with the 90% CI for the ratios of geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ being within the 80% – 125% range.
- Peak flurbiprofen concentrations were reached between approximately 30 and 40 minutes following both the lozenge and spray formulations, with a half-life ranging between 3.28 and 3.57 hr.
- There was no statistically significant difference in t_{max} between the flurbiprofen lozenge and any of the spray formulations.

Safety

- A dose of 8.75 mg flurbiprofen, administered as a lozenge or as a spray, was safe and well tolerated by the male and female subjects in this investigational study.

Date of the report: 09 November 2011

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16.3 CASE REPORT FORMS

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Pharmacokinetic parameter abbreviations and definitions may be found in Section 9.5.3.

Abbreviation	Abbreviation in Full
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of variance
BLQ	Below the limit of quantitation
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CRF	Case report form
CV	Curriculum vitae
CV%	Coefficient of variation
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GMR	Geometric mean ratios
HIV	Human immunodeficiency virus
hr	Hour(s)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LLOQ	Lower limit of quantitation
LS	Least squares
LSM	Least-squares mean
MedDRA®	Medical Dictionary for Regulatory Activities®
mL	Millilitre
N	Number of observations
ND	Not determined
NSAID	Non-steroidal anti-inflammatory drug
NTF	Note-to-file

OTC	Over-the-counter
PI	Principal Investigator
PK	Pharmacokinetic
QA	Quality Assurance
RB	Reckitt Benckiser
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
UK	United Kingdom (of Great Britain and Northern Ireland)
US	United States (of America)
µL	Microlitre
WHO	World Health Organisation

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The name of the Independent Ethics Committee (IEC) consulted is provided in Appendix 16.1.3.

The study protocol, together with subject information and consent documents, were reviewed and approved by the IEC.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the Declaration of Helsinki (Seoul, 2008), as referenced in European Union (EU) Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 Subject Information and Consent

Copies of a representative subject information sheet and a blank consent form are provided in Appendix 16.1.3.

Subjects who were considered by the Investigator to be suitable for entry into the study were given the opportunity to read the subject information sheet and consent form, and to ask questions. If they were satisfied with, and understood the information, they were asked to sign the consent form. The Investigator also signed the form. The subject was given a copy of the information sheet and signed consent form. No protocol-related procedures were performed prior to the subject signing the consent form.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Appendix 16.1.4 contains a table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their roles. The Curriculum Vitae (CV) of the Principal Investigator (PI) is also included in Appendix 16.1.4.

This study was performed under the direction of the PI:

Stephen Patrick Smith, MB, BCh, BAO
22-24 Lisburn Road
Belfast, Northern Ireland
BT9 6AD, United Kingdom (UK)
Telephone: +44 (0) 28 90 554040

The clinical laboratory tests required by this protocol were performed at Celerion (Belfast, Northern Ireland, UK).

Sample analysis for flurbiprofen in plasma was performed at Celerion (Zurich, Switzerland).

Pharmacokinetic (PK) and statistical analyses were performed and a report was prepared at Celerion, Clinical Pharmacology Sciences, under the direction of Anthea Cromie, PhD, Director, Clinical Pharmacology Sciences (Belfast, Northern Ireland, UK).

7 INTRODUCTION

Flurbiprofen is a propionic acid derivative with anti-inflammatory, analgesic and antipyretic properties. As a prescription product in tablet formulation (e.g., ANSAID, United States [US]), it is indicated for the relief of pain and inflammation in rheumatic disease and other musculoskeletal disorders, mild to moderate pain including dysmenorrhoea, migraine and postoperative analgesia in doses up to 300 mg daily.

Flurbiprofen 8.75 mg lozenges were developed by Boots Healthcare International Ltd. (now Reckitt Benckiser Healthcare (UK) Ltd.). They are indicated for the symptomatic relief of sore throat and are available as a Pharmacy medicine ('over-the-counter' [OTC]) in a number of countries including the UK, Italy, New Zealand, France, Germany, Poland, and Australia.

Previous PK studies have been completed with the original clinical trial lozenge formulation[1,2] and a further study has demonstrated that changes to the formulation[3] do not alter the PK parameters of the lozenges. A previous study has also demonstrated bioequivalence between different forms of presentation (lozenge and granules).[4] In addition, there is a comparative bioavailability study currently being planned in the US comparing 2 lozenge formulations against the non-steroidal anti-inflammatory drug (NSAID) tablet formulation (this study was completed during the preparation of this study report).

Reckitt Benckiser (RB) has developed a new 8.75 mg flurbiprofen spray formulation; this study was designed to explore different variations of the spray, differing in flavour and excipient bases. Testing different excipient bases would allow RB to explore the absorption rates of the different variations of the flurbiprofen spray formulations. The aim of the study was to identify a formulation that demonstrated bioequivalence to the existing 8.75 mg honey and lemon flurbiprofen lozenge. The pilot study facilitated further development of an 8.75 mg flurbiprofen spray, which would be used in a pivotal bioequivalence PK study.

Plasma time-concentration curves were constructed for the 4 different variants of the test product, i.e., the 8.75 mg flurbiprofen spray formulation (administered as 3 sprays per dose) compared with the 8.75 mg honey and lemon flurbiprofen lozenge (reference product). Twelve (12) healthy adult volunteers received each of the 5 products as a single dose administered by a nurse, in a random order on 5 separate occasions, with a minimum 4-day and a maximum 7-day washout period between doses. Blood samples were taken before dosing and at specified times postdosing for flurbiprofen analysis.

The healthy volunteers were not expected to derive any benefit from participation in the study. The potential risks with 8.75 mg flurbiprofen lozenge products are low and mainly confined to local reactions in the mouth, including taste disturbance and mouth ulcers; these events were minimised in the case of the lozenge by moving the lozenge around the mouth. Other potential risks are those associated with other NSAIDs, namely gastrointestinal discomfort, nausea, vomiting, diarrhoea and gastrointestinal ulceration, and bleeding. Other reported reactions to NSAIDs include dizziness, headache, renal and hepatic damage. The risks in taking single doses of 8.75 mg flurbiprofen are very low, especially in adult volunteers.

This study was conducted in accordance with the Declaration of Helsinki (Seoul, 2008), as referenced in EU Directive 2001/20/EC. It complied with ICH GCP and applicable regulatory requirements.[5]

This study was conducted to generate PK information that would help develop an 8.75 mg flurbiprofen spray formulation.

The aim of the pilot study was to identify an optimal flurbiprofen spray formulation, which provided the absorption characteristics similar to a honey and lemon Strefen formulation. This formulation would then be taken into further development.

The study was conducted in normal healthy subjects in order to minimise any bias or interference in drug absorption, distribution, metabolism, and excretion that may have occurred if subjects with an illness or disease were studied.

8 STUDY OBJECTIVES

The objective of this study was to compare the rate and extent of absorption of 4 different flavour variants of a flurbiprofen spray format (each of 4 variants delivered as a single 8.75 mg dose via 3 sprays) to the 8.75 mg honey and lemon Strefen flurbiprofen lozenge.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol is included in Appendix 16.1.1.

This was an open-label, randomised, single-dose, 5-way crossover study to compare the rate and extent of absorption of a 8.75 mg flurbiprofen lozenge with flavour and excipient base variants of a 8.75 mg/540 µL flurbiprofen administered as 3 sprays (180 µL each). There was a minimum of a 4-day and maximum of a 7-day washout period between treatments.

Twelve (12) healthy volunteers were enrolled in this study and randomised to 4 test treatments of 8.75 mg flurbiprofen administered sprays and 1 reference oral treatment of an 8.75 mg flurbiprofen lozenge. Each subject visited the centre on a maximum of 8 occasions (1 screening visit [could have been conducted over 1 or 2 visits], 5 treatment visits, and 1 post study visit) over a 5-week period. Each treatment visit required an overnight stay before dosing the following morning and subjects remained in the centre for at least 12 hours (hr) postdose. Subjects returned for a post study follow-up visit between 2 and 7 days after Day 2 of Treatment Visit 5. On the day of dosing, only those subjects who fulfilled all of the eligibility criteria were randomised into the study.

9.2 Discussion of Study Design, Including the Choice of Control Groups

This was an open-label, randomised, single-dose, 5-way crossover study to compare the rate and extent of absorption of an 8.75 mg flurbiprofen lozenge with flavour and excipient base variants of an 8.75 mg flurbiprofen spray (delivered by 3 sprays [180 µL each]). There was a 5-day washout between treatments. Twelve (12) subjects were planned to be enrolled. Subjects were assigned to 1 of 10 treatment sequences as presented in Table 9.2.1.

Table 9.2.1 Treatment Sequences

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1 (N = 2)	Treatment A	Treatment D	Treatment E	Treatment C	Treatment B
2 (N = 1)	Treatment A	Treatment E	Treatment D	Treatment B	Treatment C
3 (N = 1)	Treatment B	Treatment C	Treatment E	Treatment D	Treatment A
4 (N = 1)	Treatment B	Treatment E	Treatment C	Treatment A	Treatment D
5 (N = 1)	Treatment C	Treatment B	Treatment D	Treatment E	Treatment A
6 (N = 1)	Treatment C	Treatment D	Treatment B	Treatment A	Treatment E
7 (N = 1)	Treatment D	Treatment A	Treatment C	Treatment E	Treatment B
8 (N = 1)	Treatment D	Treatment C	Treatment A	Treatment B	Treatment E
9 (N = 2)	Treatment E	Treatment A	Treatment B	Treatment D	Treatment C
10 (N = 1)	Treatment E	Treatment B	Treatment A	Treatment C	Treatment D

9.3 Selection of Study Population

All subjects enrolled in this study were judged by the PI to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

9.3.1 Inclusion Criteria

Only subjects to whom all of the following conditions applied were included:

i) Age: > 18 to < 55 years;
ii) Sex: male or female;
iii) Status: Healthy volunteers with a body mass index (BMI) of > 20 and < 27 kg/m^2;
iv) Absence of relevant abnormalities in the clinical exploration, electrocardiogram (ECG), drug and safety analysis;
v) Subjects who had given written informed consent.

Within 14 days of first dosing, subjects were screened for eligibility. The PI assessed subjects for eligibility according to the stated inclusion and exclusion criteria and conducted a physical examination. The PI or designee recorded medical history, current medical and prior medication (taken within 14 days of the screening visit), and current concomitant medication (only hormonal contraceptives and hormone replacement therapy were allowed during the study and within 7 days of dosing). A blood sample was taken for haematology, biochemistry, and virology screening. A 5 mL blood sample was required from female subjects for pregnancy testing at each treatment visit; at the screening and follow-up visits, a separate 5 mL sample was not required. A urine sample was collected for urinalysis and testing for alcohol and drugs of abuse. On the day of dosing, only those subjects who fulfilled all of the eligibility criteria were randomised into the study.

9.3.2 Exclusion Criteria

Subjects to whom any of the following conditions applied were excluded:

i) A history of any significant disease of any body system;
ii) Any condition that may have currently interfered with the absorption, distribution, metabolism, or excretion of drugs;
iii) A history of allergy or intolerance (including angio-oedema, urticaria, bronchospasm, and rhinitis) related to treatment with flurbiprofen, ibuprofen or other NSAIDs, codeine, or the excipients of the formulations;
iv) A history of peptic or duodenal ulcers or upper gastro-intestinal bleed, or other significant gastro-intestinal disorders;
v) A history of frequent dyspepsia, e.g., heartburn or indigestion;
vi) A history of migraine;
vii) A history of psychotic illness, attempted suicide, or parasuicide;
viii) Current smokers and ex-smokers who had smoked within 6 months;

ix) A history of drug abuse (including alcohol);

x) Those with a positive drugs of abuse screen, including alcohol on any occasion throughout the study;

xi) Ingestion of a prescribed drug at any time in the 14 days before dosing with study medication (excluding hormonal contraceptives and hormone replacement therapy);

xii) Ingestion of an OTC preparation within 7 days before dosing with study medication;

xiii) Donation of blood or plasma in quantity e.g., to the Blood Transfusion service in the previous 90 days or donation of bone marrow in the previous 6 months, before enrolment into the study;

xiv) Known risk factors for Acquired Immune Deficiency Syndrome (AIDS) or known human immunodeficiency virus (HIV) positive status, or a positive viral serology screen;

xv) Those in the opinion of the PI with any clinically significant abnormal laboratory values;

xvi) Woman of childbearing potential who were pregnant or lactating, seeking pregnancy, or failing to take adequate contraceptive precautions, (i.e., an oral or injectable contraceptive, an approved hormonal implant or topical patch, an intrauterine device, abstinence [should the subject become sexually active, she was to agree to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential was defined as any female who was less than 2 years post-menopausal or had not undergone a hysterectomy or surgical sterilisation, e.g., bilateral tubal ligation, bilateral ovariectomy (oophorectomy);

xvii) Those unable, in the opinion of the PI, to comply fully with the study requirements;

xviii) Those who had been dosed in a clinical trial in the previous 90 days;

xix) Those previously randomised into the study.

9.3.3 Removal of Subjects From Therapy or Assessment

The PI may have withdrawn the subject from the study at any time. Reasons for removing a subject from the study may have included, but were not limited to:

- Adverse events (AEs) that, in the judgement of the PI, could have caused severe or permanent harm (significant clinical deterioration was an AE);
- Violation of the study protocol;
- In the PI's judgement, it was in the subject's best interest;
- Subject declined further study participation.

9.4 Treatments

9.4.1 Treatments Administered

Dosing occurred once at each of the 5 treatment visits according to the randomisation schedule. The PI or a delegated person administered the appropriate study drug to each subject orally.

Subjects randomised to Treatment A were administered a 1 x 8.75 mg flurbiprofen honey and lemon lozenge.

Subjects randomised to Treatments B, C, D, and E were administered 8.75 mg/540 µL flurbiprofen spray (delivered as a single dose of 3 sprays [each 180 µL]).

9.4.2 Identity of Investigational Product(s)

Four different flavour variants of the flurbiprofen spray format were used in this study (Treatments B – D, test) and an 8.75 mg flurbiprofen honey and lemon lozenge (Treatment A, reference). Treatment descriptions are identified in Appendix 16.1.6.

Treatment A: Flurbiprofen 8.75 mg honey and lemon lozenge (reference formulation). Manufactured by Reckitt Benckiser
Lot No.: 3EE

Treatment B: 15 mL of 8.75 mg/540 µL Flurbiprofen spray
Manufactured by Reckitt Benckiser
Lot No.: 02143/093

Treatment C: 15 mL of 8.75 mg/540 µL Flurbiprofen spray
Manufactured by Reckitt Benckiser
Lot No.: 02143/099

Treatment D: 15 mL of 8.75 mg/540 µL Flurbiprofen spray
Manufactured by Reckitt Benckiser
Lot No.: 02143/105

Treatment E: 15 mL of 8.75 mg/540 µL Flurbiprofen spray
Manufactured by Reckitt Benckiser
Lot No.: 02143/111

9.4.3 Method of Assigning Subjects to Treatment Groups

A detailed description of the randomisation schedule is presented in Appendix 16.1.7.

Drug supplies were randomised using a computer-generated randomisation schedule provided by RB. On entry to the study, subjects were allocated a unique subject number in numerical sequence. Issue of the study drug in this sequence ensured randomisation.

9.4.4 Selection of Doses in the Study

Subjects were administered one of the 4 different variants of the test product, i.e., 8.75 mg/540 µL flurbiprofen (3 sprays [each 180 µL]) and the 8.75 mg honey and lemon flurbiprofen lozenge (reference product) as a single oral dose on 5 separate occasions, according to the randomisation schedule. The potential risks with 8.75 mg flurbiprofen lozenge products are low and mainly confined to local reactions in the mouth. This study was conducted to generate PK information that would help develop an 8.75 mg flurbiprofen spray formulation.

9.4.5 Selection of Timing of Dose for Each Subject

Eligible subjects were randomised into the study and assigned a randomisation number. Each subject was dosed with 1 of the treatments described in Section 9.4.2 during Period 1 and then crossed over to the alternate treatments on the subsequent periods of the study.

Subjects were required to fast from 2200 hr until 4 hr postdose the following day. The subjects were allowed unlimited water until 2 hr before dosing. Subjects were dosed at about 0900 hr on treatment days, with dosing staggered between subjects as required. Each subject received the formulation for that treatment visit according to the randomisation schedule.

Subjects randomised to Treatment A were instructed to suck the lozenge until it had dissolved, moving the lozenge around their mouth and not to crunch or chew the lozenge.

For subjects randomised to Treatments B, C, D, and E, once the spray was primed, the nurse asked the subject to open their mouth, subsequently the nurse placed the spray head so it was aiming towards the back of the mouth and sprayed 3 times in quick succession (as per the randomisation).

9.4.6 Blinding

As this was an open-label study, no blinding mechanism was employed.

9.4.7 Prior and Concomitant Therapy

The PI or designee recorded any medications given in treatment of AEs on the concomitant medication page in the subject's case report form (CRF). Any medication taken by the subject during the course of the study was also recorded on this form. Any changes in concomitant therapy during the study were documented, including cessation of therapy, initiation of therapy, and dose changes.

The use of the following treatments was not permitted:

- Prescribed medication (excluding the contraceptive pill and hormone replacement therapy) in the 14 days prior to dosing or during the course of the study.
- OTC medication within 7 days prior to dosing or during the course of the study.
- Caffeine whilst in the centre.
- Alcohol was restricted to 2 units per day from 7 days prior to the screening visit and was to be avoided from 48 hr before screening and each admission.

9.4.8 Treatment Compliance

Appropriately trained Celerion personnel watched each subject after the treatment had been administered to ensure that each lozenge had dissolved and treatment had been consumed (as per randomisation). Upon administration, the designated personnel conducted a hand and mouth inspection to ensure compliance with dosing. Any subject who did not take the medication as required was withdrawn from the study.

9.5 Pharmacokinetic and Safety Variables

9.5.1 Pharmacokinetic and Safety Measurements Assessed and Flowchart

Table 9.5.1 Flowchart of Study Procedures

Study Period	Pre-Study Screening (1 or 2 Visits)	Treatment Visits (Visit 1 – 5) 4 – 7 Day Washout		Post Study Follow-up
Treatment Visit Day	N/A	Predose	Dosing Day	N/A
Medical history & current medical status	X			
Demographics	X			
Concomitant medication (& history at pre-study screening)	X	X	X	X
Vital signs (including 12-lead ECG)	X			X
Physical examination	X			X
Haematology	X			X
Biochemistry	X			X
Urinalysis	X			X
Viral serology	X			
Serum pregnancy test (females only)	X	X		X
Urine test for drugs of abuse and alcohol	X	X		
Confirmation of inclusion/exclusion criteria		X		
Administer medication, record time of administration			X	
Pharmacokinetic blood sampling*		X	X	
Adverse events	X	X	X	X

* Blood samples were taken at predose and at 2, 5, 10, 15, 30, 40, 50, 60, 75, 90, 120, 180, 240, 360, 480, and 720 minutes postdose on treatment days.

9.5.2 Appropriateness of Measurements

All assessments of PK and safety parameters were made using standard, widely used, published, and reliable methodologies.

The selection and timing of blood samples for PK analysis were judged appropriate for characterising the PK profiles, given the treatment and dose administered.

9.5.3 Primary Pharmacokinetic Variable(s)

Flurbiprofen plasma concentrations were listed by each subject and nominal (scheduled) sampling time, and summarised by treatment. As per Celerion Standard Operating Procedure (SOP), concentrations below the limit of quantitation (BLQ) were presented as zero prior to the first quantifiable concentration and missing thereafter, and were treated as such for the purpose of calculating PK parameters and summary statistics (the lower limit of quantitation [LLOQ] for flurbiprofen in this study was 40.00 ng/mL). Mean and individual plasma concentration-versus-time profiles were presented on linear and semi-log scales. Mean graphs were also presented with and without standard deviation (SD) bars.

A noncompartmental PK approach was used to analyse individual plasma flurbiprofen concentration-time data following each treatment. The following PK parameters were calculated based on actual sample times using WinNonlin® Professional Version 5.2.

AUC_{0-t} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t was the time of the last measurable concentration (C_t).
$AUC_{0-\infty}$ (ng·hr/mL)	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$, where k_{el} was the apparent terminal elimination rate constant.
$AUC_{\%extrap}$	Percent of $AUC_{0-\infty}$ extrapolated was calculated as $AUC_{\%extrap} = (AUC_{0-\infty} - AUC_{0-t})/ AUC_{0-\infty}*100$
AUC_{0-2} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 2 minutes postdose.
AUC_{0-5} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 5 minutes postdose.
AUC_{0-10} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 10 minutes postdose.
AUC_{0-15} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 15 minutes postdose.
AUC_{0-30} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 30 minutes postdose.
AUC_{0-40} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 40 minutes postdose.

AUC_{0-50} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 50 minutes postdose.
AUC_{0-60} (ng·hr/mL)	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 60 minutes postdose.
C_{max} (ng/mL)	Maximum observed drug concentration.
t_{max} (hr)	Time of the maximum drug concentration (obtained without interpolation). If the maximum value occurred at more than one time point, t_{max} was defined as the first time point with this value.
k_{el} (hr^{-1})	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration-versus-time curve, where slope = $-(k_{el}/2.303)$.
$t_{1/2}$ (hr)	Apparent terminal elimination half-life, calculated as $\ln(2)/k_{el}$.

Linear regressions for determination of k_{el} were performed using at least 3 data points after C_{max}. The k_{el} was not to be assigned if the terminal elimination phase was not apparent, or if the r^2 value was less than 0.8. If the k_{el} intervals were not assigned, the values of $AUC_{0-\infty}$ and $t_{1/2}$ were not to be calculated and would not have been reported.

For a given subject and treatment period, the $AUC_{0-\infty}$ was to be considered as missing if over 25% of the area under the curve was extrapolated beyond the last measurable value. If the resulting $t_{1/2}$ was more than half as long as the sampling interval, the k_{el} value and associated parameters ($AUC_{0-\infty}$, $AUC_{\%extrap}$, and $t_{1/2}$) were not to be reported.

For the calculation of partial AUCs, the nominal time rather than the actual sampling time interval was used. If the actual time at the end of the partial AUC's interval deviated from the nominal time, then methods of linear interpolation (using the 2 concentration values on either side of the nominal time) or extrapolation (when the last measurable time point was taken early) were to be used to provide an estimate of plasma flurbiprofen concentration at the nominal time. In cases where a k_{el} value could not be assigned and the extrapolation method could not be performed, the actual sampling time at the end of the interval may have been used for the calculation of partial AUCs. If the actual time point at the end of the interval was missing, the corresponding partial AUC was not to be calculated.

9.5.4 Drug Concentration Measurements

Blood samples for the analysis of flurbiprofen were collected into 4.5 mL K_3EDTA tubes at the following time points: predose and at 2, 5, 10, 15, 30, 40, 50, 60, 75, 90, 120, 180, 240, 360, 480, and 720 minutes postdose on the treatment days.

A 5 mL blood sample was drawn from female subjects for pregnancy testing at each treatment visit. At the post study visit, a further blood volume of 14.5 mL for male and female subjects was drawn for biochemistry, haematology, and pregnancy tests (females only). The total blood volume collected from each subject that completed the study for the determination of flurbiprofen concentrations was approximately 521.5 mL for females and 496.5 mL for males, including screening and follow-up visits.

If a cannula was used, 1.0 mL of blood was withdrawn prior to each collection and discarded. Once the blood sample had been obtained, 1 – 2 mL of normal saline was used to flush the cannula.

Immediately after taking the sample, the tube containing the blood was inverted approximately 4 or 5 times, and within 60 minutes the samples were transferred to a bench centrifuge and spun at 1500 g at 4˚C for 10 minutes. The plasma supernatant was then transferred using a plastic pipette into 2 polypropylene vials and frozen upright at -20˚C for storage until analysis; the samples were stored in the freezer within 90 minutes of collection. The polypropylene tubes were provided by Celerion. Plasma samples were shipped and analysed for flurbiprofen at Celerion, Zurich. The lower limit of quantitation (LLOQ) for flurbiprofen was 40.00 ng/mL.

9.6 Data Quality Assurance

Data were handled and processed according to Celerion SOPs which are written based on the principles of GCP. Training sessions are conducted once every 2 years for site personnel.

All clinical data underwent a 100% quality control check prior to database lock. Edit checks were performed as a validation process to check for missing data, data inconsistencies, etc. When the database was declared complete and accurate, access to the database was restricted. Case report forms were printed directly from the database. Each CRF was reviewed and signed by the PI. A sample CRF is presented in Appendix 16.1.2.

The final bioanalytical data were received from Celerion, Zurich Bioanalytical facility in Excel® format.

David Crossley visited Celerion to monitor the study on the following dates: 01 February 2011, 18 – 19 February 2011, 28 February 2011, 01 March 2011, and 28 – 29 March 2011.

Audit certificates are included in Appendix 16.1.8. Documentation of inter-laboratory reference ranges is included in Appendix 16.1.10.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Full details of the statistical analyses performed on the study data can be found in the final statistical analysis plan (SAP), presented in Appendix 16.1.9.

Pharmacokinetic:

Descriptive statistics

Flurbiprofen plasma concentrations and PK parameters were summarised by treatment using the following descriptive statistics: mean, SD, coefficient of variation (CV%), standard error of the mean (SEM), number of observations (N), minimum, maximum, median, and 95% confidence limits for the mean. Additionally, geometric means and geometric CV% were presented for AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. Descriptive statistics were to be calculated in each treatment only if at least 50% of flurbiprofen concentrations exceeded the LLOQ; otherwise, if more than 50% of the concentrations were below the LLOQ, the descriptive statistics were to be presented as “ND” (not determined).

Analysis of Variance

The comparisons between flurbiprofen 8.75 mg lozenge and 4 different flavour variants of the 8.75 mg flurbiprofen spray formulations were assessed using an analysis of variance (ANOVA) model. An ANOVA was also performed between the 4 different flavour variants of the 8.75 mg flurbiprofen spray formulations. The ANOVA model was based on the ln-transformed PK parameters AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. The ANOVA model included sequence, period and treatment as fixed effects, and subject nested within sequence as a random effect. Sequence and period effects were tested at a 5% level of significance. The ANOVA included calculation of least-squares mean (LSM), the difference between treatment LSM, and the standard error associated with this difference.

The potential for carryover was addressed by examination of the pre-treatment plasma concentrations in Periods 2, 3, 4, and 5. If there were any subjects for whom the flurbiprofen predose concentration was greater than 5% of the C_{max} value for the subject in that period, the statistical analysis was to be repeated with those subjects excluded for that period only. For a given PK parameter, only subjects with non-missing values for at least 1 comparison of interest were to be included in the analysis. All comparisons of interest are detailed in the section below.

The validity of all analyses was assessed by inspection of residual plots and the Shapiro-Wilks test for normality. Alternative non-parametric methods were to be considered, in discussion with the RB Statistician, if the assumptions for ANOVA were violated.

Ratios and Confidence Intervals

The geometric means of least squares (LS) were calculated using the exponentiation of the LSM. The geometric mean ratios (GMRs) of LSM were calculated using the exponentiation of the differences between the LSM from the analysis on the ln-transformed PK parameters AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. These ratios were expressed as a percentage of test relative to the reference formulation.

For each parameter, the following comparisons of interest were assessed:

(i) Each flurbiprofen spray dose (test) independently versus (vs) honey and lemon lozenge (reference): B vs A, C vs A, D vs A, and E vs A

(ii) The relationship between the flurbiprofen sprays: C vs B, D vs B, E vs B, D vs C, E vs C, and E vs D

The 90% confidence intervals (CIs) for the ratios were derived by exponentiation of the CI obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max}. The CIs were expressed as a percentage relative to the reference formulation. The p-value for each comparison was presented and assessed at the 5% level of significance.

Non-Parametric Analysis

Non-parametric analysis for t_{max} was performed to compare flurbiprofen 8.75 mg lozenge and 4 different flavour variants of the 8.75 mg flurbiprofen spray format, as well as between the 4 different flavour variants of the 8.75 mg flurbiprofen spray format. Wilcoxon Matched Pairs tests were used to perform the non-parametric analysis for the t_{max} comparisons. The corresponding 90% CIs for the differences in medians were to be reported using Walsh averages and appropriate quantile of Wilcoxon Matched Pair Test Statistic. Significant differences in t_{max} were concluded in the resulting $p < 0.05$.

Safety:

All clinical safety data were listed by subject. Continuous variables were summarised using N, mean, SD, median, minimum, and maximum. Frequency counts were reported for all categorical data. Where individual data points were missing because of dropouts or other reasons, the data were summarised based on reduced denominators.

Disposition of subjects (number of subjects dosed, completed, and discontinued early) was summarised by gender and by treatment sequence. Study completion status was listed by subject.

Quantitative demographic data (age, weight, height, and BMI) were described by summary statistics (N, mean, SD, median, minimum, and maximum). The number and percentage of subjects were presented for categorical variables.

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA®) Version 13.1.

Celerion clinics collect all changes in AE condition as separate AEs. If an AE that is reported during the study changes in severity or frequency, that AE is given a stop date/time and another AE is recorded in the database with a start date/time that matches the stop date/time of the original AE. If the AE changes again, another AE is recorded in the database with a start date/time that matches the previous AE record. For example, if a subject had a headache that started with mild severity, increased to moderate severity, then decreased back to mild before resolution, 3 separate AE records would be recorded in the database.

A treatment-emergent adverse event (TEAE) was defined as an AE that started or worsened at the time of or after study drug administration. An AE that occurred during the washout period between drug administrations was considered to be treatment-emergent to the last drug given. In the above example, the first 2 AE records would have been considered treatment-emergent, but the third would not since it represents an improvement in the condition.

All events captured in the database were listed in by-subject data listings; however, only TEAEs were summarised. Any TEAE that began more than 30 hr after the final treatment was not included in the analysis.

Summary tables include the number of subjects reporting the TEAE and percentage of subjects dosed, the number of TEAEs, and the percentage of total TEAEs. These results were summarised by treatment and overall. The number of subjects reporting each TEAE and the number of TEAEs were also summarised by treatment, severity, and relationship to treatment.

The incidence of TEAEs was compared among treatment groups using McNemar's Test for all TEAEs, for those TEAEs classified by the Investigator as probably or possibly related to study medication, and for severe adverse events (SAEs). Serious TEAEs were listed. Ratings system to determine AE severity and relationship to study treatment are presented in Table 9.7.1.

Table 9.7.1 Rating Systems Used to Determine Adverse Event Severity and Relationship to Study Medication

Variable	Category	Definition
Severity		Severity was determined by the Investigator. For symptomatic AEs, the following definitions were applied but medical experience and judgement was also used in the assessment of severity.
	Mild	The AE did not limit usual activities; the subject may experience slight discomfort.
	Moderate	The AE resulted in some limitation of usual activities; the subject may experience significant discomfort.
	Severe	The AE resulted in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain.
Relationship to study medication	Definite	An AE that followed an anticipated response to the study medication; and that was confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge).
	Probable	An AE that followed a reasonable temporal sequence from administration of the study medication, that is an anticipated response to the study medication; and that could not have been reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy.
	Possible	An AE that followed a reasonable temporal sequence from administration of the study medicines; that might have been an anticipated response to the study medication; but that could have been produced by the subject's clinical state or concomitant therapy.
	Unlikely	An AE that did not follow an anticipated response to the study medication; which may have been attributable to other than the study medication, and that was more likely to have been produced by the subject's clinical state or concomitant therapy.
	None	An AE that was known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy.

Clinical laboratory tests (serum chemistry, haematology, and urinalysis) were performed at screening and at post study, or upon early termination.

Screening for drugs of abuse and alcohol was performed at screening and on Day -1 of each period and viral serology was performed at screening.

Serum pregnancy tests for females were performed at screening, on Day -1 of each period, and at post study or upon early termination.

All clinical laboratory values (except viral serology results) were listed by subject. Additional listings were provided for all laboratory values outside the normal reference range and their associated recheck values.

If a laboratory value needed a recheck, the recheck value was used in the summary tables if the laboratory test was performed before dosing. If the laboratory test was performed after dosing, the original value was used in producing the summary tables.

For all numeric clinical laboratory results, descriptive statistics were presented for each clinical laboratory test at screening, post study, and the change from screening to post study.

Each pre-study screening baseline laboratory value was classified as low, normal, or high based on the reference range. Each post study assessment value was classified in a similar manner, producing a 3 x 3 table for each laboratory variable (within serum chemistry and haematology) for the pre-study screening and post study assessment visits. Scores of “1” were assigned to low values, “2” to normal values, and “3” to high values. Using these scores, shifts from baseline were assigned a score. For example, a laboratory value that shifted from low to high was assigned a score of 2, while a laboratory value that remained at a low value was assigned a score of 0.

Vital signs (systolic and diastolic blood pressure [BP], heart rate, and temperature) were obtained at screening and at post study, or early termination.

Vital signs were summarised at screening and post study and for the change from screening to post study using descriptive statistics. If a vital sign needed to be rechecked, the recheck value was used in the summary tables if the vital sign was taken before dosing. If the vital sign was taken after dosing, the original record was used in producing the summary.

Safety ECGs (12-lead ECGs) were performed at screening and at the end of the study, or upon early termination.

Safety ECGs were summarised at screening and at end of study as well as for change from screening to end of study using descriptive statistics.

If an ECG needed to be rechecked at screening, the recheck value was used in the summary table. If the ECG was taken after dosing, the original record was used in producing the summary.

All concomitant medications recorded during the study were coded with the World Health Organisation (WHO) Drug Dictionary (01 September 2010) and were presented in the data listings.

9.7.2 Determination of Sample Size

As this was a pilot study, no statistical justification for the sample size was performed. It was considered that the completion of 12 subjects was adequate to meet the objectives of the study.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

No changes were made in the conduct of the study.

Two note-to-files were written to clarify the content of the final protocol. File note, dated 06 December 2010, clarified information with regard to sample size; and file note, dated 08 February 2011, clarified information pertaining to safety assessments to be performed at the final study visit. Both file notes are located in Appendix 16.1.1.

As per Section 14.5 of the final protocol, incidence of AEs classified by the PI as probably or possibly related to the study treatment and severe in intensity were to be compared using Fisher's Exact Test for all events. Analysis of these events was instead compared using McNemar's Test as the data were not independent.

9.8.2 Changes in the Planned Statistical Analysis of the Study

As per Section 9.1 of the protocol (Appendix 16.1.1), partial AUC for flurbiprofen was to be calculated at predose. This was not possible; hence, it was not calculated. The SAP does not mention the calculation of partial AUC for flurbiprofen at predose.

The treatment descriptions of the test products in the tables were modified from what was mentioned in the SAP, with 3 sprays (180 µL each) added for clarification purposes.

No additional changes were made to the planned statistical analyses.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 12 subjects entered the study and were randomised to study treatment. All 12 subjects completed the study. Subject discontinuation is presented in Appendix 16.2.1, a summary of disposition is presented in Table 14.1.1, and disposition for individual subjects is presented in Table 14.1.2.

10.2 Protocol Deviations

A listing of individual subjects who deviated from the protocol is presented in Appendix 16.2.2.

Note that the SAP produced to accompany this study was labelled under the Study No. AA92772 in error, instead of the Celerion assigned Study No. of AA92722. An amended SAP is provided in Appendix 16.1.9.

In July 2011, it was discovered that during the installation of the COBAS 6000 analyser, a correction factor of -26 required for the Roche Creatinine assay was not programmed into the analyser in error, resulting in a high bias in the reporting of serum creatinine values. Details of this issue are presented in the note-to-file (NTF) titled 'Creatinine High Bias' and is located in Appendix 16.2.2. This error in serum

creatinine assay is not considered to have had any effect on the conclusions of the study, which are pharmacokinetic in nature; however, contents of the NTF should be taken into consideration when reviewing creatinine data presented in the following tables and listings: Tables 14.3.5.1 and 14.3.5.2 summarising mean and change from screening creatinine results and shifts from screening for creatinine results, respectively, and Appendix 16.2.8.1.2 presenting individual creatinine results.

11 PHARMACOKINETIC EVALUATION

Although efficacy was not evaluated in this study, analyses of PK results are described in this section.

11.1 Data Sets Analysed

The PK and statistical analyses for plasma flurbiprofen were performed on all 12 subjects who completed the study.

The strategy for the inclusion/exclusion of data in the data sets analysed was included in the SAP for the study and finalised following discussions of evaluability held after the database had been locked.

11.2 Demographic and Other Baseline Characteristics

Demographics

Demographics for individual subjects are presented in Appendix 16.2.4.1 and are summarised by gender and overall in Table 14.1.3.

Of the 12 Caucasian subjects participating in the study, 6 subjects were male and 6 were female. The mean age was 25.4 years (range: 18 – 44 years), the mean weight was 70.47 kg (range: 54 – 88 kg), the mean height was 168.8 cm (range: 152 – 183 cm), and the mean BMI was 24.568 kg/m^2 (range: 20.08 – 26.97 kg/m^2). Weight and height were observed to be lower in females than males, though overall, BMI was comparable between gender groups.

Medical History

Medical and surgical histories for individual subjects are presented in Appendix 16.2.4.3. There were a total of 3 subjects with ongoing medical events reported at screening, 2 subjects reported ongoing histories of allergies (to penicillin and tetanus vaccinations) and 1 subject reported an ongoing history of a dermatological condition (eczema). Information pertaining to inclusion and exclusion criteria is presented in Appendices 16.2.5.1.1 through 16.2.5.3.2; subjects met all the inclusion and exclusion criteria per protocol. Substance use is presented in Appendix 16.2.4.4, physical examination results are presented in Appendices 16.2.4.2.1 and 16.2.4.2.2, laboratory information pertaining to screening is presented in Appendices 16.2.8.1.1 through 16.2.8.6, and vital signs and ECG information pertaining to screening is presented by subject in Appendices 16.2.9.1 and 16.2.9.2, respectively. The PI considered all previous medical and surgical histories to be not clinically significant and approved the subjects for study participation.

Concomitant Medication

Concomitant medications for individual subjects are presented in Appendix 16.2.5.7. Prior concomitant medication intake included the use of permitted contraceptives only.

11.3 Measurements of Treatment Compliance

Individual subject data are tabulated in Appendix 16.2.5.

All study drugs presented in Section 9.4.2 were administered under the supervision of clinic personnel.

11.4 Pharmacokinetic Results

11.4.1 Analysis of Pharmacokinetics

11.4.1.1 Plasma Concentrations of Flurbiprofen

The locations of individual and mean estimates of plasma flurbiprofen concentrations are listed below:

Tables - Plasma Flurbiprofen Concentrations	Tables 14.2.1 through 14.2.5
Figures - Mean Plasma Flurbiprofen Concentrations	Figures 14.4.1 through 14.4.3
Individual Plasma Flurbiprofen Concentration Figures	Figures 14.4.4.1 through 14.4.4.12

The mean plasma flurbiprofen concentration-time profiles following Treatments A, B, C, D, and E are presented in Figures 11.4.1 – 11.4.4.

Figure 11.4.1 Mean Plasma Concentrations Versus Time Following Administration of Flurbiprofen (Linear Scale)

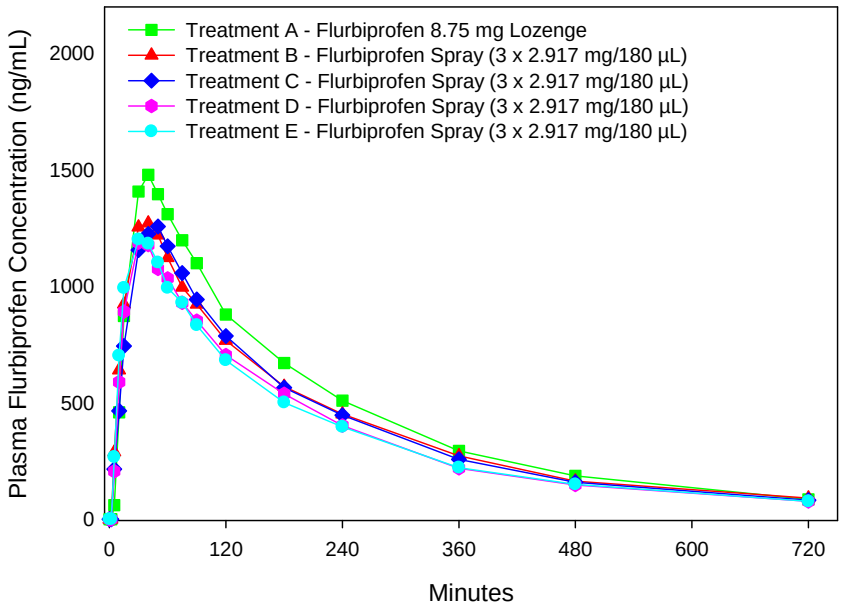


Figure 11.4.2 Mean ± SD Plasma Concentrations Versus Time Following Administration of Flurbiprofen (Linear Scale)

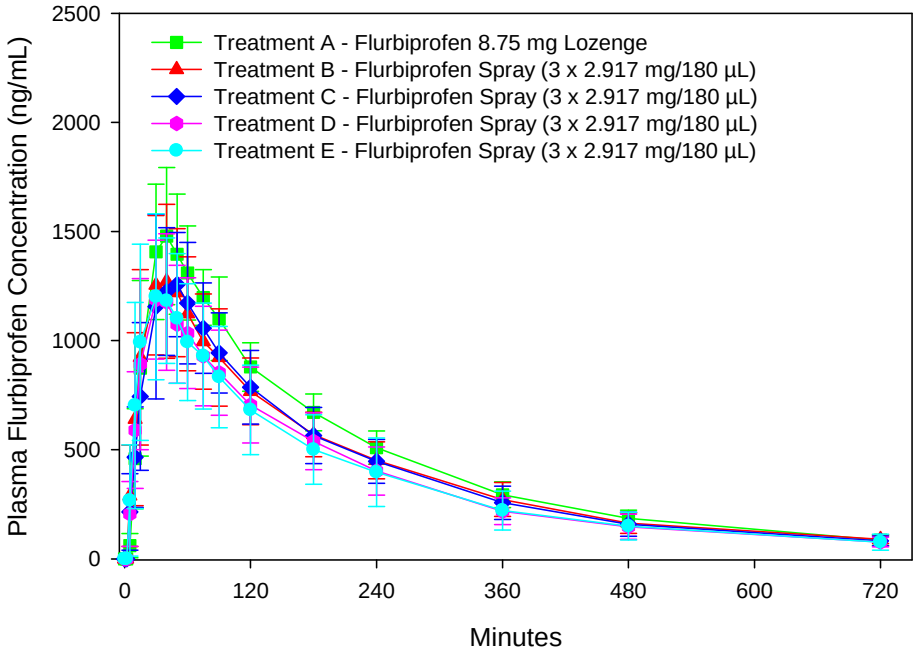


Figure 11.4.3 Mean Plasma Concentrations Versus Time Following Administration of Flurbiprofen (Semi-Log Scale)

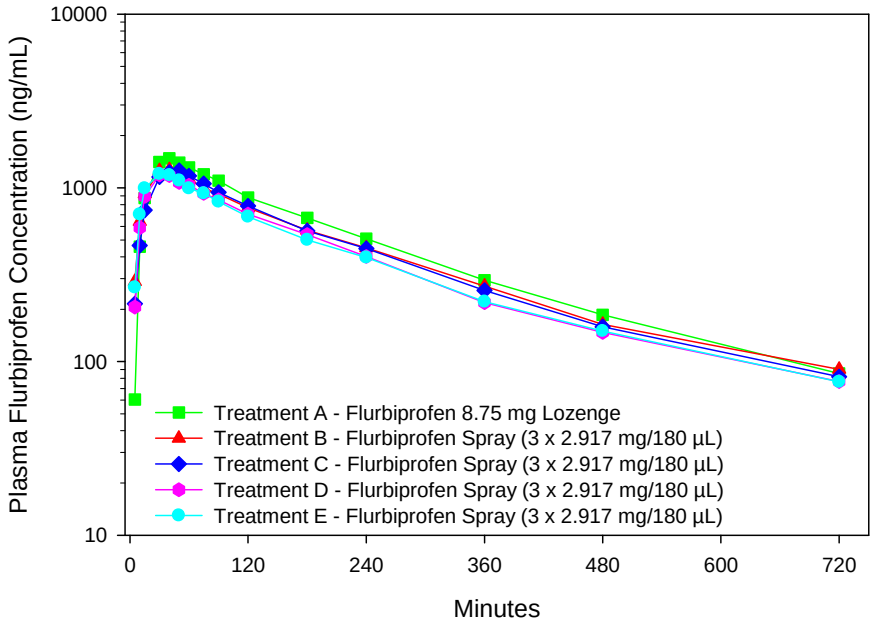
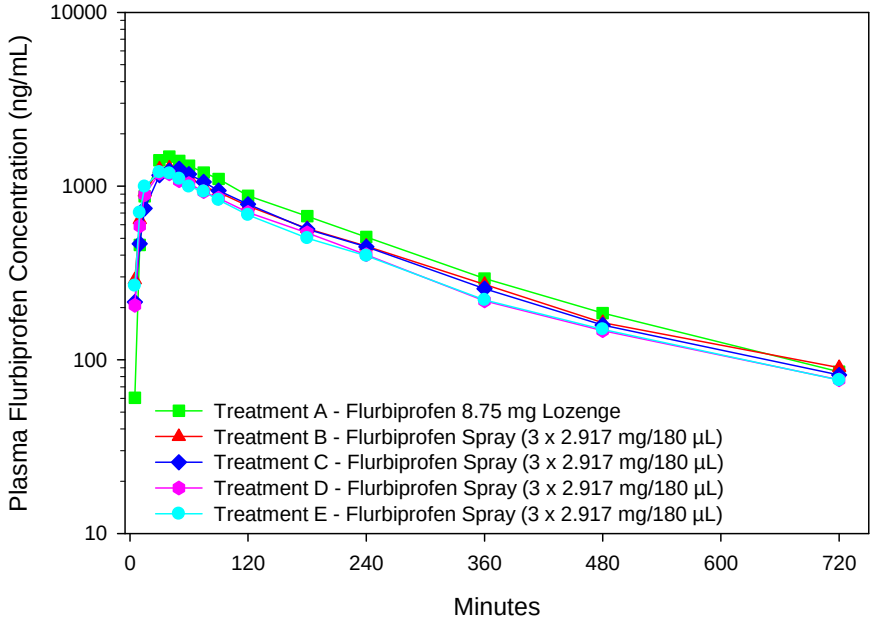


Figure 11.4.4 Mean ± SD Plasma Concentrations Versus Time Following Administration of Flurbiprofen (Semi-Log Scale)



Overall, mean peak and extent of exposure for plasma concentrations of flurbiprofen appeared to be lower for all 4 of the test spray formulations (8.75 mg/540 µL flurbiprofen, 3 sprays [180 µL each]) when compared to the reference formulation, flurbiprofen 8.75 mg lozenge. However, all 4 spray formulations appeared to have comparable mean peak and extent of exposure for flurbiprofen plasma concentration.

After drug administration, flurbiprofen was rapidly absorbed with measurable drug concentrations observed as early as 2 minutes postdose for the flurbiprofen test spray formulations. The mean peak plasma concentrations occurred approximately 30 – 50 minutes postdose, based on observed concentrations, for the tests and reference formulations. Mean flurbiprofen concentrations declined in a multi-exponential manner and remained above the LLOQ for up to 720 minutes postdose for most subjects.

11.4.1.2 Pharmacokinetic Parameters of Plasma Flurbiprofen

The locations of individual and mean estimates of plasma flurbiprofen PK parameters are listed below:

Tables – Plasma Flurbiprofen PK Parameters	Tables 14.2.6 through 14.2.10
Table - Intervals Used for Determination of Plasma Flurbiprofen k_{el} Values	Table 14.2.11
Tables - Statistical Comparisons of Plasma Flurbiprofen PK Parameters	Tables 14.2.12 through 14.2.21
Tables – Non-parametric Comparisons of Plasma Flurbiprofen t_{max}	Tables 14.2.22 and 14.2.31
Figures - Geometric Mean Ratios (%) and 90% CIs for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for Flurbiprofen	Figures 14.4.5.1 and 14.4.5.2

All of the PK parameters for flurbiprofen for each treatment are summarised in Table 11.4.1.

Table 11.4.1 Summary of the Pharmacokinetic Parameters of Plasma Flurbiprofen Following Treatments A Through E

PK Parameters	Treatment A (N = 12)	Treatment B (N = 12)	Treatment C (N = 12)	Treatment D (N = 12)	Treatment E (N = 12)
Geometric Mean (CV%)					
C_{max} (ng/mL)	1535 (13.6)	1344 (24.4)	1354 (22.4)	1205 (27.3)	1256 (31.0)
AUC_{0-t} (ng·hr/mL)	5315 (12.1)	4651 (21.5)	4512 (22.7)	4132 (25.0)	4072 (27.1)
AUC_{0-2} (ng·hr/mL)	0.000155 (295)	0.00490 (533300)	0.00185 (157)	0.00338 (2538)	0.00488 (7369)
AUC_{0-5} (ng·hr/mL)	1.81 (49.0)	5.55 (89.5)	3.65 (84.4)	4.24 (77.5)	4.75 (110)
AUC_{0-10} (ng·hr/mL)	19.9 (60.1)	37.7 (69.6)	27.4 (68.4)	33.7 (60.1)	38.2 (73.1)
AUC_{0-15} (ng·hr/mL)	69.9 (51.4)	96.1 (59.5)	72.9 (58.5)	90.0 (53.6)	102 (58.1)
AUC_{0-30} (ng·hr/mL)	344 (35.7)	360 (38.2)	295 (45.1)	340 (37.1)	364 (41.7)
AUC_{0-40} (ng·hr/mL)	580 (30.8)	568 (32.5)	488 (38.4)	534 (32.3)	559 (36.0)
AUC_{0-50} (ng·hr/mL)	816 (28.0)	771 (29.8)	695 (31.5)	716 (30.8)	747 (32.1)
AUC_{0-60} (ng·hr/mL)	1039 (26.0)	964 (27.8)	899 (27.5)	888 (29.4)	919 (30.1)
$AUC_{0-\infty}$ (ng·hr/mL)	5732 (12.6)	5097 (22.2)	4897 (22.6)	4527 (24.1)	4446 (27.8)
Median (Min - Max)					
t_{max} (hr)	0.667 (0.501 – 1.50)	0.666 (0.248 – 2.00)	0.665 (0.499 – 0.835)	0.501 (0.255 – 1.01)	0.500 (0.249 – 0.833)
Arithmetic Mean ± SD					
$t_{1/2}$ (hr)	3.34 ± 0.477	3.57 ± 0.732	3.28 ± 0.738	3.52 ± 0.879	3.43 ± 0.692
$AUC_{\%extrap}$ (%)	7.25 ± 2.54	8.72 ± 2.36	7.81 ± 2.61	8.68 ± 3.07	8.38 ± 2.62

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108

Source: Tables 14.2.6 to 14.2.10

Overall, the LLOQ of the assay (40.00 ng/mL) represented less than 5% of flurbiprofen mean C_{max} and the percent extrapolated AUC for the calculation of $AUC_{0-\infty}$ from AUC_{0-t} ($AUC_{\%extrap}$) was minimal across all studied formulations (< 10%).

Following a single administration of flurbiprofen 8.75 mg lozenge and 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL]), mean peak exposure to flurbiprofen ranged between 1205 ng/mL and 1535 ng/mL and was reached between approximately 30 and 40 minutes postdose in healthy subjects; the mean extent of exposure to flurbiprofen ranged between 4072 ng·hr/mL and 5315 ng·hr/mL (AUC_{0-t}) and between 4446 ng·hr/mL and 5732 ng·hr/mL ($AUC_{0-\infty}$). The mean peak (C_{max}) and extent of exposure (AUC_{0-t} and $AUC_{0-\infty}$) to flurbiprofen was greater for the lozenge than for the spray formulations.

The extent of exposure from dosing to 2, 5, 10, and 15 minutes postdose appeared to be greater following administration of the spray formulations relative to the lozenge. AUC_{0-5} was statistically greater for all test spray formulations relative to the lozenge. The partial extent of exposure at 30 and 40 minutes postdose appeared to be comparable between the 2 administration forms; after that point, the extent of exposure decreased for the sprays.

Following a single administration of flurbiprofen 8.75 mg lozenge and 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), the mean apparent elimination half-life ($t_{1/2}$) of flurbiprofen was comparable across all studied formulations and ranged between 3.28 and 3.57 hr in healthy subjects. In general, the elimination phase of flurbiprofen was characterised based on the last 3 to 4 measurable time points.

The results of the statistical comparisons of the AUC_{0-t}, $AUC_{0-\infty}$, partial AUCs, and C_{max} of flurbiprofen are presented in Tables 11.4.2 – 11.4.11.

Table 11.4.2 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment B Versus Treatment A

Parameters	Geometric LS Means		CIs		%Geometric
	B	A	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1325.889	1531.193	77.20 – 97.13	0.0410	86.59
AUC_{0-t}	4585.746	5348.582	77.37 – 95.02	0.0157	85.74
AUC_{0-2}	0.004	0.000	388.2 – 110460	0.0203	6548.49
AUC_{0-5}	5.715	1.619	234.3 – 532.12	< 0.0001	353.07
AUC_{0-10}	38.078	20.527	139.0 – 247.53	0.0008	185.50
AUC_{0-15}	96.144	71.195	106.3 – 171.58	0.0408	135.04
AUC_{0-30}	356.437	344.882	87.57 – 121.97	0.7396	103.35
AUC_{0-40}	560.592	579.182	84.01 – 111.52	0.7004	96.79
AUC_{0-50}	760.668	812.971	82.53 – 106.08	0.3780	93.57
AUC_{0-60}	949.795	1034.937	81.74 – 103.03	0.2191	91.77
$AUC_{0-\infty}$	5040.119	5789.319	78.45 – 96.61	0.0305	87.06

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Source: Table 14.2.12

The GMRs were 86.59%, 85.74%, and 87.06% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; however, the 90% CIs were not within the 80 - 125% range. This could be due to a lack of power from the small sample size. The 90% CIs derived from the analyses of the ln-transformed PK parameter AUC_{0-30}, AUC_{0-40}, AUC_{0-50}, and AUC_{0-60} were within the 80 – 125% range, but not for AUC_{0-2}, AUC_{0-5}, AUC_{0-10}, and AUC_{0-15}.

Given a true ratio of 85.74% (GMR for AUC_{0-t}) and an intrasubject CV of 14.9% (based on data from this study for test spray formulation Treatment B [Lot No. 02143/090]), a total of 60 subjects would be required in a pivotal study to obtain a power of at least 80% and an alpha error of 5% for a probability of having a 90% CI (Test/Reference ratio) within the acceptance criteria of 80 – 125%.

Table 11.4.3 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment C Versus Treatment A

Parameters	Geometric LS Means		CIs		%Geometric
	C	A	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1332.633	1531.193	77.59 – 97.62	0.0483	87.03
AUC_{0-t}	4454.443	5348.582	75.15 – 92.29	0.0046	83.28
AUC_{0-2}	0.002	0.000	125.8 – 89908	0.0803	3363.65
AUC_{0-5}	3.745	1.619	153.5 – 348.71	0.0014	231.37
AUC_{0-10}	27.803	20.527	101.5 – 180.74	0.0842	135.45
AUC_{0-15}	73.462	71.195	81.21 – 131.10	0.8267	103.18
AUC_{0-30}	293.351	344.882	72.07 – 100.38	0.1078	85.06
AUC_{0-40}	482.676	579.182	72.33 – 96.02	0.0361	83.34
AUC_{0-50}	686.204	812.971	74.45 – 95.70	0.0283	84.41
AUC_{0-60}	885.834	1034.937	76.24 – 96.10	0.0290	85.59
$AUC_{0-\infty}$	4846.014	5789.319	75.43 – 92.89	0.0064	83.71

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Source: Table 14.2.13

The GMRs were 87.03%, 83.28%, and 83.71% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; however, the 90% CIs were not within the 80 – 125% range. Similar results were observed for the partial extent of exposure at 15, 30, 40, 50, and 60 minutes postdose. The 90% CIs derived from the analyses of the ln-transformed PK parameters AUC_{0-2}, AUC_{0-5} and AUC_{0-10} were not within the 80 – 125% range.

Table 11.4.4 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment D Versus Treatment A

Parameters	Geometric LS Means		CIs		%Geometric
	D	A	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1199.675	1531.193	69.88 – 87.85	0.0009	78.35
AUC_{0-t}	4147.517	5348.582	70.00 – 85.90	0.0001	77.54
AUC_{0-2}	0.003	0.000	212.5 – 120771	0.0465	5066.06
AUC_{0-5}	4.283	1.619	175.9 – 398.12	0.0003	264.63
AUC_{0-10}	34.171	20.527	124.9 – 221.91	0.0048	166.47
AUC_{0-15}	90.893	71.195	100.6 – 162.07	0.0924	127.67
AUC_{0-30}	340.804	344.882	83.78 – 116.55	0.9041	98.82
AUC_{0-40}	532.195	579.182	79.79 – 105.81	0.3190	91.89
AUC_{0-50}	712.836	812.971	77.37 – 99.37	0.0844	87.68
AUC_{0-60}	884.013	1034.937	76.11 – 95.86	0.0266	85.42
$AUC_{0-\infty}$	4556.792	5789.319	70.95 – 87.32	0.0004	78.71

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Source: Table 14.2.14

The GMRs were 78.35%, 77.54%, and 78.71% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were not within the 80 – 125% range. The 90% CIs derived from the analyses of the ln-transformed PK parameter AUC_{0-30} was

within the 80 – 125% range. The partial extent of exposure at 2, 5, 10, and 15 minutes postdose CIs were not within the 80 – 125% range.

Table 11.4.5 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment E Versus Treatment A

Parameters	Geometric LS Means		CIs		%Geometric
	E	A	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1249.415	1531.193	72.78 – 91.49	0.0047	81.60
AUC_{0-t}	4078.034	5348.582	68.82 – 84.47	<0.0001	76.25
AUC_{0-2}	0.005	0.000	214.3 – 274869	0.0505	7673.97
AUC_{0-5}	4.804	1.619	197.3 – 446.53	<0.0001	296.81
AUC_{0-10}	38.291	20.527	139.9 – 248.67	0.0007	186.54
AUC_{0-15}	101.13	71.195	111.9 – 180.32	0.0175	142.05
AUC_{0-30}	359.091	344.882	88.28 – 122.81	0.6829	104.12
AUC_{0-40}	551.818	579.182	82.74 – 109.72	0.5671	95.28
AUC_{0-50}	738.238	812.971	80.13 – 102.91	0.2019	90.81
AUC_{0-60}	909.052	1034.937	78.27 – 98.57	0.0655	87.84
$AUC_{0-\infty}$	4473.022	5789.319	69.65 – 85.71	0.0001	77.26

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Table 14.2.15

The GMRs were 81.60%, 76.25%, and 77.26% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. The 90% CIs for all 3 PK parameters were not within the 80 – 125% range. The 90% CIs derived from the analyses of the ln-transformed PK parameter AUC_{0-30}, AUC_{0-40}, and AUC_{0-50} were within the 80 – 125% range. The partial extent of exposure at 2, 5, 10, and 15 minutes postdose were not within the 80 – 125% range.

Table 11.4.6 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment C Versus Treatment B

Parameters	Geometric LS Means		CIs		%Geometric
	C	B	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1332.633	1325.889	89.64 – 112.69	0.9409	100.51
AUC_{0-t}	4454.443	4585.746	87.68 – 107.61	0.6357	97.14
AUC_{0-2}	0.002	0.004	2.85 – 924.52	0.6919	51.37
AUC_{0-5}	3.745	5.715	45.26 – 94.88	0.0618	65.53
AUC_{0-10}	27.803	38.078	54.77 – 97.34	0.0729	73.02
AUC_{0-15}	73.462	96.144	60.19 – 97.00	0.0647	76.41
AUC_{0-30}	293.351	356.437	69.78 – 97.07	0.0537	82.30
AUC_{0-40}	482.676	560.592	74.77 – 99.15	0.0817	86.10
AUC_{0-50}	686.204	760.668	79.60 – 102.23	0.1733	90.21
AUC_{0-60}	885.834	949.795	83.11 – 104.67	0.3151	93.27
$AUC_{0-\infty}$	4846.014	5040.119	86.67 – 106.66	0.5278	96.15

Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Source: Table 14.2.16

The GMRs were 100.51%, 97.14%, and 96.15% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation C was comparable to B for peak and overall extent of exposure to flurbiprofen. Similar results were observed for the ln-transformed PK parameter AUC_{0-60}. The partial extent of exposure at 2, 5, 10, and 15 minutes postdose were not within the 80 – 125% range.

Table 11.4.7 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment D Versus Treatment B

Parameters	Geometric LS Means		CIs		%Geometric
	D	B	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1199.675	1325.889	80.67 – 101.49	0.1503	90.48
AUC_{0-t}	4147.517	4585.746	81.61 – 100.23	0.1076	90.44
AUC_{0-2}	0.003	0.004	5.06 – 1183.4	0.8712	77.36
AUC_{0-5}	4.283	5.715	51.69 – 108.68	0.1985	74.95
AUC_{0-10}	34.171	38.078	67.25 – 119.75	0.5314	89.74
AUC_{0-15}	90.893	96.144	74.41 – 120.11	0.6951	94.54
AUC_{0-30}	340.804	356.437	81.02 – 112.84	0.6512	95.61
AUC_{0-40}	532.195	560.592	82.40 – 109.38	0.5403	94.93
AUC_{0-50}	712.836	760.668	82.66 – 106.25	0.3892	93.71
AUC_{0-60}	884.013	949.795	82.90 – 104.49	0.3029	93.07
$AUC_{0-\infty}$	4556.792	5040.119	81.47 – 100.33	0.1109	90.41

Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Source: Table 14.2.17

The GMRs were 90.48%, 90.44%, and 90.41% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation D was comparable to B for peak and overall extent of exposure to flurbiprofen. Similar results were observed for the ln-transformed PK parameters AUC_{0-30}, AUC_{0-40}, AUC_{0-50}, and AUC_{0-60}. The partial extent of exposure at 2 and 5 minutes postdose were not within the 80 – 125% range.

Table 11.4.8 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment E Versus Treatment B

Parameters	Geometric LS Means		CIs		%Geometric
	E	B	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1249.415	1325.889	84.04 – 105.66	0.3875	94.23
AUC_{0-t}	4078.034	4585.746	80.27 – 98.52	0.0607	88.93
AUC_{0-2}	0.005	0.004	4.58 – 2998.8	0.9328	117.19
AUC_{0-5}	4.804	5.715	58.05 – 121.74	0.4340	84.06
AUC_{0-10}	38.291	38.078	75.44 – 134.05	0.9741	100.56
AUC_{0-15}	101.130	96.144	82.86 – 133.53	0.7233	105.19
AUC_{0-30}	359.091	356.437	85.42 – 118.83	0.9401	100.74
AUC_{0-40}	551.818	560.592	85.48 – 113.35	0.8518	98.43
AUC_{0-50}	738.238	760.668	85.64 – 109.98	0.6894	97.05
AUC_{0-60}	909.052	949.795	85.28 – 107.41	0.5260	95.71
$AUC_{0-\infty}$	4473.022	5040.119	80.00 – 98.45	0.0598	88.75

Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Table 14.2.18

The GMRs were 94.23%, 88.93%, and 88.75% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation E was comparable to B for peak and overall extent of exposure to flurbiprofen. Similar results were observed for the ln-transformed PK parameters AUC_{0-30}, AUC_{0-40}, AUC_{0-50}, and AUC_{0-60}.

Table 11.4.9 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment D Versus Treatment C

Parameters	Geometric LS Means		CIs		%Geometric
	D	C	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1199.675	1332.633	80.29 – 100.94	0.1299	90.02
AUC_{0-t}	4147.517	4454.443	84.05 – 103.15	0.2475	93.11
AUC_{0-2}	0.003	0.002	11.12 – 2040.5	0.7867	150.61
AUC_{0-5}	4.283	3.745	78.98 – 165.63	0.5444	114.37
AUC_{0-10}	34.171	27.803	92.19 – 163.84	0.2344	122.90
AUC_{0-15}	90.893	73.462	97.47 – 157.07	0.1409	123.73
AUC_{0-30}	340.804	293.351	98.50 – 137.03	0.1341	116.18
AUC_{0-40}	532.195	482.676	95.75 – 126.97	0.2510	110.26
AUC_{0-50}	712.836	686.204	91.67 – 117.72	0.6114	103.88
AUC_{0-60}	884.013	885.834	88.92 – 111.99	0.9762	99.79
$AUC_{0-\infty}$	4556.792	4846.014	84.76 – 104.31	0.3242	94.03

Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Source: Table 14.2.19

The GMRs were 90.02%, 93.11%, and 94.03% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation D was comparable to C for peak and overall extent of exposure to flurbiprofen. Similar results were observed with the ln-transformed PK parameters AUC_{0-50} and AUC_{0-60}. The partial extent of exposure at 2 minutes postdose was not within the 80 – 125% range.

Table 11.4.10 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment E Versus Treatment C

Parameters	Geometric LS Means		CIs		%Geometric
	E	C	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1249.415	1332.633	83.58 – 105.16	0.3503	93.76
AUC_{0-t}	4078.034	4454.443	82.61 – 101.46	0.1558	91.55
AUC_{0-2}	0.005	0.002	14.30 – 3640.0	0.6093	228.14
AUC_{0-5}	4.804	3.745	88.47 – 186.01	0.2655	128.28
AUC_{0-10}	38.291	27.803	103.2 – 183.78	0.0690	137.72
AUC_{0-15}	101.130	73.462	108.4 – 174.90	0.0301	137.66
AUC_{0-30}	359.091	293.351	103.7 – 144.46	0.0463	122.41
AUC_{0-40}	551.818	482.676	99.23 – 131.72	0.1193	114.32
AUC_{0-50}	738.238	686.204	94.89 – 121.97	0.3330	107.58
AUC_{0-60}	909.052	885.834	91.41 – 115.21	0.7088	102.62
$AUC_{0-\infty}$	4473.022	4846.014	83.18 – 102.43	0.2028	92.30

Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Table 14.2.20

The GMRs were 93.76%, 91.55%, and 92.30% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation E was comparable to C for peak and overall extent of exposure to flurbiprofen. Similar results were observed with the ln-transformed PK parameters AUC_{0-50} and AUC_{0-60}. The partial extent of exposure at 2, 5, 10, and 15 minutes postdose were not within the 80 – 125% range.

Table 11.4.11 Summary of Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters AUC_{0-t}, $AUC_{0-\infty}$, Partial AUCs and C_{max}: Treatment E Versus Treatment D

Parameters	Geometric LS Means		CIs		%Geometric
	E	D	(90% Confidence)	p-Value	Mean Ratio
C_{max}	1249.415	1199.675	92.85 – 116.82	0.5550	104.15
AUC_{0-t}	4078.034	4147.517	88.72 – 108.96	0.7835	98.32
AUC_{0-2}	0.005	0.003	7.75 – 2960.0	0.8098	151.48
AUC_{0-5}	4.804	4.283	77.35 – 162.64	0.6054	112.16
AUC_{0-10}	38.291	34.171	83.98 – 149.53	0.5105	112.06
AUC_{0-15}	101.130	90.893	87.57 – 141.36	0.4576	111.26
AUC_{0-30}	359.091	340.804	89.28 – 124.35	0.5984	105.37
AUC_{0-40}	551.818	532.195	90.00 – 119.46	0.6694	103.69
AUC_{0-50}	738.238	712.836	91.35 – 117.42	0.6414	103.56
AUC_{0-60}	909.052	884.013	91.59 – 115.45	0.6869	102.83
$AUC_{0-\infty}$	4473.022	4556.792	88.45 – 108.93	0.7659	98.16

Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Table 14.2.21

The GMRs were 104.15%, 98.32%, and 98.16% for plasma flurbiprofen C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and the 90% CIs were within the 80 – 125% range, indicating that the flurbiprofen spray Formulation E was comparable to D for peak and overall extent of exposure to flurbiprofen. Similar results were observed for ln-transformed PK parameters AUC_{0-30}, AUC_{0-40}, AUC_{0-50}, and AUC_{0-60}.

The results of the non-parametric analyses of the t_{max} of flurbiprofen are presented in Table 11.4.12.

Table 11.4.12 Non-Parametric Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameter t_{max}

Comparisons	90% CI	Median	p-Value
Difference B – A	-0.2085 – 0.0822	-0.0011	0.5557
Difference C – A	-0.1666 – 0.0811	-0.0835	0.3394
Difference D – A	-0.2881 – -0.0004	-0.1643	0.0923
Difference E – A	-0.3772 – -0.0818	-0.1682	0.0522
Difference C – B	-0.1670 – 0.2068	-0.0003	0.7334
Difference D – B	-0.2879 – 0.1664	-0.0013	0.7471
Difference E – B	-0.2044 – 0.0022	-0.1637	0.1763
Difference D – C	-0.2488 – 0.0834	-0.0833	0.4126
Difference E – C	-0.2078 – -0.0015	-0.0833	0.0117
Difference E – D	-0.2473 – 0.0839	-0.0014	0.5693

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment D = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E = 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Tables 14.2.22 to 14.2.31

Following a non-parametric evaluation using the Wilcoxon Marched Pair Test, there was no statistically significant difference in t_{max} between the flurbiprofen lozenge and any of the spray formulations ($p > 0.05$), there was, however, a small delay ranging between 0.0011 – 0.1682 hr with the administration of spray formulations relative to the lozenge.

When comparing the sprays amongst themselves, the only formulation that showed a statistically significant difference in the t_{max} was between Treatments E and C ($p < 0.05$).

Sequence Effect

A statistically significant ($p < 0.1$) sequence effect was observed for ln-transformed PK parameters C_{max}, AUC_{0-t}, AUC_{0-10}, AUC_{0-15}, AUC_{0-30}, AUC_{0-40}, AUC_{0-50}, AUC_{0-60}, and $AUC_{0-\infty}$ for flurbiprofen in plasma. However, this study meets the criteria for acceptability of studies with sequence effects: it is a single-dose study using a standard 5-treatment crossover design with normal healthy volunteers; the drug is not an endogenous entity; a more than adequate washout period of 5 days between dose administrations (corresponding to more than 7 elimination half-lives) was adequate to ensure that predose plasma drug concentrations in Periods 2, 3, 4, and 5 were below the LLOQ. The $t_{1/2}$ of flurbiprofen ranged from 3.28 – 3.57 hr; therefore, the drug is expected to be cleared from the systemic circulation by 15 – 18 hr postdose. The study was based on an acceptable protocol and used a validated assay methodology, and the study data were analysed by appropriate statistical methods. Therefore, the observed sequence effect is not expected to compromise the assessment.

11.4.2 Analytical Issues

Detailed documentation of statistical methods, as the final SAP, is presented in Appendix 16 .1.9.

11.4.2.1 Adjustments for Covariates

No adjustments were made for covariates; therefore, this section is not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

There are no missing data and no subjects dropped out of the study; therefore, this section is not applicable.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed and there was no data monitoring; therefore, this section is not applicable.

11.4.2.4 Multi-Site Studies

This was a single-site study; therefore, this section is not applicable.

11.4.2.5 Multiple Comparison/Multiplicity

No multiple comparisons were made; therefore, this section is not applicable.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

This was a PK study and no efficacy subsets of subjects were created; therefore, this section is not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This study was not designed to test equivalence; therefore, this section is not applicable.

11.4.2.8 Examination of Subgroups

No sub-groups were examined in this study; therefore, this section is not applicable.

11.4.3 Tabulation of Individual Response Data

Individual concentration and PK data can be found in Section 14.2.1. The individual PK profiles (semi-log and linear plots) are presented in Section 14.4.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

This was not a dose response study and no drug concentration-to-response relationship was explored; therefore, this section is not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

No drug/drug or drug/disease interactions were seen in this study; therefore, this section is not applicable.

11.4.6 By-Subject Displays

Group mean data represent the principal analysis in this study; therefore, this section is not applicable.

11.4.7 Pharmacokinetic Conclusions

- The peak and overall extent of exposure of the flurbiprofen spray test formulations were lower than that of the flurbiprofen 8.75 mg lozenge. The 90% CIs of the geometric mean ratios for C_{max} and AUCs of the flurbiprofen spray test formulations to the flurbiprofen 8.75 mg lozenge were outside the 80% – 125% range.
- The peak and overall extent of exposure for all 4 flurbiprofen spray formulations were comparable to each other, with the 90% CI for the ratios of geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ being within the 80% – 125% range.
- Peak flurbiprofen concentrations were reached between approximately 30 and 40 minutes following both the lozenge and spray formulations, with a half-life ranging between 3.28 and 3.57 hr.
- There was no statistically significant difference in t_{max} between the flurbiprofen lozenge and any of the spray formulations.

12 SAFETY EVALUATION

12.1 Extent of Exposure

A total of 12 subjects received 1 dose each of Treatments B, C, D, and E (test), flurbiprofen 8.75 mg/540 µL (3 sprays [180 µL]) (4 flavour variants), and Treatment A (reference), flurbiprofen 8.75 mg lozenge (honey and lemon flavoured) as part of a 5-way crossover open-label study design. Test compound administration times are presented in Appendix 16.2.5.4.2. All subjects completed the dosing regimen as per protocol and were included in the safety analysis.

12.2 Adverse Events (AEs)

All AEs for each subject, including the same event on several occasions, are listed in Appendix 16.2.7. Adverse events, giving both preferred terms according to MedDRA® (Version 13.1) and the verbatim term used by the PI, are listed for onset, duration, severity, seriousness, outcome, relationship to study drug, and action.

12.2.1 Brief Summary of Events

There were no SAEs or laboratory AEs reported in this study and no subject was discontinued due to an AE occurrence.

A total of 18 TEAEs were reported by 8 (67%) subjects overall in this study, with the highest incidence (4 [33%] subjects) occurring following Treatments B and D. Overall, AE reporting was minimal across treatments; the lowest incidence occurred following Treatment C (1 [8%] subject), with 2 (17%) subjects reporting events following Treatment A. The most common AE reported during the study was upper respiratory tract infection, 3 episodes overall following Treatment B, which were considered by the PI to be not related to the study treatment. Overall, the PI considered 14 events to be unlikely related to the study treatment and 4 events to be not related, and considered 17 events to be mild in intensity and 1 event to be moderate (upper respiratory tract infection [Treatment B]). Table 12.2.1 presents AE incidence and frequency of AEs by treatment.

Table 12.2.1 Treatment-Emergent Adverse Event Incidence

	Treatments					Total
	A (N = 12)	B (N = 12)	C (N = 12)	D (N = 12)	E (N = 12)	(N = 12)
Subject Incidence (%)	2 (17%)	4 (33%)	1 (8%)	4 (33%)	3 (25%)	8 (67%)
Number of AEs	2	4	2	5	5	18

Treatment A: Flurbiprofen 8.75 mg lozenge
Treatment B: 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/090
Treatment C: 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/096
Treatment D: 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/102
Treatment E: 15 mL of 8.75 mg/540 µL flurbiprofen (3 sprays [180 µL each]), Lot No. 02143/108
Source: Tables 14.3.1.1 and 14.3.1.2.

12.2.2 Display of Adverse Events

Treatment-emergent AEs are summarised by treatment and subject incidence in Table 14.3.1.1 and by number of AEs in Table 14.3.1.2. Treatment-emergent AEs are summarised by treatment, severity, relationship to study treatment, and subject incidence in Table 14.3.1.3; the same information by number of events is presented in Table 14.3.1.4. Incidence of all TEAEs (McNemar's Test) is presented in Table 14.3.1.5. Incidence of probably or possibly related TEAEs (McNemar's Test [none reported]) is presented in Table 14.3.1.6. Severe TEAEs (McNemar's Test [none reported]) are presented in Table 14.3.1.7. Serious AEs (none reported) are presented in Table 14.3.2. Individual AEs are presented in Appendices 16.2.7.1 through 16.2.7.3.

12.2.3 Analysis of Adverse Events

Upper respiratory tract infection was reported 3 times by a total of 3 (25%) subjects following Treatment B. Onset was approximately 2 days for all episodes and duration ranged from approximately 3 to 14 days. All events were considered by the PI to be not related to the study treatment. Two events were considered to be mild in intensity and 1 event to be moderate. All events resolved without sequelae and without the intervention of concomitant medications.

Mild cheilitis was reported twice by 2 (17%) subjects, with 1 subject each following Treatments D and E. Both events resolved without sequelae within a timeframe of 3 to 11 days, respectively, and were considered by the PI to be unlikely related to the study treatment.

Mild headache was reported twice by 2 (17%) subjects, with 1 subject each following Treatments C and E. Both events resolved without sequelae within a timeframe of 2 to 3 hr, respectively, and were considered by the PI to be unlikely related to the study treatment.

Remaining events were reported by 1 (8%) subject, all of which were mild in intensity and were considered to be unlikely related or not related to the study treatment.

Rash, rash macular, rash maculo-papular, and rash pustular were each reported by 1 (8%) subject following Treatments D, C, and E. All rash events were considered by the PI to be unlikely related to the study treatment and were mild in intensity. Subjects experiencing these TEAEs did not require concomitant medication. Subject 12 (Treatment C) received Loratadine® and Diprobase® ointment for treatment of predose events of pruritic rash and acarodermatitis. All events resolved without sequelae.

Concomitant medications are presented by individual subject in Appendix 16.2.5.7. In addition to the medications received by Subject 12, Subject 8 received Vaseline for chapped lips reported following Treatment D.

Postural dizziness AEs are described in Section 12.5.1.

12.3 Other Serious Adverse Events (SAEs) and other Significant Adverse Events

There were no deaths or other serious or significant AEs in this study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Clinically Significant Abnormal Laboratory Value

Laboratory information is presented in the following locations:

Out-of-range values and recheck results - serum chemistry	Tables 14.3.4.1.1 and 14.3.4.1.2
Out-of-range values and recheck results - haematology	Tables 14.3.4.2.1 and 14.3.4.2.2
Out-of-range values and recheck results - urinalysis	Table 14.3.4.3
Clinical laboratory summary and change from screening - serum chemistry	Table 14.3.5.1
Clinical laboratory shift from screening - serum chemistry	Table 14.3.5.2
Clinical laboratory summary and change from screening - haematology	Table 14.3.5.3
Clinical laboratory shift from screening - haematology	Table 14.3.5.4
Clinical laboratory summary and change from screening - urinalysis	Table 14.3.5.5
Individual results - serum chemistry	Appendices 16.2.8.1.1 through 16.2.8.1.3
Individual results - haematology	Appendices 16.2.8.2.1 through 16.2.8.2.3
Individual results - urinalysis	Appendices 16.2.8.3.1 through 16.2.8.3.3
Urine drug screening results	Appendices 16.2.8.4.1 and 16.2.8.4.2
Laboratory individual results - other	Appendix 16.2.8.5.
Clinical laboratory Investigator comments	Appendix 16.2.8.6

12.4.2 Evaluation of Each Laboratory Parameter

Mean laboratory parameters remained within reference range at the post study assessment with minimal changes from screening for serum chemistry, haematology, and urinalysis.

12.4.2.1 Laboratory Values Over Time

Laboratory shifts from screening to post study were minimal for serum chemistry, haematology, and urinalysis. All post study out-of-range results were considered by the PI to be not clinically significant.

12.4.2.2 Individual Subject Changes

Not applicable.

12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

12.5.1 Vital signs

Vital sign results and change from screening are summarised in Table 14.3.5.6. Individual vital signs are presented in Appendix 16.2.9.1.

Mean vital sign results were within normal range, with minimal changes from screening at the post study assessment.

Two (2) subjects experienced vital sign-related AEs of postural dizziness. Subject 6 had mild postural dizziness 2.7 hr following Treatment A in Period 3, with a duration of 7.5 hr. During the time of the dizziness event, vital sign measurements were: 86/43 mmHg, pulse 63 beats per minute (bpm) on supine and 81/62 mmHg, pulse 104 bpm on standing (~5.5 hr post onset); 84/55 mmHg, pulse 71 bpm on supine and 98/52 mmHg, pulse 109 bpm on standing (~6.8 hr post onset); and 92/60 mmHg, pulse 68 bpm on supine and 99/59 mmHg, pulse 106 bpm on standing (~8.6 hr post onset) (source data on file at Celerion). The subject was asymptomatic and considered fit for discharge from the clinic. Screening vital sign results (seated) for this subject were noted to be comparatively low at 95/72 mmHg, pulse 80 bpm. The PI considered the event to be unlikely related to the study treatment. The subject did not experience this event in any other treatment period.

Subject 12 had mild postural dizziness approximately 3.7 hr following Treatment D in Period 4, with a duration of 3 hr. Vital sign measurements were 117/53 mmHg, pulse 46 bpm on supine and 122/59 mmHg, pulse 57 bpm on standing (~23 minutes post onset) (source data on file at Celerion). The PI considered the event to be unlikely related to the study treatment. The subject did not experience this event in any other treatment period.

12.5.2. Electrocardiograms

Mean summary results and change from screening for ECGs are presented in Table 14.3.5.7. Individual ECG results are presented in Appendix 16.2.9.2.

Mean ECG results were within normal limits at the post study assessment with minimal changes from screening. There were 4 subjects with post study ECG abnormalities which the PI considered not clinically significant or a normal variant.

12.5.3 Physical Examinations

Physical examination assessments are presented in Appendices 16.2.4.2.1 through 16.2.4.2.3. With the exception of rash events (see Section 12.2.3), no other post treatment physical findings were noted.

12.6 Safety Conclusions

There were no SAEs or laboratory AEs reported in this study and no subject was discontinued due to an AE.

A total of 18 TEAEs were reported by 8 (67%) subjects overall in this study, with the highest incidence (4 [33%] subjects) occurring following Treatments B and D. Two (2) subjects reported events following Treatment A. The most common AE reported during the study was upper respiratory tract infection; 3 episodes overall following Treatment B, which were considered by the PI to be not related to the study treatment. Overall, the PI considered all events to be unlikely related or not related to the study treatment. The majority of the events were mild in intensity, with 1 moderate event of upper respiratory tract infection (following Treatment B).

There were 2 vital sign events of postural dizziness reported during the study, 1 each following Treatments A and D. Both events were considered by the PI to be mild in intensity and unlikely related to the study treatment.

Overall, there were no clinically significant observations in the AE, clinical laboratory, ECG, or physical examination assessments in this study.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

Pharmacokinetic

The peak and overall extent of exposure of the flurbiprofen spray test formulations were lower than that of the flurbiprofen 8.75 mg lozenge. The 90% CIs of the geometric mean ratios for C_{max} and AUCs of the flurbiprofen spray test formulations to the flurbiprofen 8.75 mg lozenge were outside the 80% – 125% range.

The absorption phase of flurbiprofen for both the lozenge and spray formulations appeared to be highly variable. The %CV for the partial AUCs ranged between 26.0 and 110%. It should be noted that the PK parameter AUC_{0-2} was not robustly assessed because the majority of concentrations were BLQ; hence, this parameter was presented for information purposes only.

The extent of exposure from dosing to 2, 5, 10, and 15 minutes postdose appeared to be greater following administration of the spray formulations relative to the lozenge. AUC_{0-5} was statistically greater for all test spray formulations relative to the lozenge. The partial extent of exposure at 30 and 40 minutes postdose appeared to be comparable between the 2 administration forms; after that point the extent of exposure decreased for the spray formulations.

The peak exposure was reached between approximately 30 and 40 minutes postdose for the lozenge and spray formulations. The mean apparent elimination $t_{1/2}$ of flurbiprofen was comparable across all studied formulations and ranged between 3.28 and 3.57 hr in healthy subjects. The peak and overall extent of exposure for all 4 flurbiprofen spray formulations were comparable to each other, with the 90% CI for the ratios of geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ being within the 80 – 125% range.

An investigation was performed by the Sponsor to investigate the possibility that the complete dose of flurbiprofen may not have been delivered during administration of the test (spray) formulations. The results of the investigation showed that using the dosing instructions provided, it was possible that on average only approximately 80% of the dose was dispensed. A further investigation was performed to investigate other methods for pump operation and it was found that by changing the method for pump operation it is possible to increase the amount of product dosed and to decrease the level of variability between users.

It was concluded that changing the methodology in future studies could potentially bring the results for the spray formulations closer to the reference, both in terms of %CV and AUC/C_{max}.

Safety

Overall, there were no clinically significant safety findings in this investigational study. Adverse event reporting was, overall, minimal across treatment groups. The PI considered all reported events to be unlikely related or not related to the study treatment, with the majority of reported events being mild in intensity. Clinical laboratory, vital sign, and ECG assessments largely remained within normal limits at the post study assessment, with any out-of-range post-treatment results considered by the PI to be not clinically significant.

13.2 Conclusion

Pharmacokinetic

- The peak and overall extent of exposure of the flurbiprofen spray test formulations were lower than that of the flurbiprofen 8.75 mg lozenge. The 90% CIs of the geometric mean ratios for C_{max} and AUCs of the flurbiprofen spray test formulations to the flurbiprofen 8.75 mg lozenge were outside the 80% – 125% range.
- The peak and overall extent of exposure for all 4 flurbiprofen spray formulations were comparable to each other, with the 90% CI for the ratios of geometric means for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ being within the 80% – 125% range.
- Peak flurbiprofen concentrations were reached between approximately 30 and 40 minutes following both the lozenge and spray formulations, with a half-life ranging between 3.28 and 3.57 hr.
- There was no statistically significant difference in t_{max} between the flurbiprofen lozenge and any of the spray formulations.

Safety

- A dose of 8.75 mg flurbiprofen, administered as a lozenge or as a spray, was safe and well tolerated by the male and female subjects in this investigational study.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Table 14.1.1. Summary of Disposition

Disposition	Male	Female	Overall
Enrolled	6	6	12
Completed	6	6	12
Discontinued Early	0	0	0

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Table 14.1.2. Disposition of Subjects

Subject Number	Treatment Sequence	Dosed					Completed					Study Completion	
		A	B	C	D	E	A	B	C	D	E	Status	Date
0001	AEDBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0002	BECAD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0003	DACEB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0004	EABDC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0005	CDBAE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0006	DCABE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0007	BCEDA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0008	CBDEA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0009	EBACD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0010	ADECB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0011	ADECB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
0012	EABDC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Completed Study	10MAR2011
		12	12	12	12	12	12	12	12	12	12		

Note: Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

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Table 14.1.3. Demographic Summary

Variable		Male	Female	Overall
Gender	Male	6 (100%)	0 (0%)	6 (50%)
	Female	0 (0%)	6 (100%)	6 (50%)
Race	Caucasian	6 (100%)	6 (100%)	12 (100%)
Age (yrs)	N	6	6	12
	Mean	23.8	27.0	25.4
	SD	3.97	9.59	7.19
	Median	23.5	25.5	24.0
	Minimum	19	18	18
	Maximum	30	44	44
Weight (kg)	N	6	6	12
	Mean	78.30	62.63	70.47
	SD	9.862	7.593	11.720
	Median	81.20	62.60	68.70
	Minimum	62.8	54.0	54.0
	Maximum	88.0	73.6	88.0
Height (cm)	N	6	6	12
	Mean	175.0	162.7	168.8
	SD	8.10	5.96	9.35
	Median	176.0	163.5	168.0
	Minimum	161	152	152
	Maximum	183	169	183
Body Mass Index (kg/m²)	N	6	6	12
	Mean	25.470	23.665	24.568
	SD	1.4404	2.4472	2.1340
	Median	26.075	24.225	25.230
	Minimum	23.19	20.08	20.08
	Maximum	26.97	26.39	26.97

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14.2 Pharmacokinetic Data Summary Tables and Figures

Table 14.2.1. Plasma Flurbiprofen Concentrations (ng/mL) Following Flurbiprofen 8.75 mg lozenge (Treatment A) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) Predose	2	5	10	15	30	40	50
1	A	1	BLQ	BLQ	55.19	224.7	420.3	962.2	1116	1368
2	A	4	BLQ	BLQ	72.19	511.5	1017	1375	1529	1510
3	A	2	BLQ	BLQ	51.56	311.5	413.0	788.8	788.3	727.4
4	A	2	BLQ	BLQ	BLQ	238.1	482.0	1281	1379	1376
5	A	4	BLQ	BLQ	60.95	412.3	667.0	1215	1324	1405
6	A	3	BLQ	BLQ	202.9	1024	1740	1687	1815	1655
7	A	5	BLQ	BLQ	BLQ	317.6	649.0	1380	1309	1062
8	A	5	BLQ	BLQ	91.51	596.2	1080	1757	1799	1558
9	A	3	BLQ	BLQ	52.87	457.4	1058	1633	1623	1310
10	A	1	BLQ	BLQ	88.56	575.7	1300	1791	1819	1721
11	A	1	BLQ	BLQ	BLQ	227.6	618.4	1466	1519	1434
12	A	2	BLQ	BLQ	49.32	610.2	1034	1550	1724	1630
Mean			0	0	60.42	458.9	873.2	1407	1479	1396
SD			0	0	55.13	229.3	402.8	310.1	314.4	275.6
CV (%)			.	.	91.25	49.97	46.13	22.04	21.26	19.74
SEM			0	0	15.92	66.20	116.3	89.52	90.77	79.55
N			12	12	12	12	12	12	12	12
Minimum			0	0	0	224.7	413.0	788.8	788.3	727.4
Maximum			0	0	202.9	1024	1740	1791	1819	1721
Median			0	0	54.03	434.9	842.0	1423	1524	1420
Lower 95% CI			0	0	31.84	340.0	664.4	1246	1316	1253
Upper 95% CI			0	0	89.00	577.8	1082	1568	1642	1539

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.
. = Value missing or not reportable.
ND = Not Determined

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Table 14.2.1. Plasma Flurbiprofen Concentrations (ng/mL) Following Flurbiprofen 8.75 mg lozenge (Treatment A) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) 60	75	90	120	180	240	360	480	720
1	A	1	1293	1047	954.1	712.8	625.6	491.6	291.2	202.7	92.63
2	A	4	1390	1153	1002	867.7	580.7	430.3	216.3	127.1	42.78
3	A	2	762.2	1113	1205	956.7	760.0	591.3	291.4	227.8	104.9
4	A	2	1370	1141	1293	812.6	631.9	472.2	238.9	154.1	65.67
5	A	4	1249	1308	989.8	734.6	559.7	406.4	183.7	120.7	47.42
6	A	3	1489	1322	1155	1027	795.0	656.0	393.2	226.6	107.2
7	A	5	1048	1009	831.5	838.1	580.2	437.5	343.6	222.5	117.5
8	A	5	1506	1326	1034	911.5	712.9	551.7	332.4	185.9	94.13
9	A	3	1305	1147	1029	833.2	718.5	547.5	275.2	221.0	101.9
10	A	1	1485	1414	1559	1100	800.2	583.8	330.3	175.3	81.25
11	A	1	1359	1115	986.5	886.2	656.0	460.3	329.6	189.9	91.53
12	A	2	1464	1283	1159	869.4	629.4	485.4	295.3	176.6	77.09
Mean			1310	1198	1100	879.2	670.8	509.5	293.4	185.9	85.33
SD			215.3	127.3	191.4	110.7	84.39	76.10	58.75	37.17	23.47
CV (%)			16.44	10.62	17.40	12.59	12.58	14.94	20.02	20.00	27.50
SEM			62.16	36.75	55.25	31.95	24.36	21.97	16.96	10.73	6.775
N			12	12	12	12	12	12	12	12	12
Minimum			762.2	1009	831.5	712.8	559.7	406.4	183.7	120.7	42.78
Maximum			1506	1414	1559	1100	800.2	656.0	393.2	227.8	117.5
Median			1365	1150	1032	868.6	644.0	488.5	293.4	187.9	92.08
Lower 95% CI			1198	1132	1001	821.8	627.1	470.0	263.0	166.6	73.17
Upper 95% CI			1422	1264	1199	936.5	714.6	549.0	323.9	205.1	97.50

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.

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Table 14.2.2. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (Treatment B) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) Predose	2	5	10	15	30	40	50
1	B	4	BLQ	43.66	123.0	362.8	667.0	1567	1375	1243
2	B	1	BLQ	88.92	508.4	948.1	1149	1088	1011	888.6
3	B	5	BLQ	BLQ	164.7	226.5	348.6	694.0	648.5	767.2
4	B	3	BLQ	BLQ	546.5	926.2	1527	1320	1284	1082
5	B	3	BLQ	BLQ	164.0	405.3	625.1	1161	1250	1225
6	B	4	BLQ	BLQ	836.4	1630	1712	1775	1878	1604
7	B	1	BLQ	BLQ	120.0	495.7	820.8	881.9	811.5	851.4
8	B	2	BLQ	BLQ	393.2	821.3	1001	1739	1556	1608
9	B	2	BLQ	BLQ	161.5	440.4	791.9	1114	1319	1165
10	B	5	BLQ	BLQ	116.0	278.0	505.3	1304	1651	1603
11	B	5	BLQ	BLQ	124.4	440.9	825.0	1213	1455	1393
12	B	3	BLQ	BLQ	204.3	708.2	1108	1192	1028	1209
Mean			0	11.05	288.5	640.3	923.4	1254	1272	1220
SD			0	27.55	232.1	396.4	401.7	319.8	352.5	293.6
CV (%)			.	249.3	80.44	61.91	43.50	25.50	27.71	24.07
SEM			0	7.953	67.00	114.4	115.9	92.31	101.8	84.75
N			12	12	12	12	12	12	12	12
Minimum			0	0	116.0	226.5	348.6	694.0	648.5	767.2
Maximum			0	88.92	836.4	1630	1712	1775	1878	1608
Median			0	0	164.4	468.3	822.9	1203	1302	1217
Lower 95% CI			0	-3.234	168.2	434.8	715.2	1088	1089	1068
Upper 95% CI			0	25.33	408.9	845.8	1132	1420	1455	1372

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.
. = Value missing or not reportable.
ND = Not Determined

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Table 14.2.2. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (Treatment B) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) 60	75	90	120	180	240	360	480	720
1	B	4	1179	991.6	938.2	761.8	599.7	457.7	291.4	181.2	100.9
2	B	1	803.9	710.0	697.2	501.3	344.5	251.3	114.9	57.08	BLQ
3	B	5	742.8	752.6	745.5	914.5	569.9	412.1	299.7	163.6	91.35
4	B	3	1021	986.7	789.7	581.2	514.6	392.5	237.3	130.8	56.10
5	B	3	1211	1072	992.8	860.4	555.6	511.8	396.2	190.0	105.0
6	B	4	1498	1282	1138	943.4	726.6	584.9	358.3	246.3	125.9
7	B	1	764.3	774.8	640.5	628.7	495.7	437.8	192.1	132.4	81.75
8	B	2	1411	1128	970.6	773.7	594.6	480.0	233.0	159.5	78.39
9	B	2	1105	878.3	845.3	723.3	575.1	477.4	283.9	190.6	91.33
10	B	5	1418	1441	1465	1014	734.0	539.4	287.1	169.6	82.72
11	B	5	1302	1053	1009	821.9	597.2	476.0	346.3	206.4	108.4
12	B	3	1024	880.4	840.8	689.6	529.3	398.8	221.3	137.8	70.21
Mean			1123	995.9	922.7	767.8	569.7	451.6	271.8	163.8	90.19
SD			261.0	218.2	223.1	153.1	102.2	84.94	77.62	47.21	19.42
CV (%)			23.23	21.91	24.18	19.94	17.94	18.81	28.56	28.83	21.53
SEM			75.33	62.98	64.41	44.20	29.51	24.52	22.41	13.63	5.855
N			12	12	12	12	12	12	12	12	11
Minimum			742.8	710.0	640.5	501.3	344.5	251.3	114.9	57.08	56.10
Maximum			1498	1441	1465	1014	734.0	584.9	396.2	246.3	125.9
Median			1142	989.2	891.8	767.8	572.5	466.9	285.5	166.6	91.33
Lower 95% CI			988.0	882.8	807.0	688.4	516.7	407.6	231.6	139.3	79.57
Upper 95% CI			1259	1109	1038	847.2	622.7	495.7	312.0	188.3	100.8

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.

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Table 14.2.3. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (Treatment C) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) Predose	2	5	10	15	30	40	50
1	C	5	BLQ	BLQ	83.17	223.5	354.0	689.5	757.2	1352
2	C	3	BLQ	BLQ	376.4	676.2	936.4	1188	1197	1658
3	C	3	BLQ	BLQ	357.0	505.9	724.6	962.3	1327	1214
4	C	5	BLQ	BLQ	634.1	787.3	1016	1462	1415	1292
5	C	1	BLQ	BLQ	50.02	216.0	553.5	936.9	1279	1200
6	C	2	BLQ	BLQ	233.4	690.6	1102	1517	1408	1413
7	C	2	BLQ	BLQ	51.78	197.4	354.7	687.3	986.9	1029
8	C	1	BLQ	BLQ	127.6	590.8	1337	2077	1655	1464
9	C	4	BLQ	BLQ	220.9	748.9	1011	1186	1174	963.0
10	C	4	BLQ	BLQ	84.32	192.4	314.2	679.2	875.4	1079
11	C	4	BLQ	BLQ	88.97	335.4	470.6	982.4	955.3	888.3
12	C	5	BLQ	BLQ	272.1	422.6	752.3	1500	1675	1534
Mean			0	0	215.0	465.6	743.9	1156	1225	1257
SD			0	0	175.1	230.1	338.7	423.5	293.0	238.6
CV (%)			.	.	81.46	49.42	45.53	36.65	23.91	18.98
SEM			0	0	50.55	66.42	97.78	122.3	84.57	68.87
N			12	12	12	12	12	12	12	12
Minimum			0	0	50.02	192.4	314.2	679.2	757.2	888.3
Maximum			0	0	634.1	787.3	1337	2077	1675	1658
Median			0	0	174.3	464.3	738.5	1084	1238	1253
Lower 95% CI			0	0	124.2	346.3	568.3	936.1	1074	1134
Upper 95% CI			0	0	305.8	584.9	919.5	1375	1377	1381

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.
. = Value missing or not reportable.
ND = Not Determined

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Table 14.2.3. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (Treatment C) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) 60	75	90	120	180	240	360	480	720
1	C	5	1351	1230	1170	875.4	739.6	614.4	379.3	244.1	117.5
2	C	3	1513	1260	1054	902.5	602.6	404.0	186.8	98.35	BLQ
3	C	3	1323	1127	1110	1014	668.2	497.6	371.1	205.7	101.9
4	C	5	1344	1347	1075	1020	766.9	577.6	324.7	193.5	87.50
5	C	1	958.2	946.9	899.1	670.1	427.7	301.7	167.6	74.19	BLQ
6	C	2	1472	1197	1034	905.3	664.3	561.5	285.7	221.4	98.74
7	C	2	739.0	692.7	647.7	500.6	408.3	354.9	221.9	158.7	91.77
8	C	1	1181	1064	1002	813.4	558.1	451.1	239.4	141.8	66.75
9	C	4	961.8	842.6	696.6	695.7	505.4	446.5	234.9	173.1	75.14
10	C	4	975.3	1015	919.2	610.6	417.6	338.4	159.6	82.96	43.76
11	C	4	777.9	771.3	649.2	598.8	425.3	363.6	200.6	127.5	57.15
12	C	5	1470	1196	1066	830.7	596.1	449.0	312.2	181.9	77.19
Mean			1172	1057	943.6	786.4	565.0	446.7	257.0	158.6	81.74
SD			278.1	207.4	184.1	169.0	128.8	100.4	76.31	54.91	22.22
CV (%)			23.73	19.62	19.51	21.49	22.79	22.48	29.69	34.62	27.19
SEM			80.29	59.88	53.14	48.78	37.17	28.99	22.03	15.85	7.027
N			12	12	12	12	12	12	12	12	10
Minimum			739.0	692.7	647.7	500.6	408.3	301.7	159.6	74.19	43.76
Maximum			1513	1347	1170	1020	766.9	614.4	379.3	244.1	117.5
Median			1252	1096	1018	822.1	577.1	447.8	237.2	165.9	82.35
Lower 95% CI			1028	949.9	848.1	698.8	498.3	394.6	217.4	130.1	68.86
Upper 95% CI			1316	1165	1039	874.0	631.8	498.8	296.5	187.1	94.62

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.

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Table 14.2.4. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (Treatment D) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) Predose	2	5	10	15	30	40	50
1	D	3	BLQ	BLQ	427.3	754.1	788.8	845.9	789.2	652.3
2	D	5	BLQ	45.27	393.2	918.0	1034	1149	1137	978.2
3	D	1	BLQ	BLQ	96.99	327.5	405.2	912.0	749.0	759.0
4	D	4	BLQ	BLQ	173.1	716.6	1000	1385	1608	1328
5	D	2	BLQ	BLQ	79.66	260.7	486.7	1112	1112	1147
6	D	1	BLQ	BLQ	501.6	965.4	1493	1626	1576	1406
7	D	4	BLQ	BLQ	75.36	248.0	381.4	703.8	633.0	586.2
8	D	3	BLQ	BLQ	137.5	664.5	1200	1497	1385	1291
9	D	5	BLQ	BLQ	88.65	393.8	679.6	1150	1244	1184
10	D	2	BLQ	BLQ	126.8	324.3	614.8	1174	1229	1186
11	D	2	BLQ	BLQ	167.0	623.5	1137	1346	1324	1158
12	D	4	BLQ	BLQ	201.0	880.1	1483	1360	1337	1219
Mean			0	3.773	205.7	589.7	892.0	1188	1177	1075
SD			0	13.07	148.8	267.3	392.2	272.6	313.0	270.4
CV (%)			.	346.4	72.36	45.32	43.97	22.94	26.60	25.16
SEM			0	3.773	42.97	77.15	113.2	78.69	90.37	78.05
N			12	12	12	12	12	12	12	12
Minimum			0	0	75.36	248.0	381.4	703.8	633.0	586.2
Maximum			0	45.27	501.6	965.4	1493	1626	1608	1406
Median			0	0	152.3	644.0	894.4	1162	1237	1171
Lower 95% CI			0	-3.002	128.5	451.2	688.6	1047	1015	934.4
Upper 95% CI			0	10.55	282.8	728.3	1095	1330	1339	1215

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.
. = Value missing or not reportable.
ND = Not Determined

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Table 14.2.4. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (Treatment D) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) 60	75	90	120	180	240	360	480	720
1	D	3	652.1	594.6	553.7	532.6	396.6	358.7	219.5	125.4	70.32
2	D	5	885.7	803.1	675.3	547.7	428.3	293.3	156.6	82.69	BLQ
3	D	1	872.2	741.6	787.7	583.3	548.1	357.9	237.7	108.4	64.06
4	D	4	1312	1176	991.9	834.4	596.0	446.4	247.6	198.2	75.61
5	D	2	995.4	873.3	777.1	618.3	431.1	290.6	149.4	88.08	BLQ
6	D	1	1313	1252	1143	970.7	683.2	582.4	325.0	227.1	92.22
7	D	4	592.5	579.1	571.8	449.8	368.7	275.6	154.9	136.5	74.47
8	D	3	1187	950.3	921.1	680.3	573.5	389.8	165.8	126.3	56.62
9	D	5	1369	1164	1145	1013	831.2	632.7	329.0	267.1	132.6
10	D	2	1195	1166	949.6	793.0	576.0	359.1	185.5	100.8	57.61
11	D	2	1016	987.6	804.3	727.0	504.2	434.4	227.7	152.2	78.08
12	D	4	1024	866.5	915.1	706.8	522.5	408.0	221.2	153.6	65.51
Mean			1034	929.5	853.0	704.7	538.3	402.4	218.3	147.2	76.71
SD			253.6	228.2	195.2	174.0	130.3	110.7	61.33	57.02	22.28
CV (%)			24.52	24.55	22.88	24.69	24.20	27.51	28.09	38.74	29.04
SEM			73.21	65.88	56.35	50.22	37.61	31.96	17.71	16.46	7.045
N			12	12	12	12	12	12	12	12	10
Minimum			592.5	579.1	553.7	449.8	368.7	275.6	149.4	82.69	56.62
Maximum			1369	1252	1145	1013	831.2	632.7	329.0	267.1	132.6
Median			1020	911.8	859.7	693.6	535.3	374.5	220.4	131.4	72.40
Lower 95% CI			903.0	811.2	751.8	614.5	470.7	345.0	186.5	117.6	63.80
Upper 95% CI			1166	1048	954.2	794.9	605.8	459.8	250.1	176.8	89.62

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.

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Table 14.2.5. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (Treatment E) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) Predose	2	5	10	15	30	40	50
1	E	2	BLQ	BLQ	114.1	293.9	447.0	627.3	676.5	693.3
2	E	2	BLQ	90.05	680.3	1184	1282	1153	1067	1013
3	E	4	BLQ	BLQ	221.1	402.2	694.8	926.5	1202	1140
4	E	1	BLQ	BLQ	270.2	772.0	1268	1264	1173	817.0
5	E	5	BLQ	BLQ	55.77	325.2	826.7	1515	1486	1343
6	E	5	BLQ	BLQ	202.3	856.3	1413	1937	1755	1777
7	E	3	BLQ	BLQ	98.76	355.5	655.7	745.4	823.2	692.4
8	E	4	BLQ	BLQ	859.9	1919	2063	1723	1398	1156
9	E	1	BLQ	BLQ	376.1	863.5	975.9	1167	1102	1166
10	E	3	BLQ	BLQ	132.5	474.7	750.2	1087	1199	1149
11	E	3	BLQ	BLQ	68.41	607.9	925.6	1271	1022	1042
12	E	1	BLQ	BLQ	126.1	373.3	605.5	994.5	1287	1237
Mean			0	7.504	267.1	702.3	992.3	1201	1183	1102
SD			0	26.00	254.8	472.4	449.5	380.5	287.4	297.0
CV (%)			.	346.4	95.39	67.27	45.30	31.69	24.30	26.95
SEM			0	7.504	73.56	136.4	129.8	109.8	82.97	85.73
N			12	12	12	12	12	12	12	12
Minimum			0	0	55.77	293.9	447.0	627.3	676.5	692.4
Maximum			0	90.05	859.9	1919	2063	1937	1755	1777
Median			0	0	167.4	541.3	876.2	1160	1186	1145
Lower 95% CI			0	-5.972	135.0	457.4	759.2	1004	1034	948.2
Upper 95% CI			0	20.98	399.2	947.2	1225	1398	1332	1256

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.
. = Value missing or not reportable.
ND = Not Determined

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Table 14.2.5. Plasma Flurbiprofen Concentrations (ng/mL) Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (Treatment E) (PK Population)

Subject Number	Treatment	Period	Sample Times (min) 60	75	90	120	180	240	360	480	720
1	E	2	682.4	586.4	516.3	466.6	340.9	278.7	176.2	129.4	64.07
2	E	2	949.9	799.5	713.5	569.0	395.2	290.5	127.2	69.28	BLQ
3	E	4	1037	1025	858.5	811.3	519.2	516.7	223.0	196.0	91.54
4	E	1	835.2	718.0	698.6	522.2	365.2	309.3	152.3	107.4	46.19
5	E	5	1126	1065	911.1	674.4	505.2	319.3	179.9	112.3	BLQ
6	E	5	1630	1500	1420	1230	954.9	834.4	472.1	314.5	168.6
7	E	3	581.2	628.7	525.5	451.2	380.4	260.9	228.3	153.6	74.24
8	E	4	1071	984.9	874.3	746.7	515.5	417.8	221.5	148.4	67.68
9	E	1	978.7	1054	931.8	693.7	543.5	427.0	282.4	195.9	87.18
10	E	3	1066	987.5	898.5	688.8	477.2	324.3	167.4	102.8	40.45
11	E	3	808.4	890.7	824.9	639.8	490.6	404.4	221.8	148.2	72.53
12	E	1	1150	912.7	825.7	698.1	523.1	377.7	201.8	120.5	51.73
Mean			993.0	929.4	833.2	682.7	500.9	396.8	221.2	149.9	76.42
SD			267.7	242.4	232.5	204.8	159.4	156.8	89.10	63.66	36.37
CV (%)			26.96	26.09	27.90	30.00	31.81	39.51	40.29	42.48	47.60
SEM			77.29	69.98	67.10	59.13	46.00	45.25	25.72	18.38	11.50
N			12	12	12	12	12	12	12	12	10
Minimum			581.2	586.4	516.3	451.2	340.9	260.9	127.2	69.28	40.45
Maximum			1630	1500	1420	1230	954.9	834.4	472.1	314.5	168.6
Median			1008	948.8	842.1	681.6	497.9	351.0	211.7	138.8	70.11
Lower 95% CI			854.2	803.7	712.7	576.5	418.3	315.5	175.0	116.9	55.34
Upper 95% CI			1132	1055	953.7	788.8	583.5	478.0	267.4	182.9	97.51

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of 40.00 ng/mL are treated as 0 before the first quantifiable concentration and as missing thereafter.

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Table 14.2.6. Plasma Flurbiprofen Pharmacokinetic Parameters Following Flurbiprofen 8.75 mg lozenge (Treatment A) (PK Population)

Subject Number	Treatment	Period	Parameters: Cmax ng/mL	tmax hr	kel 1/hr	t1/2 hr	AUC0-t ng*hr/mL	AUC0-2 ng*hr/mL	AUC0-5 ng*hr/mL	AUC0-10 ng*hr/mL	AUC0-15 ng*hr/mL	AUC0-30 ng*hr/mL	AUC0-40 ng*hr/mL
1	A	1	1368	0.8311	0.1911	3.627	4870	0.000127	1.301	12.74	39.61	212.4	385.7
2	A	4	1529	0.6686	0.2716	2.552	4736	0.000181	1.853	26.43	87.58	384.1	626.0
3	A	2	1205	1.503	0.1746	3.970	5234	0.00	1.294	13.33	40.50	190.7	322.1
4	A	2	1379	0.6664	0.2165	3.202	4901	0.00	0.00	9.414	38.98	260.2	482.0
5	A	4	1405	0.8339	0.2277	3.044	4355	0.000155	1.593	21.52	66.19	300.9	512.7
6	A	3	1815	0.6689	0.2259	3.068	6616	0.00	5.283	57.66	173.6	602.0	893.5
7	A	5	1380	0.5014	0.1771	3.913	5053	0.00	0.00	12.58	52.55	305.5	529.6
8	A	5	1799	0.6653	0.2056	3.371	5821	0.00	2.389	31.76	101.9	457.0	753.4
9	A	3	1633	0.5006	0.1695	4.088	5566	0.001324	1.378	22.76	85.78	421.9	693.3
10	A	1	1819	0.6656	0.2463	2.815	6329	0.00	2.016	29.87	108.0	493.5	794.4
11	A	1	1519	0.6658	0.2061	3.363	5270	0.00	0.00	9.725	45.55	305.5	554.3
12	A	2	1724	0.6672	0.2234	3.103	5456	0.000018	1.191	28.30	96.23	418.0	690.7
Mean			1548	0.7364	0.2113	3.343	5350	0.000150	1.525	23.01	78.03	362.6	603.1
SD			207.7	0.2611	0.03050	0.4769	657.1	0.000376	1.428	13.60	39.69	121.9	169.7
CV (%)			13.42	35.46	14.44	14.27	12.28	249.6	93.66	59.13	50.86	33.61	28.13
SEM			59.95	0.07538	0.008805	0.1377	189.7	0.000108	0.4123	3.927	11.46	35.18	48.98
N			12	12	12	12	12	12	12	12	12	12	12
Minimum			1205	0.5006	0.1695	2.552	4355	0.00	0.00	9.414	38.98	190.7	322.1
Maximum			1819	1.503	0.2716	4.088	6616	0.001324	5.283	57.66	173.6	602.0	893.5
Median			1524	0.6668	0.2113	3.283	5252	0.00	1.339	22.14	75.99	344.8	590.2
Lower 95% CI			1440	0.6011	0.1955	3.096	5010	-0.00004	0.7844	15.95	57.46	299.5	515.2
Upper 95% CI			1656	0.8718	0.2271	3.590	5691	0.000345	2.265	30.06	98.61	425.8	691.1
Geom.Mean			1535	.	.	.	5315	0.000155	1.809	19.93	69.93	343.7	579.9
Geom. CV(%)			13.61	.	.	.	12.09	295.2	49.04	60.05	51.44	35.72	30.76

. = Value missing or not reportable.

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Table 14.2.6. Plasma Flurbiprofen Pharmacokinetic Parameters Following Flurbiprofen 8.75 mg lozenge (Treatment A) (PK Population)

Subject Number	Treatment	Period	Parameters: AUC0-50 ng*hr/mL	AUC0-60 ng*hr/mL	AUC0-inf ng*hr/mL	AUC%extrap %	ln-Parameters: ln(Cmax)	ln(AUC0-t)	ln(AUC0-2)	ln(AUC0-5)	ln(AUC0-10)
1	A	1	593.1	814.8	5355	9.051	7.221	8.491	-8.967	0.2630	2.545
2	A	4	879.2	1122	4893	3.220	7.332	8.463	-8.614	0.6170	3.275
3	A	2	449.4	573.1	5835	10.30	7.094	8.563	.	0.2581	2.590
4	A	2	711.4	940.3	5205	5.829	7.229	8.497	.	.	2.242
5	A	4	740.1	961.7	4563	4.564	7.248	8.379	-8.767	0.4656	3.069
6	A	3	1183	1445	7091	6.692	7.504	8.797	.	1.664	4.055
7	A	5	727.0	903.0	5716	11.60	7.230	8.528	.	.	2.532
8	A	5	1033	1288	6279	7.291	7.495	8.669	.	0.8709	3.458
9	A	3	937.6	1156	6167	9.746	7.398	8.624	-6.627	0.3205	3.125
10	A	1	1089	1356	6659	4.955	7.506	8.753	.	0.7010	3.397
11	A	1	800.0	1033	5714	7.772	7.326	8.570	.	.	2.275
12	A	2	970.0	1228	5801	5.949	7.452	8.604	-10.88	0.1744	3.343
Mean			842.7	1068	5773	7.248	7.336	8.578	-8.770	0.5928	2.992
SD			213.0	247.6	718.5	2.536	0.1355	0.1205	1.508	0.4643	0.5549
CV (%)			25.27	23.18	12.45	34.99	1.847	1.404	-17.19	78.32	18.55
SEM			61.47	71.46	207.4	0.7321	0.03912	0.03478	0.6743	0.1548	0.1602
N			12	12	12	12	12	12	5	9	12
Minimum			449.4	573.1	4563	3.220	7.094	8.379	-10.88	0.1744	2.242
Maximum			1183	1445	7091	11.60	7.506	8.797	-6.627	1.664	4.055
Median			839.6	1077	5758	6.992	7.329	8.566	-8.767	0.4656	3.097
Lower 95% CI			732.3	939.9	5401	5.933	7.266	8.516	-10.21	0.3050	2.704
Upper 95% CI			953.1	1197	6146	8.562	7.407	8.641	-7.333	0.8806	3.280
Geom.Mean			815.7	1039	5732	.	.	.	.	.	.
Geom. CV(%)			28.01	26.00	12.58	.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.6. Plasma Flurbiprofen Pharmacokinetic Parameters Following Flurbiprofen 8.75 mg lozenge (Treatment A) (PK Population)

Subject Number	Treatment	Period	ln-Parameters ln(AUC0-15)	ln(AUC0-30)	ln(AUC0-40)	ln(AUC0-50)	ln(AUC0-60)	ln(AUC0-inf)
1	A	1	3.679	5.358	5.955	6.385	6.703	8.586
2	A	4	4.473	5.951	6.439	6.779	7.023	8.496
3	A	2	3.701	5.251	5.775	6.108	6.351	8.672
4	A	2	3.663	5.561	6.178	6.567	6.846	8.557
5	A	4	4.193	5.707	6.240	6.607	6.869	8.426
6	A	3	5.157	6.400	6.795	7.076	7.276	8.867
7	A	5	3.962	5.722	6.272	6.589	6.806	8.651
8	A	5	4.624	6.125	6.625	6.940	7.161	8.745
9	A	3	4.452	6.045	6.541	6.843	7.052	8.727
10	A	1	4.682	6.202	6.678	6.993	7.212	8.804
11	A	1	3.819	5.722	6.318	6.685	6.940	8.651
12	A	2	4.567	6.035	6.538	6.877	7.113	8.666
Mean			4.248	5.840	6.363	6.704	6.946	8.654
SD			0.4845	0.3465	0.3007	0.2748	0.2557	0.1254
CV (%)			11.41	5.934	4.725	4.100	3.682	1.449
SEM			0.1399	0.1000	0.08679	0.07934	0.07382	0.03619
N			12	12	12	12	12	12.00
Minimum			3.663	5.251	5.775	6.108	6.351	8.426
Maximum			5.157	6.400	6.795	7.076	7.276	8.867
Median			4.322	5.836	6.379	6.732	6.981	8.658
Lower 95% CI			3.996	5.660	6.207	6.562	6.813	8.589
Upper 95% CI			4.499	6.020	6.519	6.847	7.078	8.719
Geom.Mean			.	.	.	.	.	.
Geom. CV(%)			.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.7. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (Treatment B) (PK Population)

Subject Number	Treatment	Period	Parameters										
			Cmax ng/mL	tmax hr	kel 1/hr	t1/2 hr	AUC0-t ng*hr/mL	AUC0-2 ng*hr/mL	AUC0-5 ng*hr/mL	AUC0-10 ng*hr/mL	AUC0-15 ng*hr/mL	AUC0-30 ng*hr/mL	AUC0-40 ng*hr/mL
1	B	4	1567	0.5014	0.1737	3.989	4944	0.7449	4.855	24.77	67.38	345.4	590.6
2	B	1	1149	0.2506	0.3678	1.885	2845	1.454	16.37	76.80	163.9	443.4	618.3
3	B	5	914.5	1.998	0.1940	3.572	4224	0.00	2.562	17.08	39.87	166.3	278.2
4	B	3	1527	0.2481	0.2439	2.842	4320	0.009936	13.39	74.63	177.9	533.8	750.9
5	B	3	1250	0.6664	0.2070	3.348	5235	0.000063	4.028	27.74	70.95	294.4	495.3
6	B	4	1878	0.6656	0.1738	3.987	6504	0.000336	21.20	124.1	263.2	699.1	1004
7	B	1	881.9	0.5025	0.1390	4.986	3808	0.00	2.630	27.60	82.67	295.4	436.6
8	B	2	1739	0.5008	0.1820	3.809	5081	0.004601	9.930	60.75	136.3	476.2	750.9
9	B	2	1319	0.6669	0.1891	3.666	4742	0.000064	4.030	28.72	79.67	318.0	520.7
10	B	5	1651	0.6667	0.2037	3.403	5682	0.00	2.583	18.58	51.12	278.3	525.1
11	B	5	1455	0.6708	0.1892	3.663	5277	0.00	2.988	25.95	78.30	333.3	555.3
12	B	3	1209	0.8306	0.1878	3.690	4263	0.00	4.505	42.43	118.5	406.2	591.2
Mean			1378	0.6807	0.2043	3.570	4744	0.1845	7.423	45.76	110.8	382.5	593.1
SD			313.4	0.4500	0.05701	0.7318	944.8	0.4534	6.322	32.34	64.76	140.5	181.8
CV (%)			22.74	66.11	27.91	20.50	19.92	245.7	85.17	70.66	58.45	36.73	30.65
SEM			90.47	0.1299	0.01646	0.2112	272.7	0.1309	1.825	9.334	18.70	40.55	52.47
N			12	12	12	12	12	12	12	12	12	12	12
Minimum			881.9	0.2481	0.1390	1.885	2845	0.00	2.562	17.08	39.87	166.3	278.2
Maximum			1878	1.998	0.3678	4.986	6504	1.454	21.20	124.1	263.2	699.1	1004
Median			1387	0.6660	0.1892	3.664	4843	0.000064	4.267	28.23	81.17	339.3	572.9
Lower 95% CI			1216	0.4474	0.1747	3.191	4254	-0.05055	4.145	29.00	77.23	309.6	498.8
Upper 95% CI			1541	0.9140	0.2338	3.949	5234	0.4196	10.70	62.52	144.4	455.3	687.3
Geom.Mean			1344	.	.	.	4651	0.004904	5.549	37.69	96.13	359.8	567.5
Geom. CV(%)			24.36	.	.	.	21.52	533300	89.49	69.56	59.52	38.19	32.46

. = Value missing or not reportable.

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Table 14.2.7. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (Treatment B) (PK Population)

Subject Number	Treatment	Period	Parameters AUC0-50 ng*hr/mL	AUC0-60 ng*hr/mL	AUC0-inf ng*hr/mL	AUC%extrap %	ln-Parameters ln(Cmax)	ln(AUC0-t)	ln(AUC0-2)	ln(AUC0-5)	ln(AUC0-10)
1	B	4	808.5	1010	5525	10.51	7.357	8.506	-0.2945	1.580	3.210
2	B	1	776.5	917.5	3001	5.172	7.047	7.953	0.3745	2.795	4.341
3	B	5	394.3	520.2	4694	10.03	6.818	8.348	.	0.9407	2.838
4	B	3	947.6	1123	4550	5.055	7.331	8.371	-4.612	2.595	4.313
5	B	3	701.4	904.5	5742	8.832	7.131	8.563	-9.658	1.393	3.323
6	B	4	1294	1552	7228	10.02	7.538	8.780	-7.997	3.054	4.821
7	B	1	575.2	709.9	4396	13.38	6.782	8.245	.	0.9670	3.318
8	B	2	1014	1266	5512	7.816	7.461	8.533	-5.381	2.296	4.107
9	B	2	727.5	916.7	5225	9.243	7.185	8.464	-9.657	1.394	3.358
10	B	5	796.1	1047	6089	6.670	7.409	8.645	.	0.9488	2.922
11	B	5	792.7	1017	5850	9.792	7.283	8.571	.	1.095	3.256
12	B	3	777.7	963.5	4637	8.062	7.098	8.358	.	1.505	3.748
Mean			800.5	995.7	5204	8.715	7.203	8.445	-5.318	1.714	3.630
SD			222.2	258.0	1057	2.359	0.2401	0.2128	4.143	0.7670	0.6282
CV (%)			27.75	25.91	20.32	27.06	3.333	2.520	-77.91	44.76	17.31
SEM			64.13	74.47	305.3	0.6808	0.06930	0.06143	1.566	0.2214	0.1813
N			12	12	12	12	12	12	7	12	12
Minimum			394.3	520.2	3001	5.055	6.782	7.953	-9.658	0.9407	2.838
Maximum			1294	1552	7228	13.38	7.538	8.780	0.3745	3.054	4.821
Median			785.2	986.9	5368	9.037	7.234	8.485	-5.381	1.449	3.340
Lower 95% CI			685.3	862.0	4656	7.492	7.079	8.335	-8.361	1.316	3.304
Upper 95% CI			915.6	1129	5752	9.937	7.328	8.555	-2.275	2.111	3.955
Geom.Mean			771.3	963.9	5097	.	.	.	.	.	.
Geom. CV(%)			29.83	27.82	22.24	.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.7. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (Treatment B) (PK Population)

Subject Number	Treatment	Period	ln-Parameters ln(AUC0-15)	ln(AUC0-30)	ln(AUC0-40)	ln(AUC0-50)	ln(AUC0-60)	ln(AUC0-inf)
1	B	4	4.210	5.845	6.381	6.695	6.918	8.617
2	B	1	5.099	6.095	6.427	6.655	6.822	8.007
3	B	5	3.686	5.114	5.628	5.977	6.254	8.454
4	B	3	5.181	6.280	6.621	6.854	7.024	8.423
5	B	3	4.262	5.685	6.205	6.553	6.807	8.656
6	B	4	5.573	6.550	6.911	7.165	7.348	8.886
7	B	1	4.415	5.688	6.079	6.355	6.565	8.388
8	B	2	4.915	6.166	6.621	6.922	7.144	8.615
9	B	2	4.378	5.762	6.255	6.590	6.821	8.561
10	B	5	3.934	5.629	6.264	6.680	6.954	8.714
11	B	5	4.361	5.809	6.320	6.675	6.925	8.674
12	B	3	4.775	6.007	6.382	6.656	6.871	8.442
Mean			4.566	5.886	6.341	6.648	6.871	8.536
SD			0.5507	0.3690	0.3165	0.2920	0.2730	0.2198
CV (%)			12.06	6.269	4.991	4.392	3.973	2.574
SEM			0.1590	0.1065	0.09136	0.08429	0.07880	0.06344
N			12	12	12	12	12	12.00
Minimum			**3.686**	**5.114**	**5.628**	**5.977**	**6.254**	**8.007**
Maximum			5.573	6.550	6.911	7.165	7.348	8.886
Median			4.396	5.827	6.350	6.666	6.894	8.588
Lower 95% CI			4.280	5.694	6.177	6.497	6.729	8.422
Upper 95% CI			4.851	6.077	6.505	6.799	7.012	8.650
Geom.Mean			.	.	.	.	.	.
Geom. CV(%)			.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.8. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (Treatment C) (PK Population)

Subject Number	Treatment	Period	Parameters: Cmax ng/mL	tmax hr	kel 1/hr	t1/2 hr	AUC0-t ng*hr/mL	AUC0-2 ng*hr/mL	AUC0-5 ng*hr/mL	AUC0-10 ng*hr/mL	AUC0-15 ng*hr/mL	AUC0-30 ng*hr/mL	AUC0-40 ng*hr/mL
1	C	5	1352	0.8350	0.1947	3.560	5645	0.00	2.042	14.91	39.16	170.2	290.8
2	C	3	1658	0.8306	0.3528	1.965	4332	0.003389	7.313	48.16	115.5	381.3	580.1
3	C	3	1327	0.6675	0.2042	3.394	5520	0.005910	7.966	43.27	94.60	305.6	496.4
4	C	5	1462	0.5022	0.2178	3.183	5862	0.00	10.83	66.53	140.3	447.2	687.3
5	C	1	1279	0.6653	0.3449	2.010	3286	0.00	1.189	11.92	43.46	229.8	414.8
6	C	2	1517	0.5000	0.1811	3.827	5651	0.000570	5.824	44.29	118.9	446.3	690.2
7	C	2	1029	0.8325	0.1464	4.733	3544	0.001003	1.352	11.90	35.12	165.6	305.1
8	C	1	2077	0.5014	0.2093	3.311	5011	0.00	3.184	33.59	114.3	540.4	851.9
9	C	4	1186	0.4994	0.1933	3.585	4351	0.008023	5.990	47.00	120.1	394.7	591.4
10	C	4	1079	0.8336	0.2084	3.326	3376	0.001659	2.236	13.88	34.96	159.2	289.0
11	C	4	982.4	0.5008	0.2089	3.318	3533	0.00	2.211	19.91	53.30	233.9	395.4
12	C	5	1675	0.6642	0.2246	3.086	5262	0.000478	4.880	31.53	80.57	362.0	626.8
Mean			1385	0.6527	0.2239	3.275	4614	0.001753	4.585	32.24	82.53	319.7	518.3
SD			316.0	0.1495	0.06177	0.7380	993.2	0.002667	3.060	17.92	39.42	127.8	182.5
CV (%)			22.81	22.91	27.59	22.54	21.52	152.1	66.75	55.58	47.77	39.99	35.22
SEM			91.23	0.04316	0.01783	0.2130	286.7	0.000769	0.8835	5.173	11.38	36.90	52.69
N			12	12	12	12	12	12	12	12	12	12	12
Minimum			982.4	0.4994	0.1464	1.965	3286	0.00	1.189	11.90	34.96	159.2	289.0
Maximum			2077	0.8350	0.3528	4.733	5862	0.008023	10.83	66.53	140.3	540.4	851.9
Median			1340	0.6648	0.2087	3.322	4681	0.000524	4.032	32.56	87.59	333.8	538.3
Lower 95% CI			1221	0.5752	0.1919	2.892	4100	0.000370	2.998	22.95	62.09	253.4	423.6
Upper 95% CI			1549	0.7302	0.2559	3.657	5129	0.003135	6.171	41.53	103.0	385.9	612.9
Geom.Mean			1354	.	.	.	4512	0.001846	3.648	27.39	72.88	294.9	487.8
Geom. CV(%)			22.41	.	.	.	22.65	157.2	84.38	68.37	58.47	45.12	38.38

. = Value missing or not reportable.

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Table 14.2.8. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (Treatment C) (PK Population)

Subject Number	Treatment	Period	Parameters AUC0-50 ng*hr/mL	AUC0-60 ng*hr/mL	AUC0-inf ng*hr/mL	AUC%extrap %	ln-Parameters ln(Cmax)	ln(AUC0-t)	ln(AUC0-2)	ln(AUC0-5)	ln(AUC0-10)
1	C	5	465.6	690.9	6249	9.658	7.209	8.639	.	0.7140	2.702
2	C	3	818.3	1082	4611	6.045	7.413	8.374	-5.687	1.990	3.874
3	C	3	708.2	919.6	6019	8.290	7.191	8.616	-5.131	2.075	3.767
4	C	5	913.4	1133	6263	6.415	7.288	8.676	.	2.382	4.198
5	C	1	621.2	800.9	3501	6.144	7.154	8.097	.	0.1731	2.479
6	C	2	925.2	1166	6196	8.799	7.324	8.640	-7.468	1.762	3.791
7	C	2	473.0	620.0	4170	15.03	6.936	8.173	-6.905	0.3016	2.477
8	C	1	1115	1342	5330	5.982	7.639	8.519	.	1.158	3.514
9	C	4	769.0	929.4	4740	8.200	7.078	8.378	-4.825	1.790	3.850
10	C	4	452.0	623.3	3586	5.856	6.984	8.125	-6.401	0.8047	2.630
11	C	4	549.0	687.9	3806	7.187	6.890	8.170	.	0.7934	2.991
12	C	5	895.7	1148	5606	6.130	7.424	8.568	-7.645	1.585	3.451
Mean			725.5	928.6	5006	7.811	7.211	8.415	-6.295	1.294	3.310
SD			216.3	244.9	1073	2.612	0.2214	0.2237	1.115	0.7333	0.6193
CV (%)			29.82	26.37	21.44	33.44	3.070	2.658	-17.72	56.66	18.71
SEM			62.44	70.70	309.9	0.7541	0.06391	0.06457	0.4216	0.2117	0.1788
N			12	12	12	12	12	12	7	12	12
Minimum			452.0	620.0	3501	5.856	6.890	8.097	-7.645	0.1731	2.477
Maximum			1115	1342	6263	15.03	7.639	8.676	-4.825	2.382	4.198
Median			738.6	924.5	5035	6.801	7.200	8.449	-6.401	1.372	3.483
Lower 95% CI			613.3	801.6	4450	6.457	7.096	8.299	-7.114	0.9140	2.989
Upper 95% CI			837.6	1056	5563	9.165	7.326	8.531	-5.476	1.674	3.631
Geom.Mean			695.3	898.5	4897	.	.	.	.	.	.
Geom. CV(%)			31.54	27.53	22.58	.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.8. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (Treatment C) (PK Population)

Subject Number	Treatment	Period	ln-Parameters ln(AUC0-15)	ln(AUC0-30)	ln(AUC0-40)	ln(AUC0-50)	ln(AUC0-60)	ln(AUC0-inf)
1	C	5	3.668	5.137	5.673	6.143	6.538	8.740
2	C	3	4.749	5.944	6.363	6.707	6.987	8.436
3	C	3	4.550	5.722	6.207	6.563	6.824	8.703
4	C	5	4.944	6.103	6.533	6.817	7.033	8.742
5	C	1	3.772	5.437	6.028	6.432	6.686	8.161
6	C	2	4.779	6.101	6.537	6.830	7.061	8.732
7	C	2	3.559	5.109	5.720	6.159	6.430	8.336
8	C	1	4.739	6.292	6.748	7.017	7.202	8.581
9	C	4	4.788	5.978	6.382	6.645	6.835	8.464
10	C	4	3.554	5.070	5.667	6.114	6.435	8.185
11	C	4	3.976	5.455	5.980	6.308	6.534	8.244
12	C	5	4.389	5.892	6.441	6.798	7.046	8.632
Mean			4.289	5.687	6.190	6.544	6.801	8.496
SD			0.5423	0.4304	0.3707	0.3080	0.2703	0.2230
CV (%)			12.64	7.569	5.989	4.706	3.975	2.624
SEM			0.1565	0.1243	0.1070	0.08890	0.07803	0.06437
N			12	12	12	12	12	12.00
Minimum			3.554	5.070	5.667	6.114	6.430	8.161
Maximum			4.944	6.292	6.748	7.017	7.202	8.742
Median			4.469	5.807	6.285	6.604	6.829	8.522
Lower 95% CI			4.008	5.464	5.998	6.385	6.661	8.381
Upper 95% CI			4.570	5.910	6.382	6.704	6.941	8.612
Geom.Mean			.	.	.	.	.	.
Geom. CV(%)			.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.9. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (Treatment D) (PK Population)

Subject Number	Treatment	Period	Parameters: Cmax ng/mL	tmax hr	kel 1/hr	t1/2 hr	AUC0-t ng*hr/mL	AUC0-2 ng*hr/mL	AUC0-5 ng*hr/mL	AUC0-10 ng*hr/mL	AUC0-15 ng*hr/mL	AUC0-30 ng*hr/mL	AUC0-40 ng*hr/mL
1	D	3	845.9	0.4989	0.2036	3.404	3416	0.002660	10.73	59.99	124.3	328.7	464.9
2	D	5	1149	0.4989	0.3166	2.189	3185	0.7339	11.68	66.85	148.3	421.2	611.8
3	D	1	912.0	0.5017	0.2213	3.131	3654	0.00	2.342	19.76	50.12	214.0	352.5
4	D	4	1608	0.6697	0.2149	3.225	5090	0.00	4.331	41.59	112.7	410.2	659.4
5	D	2	1147	0.8328	0.2981	2.325	3150	0.00	1.992	16.29	47.61	246.7	432.0
6	D	1	1626	0.4992	0.2117	3.274	6015	0.003141	12.67	74.25	177.0	566.9	833.7
7	D	4	703.8	0.4992	0.1266	5.474	2907	0.000490	1.977	15.69	41.70	176.8	288.1
8	D	3	1497	0.5006	0.1820	3.808	4345	0.000331	3.378	36.53	114.6	451.8	692.0
9	D	5	1369	1.009	0.1554	4.461	6058	0.000564	2.274	22.44	67.12	295.6	495.1
10	D	2	1229	0.6669	0.1879	3.689	4177	0.001475	3.184	22.11	61.26	284.4	484.7
11	D	2	1346	0.5019	0.1774	3.908	4473	0.00	4.100	37.18	110.7	420.9	643.4
12	D	4	1483	0.2550	0.2067	3.353	4522	0.02053	5.357	50.37	147.3	502.9	727.8
Mean			1243	0.5778	0.2085	3.520	4249	0.06359	5.334	38.59	100.2	360.0	557.1
SD			302.2	0.1940	0.05358	0.8792	1063	0.2112	3.987	20.43	45.51	120.7	163.0
CV (%)			24.31	33.58	25.70	24.98	25.01	332.1	74.74	52.94	45.41	33.52	29.26
SEM			87.25	0.05601	0.01547	0.2538	306.8	0.06096	1.151	5.897	13.14	34.84	47.05
N			12	12	12	12	12	12	12	12	12	12	12
Minimum			703.8	0.2550	0.1266	2.189	2907	0.00	1.977	15.69	41.70	176.8	288.1
Maximum			1626	1.009	0.3166	5.474	6058	0.7339	12.67	74.25	177.0	566.9	833.7
Median			1288	0.5012	0.2051	3.379	4261	0.000527	3.739	36.86	111.7	369.5	553.4
Lower 95% CI			1086	0.4773	0.1807	3.065	3698	-0.04589	3.267	28.00	76.62	297.4	472.6
Upper 95% CI			1400	0.6784	0.2363	3.976	4800	0.1731	7.401	49.18	123.8	422.6	641.6
Geom.Mean			1205	.	.	.	4132	0.003379	4.243	33.67	89.96	340.3	533.7
Geom. CV(%)			27.27	.	.	.	24.95	2538	77.45	60.06	53.61	37.12	32.30

. = Value missing or not reportable.

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Table 14.2.9. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (Treatment D) (PK Population)

Subject Number	Treatment	Period	Parameters AUC0-50 ng*hr/mL	AUC0-60 ng*hr/mL	AUC0-inf ng*hr/mL	AUC%extrap %	ln-Parameters ln(Cmax)	ln(AUC0-t)	ln(AUC0-2)	ln(AUC0-5)	ln(AUC0-10)
1	D	3	585.0	693.7	3761	9.182	6.740	8.136	-5.929	2.373	4.094
2	D	5	787.9	943.1	3446	7.578	7.047	8.066	-0.3094	2.458	4.203
3	D	1	478.1	613.5	3943	7.340	6.816	8.204	.	0.8511	2.984
4	D	4	904.6	1125	5442	6.465	7.383	8.535	.	1.466	3.728
5	D	2	620.2	798.7	3446	8.574	7.045	8.055	.	0.6889	2.790
6	D	1	1082	1308	6451	6.753	7.394	8.702	-5.763	2.539	4.307
7	D	4	389.7	487.9	3496	16.82	6.556	7.975	-7.621	0.6816	2.753
8	D	3	914.8	1121	4656	6.682	7.311	8.377	-8.013	1.217	3.598
9	D	5	697.3	909.6	6911	12.35	7.222	8.709	-7.480	0.8217	3.111
10	D	2	685.8	884.3	4483	6.839	7.114	8.337	-6.519	1.158	3.096
11	D	2	850.3	1031	4913	8.960	7.205	8.406	.	1.411	3.616
12	D	4	940.8	1130	4839	6.549	7.302	8.417	-3.886	1.678	3.919
Mean			744.7	920.5	4649	8.675	7.095	8.327	-5.690	1.445	3.517
SD			205.2	240.8	1154	3.070	0.2678	0.2457	2.544	0.6855	0.5550
CV (%)			27.56	26.16	24.81	35.39	3.775	2.951	-44.70	47.43	15.78
SEM			59.25	69.52	333.0	0.8862	0.07730	0.07093	0.8993	0.1979	0.1602
N			12	12	12	12	12	12	8	12	12
Minimum			389.7	487.9	3446	6.465	6.556	7.975	-8.013	0.6816	2.753
Maximum			1082	1308	6911	16.82	7.394	8.709	-0.3094	2.539	4.307
Median			742.6	926.3	4570	7.459	7.159	8.357	-6.224	1.314	3.607
Lower 95% CI			638.3	795.6	4051	7.083	6.956	8.199	-7.394	1.090	3.229
Upper 95% CI			851.1	1045	5247	10.27	7.233	8.454	-3.986	1.801	3.804
Geom.Mean			716.3	888.4	4527	.	.	.	.	.	.
Geom. CV(%)			30.78	29.41	24.07	.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.9. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (Treatment D) (PK Population)

Subject Number	Treatment	Period	ln-Parameters ln(AUC0-15)	ln(AUC0-30)	ln(AUC0-40)	ln(AUC0-50)	ln(AUC0-60)	ln(AUC0-inf)
1	D	3	4.823	5.795	6.142	6.372	6.542	8.233
2	D	5	4.999	6.043	6.416	6.669	6.849	8.145
3	D	1	3.914	5.366	5.865	6.170	6.419	8.280
4	D	4	4.724	6.017	6.491	6.807	7.025	8.602
5	D	2	3.863	5.508	6.068	6.430	6.683	8.145
6	D	1	5.176	6.340	6.726	6.986	7.176	8.772
7	D	4	3.731	5.175	5.663	5.965	6.190	8.159
8	D	3	4.741	6.113	6.540	6.819	7.022	8.446
9	D	5	4.206	5.689	6.205	6.547	6.813	8.841
10	D	2	4.115	5.650	6.183	6.531	6.785	8.408
11	D	2	4.707	6.042	6.467	6.746	6.939	8.500
12	D	4	4.993	6.220	6.590	6.847	7.030	8.485
Mean			4.499	5.830	6.280	6.574	6.789	8.418
SD			0.5026	0.3593	0.3150	0.3008	0.2880	0.2373
CV (%)			11.17	6.163	5.017	4.576	4.242	2.819
SEM			0.1451	0.1037	0.09094	0.08684	0.08314	0.06850
N			12	12	12	12	12	12.00
Minimum			3.731	5.175	5.663	5.965	6.190	8.145
Maximum			5.176	6.340	6.726	6.986	7.176	8.841
Median			4.716	5.906	6.311	6.608	6.831	8.427
Lower 95% CI			4.239	5.644	6.116	6.418	6.640	8.295
Upper 95% CI			4.760	6.016	6.443	6.730	6.939	8.541
Geom.Mean			.	.	.	.	.	.
Geom. CV(%)			.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.10. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (Treatment E) (PK Population)

Subject Number	Treatment	Period	Parameters: Cmax ng/mL	tmax hr	kel 1/hr	t1/2 hr	AUC0-t ng*hr/mL	AUC0-2 ng*hr/mL	AUC0-5 ng*hr/mL	AUC0-10 ng*hr/mL	AUC0-15 ng*hr/mL	AUC0-30 ng*hr/mL	AUC0-40 ng*hr/mL
1	E	2	693.3	0.8331	0.1702	4.073	2923	0.002175	2.932	19.97	50.92	185.3	293.9
2	E	2	1282	0.2489	0.3579	1.937	3195	1.523	20.61	98.50	201.3	505.7	690.8
3	E	4	1202	0.6664	0.1554	4.461	4661	0.002691	5.806	31.90	77.13	279.4	456.8
4	E	1	1268	0.2514	0.2010	3.449	3444	0.00	6.455	48.18	131.4	447.9	651.1
5	E	5	1515	0.4992	0.2619	2.646	3760	0.00	1.272	16.90	64.61	357.0	607.1
6	E	5	1937	0.4994	0.1704	4.069	7914	0.00	4.921	49.42	144.2	563.4	871.0
7	E	3	823.2	0.6667	0.1864	3.720	3209	0.003468	2.588	21.78	64.22	239.4	370.2
8	E	4	2063	0.2533	0.1981	3.498	4867	0.00	22.34	140.3	306.0	780.0	1040
9	E	1	1167	0.5003	0.1979	3.502	4725	0.00	8.973	60.52	137.1	404.8	594.5
10	E	3	1199	0.6689	0.2361	2.936	3802	0.000338	3.457	29.05	79.95	309.4	499.8
11	E	3	1271	0.4989	0.1852	3.742	4125	0.001289	1.738	30.16	94.34	369.2	560.4
12	E	1	1287	0.6694	0.2235	3.102	4028	0.00	2.962	23.79	64.87	264.8	454.3
Mean			1309	0.5213	0.2120	3.428	4221	0.1278	7.005	47.53	118.0	392.2	590.8
SD			389.5	0.1916	0.05483	0.6922	1325	0.4395	7.110	37.15	74.02	165.0	208.2
CV (%)			29.75	36.76	25.86	20.19	31.38	344.0	101.5	78.15	62.72	42.08	35.24
SEM			112.4	0.05532	0.01583	0.1998	382.4	0.1269	2.052	10.72	21.37	47.64	60.10
N			12	12	12	12	12	12	12	12	12	12	12
Minimum			693.3	0.2489	0.1554	1.937	2923	0.00	1.272	16.90	50.92	185.3	293.9
Maximum			2063	0.8331	0.3579	4.461	7914	1.523	22.34	140.3	306.0	780.0	1040
Median			1270	0.4999	0.1980	3.500	3915	0.000169	4.189	31.03	87.15	363.1	577.5
Lower 95% CI			1107	0.4220	0.1836	3.069	3534	-0.1001	3.319	28.28	79.64	306.6	482.9
Upper 95% CI			1511	0.6207	0.2404	3.787	4908	0.3556	10.69	66.79	156.4	477.7	698.8
Geom.Mean			1256	.	.	.	4072	0.004880	4.747	38.22	102.1	363.9	559.0
Geom. CV(%)			31.03	.	.	.	27.08	7369	110.4	73.11	58.05	41.71	36.00

. = Value missing or not reportable.

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Table 14.2.10. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (Treatment E) (PK Population)

Subject Number	Treatment	Period	Parameters AUC0-50 ng*hr/mL	AUC0-60 ng*hr/mL	AUC0-inf ng*hr/mL	AUC%extrap %	ln-Parameters ln(Cmax)	ln(AUC0-t)	ln(AUC0-2)	ln(AUC0-5)	ln(AUC0-10)
1	E	2	408.0	522.7	3299	11.41	6.541	7.980	-6.131	1.076	2.994
2	E	2	864.2	1028	3388	5.713	7.156	8.069	0.4209	3.026	4.590
3	E	4	651.9	833.2	5250	11.22	7.092	8.447	-5.918	1.759	3.463
4	E	1	817.3	955.0	3674	6.256	7.145	8.144	.	1.865	3.875
5	E	5	842.7	1048	4189	10.23	7.323	8.232	.	0.2408	2.827
6	E	5	1165	1449	8903	11.12	7.569	8.976	.	1.593	3.900
7	E	3	496.3	602.2	3607	11.04	6.713	8.074	-5.664	0.9508	3.081
8	E	4	1253	1438	5208	6.558	7.632	8.490	.	3.107	4.944
9	E	1	782.8	961.7	5165	8.528	7.062	8.461	.	2.194	4.103
10	E	3	695.4	880.1	3973	4.313	7.089	8.243	-7.990	1.240	3.369
11	E	3	732.3	886.3	4516	8.670	7.148	8.325	-6.654	0.5526	3.406
12	E	1	664.6	863.6	4260	5.434	7.160	8.301	.	1.086	3.169
Mean			781.1	955.6	4619	8.375	7.136	8.312	-5.323	1.558	3.643
SD			241.6	275.7	1517	2.621	0.3032	0.2661	2.933	0.8926	0.6543
CV (%)			30.93	28.85	32.84	31.29	4.249	3.201	-55.10	57.31	17.96
SEM			69.75	79.60	437.9	0.7565	0.08753	0.07680	1.197	0.2577	0.1889
N			12	12	12	12	12	12	6	12	12
Minimum			408.0	522.7	3299	4.313	6.541	7.980	-7.990	0.2408	2.827
Maximum			1253	1449	8903	11.41	7.632	8.976	0.4209	3.107	4.944
Median			757.6	920.6	4224	8.599	7.146	8.272	-6.024	1.417	3.435
Lower 95% CI			655.8	812.7	3833	7.016	6.979	8.174	-7.735	1.095	3.304
Upper 95% CI			906.4	1099	5406	9.734	7.293	8.450	-2.910	2.020	3.983
Geom.Mean			747.4	919.3	4446	.	.	.	.	.	.
Geom. CV(%)			32.14	30.11	27.79	.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.10. Plasma Flurbiprofen Pharmacokinetic Parameters Following
15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (Treatment E) (PK Population)

Subject Number	Treatment	Period	ln-Parameters ln(AUC0-15)	ln(AUC0-30)	ln(AUC0-40)	ln(AUC0-50)	ln(AUC0-60)	ln(AUC0-inf)
1	E	2	3.930	5.222	5.683	6.011	6.259	8.101
2	E	2	5.305	6.226	6.538	6.762	6.935	8.128
3	E	4	4.345	5.633	6.124	6.480	6.725	8.566
4	E	1	4.878	6.105	6.479	6.706	6.862	8.209
5	E	5	4.168	5.878	6.409	6.737	6.955	8.340
6	E	5	4.971	6.334	6.770	7.061	7.279	9.094
7	E	3	4.162	5.478	5.914	6.207	6.401	8.191
8	E	4	5.724	6.659	6.947	7.133	7.271	8.558
9	E	1	4.920	6.003	6.388	6.663	6.869	8.550
10	E	3	4.381	5.735	6.214	6.545	6.780	8.287
11	E	3	4.547	5.911	6.329	6.596	6.787	8.415
12	E	1	4.172	5.579	6.119	6.499	6.761	8.357
Mean			4.626	5.897	6.326	6.617	6.824	8.400
SD			0.5389	0.4005	0.3490	0.3136	0.2946	0.2728
CV (%)			11.65	6.791	5.518	4.739	4.318	3.248
SEM			0.1556	0.1156	0.1008	0.09052	0.08505	0.07875
N			12	12	12	12	12	12.00
Minimum			3.930	5.222	5.683	6.011	6.259	8.101
Maximum			5.724	6.659	6.947	7.133	7.279	9.094
Median			4.464	5.895	6.358	6.630	6.824	8.349
Lower 95% CI			4.346	5.689	6.145	6.454	6.671	8.258
Upper 95% CI			4.905	6.104	6.507	6.779	6.976	8.541
Geom.Mean			.	.	.	.	.	.
Geom. CV(%)			.	.	.	.	.	.

. = Value missing or not reportable.

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Table 14.2.11. Intervals (Hours) Used for Determination of Plasma Flurbiprofen kel Values Following Treatments A to E

Subject Number	Treatment A Interval	Treatment A R^2	Treatment A N	Treatment B Interval	Treatment B R^2	Treatment B N	Treatment C Interval	Treatment C R^2	Treatment C N	Treatment D Interval	Treatment D R^2	Treatment D N	Treatment E Interval	Treatment E R^2	Treatment E N
1	6.0 - 12.0	1.000	3	6.0 - 12.0	0.985	3	6.0 - 12.0	0.998	3	4.0 - 12.0	0.975	4	6.0 - 12.0	0.999	3
2	6.0 - 12.0	1.000	3	3.0 - 8.0	0.999	4	4.0 - 8.0	0.997	3	4.0 - 8.0	1.000	3	4.0 - 8.0	0.992	3
3	6.0 - 12.0	0.990	3	4.0 - 12.0	0.979	4	4.0 - 12.0	0.988	4	4.0 - 12.0	0.952	4	6.0 - 12.0	0.958	3
4	6.0 - 12.0	1.000	3	4.0 - 12.0	0.995	4	6.0 - 12.0	0.995	3	4.0 - 12.0	0.986	4	6.0 - 12.0	0.998	3
5	6.0 - 12.0	0.999	3	4.0 - 12.0	0.965	4	3.0 - 8.0	0.995	4	4.0 - 8.0	0.995	3	4.0 - 8.0	0.997	3
6	4.0 - 12.0	0.991	4	6.0 - 12.0	0.999	3	6.0 - 12.0	0.989	3	6.0 - 12.0	0.997	3	6.0 - 12.0	0.996	3
7	6.0 - 12.0	0.994	3	6.0 - 12.0	0.986	3	6.0 - 12.0	0.998	3	6.0 - 12.0	0.972	3	6.0 - 12.0	1.000	3
8	6.0 - 12.0	0.980	3	6.0 - 12.0	1.000	3	6.0 - 12.0	0.992	3	6.0 - 12.0	0.992	3	6.0 - 12.0	1.000	3
9	6.0 - 12.0	0.985	3	6.0 - 12.0	1.000	3	6.0 - 12.0	0.995	3	6.0 - 12.0	0.987	3	4.0 - 12.0	1.000	4
10	4.0 - 12.0	0.985	4	6.0 - 12.0	0.990	3	6.0 - 12.0	0.962	3	6.0 - 12.0	0.955	3	6.0 - 12.0	1.000	3
11	4.0 - 12.0	0.993	4	4.0 - 12.0	0.991	4	6.0 - 12.0	0.999	3	6.0 - 12.0	0.998	3	6.0 - 12.0	0.999	3
12	6.0 - 12.0	0.998	3	6.0 - 12.0	0.992	3	4.0 - 12.0	0.997	4	6.1 - 12.0	0.999	3	6.0 - 12.0	0.997	3

Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

R^2 = Correlation of the linear regression
N = Number of points used in kel calculation

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Table 14.2.12. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment B Versus Treatment A

Parameter	Geometric LS Means B	Geometric LS Means A	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1325.889	1531.193	77.20 - 97.13	0.0410	86.59
AUC0-t	4585.746	5348.582	77.37 - 95.02	0.0157	85.74
AUC0-2	0.004	0.000	388.2 - 110460	0.0203	6548.49
AUC0-5	5.715	1.619	234.3 - 532.12	<.0001	353.07
AUC0-10	38.078	20.527	139.0 - 247.53	0.0008	185.50
AUC0-15	96.144	71.195	106.3 - 171.58	0.0408	135.04
AUC0-30	356.437	344.882	87.57 - 121.97	0.7396	103.35
AUC0-40	560.592	579.182	84.01 - 111.52	0.7004	96.79
AUC0-50	760.668	812.971	82.53 - 106.08	0.3780	93.57
AUC0-60	949.795	1034.937	81.74 - 103.03	0.2191	91.77
AUC0-inf	5040.119	5789.319	78.45 - 96.61	0.0305	87.06

Treatment B: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (test)
Treatment A: Flurbiprofen 8.75 mg lozenge (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.13. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment C Versus Treatment A

Parameter	Geometric LS Means C	Geometric LS Means A	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1332.633	1531.193	77.59 - 97.62	0.0483	87.03
AUC0-t	4454.443	5348.582	75.15 - 92.29	0.0046	83.28
AUC0-2	0.002	0.000	125.8 - 89908	0.0803	3363.65
AUC0-5	3.745	1.619	153.5 - 348.71	0.0014	231.37
AUC0-10	27.803	20.527	101.5 - 180.74	0.0842	135.45
AUC0-15	73.462	71.195	81.21 - 131.10	0.8267	103.18
AUC0-30	293.351	344.882	72.07 - 100.38	0.1078	85.06
AUC0-40	482.676	579.182	72.33 - 96.02	0.0361	83.34
AUC0-50	686.204	812.971	74.45 - 95.70	0.0283	84.41
AUC0-60	885.834	1034.937	76.24 - 96.10	0.0290	85.59
AUC0-inf	4846.014	5789.319	75.43 - 92.89	0.0064	83.71

Treatment C: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (test)
Treatment A: Flurbiprofen 8.75 mg lozenge (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.14. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment D Versus Treatment A

Parameter	Geometric LS Means D	Geometric LS Means A	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1199.675	1531.193	69.88 - 87.85	0.0009	78.35
AUC0-t	4147.517	5348.582	70.00 - 85.90	0.0001	77.54
AUC0-2	0.003	0.000	212.5 - 120771	0.0465	5066.06
AUC0-5	4.283	1.619	175.9 - 398.12	0.0003	264.63
AUC0-10	34.171	20.527	124.9 - 221.91	0.0048	166.47
AUC0-15	90.893	71.195	100.6 - 162.07	0.0924	127.67
AUC0-30	340.804	344.882	83.78 - 116.55	0.9041	98.82
AUC0-40	532.195	579.182	79.79 - 105.81	0.3190	91.89
AUC0-50	712.836	812.971	77.37 - 99.37	0.0844	87.68
AUC0-60	884.013	1034.937	76.11 - 95.86	0.0266	85.42
AUC0-inf	4556.792	5789.319	70.95 - 87.32	0.0004	78.71

Treatment D: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (test)
Treatment A: Flurbiprofen 8.75 mg lozenge (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.15. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment E Versus Treatment A

Parameter	Geometric LS Means E	Geometric LS Means A	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1249.415	1531.193	72.78 - 91.49	0.0047	81.60
AUC0-t	4078.034	5348.582	68.82 - 84.47	<.0001	76.25
AUC0-2	0.005	0.000	214.3 - 274869	0.0505	7673.97
AUC0-5	4.804	1.619	197.3 - 446.53	<.0001	296.81
AUC0-10	38.291	20.527	139.9 - 248.67	0.0007	186.54
AUC0-15	101.130	71.195	111.9 - 180.32	0.0175	142.05
AUC0-30	359.091	344.882	88.28 - 122.81	0.6829	104.12
AUC0-40	551.818	579.182	82.74 - 109.72	0.5671	95.28
AUC0-50	738.238	812.971	80.13 - 102.91	0.2019	90.81
AUC0-60	909.052	1034.937	78.27 - 98.57	0.0655	87.84
AUC0-inf	4473.022	5789.319	69.65 - 85.71	0.0001	77.26

Treatment E: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (test)
Treatment A: Flurbiprofen 8.75 mg lozenge (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.16. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment C Versus Treatment B

Parameter	Geometric LS Means C	Geometric LS Means B	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1332.633	1325.889	89.64 - 112.69	0.9409	100.51
AUC0-t	4454.443	4585.746	87.68 - 107.61	0.6357	97.14
AUC0-2	0.002	0.004	2.85 - 924.52	0.6919	51.37
AUC0-5	3.745	5.715	45.26 - 94.88	0.0618	65.53
AUC0-10	27.803	38.078	54.77 - 97.34	0.0729	73.02
AUC0-15	73.462	96.144	60.19 - 97.00	0.0647	76.41
AUC0-30	293.351	356.437	69.78 - 97.07	0.0537	82.30
AUC0-40	482.676	560.592	74.77 - 99.15	0.0817	86.10
AUC0-50	686.204	760.668	79.60 - 102.23	0.1733	90.21
AUC0-60	885.834	949.795	83.11 - 104.67	0.3151	93.27
AUC0-inf	4846.014	5040.119	86.67 - 106.66	0.5278	96.15

Treatment C: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (test)
Treatment B: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.17. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment D Versus Treatment B

Parameter	Geometric LS Means D	Geometric LS Means B	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1199.675	1325.889	80.67 - 101.49	0.1503	90.48
AUC0-t	4147.517	4585.746	81.61 - 100.23	0.1076	90.44
AUC0-2	0.003	0.004	5.06 - 1183.4	0.8712	77.36
AUC0-5	4.283	5.715	51.69 - 108.68	0.1985	74.95
AUC0-10	34.171	38.078	67.25 - 119.75	0.5314	89.74
AUC0-15	90.893	96.144	74.41 - 120.11	0.6951	94.54
AUC0-30	340.804	356.437	81.02 - 112.84	0.6512	95.61
AUC0-40	532.195	560.592	82.40 - 109.38	0.5403	94.93
AUC0-50	712.836	760.668	82.66 - 106.25	0.3892	93.71
AUC0-60	884.013	949.795	82.90 - 104.49	0.3029	93.07
AUC0-inf	4556.792	5040.119	81.47 - 100.33	0.1109	90.41

Treatment D: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (test)
Treatment B: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.18. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment E Versus Treatment B

Parameter	Geometric LS Means E	Geometric LS Means B	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1249.415	1325.889	84.04 - 105.66	0.3875	94.23
AUC0-t	4078.034	4585.746	80.27 - 98.52	0.0607	88.93
AUC0-2	0.005	0.004	4.58 - 2998.8	0.9328	117.19
AUC0-5	4.804	5.715	58.05 - 121.74	0.4340	84.06
AUC0-10	38.291	38.078	75.44 - 134.05	0.9741	100.56
AUC0-15	101.130	96.144	82.86 - 133.53	0.7233	105.19
AUC0-30	359.091	356.437	85.42 - 118.83	0.9401	100.74
AUC0-40	551.818	560.592	85.48 - 113.35	0.8518	98.43
AUC0-50	738.238	760.668	85.64 - 109.98	0.6894	97.05
AUC0-60	909.052	949.795	85.28 - 107.41	0.5260	95.71
AUC0-inf	4473.022	5040.119	80.00 - 98.45	0.0598	88.75

Treatment E: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (test)
Treatment B: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.19. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment D Versus Treatment C

Parameter	Geometric LS Means D	Geometric LS Means C	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1199.675	1332.633	80.29 - 100.94	0.1299	90.02
AUC0-t	4147.517	4454.443	84.05 - 103.15	0.2475	93.11
AUC0-2	0.003	0.002	11.12 - 2040.5	0.7867	150.61
AUC0-5	4.283	3.745	78.98 - 165.63	0.5444	114.37
AUC0-10	34.171	27.803	92.19 - 163.84	0.2344	122.90
AUC0-15	90.893	73.462	97.47 - 157.07	0.1409	123.73
AUC0-30	340.804	293.351	98.50 - 137.03	0.1341	116.18
AUC0-40	532.195	482.676	95.75 - 126.97	0.2510	110.26
AUC0-50	712.836	686.204	91.67 - 117.72	0.6114	103.88
AUC0-60	884.013	885.834	88.92 - 111.99	0.9762	99.79
AUC0-inf	4556.792	4846.014	84.76 - 104.31	0.3242	94.03

Treatment D: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (test)
Treatment C: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.20. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment E Versus Treatment C

Parameter	Geometric LS Means E	Geometric LS Means C	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1249.415	1332.633	83.58 - 105.16	0.3503	93.76
AUC0-t	4078.034	4454.443	82.61 - 101.46	0.1558	91.55
AUC0-2	0.005	0.002	14.30 - 3640.0	0.6093	228.14
AUC0-5	4.804	3.745	88.47 - 186.01	0.2655	128.28
AUC0-10	38.291	27.803	103.2 - 183.78	0.0690	137.72
AUC0-15	101.130	73.462	108.4 - 174.90	0.0301	137.66
AUC0-30	359.091	293.351	103.7 - 144.46	0.0463	122.41
AUC0-40	551.818	482.676	99.23 - 131.72	0.1193	114.32
AUC0-50	738.238	686.204	94.89 - 121.97	0.3330	107.58
AUC0-60	909.052	885.834	91.41 - 115.21	0.7088	102.62
AUC0-inf	4473.022	4846.014	83.18 - 102.43	0.2028	92.30

Treatment E: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (test)
Treatment C: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.21. Statistical Comparisons of Plasma Flurbiprofen Pharmacokinetic Parameters: Treatment E Versus Treatment D

Parameter	Geometric LS Means E	Geometric LS Means D	Confidence Intervals (90% Confidence)	p-Value	% Geometric Mean Ratio
Cmax	1249.415	1199.675	92.85 - 116.82	0.5550	104.15
AUC0-t	4078.034	4147.517	88.72 - 108.96	0.7835	98.32
AUC0-2	0.005	0.003	7.75 - 2960.0	0.8098	151.48
AUC0-5	4.804	4.283	77.35 - 162.64	0.6054	112.16
AUC0-10	38.291	34.171	83.98 - 149.53	0.5105	112.06
AUC0-15	101.130	90.893	87.57 - 141.36	0.4576	111.26
AUC0-30	359.091	340.804	89.28 - 124.35	0.5984	105.37
AUC0-40	551.818	532.195	90.00 - 119.46	0.6694	103.69
AUC0-50	738.238	712.836	91.35 - 117.42	0.6414	103.56
AUC0-60	909.052	884.013	91.59 - 115.45	0.6869	102.83
AUC0-inf	4473.022	4556.792	88.45 - 108.93	0.7659	98.16

Treatment E: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108) (test)
Treatment D: 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102) (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

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Table 14.2.22. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment B Versus Treatment A

	Difference B - A		
Parameter	90% CI	Median	p-Value
tmax	-0.2085 - 0.0822	-0.0011	0.5557

Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment A = Flurbiprofen 8.75 mg lozenge

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.23. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment C Versus Treatment A

	Difference C - A		
Parameter	90% CI	Median	p-Value
tmax	-0.1666 - 0.0811	-0.0835	0.3394

Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment A = Flurbiprofen 8.75 mg lozenge

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.24. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment D Versus Treatment A

	Difference D - A		
Parameter	90% CI	Median	p-Value
tmax	-0.2881 - -0.0004	-0.1643	0.0923

Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment A = Flurbiprofen 8.75 mg lozenge

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.25. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment E Versus Treatment A

	Difference E - A		
Parameter	90% CI	Median	p-Value
tmax	-0.3772 - -0.0818	-0.1682	0.0522

Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)
Treatment A = Flurbiprofen 8.75 mg lozenge

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.26. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment C Versus Treatment B

	Difference C - B		
Parameter	90% CI	Median	p-Value
tmax	-0.1670 - 0.2068	-0.0003	0.7334

Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.27. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment D Versus Treatment B

	Difference D - B		
Parameter	90% CI	Median	p-Value
tmax	-0.2879 - 0.1664	-0.0013	0.7471

Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.28. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment E Versus Treatment B

	Difference E - B		
Parameter	90% CI	Median	p-Value
tmax	-0.2044 - 0.0022	-0.1637	0.1763

Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.29. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment D Versus Treatment C

	Difference D - C		
Parameter	90% CI	Median	p-Value
tmax	-0.2488 - 0.0834	-0.0833	0.4126

Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.30. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment E Versus Treatment C

	Difference E - C		
Parameter	90% CI	Median	p-Value
tmax	-0.2078 - -0.0015	-0.0833	0.0117

Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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Table 14.2.31. Non-Parametric Statistical Comparison of Plasma Flurbiprofen tmax:
Treatment E Versus Treatment D

	Difference E - D		
Parameter	90% CI	Median	p-Value
tmax	-0.2473 - 0.0839	-0.0014	0.5693

Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)

The Confidence Interval is constructed using Walsh Averages and
appropriate quantile of the Wilcoxon Matched Pair Test Statistic.
CI = Confidence Interval

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14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 14.3.1.1. Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event*	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Total
Number of Subjects Dosed	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)
Number of Subjects With Adverse Events	2 (17%)	4 (33%)	1 (8%)	4 (33%)	3 (25%)	8 (67%)
Number of Subjects Without Adverse Events	10 (83%)	8 (67%)	11 (92%)	8 (67%)	9 (75%)	4 (33%)
Gastrointestinal disorders	0 (0%)	0 (0%)	0 (0%)	2 (17%)	1 (8%)	3 (25%)
Chapped lips	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (8%)
Cheilitis	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)	2 (17%)
Lip dry	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)
Nausea	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (8%)
Infections and infestations	0 (0%)	3 (25%)	0 (0%)	0 (0%)	1 (8%)	4 (33%)
Rash pustular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)
Upper respiratory tract infection	0 (0%)	3 (25%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Arthralgia	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Nervous system disorders	1 (8%)	0 (0%)	1 (8%)	1 (8%)	1 (8%)	4 (33%)
Dizziness postural	1 (8%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	2 (17%)
Headache	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (8%)	2 (17%)
Skin and subcutaneous tissue disorders	1 (8%)	0 (0%)	1 (8%)	1 (8%)	1 (8%)	4 (33%)
Dry skin	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Rash	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (8%)
Rash macular	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (8%)
Rash maculo-papular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)

Note: * Adverse events are classified according to MedDRA Version 13.1.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

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Table 14.3.1.2. Treatment-Emergent Adverse Event Frequency by Treatment - Number of Adverse Events (% of Total Adverse Events)

	Treatment					
Adverse Event*	A	B	C	D	E	Total
Number of Adverse Events	2 (100%)	4 (100%)	2 (100%)	5 (100%)	5 (100%)	18 (100%)
Gastrointestinal disorders	0 (0%)	0 (0%)	0 (0%)	3 (60%)	2 (40%)	5 (28%)
Chapped lips	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (6%)
Cheilitis	0 (0%)	0 (0%)	0 (0%)	1 (20%)	1 (20%)	2 (11%)
Lip dry	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	1 (6%)
Nausea	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (6%)
Infections and infestations	0 (0%)	3 (75%)	0 (0%)	0 (0%)	1 (20%)	4 (22%)
Rash pustular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	1 (6%)
Upper respiratory tract infection	0 (0%)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	3 (17%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Arthralgia	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Nervous system disorders	1 (50%)	0 (0%)	1 (50%)	1 (20%)	1 (20%)	4 (22%)
Dizziness postural	1 (50%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	2 (11%)
Headache	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (20%)	2 (11%)
Skin and subcutaneous tissue disorders	1 (50%)	0 (0%)	1 (50%)	1 (20%)	1 (20%)	4 (22%)
Dry skin	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
Rash	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (6%)
Rash macular	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	1 (6%)
Rash maculo-papular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	1 (6%)

Note: * Adverse events are classified according to MedDRA Version 13.1.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

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Table 14.3.1.3. Treatment-Emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Study Drug - Number of Subjects Reporting Events

Adverse Event*	Treatment	Number of Subjects with Adverse Events	Severity			Relationship to Study Drug				
			Mild	Moderate	Severe	Definite	Probable	Possible	Unlikely	None
Arthralgia	B	1	1	0	0	0	0	0	0	1
Chapped lips	D	1	1	0	0	0	0	0	1	0
Cheilitis	D	1	1	0	0	0	0	0	1	0
	E	1	1	0	0	0	0	0	1	0
Dizziness postural	A	1	1	0	0	0	0	0	1	0
	D	1	1	0	0	0	0	0	1	0
Dry skin	A	1	1	0	0	0	0	0	1	0
Headache	**C**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
	E	1	1	0	0	0	0	0	1	0
Lip dry	E	1	1	0	0	0	0	0	1	0
Nausea	D	1	1	0	0	0	0	0	1	0
Rash	D	1	1	0	0	0	0	0	1	0
Rash macular	C	1	1	0	0	0	0	0	1	0
Rash maculo-papular	**E**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
Rash pustular	E	1	1	0	0	0	0	0	1	0
Upper respiratory tract infection	B	3	2	1	0	0	0	0	0	3
Treatment A		2	2	0	0	0	0	0	2	0
Treatment B		4	3	1	0	0	0	0	0	4
Treatment C		1	1	0	0	0	0	0	1	0
Treatment D		4	4	0	0	0	0	0	4	0
Treatment E		3	3	0	0	0	0	0	3	0
Overall		8	8	1	0	0	0	0	7	4

Note: * Adverse events are classified according to MedDRA Version 13.1.
When a subject experienced the same AE at more than one level of severity during a treatment period, each AE was counted separately. When a subject experienced the same AE at more than one level of drug relationship during a treatment period, each AE was counted separately.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

Table 14.3.1.4. Treatment-Emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Study Drug - Number of Adverse Events

Adverse Event*	Treatment	Number of Adverse Events	Severity			Relationship to Study Drug				
			Mild	Moderate	Severe	Definite	Probable	Possible	Unlikely	None
Arthralgia	B	1	1	0	0	0	0	0	0	1
Chapped lips	D	1	1	0	0	0	0	0	1	0
Cheilitis	D	1	1	0	0	0	0	0	1	0
	E	1	1	0	0	0	0	0	1	0
Dizziness postural	A	1	1	0	0	0	0	0	1	0
	D	1	1	0	0	0	0	0	1	0
Dry skin	A	1	1	0	0	0	0	0	1	0
Headache	C	1	1	0	0	0	0	0	1	0
	E	1	1	0	0	0	0	0	1	0
Lip dry	E	1	1	0	0	0	0	0	1	0
Nausea	D	1	1	0	0	0	0	0	1	0
Rash	D	1	1	0	0	0	0	0	1	0
Rash macular	C	1	1	0	0	0	0	0	1	0
Rash maculo-papular	E	1	1	0	0	0	0	0	1	0
Rash pustular	E	1	1	0	0	0	0	0	1	0
Upper respiratory tract infection	B	3	2	1	0	0	0	0	0	3
Treatment A		2	2	0	0	0	0	0	2	0
Treatment B		4	3	1	0	0	0	0	0	4
Treatment C		2	2	0	0	0	0	0	2	0
Treatment D		5	5	0	0	0	0	0	5	0
Treatment E		5	5	0	0	0	0	0	5	0
Overall		18	17	1	0	0	0	0	14	4

Note: * Adverse events are classified according to MedDRA Version 13.1.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae4a_auto.sas 18APR2011 12:38

Table 14.3.1.5. Incidence of All Treatment-Emergent Adverse Events - McNemar's Test

Adverse Event*	Treatment	Adverse Event	Test	Reference	P-value from McNemars Exact Test
Arthralgia	B vs A	Yes	1	0	0.00098
		No	11	12	
Chapped lips	D vs A	Yes	1	0	0.00098
		No	11	12	
Cheilitis	D vs A	Yes	1	0	0.00098
		No	11	12	
	E vs A	Yes	1	0	0.00098
		No	11	12	
Dizziness postural	B vs A	Yes	0	1	0.00342
		No	12	11	
	C vs A	Yes	0	1	0.00342
		No	12	11	
	D vs A	Yes	1	1	0.00635
		No	11	11	
	E vs A	Yes	0	1	0.00342
		No	12	11	
Dry skin	B vs A	Yes	0	1	0.00342
		No	12	11	
	C vs A	Yes	0	1	0.00342
		No	12	11	
	D vs A	Yes	0	1	0.00342
		No	12	11	
	E vs A	Yes	0	1	0.00342
		No	12	11	

Note: * Adverse events are classified according to MedDRA Version 13.1.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae5a_auto.sas 18MAY2011 14:43

Table 14.3.1.5. Incidence of All Treatment-Emergent Adverse Events - McNemar's Test

Adverse Event*	Treatment	Adverse Event	Test	Reference	P-value from McNemars Exact Test
Headache	C vs A	Yes	1	0	0.00098
		No	11	12	
	E vs A	Yes	1	0	0.00098
		No	11	12	
Lip dry	E vs A	Yes	1	0	0.00098
		No	11	12	
Nausea	D vs A	Yes	1	0	0.00098
		No	11	12	
Rash	D vs A	Yes	1	0	0.00098
		No	11	12	
Rash macular	C vs A	Yes	1	0	0.00098
		No	11	12	
Rash maculo-papular	E vs A	Yes	1	0	0.00098
		No	11	12	
Rash pustular	E vs A	Yes	1	0	0.00098
		No	11	12	
Upper respiratory tract infect	B vs A	Yes	3	0	0.00391
		No	9	12	

Note: * Adverse events are classified according to MedDRA Version 13.1.
Treatment A = Flurbiprofen 8.75 mg lozenge
Treatment B = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/090)
Treatment C = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/096)
Treatment D = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/102)
Treatment E = 15 mL of 8.75 mg/540 µL Flurbiprofen (3 sprays (180 µL each)) (Batch No. 02143/108)

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae5a_auto.sas 18MAY2011 14:43

Table 14.3.1.6. Incidence of Probably or Possibly Related Treatment-Emergent Adverse Events - McNemar's Test

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There were no probably or possibly related treatment-emergent adverse events recorded during the study.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae6a_auto.sas 28APR2011 10:29

Table 14.3.1.7. Incidence of Severe Treatment-Emergent Adverse Events - McNemar's Test

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There were no severe treatment-emergent adverse events recorded during the study.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae7a_auto.sas 28APR2011 10:29

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2. Serious Adverse Events

There were no serious adverse events recorded during the study.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_tblae_ser.sas 18APR2011 12:38

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable for this study.

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

Table 14.3.4.1.1 Out-of-Range Values and Recheck Results - Serum Chemistry (I of II)

Subject Number	Age/ Gender	Study Period	Date	Alpha HBD 80-220 (U/L)	Potassium 3.8-5.3 (mmol/L)	Sodium 133-142 (mmol/L)	Albumin 42-52 (g/L)	Glucose 4.2-5.9 (mmol/L)	Total Protein 67-83 (g/L)
2	44/F	Post	10MAR2011		3.6 LN		41 LN		
3	25/M	Post	10MAR2011			144 HN			
4	28/F	Post	10MAR2011					4.1 LN	66 LN
5	21/M	Screen	02FEB2011		3.7 LN				
		Post	10MAR2011	79 L -	3.4 LY-				
6	19/F	Post	10MAR2011	252 H -				4.1 LN	
7	26/M	Screen	02FEB2011				53 HN		
		Post	10MAR2011					4.1 LN	
8	18/F	Screen	02FEB2011		3.7 LN			4.1 LN	
		Post	10MAR2011						64 LN
10	30/F	Post	10MAR2011						64 LN
12	23/F	Screen	02FEB2011		3.7 LN		54 HN		

Note: H = Above Normal Range, L = Below Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_lababn.sas 18APR2011 12:38

Table 14.3.4.1.2 Out-of-Range Values and Recheck Results - Serum Chemistry (II of II)

Subject Number	Age/ Gender	Study Period	Date	Uric Acid F: 155-392 M: 214-435 (umol/L)	Alanine Amino-transferase 12-60 (U/L)	Direct Bilirubin M: 0-5 (umol/L)	Indirect Bilirubin M: 0-20 (umol/L)	Total Bilirubin 3.4-27.4 (umol/L)	GGT 8-81 (U/L)	Creatine Kinase 25-260 (U/L)
1	30/M	Screen	02FEB2011							294 HY-
		Post	10MAR2011							290 HY-
5	21/M	Post	10MAR2011						7 LN	
6	19/F	Screen	02FEB2011		11 LN					
		Post	10MAR2011		11 LN				7 LN	
7	26/M	Screen	02FEB2011							285 HN
		Post	10MAR2011							310 HY-
8	18/F	Post	10MAR2011		9 LN					
9	18/M	Post	10MAR2011					3 LN		
11	22/M	Screen	02FEB2011	445 HN				34 HY-		
		Recheck	02FEB2011			6 HN	29 H -	35 HY-		
12	23/F	Post	10MAR2011		11 LN					

Note: H = Above Normal Range, L = Below Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labab n.sas 18APR2011 12:38

Table 14.3.4.2.1 Out-of-Range Values and Recheck Results - Haematology (I of II)

Subject Number	Age/ Gender	Study Period	Date	Haemoglobin F: 11.7-15.2 M: 13.4-17 (g/dL)	Haematocrit F: 34.7-41.1 M: 40.8-50.1 (%)	Red Blood Cell Count F: 3.98-4.62 M: 4.65-5.71 (mil/uL)	White Blood Cell Count 3.6-10.4 (thou/uL)
1	30/M	Screen	02FEB2011		39.90 LN	4.54 LN	
		Post	10MAR2011		39.10 LN	4.46 LN	
4	28/F	Screen	02FEB2011		41.60 HN		
6	19/F	Post	10MAR2011	10.8 LY-	32.90 LN	3.60 LN	
7	26/M	Screen	02FEB2011				3.5 LN
		Post	10MAR2011			4.56 LN	
8	18/F	Screen	02FEB2011		41.80 HN		
9	18/M	Screen	02FEB2011			4.46 LN	
		Post	10MAR2011		39.70 LN	4.37 LN	
10	30/F	Post	10MAR2011	11.1 LY-	33.50 LN	3.78 LN	
11	22/M	Screen	02FEB2011				3.4 LY-

Note: H = Above Normal Range, L = Below Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_lababn.sas 18APR2011 12:38

Table 14.3.4.2.2 Out-of-Range Values and Recheck Results - Haematology (II of II)

Subject Number	Age/ Gender	Study Period	Date	Basophils .4-1.6 (%)	Eosinophils .3-8.7 (%)	Eosinophil Count 0-.5 (thou/uL)	Lymphocytes 14.9-43.2 (%)	Neutrophil Count 1.7-7.7 (thou/uL)
1	30/M	Post	10MAR2011		11.2 HY-	.6 H -		
3	25/M	Screen	02FEB2011				46.0 HN	
		Post	10MAR2011				46.5 HN	
4	28/F	Screen	02FEB2011	.3 LN				
5	21/M	Screen	02FEB2011	.3 LN				
		Post	10MAR2011	.3 LN				
6	19/F	Post	10MAR2011	.3 LN				
7	26/M	Screen	02FEB2011	.3 LN				
		Post	10MAR2011	.3 LN				
11	22/M	Screen	02FEB2011	.3 LN			47.2 HN	1.5 L -
		Post	10MAR2011	.2 LN			43.9 HN	
12	23/F	Screen	02FEB2011	.1 LN				
		Post	10MAR2011	.2 LN				

Note: H = Above Normal Range, L = Below Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labab n.sas 18APR2011 12:38

Table 14.3.4.3 Out-of-Range Values and Recheck Results - Urinalysis

Subject Number	Age/ Gender	Study Period	Date	Blood NEGATIVE	Ketones NEGATIVE	Bilirubin NEGATIVE	Bacteria F: NEGATIVE	RBC F: < 0-3 (/hpf)
3	25/M	Screen	02FEB2011		TRACE *Y-			
		Post	10MAR2011		TRACE *Y-			
4	28/F	Post	10MAR2011		TRACE *Y-			
5	21/M	Post	10MAR2011		TRACE *Y-	1+ *Y-		
6	19/F	Screen	02FEB2011		TRACE *Y-			
		Post	10MAR2011	TRACE *Y-			1+ *N	
7	26/M	Screen	02FEB2011		TRACE *Y-			
		Post	10MAR2011		TRACE *Y-			
10	30/F	Post	10MAR2011	2+ *Y-			1+ *N	3-5 HY-

Note: * = No Match to Normal Range, H = Above Normal Range
Computer: N = Not Clinically Significant, Y = Clinically Significant
PI interpretation: - = Not Clinically Significant

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_lababn.sas 18APR2011 12:38

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1. Clinical Laboratory Summary and Change From Screening - Serum Chemistry

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Calcium (mmol/L)	2.18-2.56	N	12	12	12
		Mean	2.362	2.371	0.009
		SD	0.0544	0.0944	0.0658
		Minimum	2.30	2.25	-0.08
		Median	2.355	2.340	-0.010
		Maximum	2.47	2.54	0.14
Potassium (mmol/L)	3.8-5.3	N	12	12	12
		Mean	3.95	4.10	0.15
		SD	0.211	0.352	0.408
		Minimum	3.7	3.4	-0.3
		Median	3.95	4.15	0.00
		Maximum	4.3	4.6	0.9
Phosphorus (mmol/L)	.68-1.36	N	12	12	12
		Mean	1.085	1.126	0.041
		SD	0.1262	0.1482	0.0966
		Minimum	0.81	0.89	-0.10
		Median	1.090	1.130	0.025
		Maximum	1.23	1.35	0.20
Sodium (mmol/L)	133-142	N	12	12	12
		Mean	140.8	140.6	-0.3
		SD	0.72	1.44	1.22
		Minimum	140	139	-2
		Median	141.0	140.5	0.0
		Maximum	142	144	2

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.1. Clinical Laboratory Summary and Change From Screening - Serum Chemistry

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Albumin (g/L)	42-52	N	12	12	12
		Mean	49.9	45.9	-4.0
		SD	2.54	3.03	1.76
		Minimum	45	41	-7
		Median	50.0	46.0	-4.0
		Maximum	54	50	-1
Blood Urea Nitrogen (mmol/L)	1.9-6.7	N	12	12	12
		Mean	4.28	5.00	0.73
		SD	1.029	0.714	1.364
		Minimum	2.6	3.7	-2.0
		Median	4.20	5.00	0.70
		Maximum	6.1	6.0	3.3
Creatinine (umol/L)	46-123 #	N	12	12	12
		Mean	87.3	92.8	5.6
		SD	10.56	9.50	5.98
		Minimum	73	81	-7
		Median	84.0	90.5	5.0
		Maximum	109	109	18
Glucose (mmol/L)	4.2-5.9	N	12	12	12
		Mean	4.88	4.68	-0.20
		SD	0.379	0.389	0.548
		Minimum	4.1	4.1	-1.2
		Median	4.90	4.75	-0.20
		Maximum	5.5	5.3	0.8

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.1. Clinical Laboratory Summary and Change From Screening - Serum Chemistry

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Total Protein (g/L)	67-83	N	12	12	12
		Mean	72.3	68.3	-3.9
		SD	2.63	2.74	2.68
		Minimum	69	64	-8
		Median	72.0	69.0	-4.0
		Maximum	77	72	0
Uric Acid (umol/L)	155-435 #	N	12	12	12
		Mean	293.9	298.8	4.8
		SD	73.73	46.73	42.07
		Minimum	172	221	-71
		Median	273.5	292.0	-2.0
		Maximum	445	374	80
Alkaline Phosphatase (U/L)	35-110	N	12	12	12
		Mean	84.4	80.7	-3.8
		SD	18.66	17.84	6.86
		Minimum	51	48	-21
		Median	85.0	83.0	-2.5
		Maximum	109	107	5
Alanine Aminotransferase (U/L)	12-60	N	12	12	12
		Mean	17.7	16.7	-1.0
		SD	7.81	5.94	6.18
		Minimum	11	9	-19
		Median	14.5	14.5	1.0
		Maximum	39	26	4

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.1. Clinical Laboratory Summary and Change From Screening - Serum Chemistry

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Aspartate Aminotransferase (U/L)	8-37	N	12	12	12
		Mean	19.3	18.8	-0.5
		SD	3.58	3.93	4.19
		Minimum	16	15	-10
		Median	18.0	17.0	-1.0
		Maximum	28	27	6
Total Bilirubin (umol/L)	3.4-27.4	N	12	12	12
		Mean	13.5	12.1	-1.4
		SD	8.35	8.64	6.76
		Minimum	4	3	-12
		Median	11.0	8.0	-2.0
		Maximum	35	27	13
GGT (U/L)	8-81	N	12	12	12
		Mean	11.7	10.5	-1.2
		SD	3.06	2.43	1.90
		Minimum	8	7	-5
		Median	11.0	10.0	-1.5
		Maximum	17	15	3
Cholesterol (mmol/L)	2.8-7.1	N	12	12	12
		Mean	4.58	4.44	-0.13
		SD	1.292	1.258	0.235
		Minimum	2.9	2.9	-0.4
		Median	4.10	3.90	-0.15
		Maximum	6.7	6.4	0.4

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.1. Clinical Laboratory Summary and Change From Screening - Serum Chemistry

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Creatine Kinase (U/L)	25-260	N	12	12	12
		Mean	130.6	139.5	8.9
		SD	75.99	80.46	21.12
		Minimum	79	61	-23
		Median	98.5	114.5	6.0
		Maximum	294	310	42
Triglycerides (mmol/L)	.38-2.59	N	12	12	12
		Mean	0.833	0.946	0.113
		SD	0.3260	0.3088	0.2891
		Minimum	0.41	0.50	-0.39
		Median	0.685	0.925	0.100
		Maximum	1.40	1.52	0.83

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.2. Clinical Laboratory Shift From Screening - Serum Chemistry

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
Calcium (mmol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Potassium (mmol/L)	1	1	1	0	0	1	9	2	0
	2	2	8	0					
	3	0	0	0					
Phosphorus (mmol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Sodium (mmol/L)	1	0	0	0	0	0	11	1	0
	2	0	11	0					
	3	0	1	0					
Albumin (g/L)	1	0	1	0	0	3	9	0	0
	2	0	9	2					
	3	0	0	0					
Blood Urea Nitrogen (mmol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Creatinine (umol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.2. Clinical Laboratory Shift From Screening - Serum Chemistry

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
Glucose (mmol/L)	1	0	3	0	0	3	8	1	0
	2	1	8	0					
	3	0	0	0					
Total Protein (g/L)	1	0	3	0	0	3	9	0	0
	2	0	9	0					
	3	0	0	0					
Uric Acid (umol/L)	1	0	0	0	0	1	11	0	0
	2	0	11	1					
	3	0	0	0					
Alkaline Phosphatase (U/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Alanine Aminotransferase (U/L)	1	1	2	0	0	2	10	0	0
	2	0	9	0					
	3	0	0	0					
Aspartate Aminotransferase (U/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Total Bilirubin (umol/L)	1	0	1	0	0	2	10	0	0
	2	0	10	1					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.2. Clinical Laboratory Shift From Screening - Serum Chemistry

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
GGT (U/L)	1	0	2	0	0	2	10	0	0
	2	0	10	0					
	3	0	0	0					
Cholesterol (mmol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Creatine Kinase (U/L)	1	0	0	0	0	0	12	0	0
	2	0	10	0					
	3	0	0	2					
Triglycerides (mmol/L)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.3. Clinical Laboratory Summary and Change From Screening - Haematology

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Haemoglobin (g/dL)	11.7-17 #	N	12	12	12
		Mean	14.13	13.29	-0.83
		SD	1.239	1.421	0.550
		Minimum	12.1	10.8	-1.7
		Median	14.15	13.40	-0.80
		Maximum	16.3	15.4	0.1
Haematocrit (%)	34.7-50.1 #	N	12	12	12
		Mean	41.35	38.86	-2.49
		SD	2.903	3.425	1.499
		Minimum	36.5	32.9	-4.7
		Median	41.35	39.00	-2.70
		Maximum	47.0	43.6	0.2
Platelet Count (thou/uL)	150-400	N	12	12	12
		Mean	245.7	242.5	-3.2
		SD	57.15	56.75	23.40
		Minimum	176	155	-41
		Median	231.5	221.0	-3.0
		Maximum	341	335	37
Red Blood Cell Count (mil/uL)	3.98-5.71 #	N	12	12	12
		Mean	4.638	4.403	-0.234
		SD	0.4257	0.4807	0.1858
		Minimum	3.99	3.60	-0.52
		Median	4.560	4.415	-0.210
		Maximum	5.60	5.23	0.09

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.3. Clinical Laboratory Summary and Change From Screening - Haematology

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
MCH (pg)	26-33.5 #	N	12	12	12
		Mean	30.48	30.19	-0.29
		SD	1.036	1.068	0.243
		Minimum	28.9	28.6	-0.7
		Median	30.40	30.15	-0.30
		Maximum	32.5	32.0	0.3
MCHC (g/dL)	31.9-36.5 #	N	12	12	12
		Mean	34.13	34.15	0.02
		SD	0.848	0.827	0.359
		Minimum	32.7	32.8	-0.6
		Median	34.10	34.25	0.00
		Maximum	35.3	35.3	0.5
MCV (fL)	81-99 #	N	12	12	12
		Mean	89.4	88.5	-0.9
		SD	3.12	3.21	1.00
		Minimum	84	83	-3
		Median	89.5	88.5	-1.0
		Maximum	94	93	1
White Blood Cell Count (thou/uL)	3.6-10.4	N	12	12	12
		Mean	5.32	5.64	0.33
		SD	1.220	1.448	1.610
		Minimum	3.4	3.6	-2.0
		Median	5.10	5.60	-0.20
		Maximum	7.5	9.4	4.4

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.3. Clinical Laboratory Summary and Change From Screening - Haematology

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Basophils (%)	.4-1.6	N	12	12	12
		Mean	0.52	0.48	-0.03
		SD	0.272	0.233	0.161
		Minimum	0.1	0.2	-0.3
		Median	0.50	0.50	0.00
		Maximum	1.0	0.9	0.2
Basophil Count (thou/uL)	0-.1	N	12	12	12
		Mean	0.02	0.00	-0.02
		SD	0.039	0.000	0.039
		Minimum	0.0	0.0	-0.1
		Median	0.00	0.00	0.00
		Maximum	0.1	0.0	0.0
Eosinophils (%)	.3-8.7	N	12	12	12
		Mean	2.28	3.86	1.58
		SD	1.236	2.869	1.849
		Minimum	0.8	1.3	0.1
		Median	2.20	2.85	0.75
		Maximum	5.0	11.2	6.2
Eosinophil Count (thou/uL)	0-.5	N	12	12	12
		Mean	0.13	0.23	0.10
		SD	0.087	0.154	0.095
		Minimum	0.0	0.1	0.0
		Median	0.10	0.20	0.10
		Maximum	0.3	0.6	0.3

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.3. Clinical Laboratory Summary and Change From Screening - Haematology

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Lymphocytes (%)	14.9-43.2	N	12	12	12
		Mean	33.48	31.10	-2.38
		SD	7.225	8.792	4.947
		Minimum	25.8	16.8	-12.8
		Median	33.40	31.05	-2.65
		Maximum	47.2	46.5	3.8
Lymphocyte Count (thou/uL)	1-2.8	N	12	12	12
		Mean	1.73	1.67	-0.06
		SD	0.355	0.326	0.318
		Minimum	1.3	1.2	-0.6
		Median	1.65	1.60	-0.10
		Maximum	2.6	2.1	0.4
Monocytes (%)	4.7-13.2	N	12	12	12
		Mean	7.50	8.52	1.02
		SD	1.545	1.961	1.756
		Minimum	4.9	5.8	-2.8
		Median	7.40	8.05	1.45
		Maximum	10.5	12.2	3.6
Monocyte Count (thou/uL)	0-.9	N	12	12	12
		Mean	0.39	0.46	0.07
		SD	0.100	0.124	0.089
		Minimum	0.2	0.3	-0.1
		Median	0.40	0.40	0.10
		Maximum	0.6	0.7	0.2

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.3. Clinical Laboratory Summary and Change From Screening - Haematology

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
Neutrophils (%)	42.1-76.3	N	12	12	12
		Mean	56.23	56.04	-0.18
		SD	6.676	8.618	6.899
		Minimum	44.3	42.2	-11.1
		Median	57.85	56.05	-1.00
		Maximum	65.3	74.2	14.2
Neutrophil Count (thou/uL)	1.7-7.7	N	12	12	12
		Mean	3.04	3.26	0.22
		SD	0.976	1.375	1.389
		Minimum	1.5	1.8	-1.4
		Median	2.90	3.30	-0.15
		Maximum	4.5	6.9	3.9

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1. for the breakdown.

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.4. Clinical Laboratory Shift From Screening - Haematology

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
Haemoglobin (g/dL)	1	0	2	0	0	2	10	0	0
	2	0	10	0					
	3	0	0	0					
Haematocrit (%)	1	1	3	0	0	5	7	0	0
	2	0	6	2					
	3	0	0	0					
Platelet Count (thou/uL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Red Blood Cell Count (mil/uL)	1	2	3	0	0	3	9	0	0
	2	0	7	0					
	3	0	0	0					
MCH (pg)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
MCHC (g/dL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
MCV (fL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.4. Clinical Laboratory Shift From Screening - Haematology

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
White Blood Cell Count (thou/uL)	1	0	0	0	0	0	10	2	0
	2	2	10	0					
	3	0	0	0					
Basophils (%)	1	4	1	0	0	1	10	1	0
	2	1	6	0					
	3	0	0	0					
Basophil Count (thou/uL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Eosinophils (%)	1	0	0	0	0	0	11	1	0
	2	0	11	0					
	3	0	1	0					
Eosinophil Count (thou/uL)	1	0	0	0	0	0	11	1	0
	2	0	11	0					
	3	0	1	0					
Lymphocytes (%)	1	0	0	0	0	0	12	0	0
	2	0	10	0					
	3	0	0	2					
Lymphocyte Count (thou/uL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.4. Clinical Laboratory Shift From Screening - Haematology

Laboratory Test (units)	Post Score*	Screening Score* 1	2	3	Shift Score** -2	-1	0	1	2
Monocytes (%)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Monocyte Count (thou/uL)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Neutrophils (%)	1	0	0	0	0	0	12	0	0
	2	0	12	0					
	3	0	0	0					
Neutrophil Count (thou/uL)	1	0	0	0	0	0	11	1	0
	2	1	11	0					
	3	0	0	0					

Note: * Score: 1 = Low, 2 = Normal, 3 = High
** Shift Score: Difference between score at Post and score at Screening

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labshift.sas 18APR2011 12:38

Table 14.3.5.5. Clinical Laboratory Summary and Change From Screening - Urinalysis

Laboratory Test (units)	Normal Range	Statistic	Screening	Post	Change
pH, Urine	5.0-8.0	N	12	12	12
		Mean	6.63	6.08	-0.54
		SD	0.569	0.669	0.811
		Minimum	5.5	5.0	-2.0
		Median	6.75	6.00	-0.50
		Maximum	7.5	7.5	0.5
Specific Gravity	1.005-1.030	N	12	12	12
		Mean	1.0139	1.0165	0.0026
		SD	0.00715	0.00879	0.00632
		Minimum	1.005	1.005	-0.005
		Median	1.0125	1.0150	0.0010
		Maximum	1.025	1.028	0.012

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_labsummary.sas 18APR2011 12:38

Table 14.3.5.6. Vital Sign Summary

Vital Sign (units)	Statistic	Screening	Post	Change
Systolic Blood Pressure (mm Hg)	N	12	12	12
	Mean	116.0	111.3	-4.7
	SD	10.54	4.44	10.38
	Minimum	95	103	-20
	Median	117.0	111.0	-4.5
	Maximum	133	119	14
Diastolic Blood Pressure (mm Hg)	N	12	12	12
	Mean	70.8	65.7	-5.2
	SD	4.30	6.57	8.82
	Minimum	63	53	-18
	Median	70.5	66.0	-3.0
	Maximum	78	77	14
Pulse Rate (bpm)	N	12	12	12
	Mean	71.8	68.6	-3.3
	SD	10.68	11.54	10.85
	Minimum	49	50	-16
	Median	73.0	67.5	-6.0
	Maximum	86	94	22

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_vitsummary.sas 18APR2011 12:38

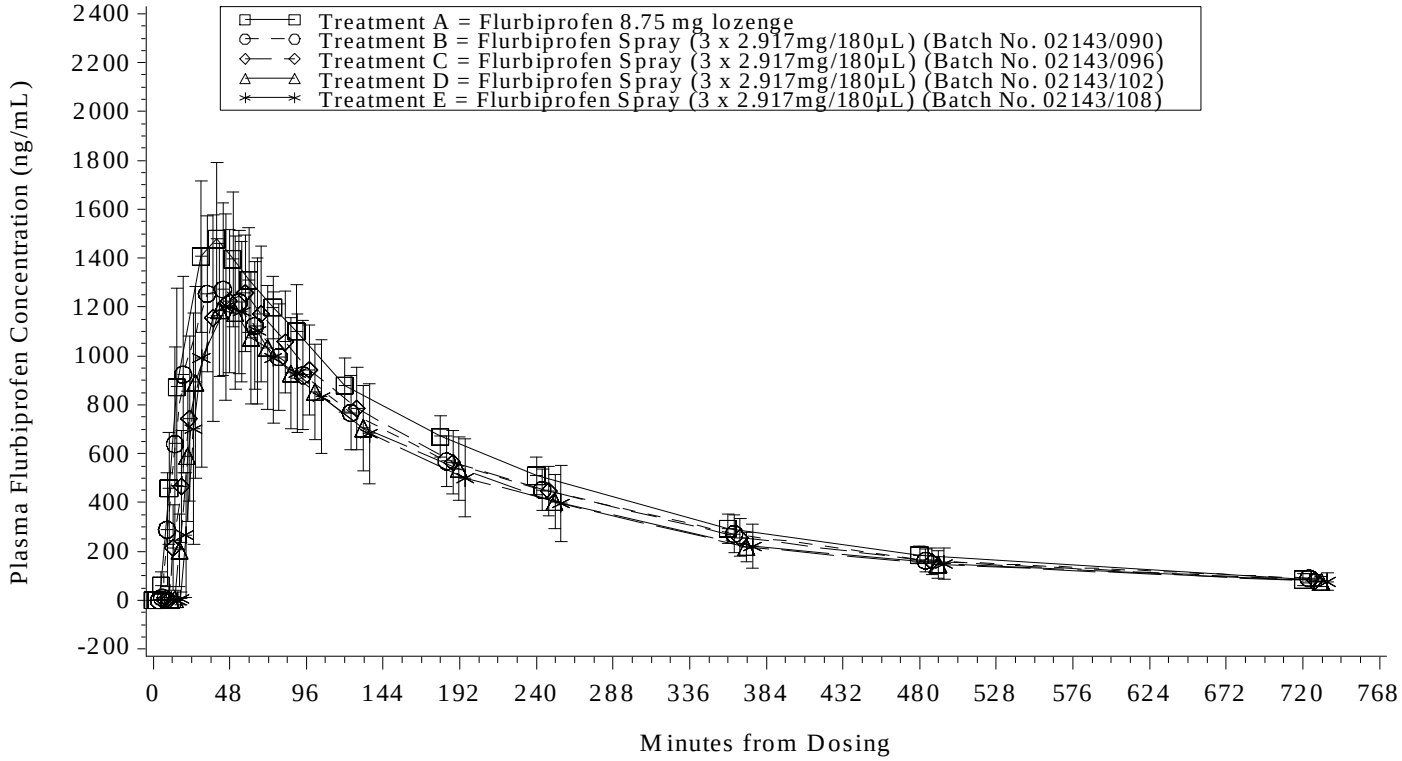
Table 14.3.5.7. 12-Lead Electrocardiogram Summary

Parameter (units)	Statistic	Screening	Post	Change
Heart Rate (bpm)	N	12	12	12
	Mean	67.3	62.2	-5.1
	SD	7.46	12.04	11.20
	Minimum	51	44	-26
	Median	68.5	59.5	-8.0
	Maximum	77	89	14
PR (msec)	N	12	12	12
	Mean	146.5	149.3	2.8
	SD	21.39	20.44	18.73
	Minimum	120	120	-36
	Median	147.0	151.0	6.0
	Maximum	196	184	34
QRS (msec)	N	12	12	12
	Mean	88.8	88.2	-0.7
	SD	12.34	12.60	6.29
	Minimum	68	70	-12
	Median	87.0	85.0	2.0
	Maximum	110	112	8
QT (msec)	N	12	12	12
	Mean	395.5	412.5	17.0
	SD	23.62	24.33	27.59
	Minimum	376	368	-30
	Median	384.0	412.0	17.0
	Maximum	456	444	64
QTcB (msec)	N	12	12	12
	Mean	416.4	415.3	-1.1
	SD	17.03	20.88	19.51
	Minimum	388	372	-40
	Median	414.5	413.5	-2.0
	Maximum	444	447	31

Program: /AA92722/ECR/sas_prg/stsas/tab cdash_ecgsummary.sas 18APR2011 12:38

14.4 Figures

Figure 14.4.1
Mean (± SD) Plasma Flurbiprofen Concentrations Versus Time Curves
(Linear Scale)



Treatments B, C, D and E are shifted to the right for ease of reading
Celerion Project AA92722
Program: /AA92722/ECR/sas_prg/pksas meangraph_rtf.sas 15APR2011 08:29

Figure 14.4.2
Mean Plasma Flurbiprofen Concentrations Versus Time Curves
(Linear Scale)

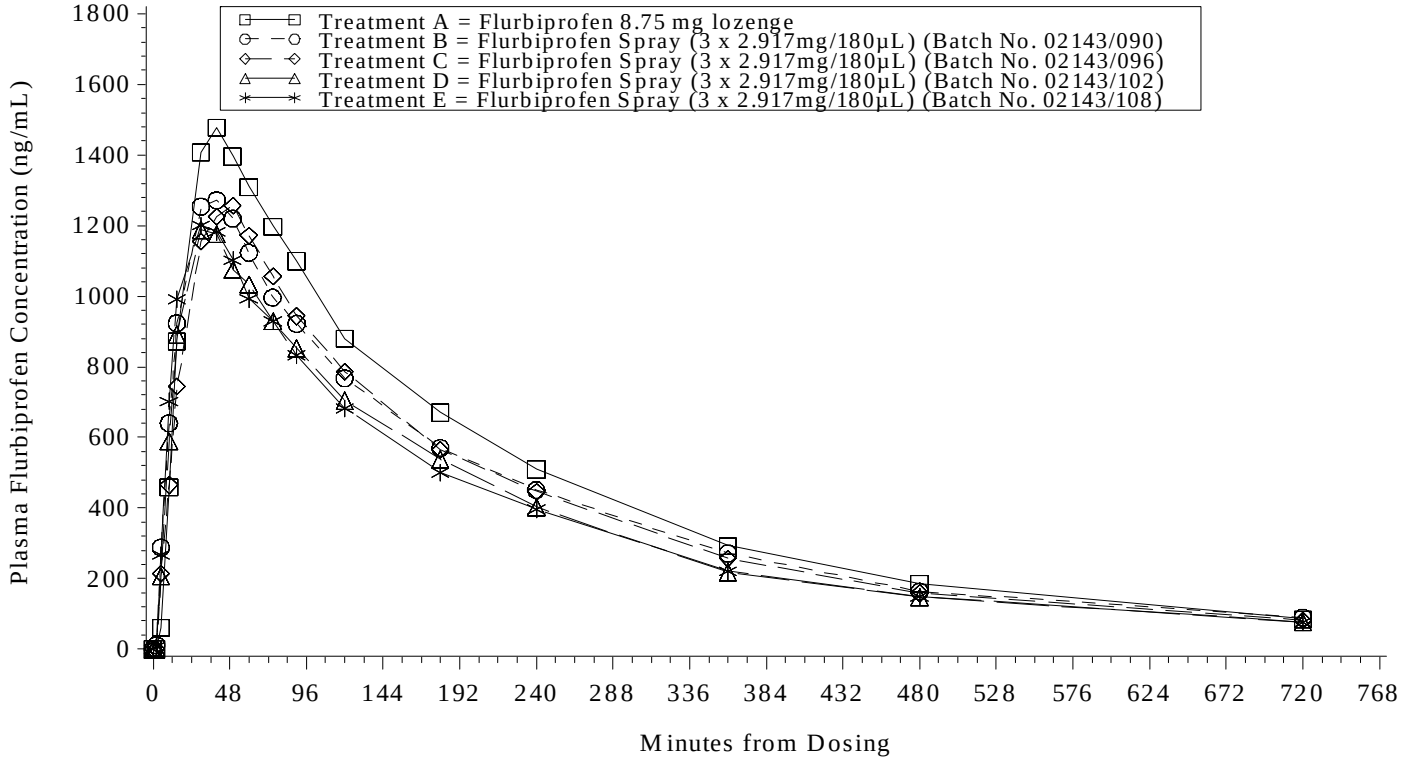


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Figure 14.4.3
Mean Plasma Flurbiprofen Concentrations Versus Time Curves
(Semi-Log Scale)

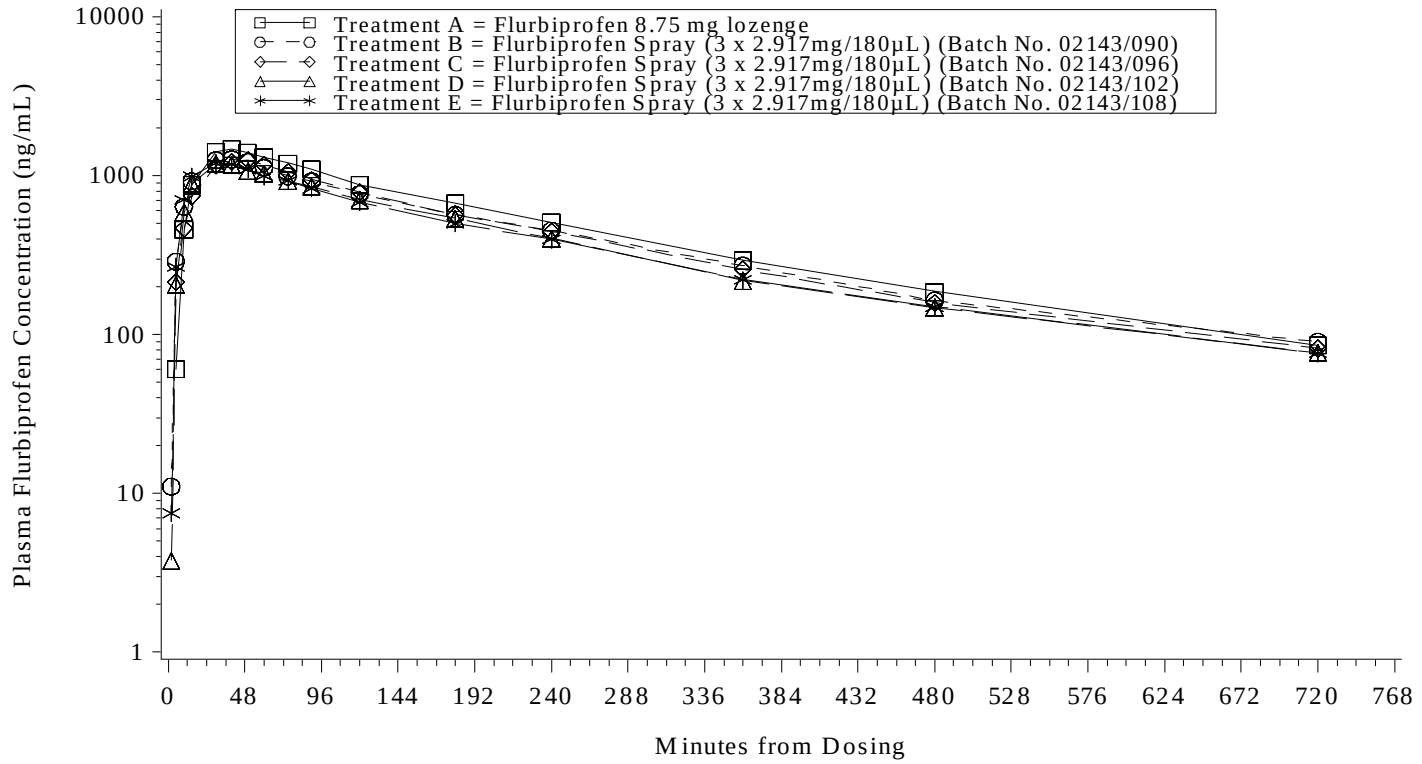

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Figure 14.4.4.1
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 1

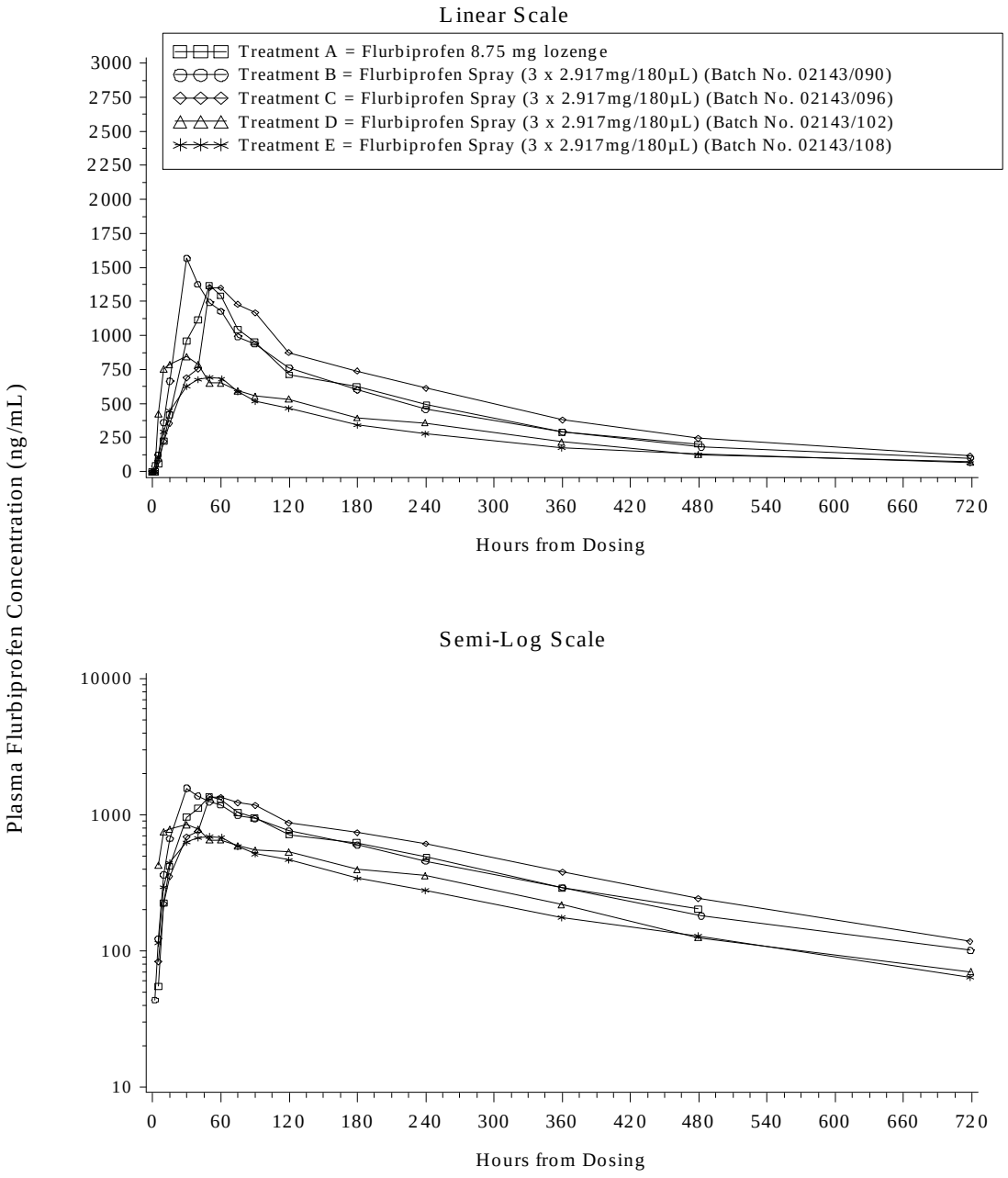

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Figure 14.4.4.2
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 2

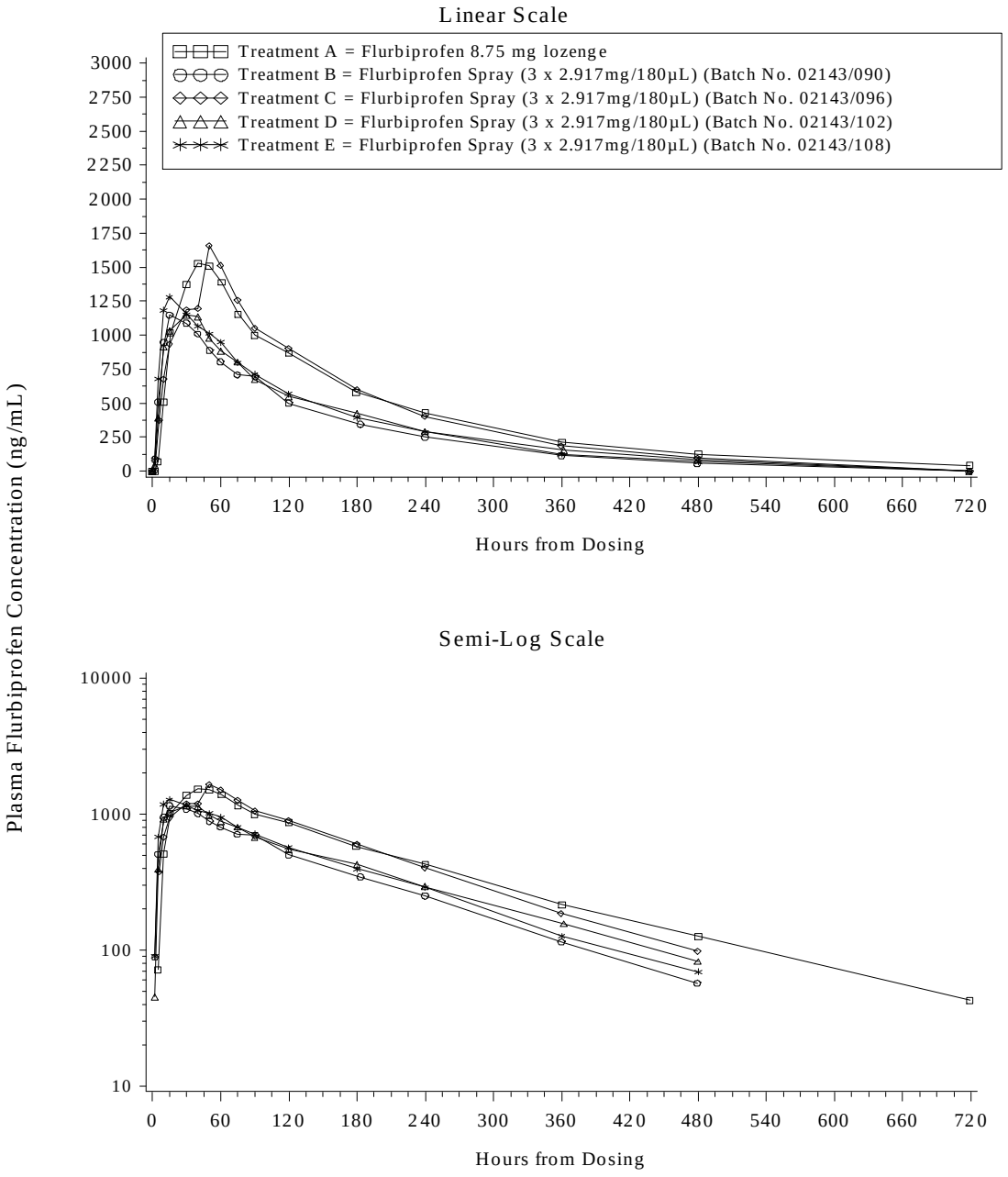

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Figure 14.4.4.3
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 3

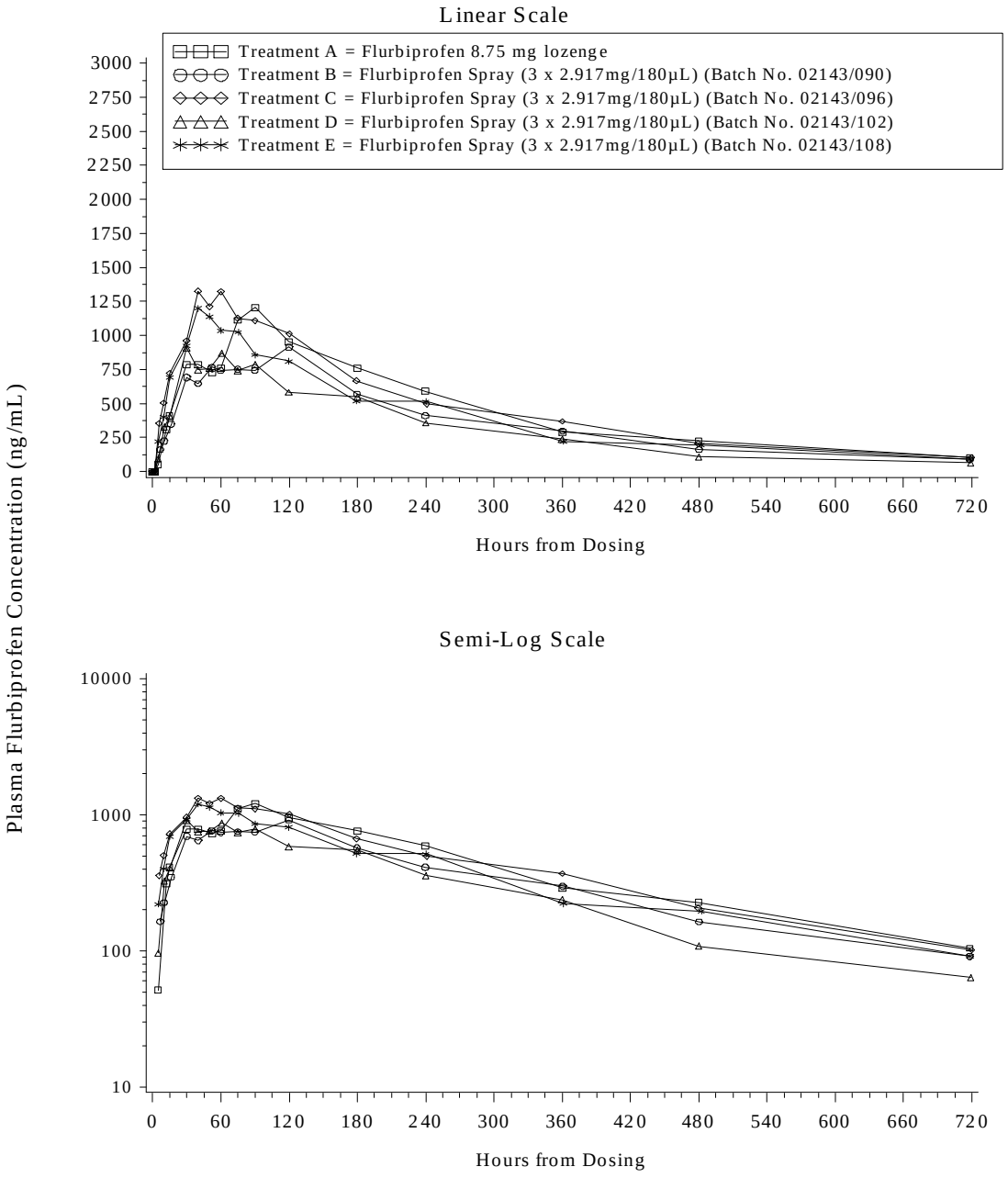

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Figure 14.4.4.4
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 4

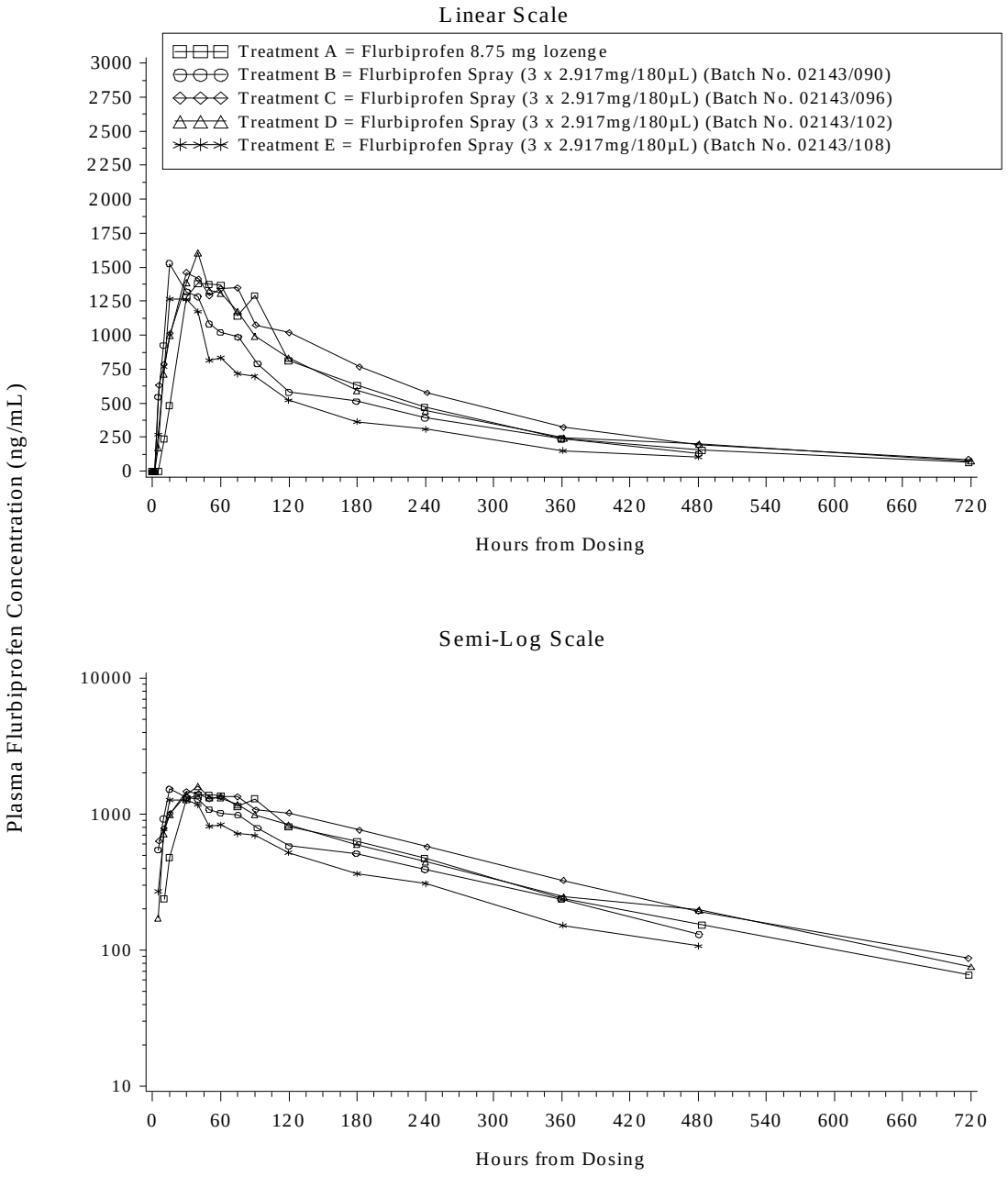

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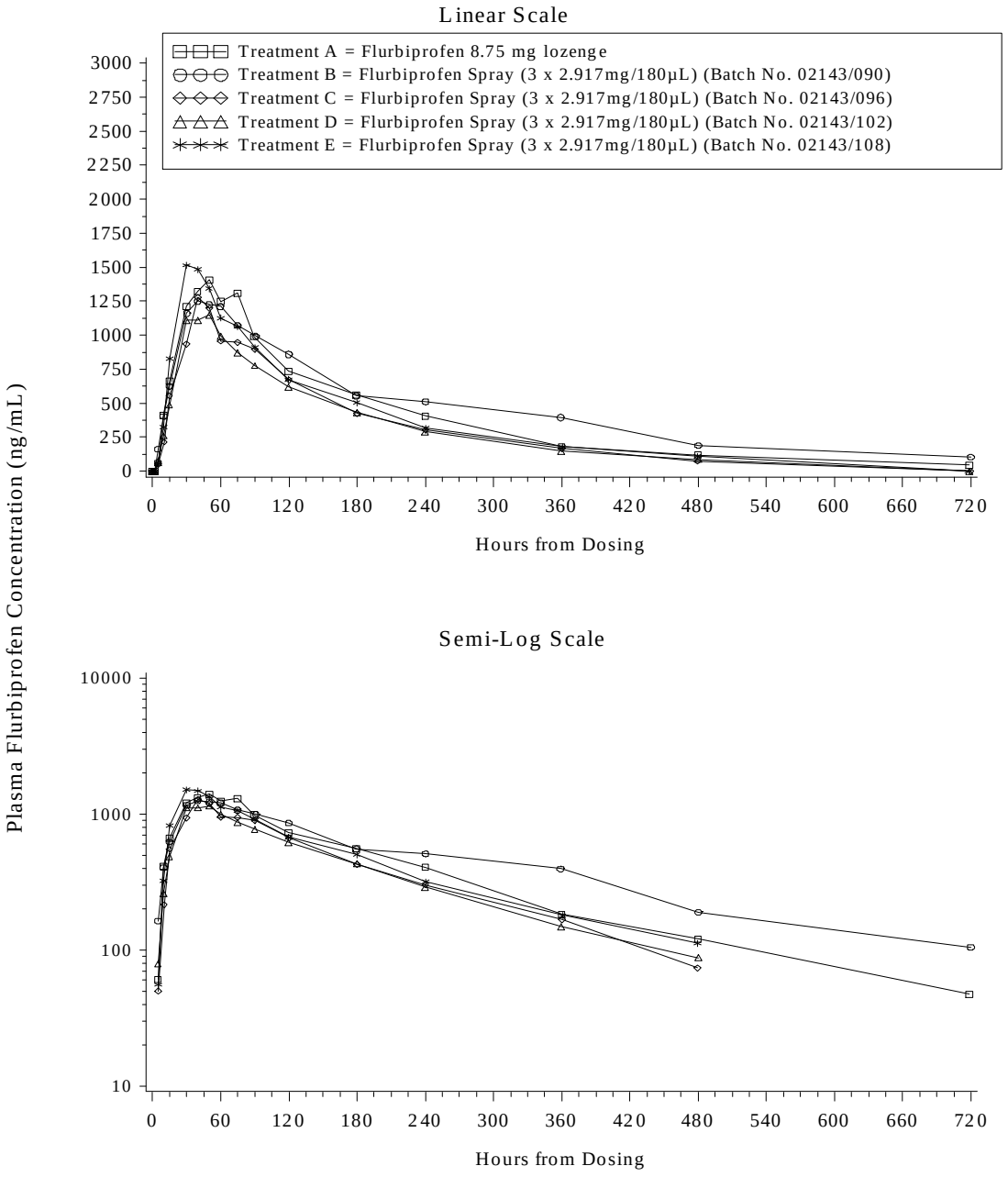
Figure 14.4.4.5
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 5



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Program: /AA92722/ECR/sas_prg/pksas indgraph-all.sas 15APR2011 10:39

Figure 14.4.4.6
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 6

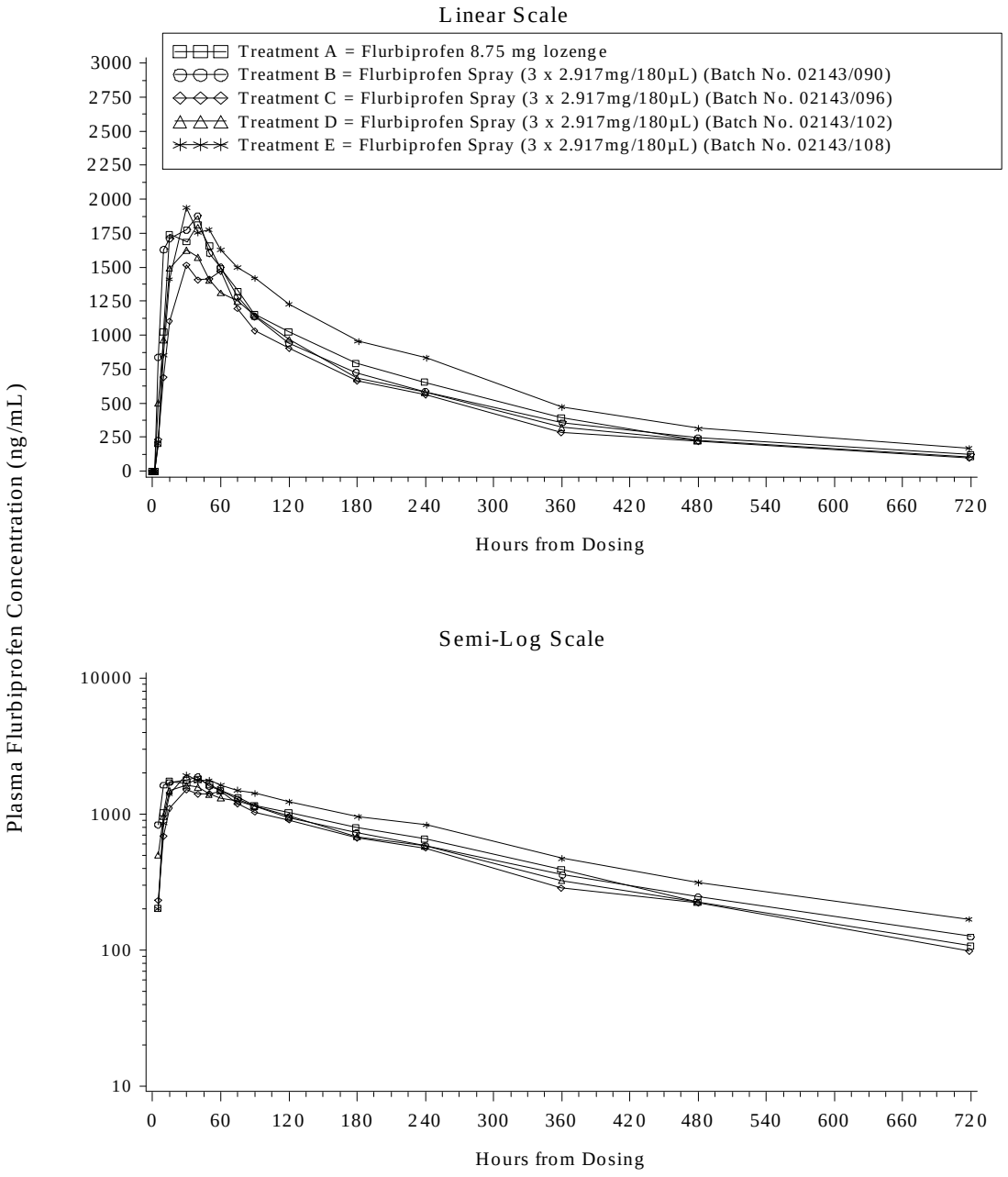

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Figure 14.4.4.7
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 7

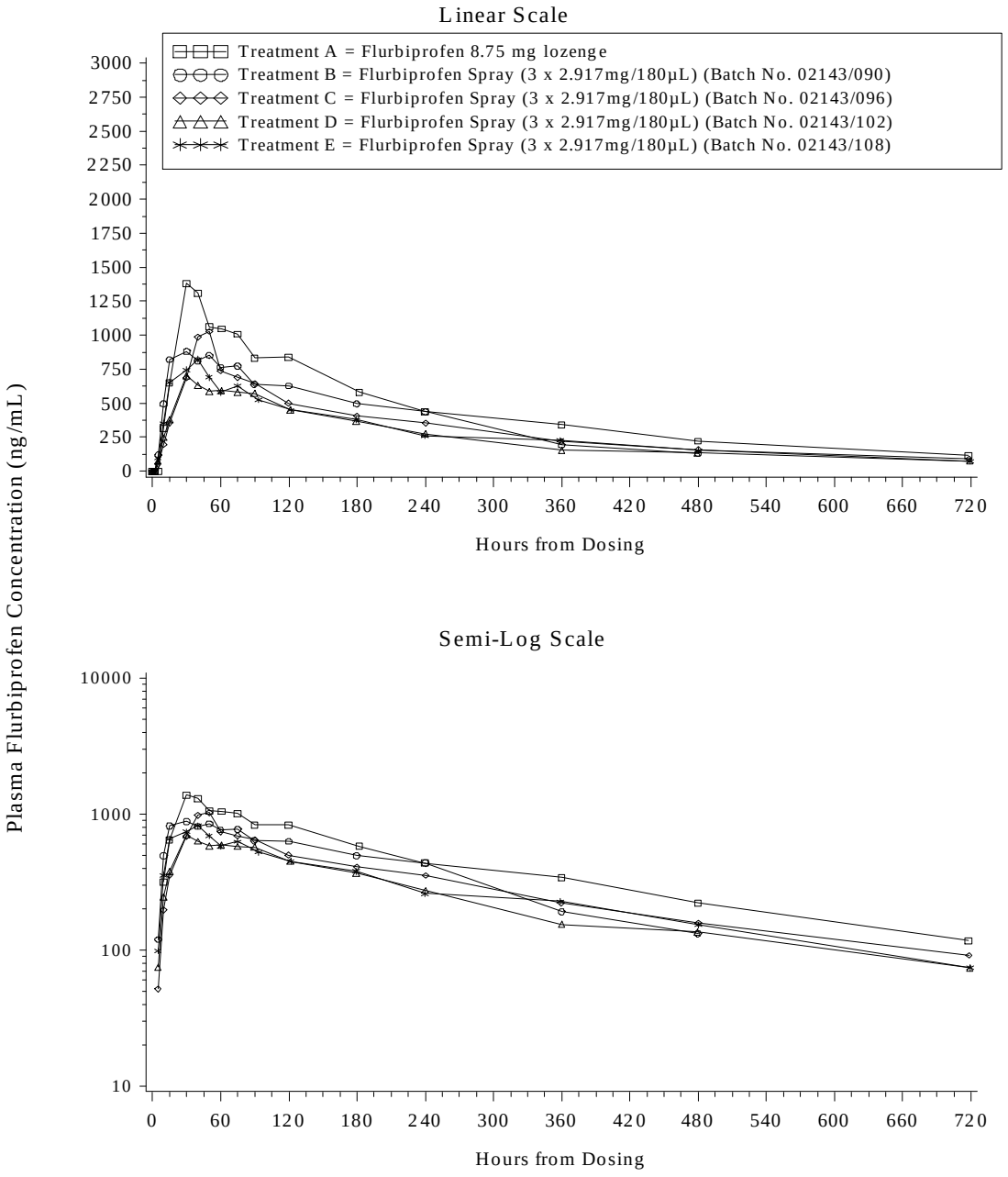

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Figure 14.4.4.8
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 8

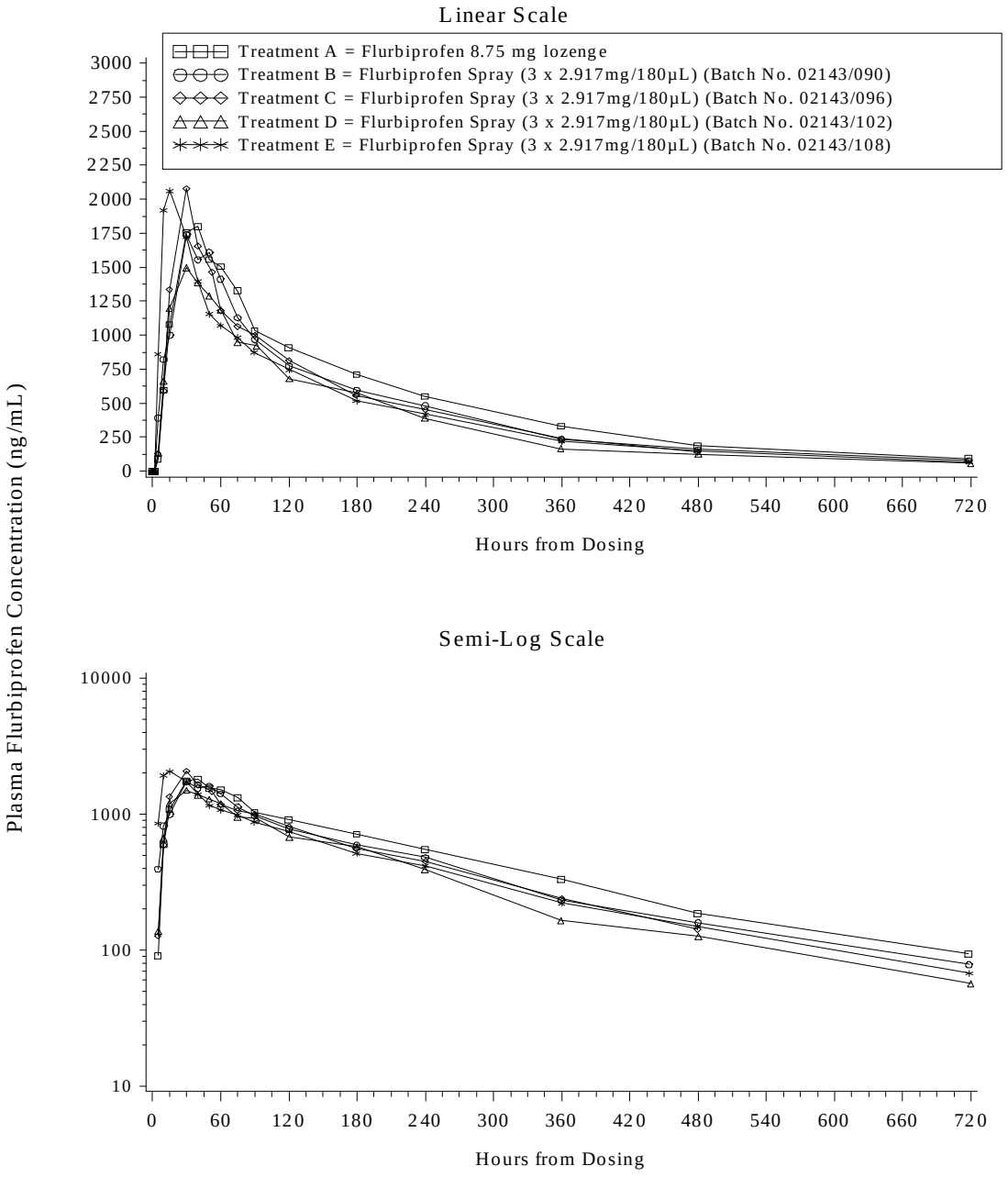

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Figure 14.4.4.9
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 9

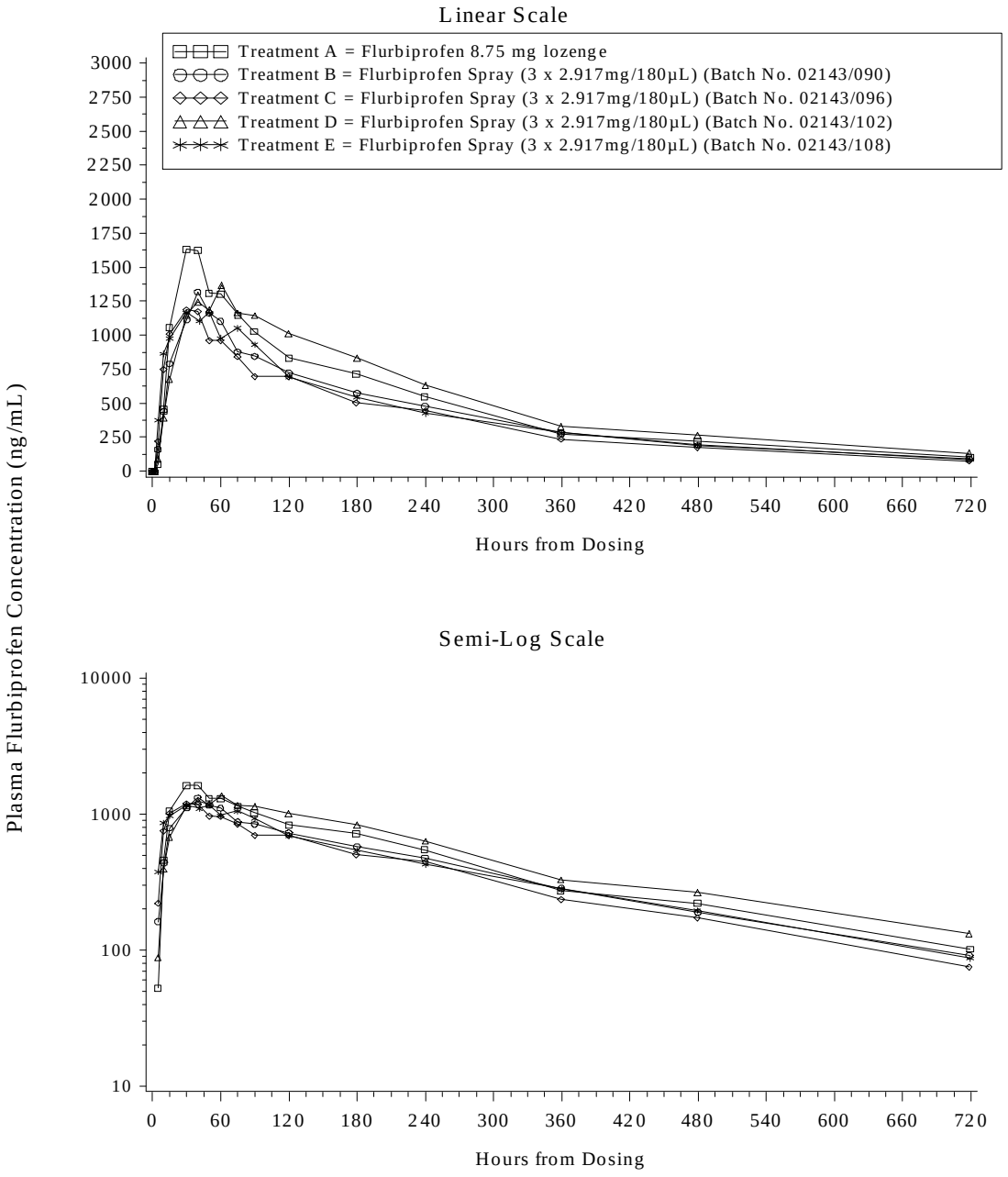

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Figure 14.4.4.10
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 10

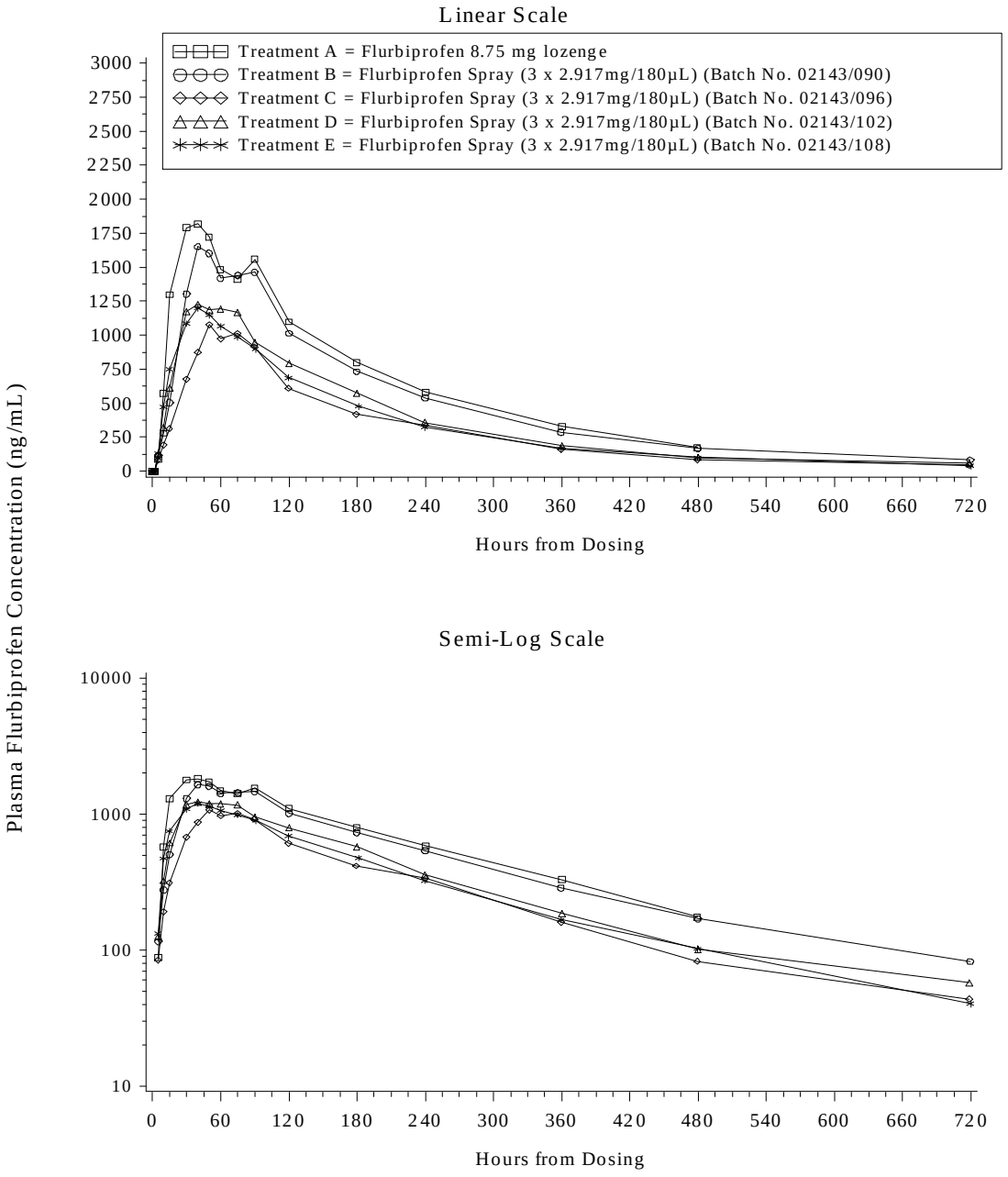

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Figure 14.4.4.12
Individual Plasma Flurbiprofen Concentrations Versus Time
Subject 12

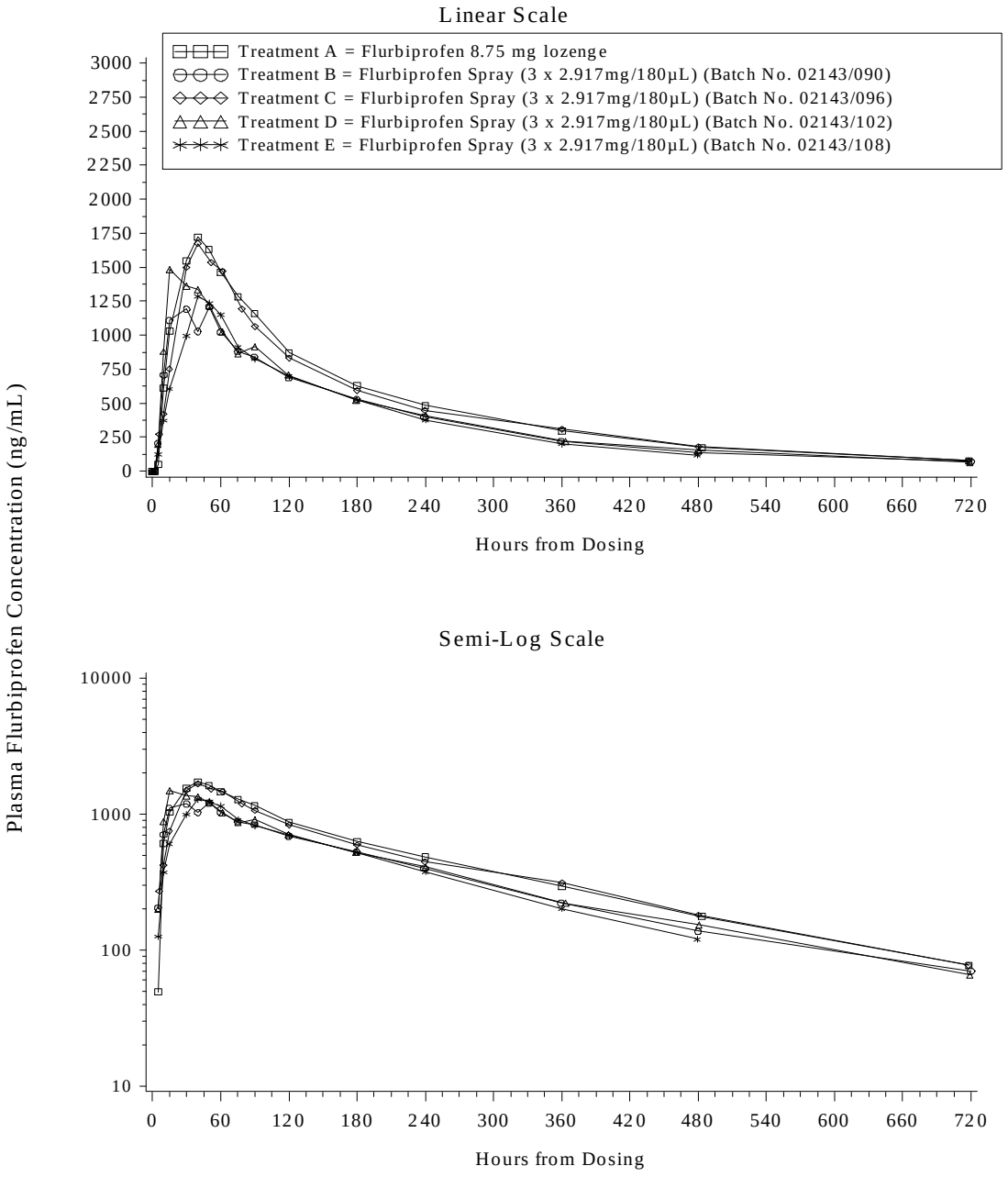

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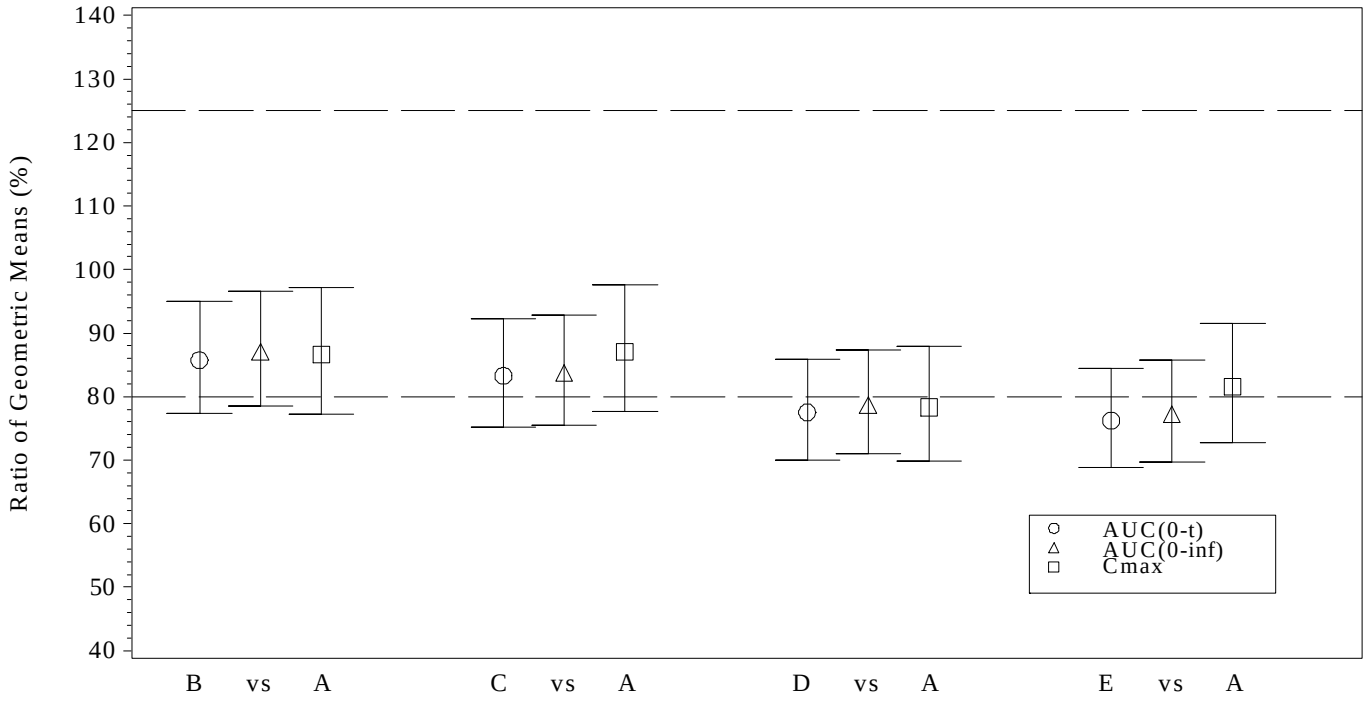
Figure 14.4.5.1
Geometric Mean Ratios (%) and 90% Confidence Intervals for AUC0-t, AUC0-inf and Cmax for Treatment B Versus Treatment A, Treatment C Versus Treatment A, Treatment D Versus Treatment A and Treatment E Versus Treatment A for Flurbiprofen (Spray versus Lozenge Comparisons)



Celerion Project AA92722
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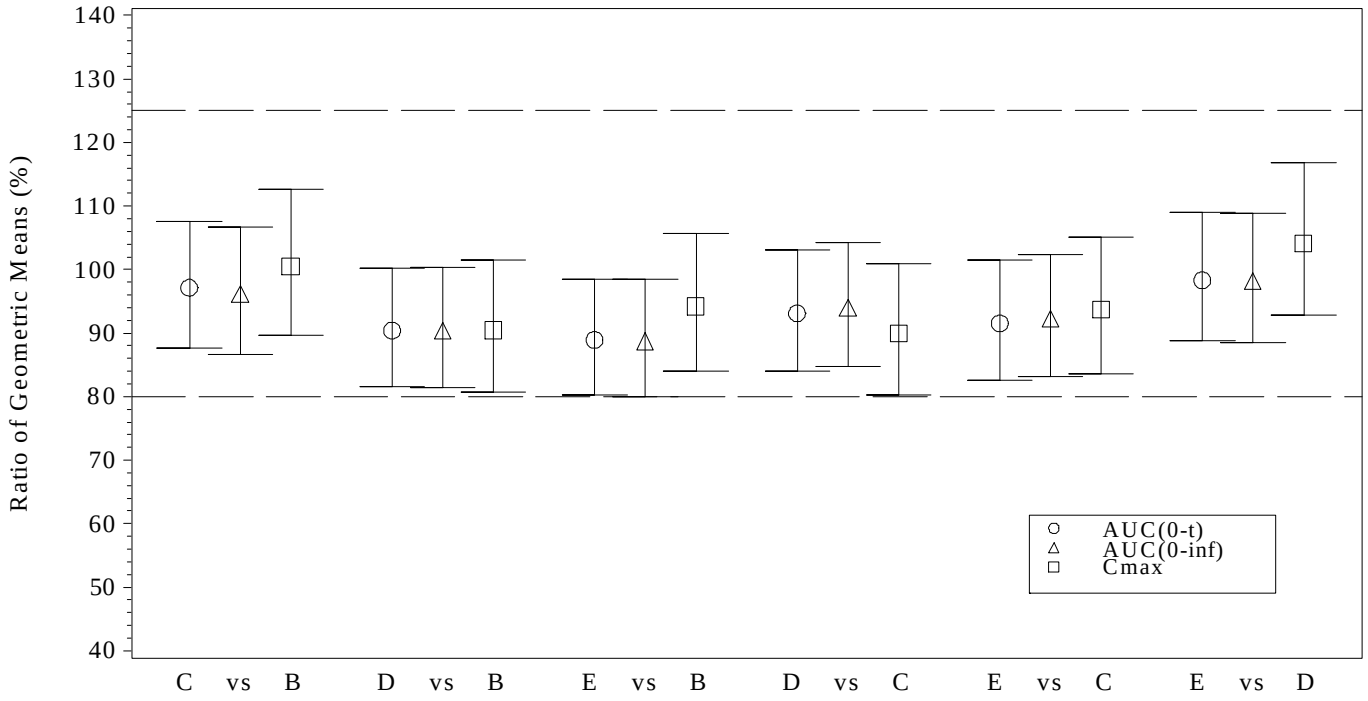
Figure 14.4.5.2
Geometric Mean Ratios (%) and 90% Confidence Intervals for AUC0-t, AUC0-inf and Cmax for Treatment C Versus Treatment B, Treatment D Versus Treatment B, Treatment E Versus Treatment B Treatment D Versus Treatment C, Treatment E Versus Treatment C and Treatment E Versus Treatment D for Flurbiprofen (Spray versus Spray Comparisons)



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Program: /AA92722/ECR/sas_prg/pksas ratiograph2.sas 14APR2011 16:36

15 REFERENCE LIST

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