Sponsor Novartis
Generic Drug Name SAF312
Therapeutic Area of Trial Postoperative dental pain patients
Approved Indication Investigational
Protocol Number CSAF312A2103
Title A double-blind, randomized, single dose, placebo-controlled, three part study to evaluate the safety and tolerability of SAF312 in postoperative dental pain patients (Part A), to evaluate the analgesic effect of SAF312 in comparison to placebo in the treatment of postoperative dental pain using ibuprofen as a positive control (Part B) and to evaluate a dose response (Part C).
Phase of Development IIa/IIb
Study Start/End Dates 29-Sep-2009 to 31-May-2011
Study Design/Methodology A double-blind, randomized, single dose, placebo controlled, three part study to evaluate the safety and tolerability of SAF312 in postoperative dental pain patients (Part A), to evaluate the analgesic effect of SAF312 in comparison to placebo in the treatment of postoperative dental pain using ibuprofen as a positive control (Part B) and to evaluate a dose response (Part C).
Centres Single centre: United States
Publication NA

Outcome measures

Primary outcome measures

- The primary efficacy measure was summed pain intensity difference [SPID(0-6)] from 0 to 6 hours.

Secondary outcome measures

- Time-specific PID and pain relief (PR) based on the categorical scale and PID based on the visual analog scale (VAS) at different time intervals up to 24 hours post dose.
- Total Pain Relief (TOTPAR) scores from 0 to 24 hours.
- Time to onset of analgesia, time to rescue medication intake, proportion of patients requiring rescue medication in the first six (6) hours, and patient global evaluation.
- Safety and tolerability assessments consisted mainly of vital signs, body temperature, thermal perception (Part C only), ECG evaluation, cardiac Holter monitoring (Part A only), and collecting all adverse events (AEs).
- The following PK parameters were determined using non-compartmental analysis from the plasma concentration-time data of SAF312 and ibuprofen (for Part A and Part B only): AUCinf, AUClast, Cmax, Tmax, Lambda z and T1/2.

Test Product (s), Dose(s), and Mode(s) of Administration

Test drug, ibuprofen and placebo were administered orally as a single dose in the form of hard gelatin capsules (SAF312: 2.5 mg, 10 mg, 25 mg and 100 mg; Ibuprofen 200 mg).

Statistical Methods

All data for background and demographic variables, relevant medical history/current medical conditions and teeth extraction record, safety and tolerability variables were listed by treatment group and patient, and summarized in a descriptive manner based on the safety population. Descriptive statistics (including geometric mean) were provided for the PK parameters.

Summaries of PID(-categorical), PR and VAS were presented. TOTPAR and SPID(0-6) were calculated as the area under the PR or PID curves over time, respectively, standardized by the time range. For patients that drop out or take the rescue medication after the first 90 minutes, the LOCF was applied. The primary analysis, was performed at the final analysis of study part B (and including data from study part A), following Bayesian approach, assessing the efficacy of single doses of SAF312 (high dose and ¼ of the high dose) as compared to placebo, measured by the SPID(0-6). In addition, ANCOVA models were fitted separately to TOTPAR, SPID(0-6) and the VAS data, including treatment/dose and number of removed teeth as factors, and the baseline PR, PI or VAS value, respectively, as a covariate. Cochran-Mantel-Haenszel tests were used for PID (each time point), PR (each time point), adjusting for number of teeth removed. Treatment group comparisons were made for each active treatment and dose against placebo.
The median time to onset of analgesia, to meaningful pain relief and to use of rescue medication was estimated using the Kaplan-Meier product limit method, and each active drug and dose were compared to placebo using the log-rank test. Patient global evaluation was summarized by treatment group and comparisons to placebo was performed using Cochran-Mantel-Haenszel tests, adjusting for the number of teeth removed. The proportion of patients requiring rescue medication in the first 6 hours was analyzed analogously. No adjustments for multiplicity were made in any of the secondary analyses.
In part C, patients were allocated to different doses using the optimization algorithm proposed by depending on the observations from parts A and B in order to maximize the dose-response information obtained in this part. Parts A, B and C were pooled for the estimation of dose-

response and the minimal effective dose.

Study Population: Inclusion/Exclusion Criteria and Demographics

This study was conducted in male and female (WONCBP) patients aged 18 – 45 years, in good health as determined by past medical history, physical examination, vital signs, electrocardiogram and laboratory tests at screening. The key main criteria for inclusion included extraction of two or more impacted third molars (at least one of the mandibular) with a moderate to severe post-surgical pain intensity. Key exclusion criteria included history of hypersensitivity to analgesics, use of antipyretic/analgesic drugs from 48 hrs pre-dose to 24 hrs post-dose, unless initiated by the Investigator, presence/ history of, or family history of malignant hyperthermia or anesthesia-related events, and abnormal ECG.

Participant Flow

Table 10-1 Subject disposition – n (%) of subjects

Category	Placebo N=37 n (%)	SAF312 7.5 mg N=31 n (%)	SAF312 15 mg N=15 n (%)	SAF312 25 mg N=16 n (%)	SAF312 50 mg N=30 n (%)	SAF312 200 mg N=30 n (%)	SAF312 600 mg N=16 n (%)	Ibuprofen 400 mg N=28 n (%)
Completed	35 (94.6)	31 (100.0)	14 (93.3)	14 (87.5)	29 (96.7)	28 (93.3)	16 (100.0)	26 (92.9)
Discontinued from study	2 (5.4)	0 (0.0)	1 (6.7)	2 (12.5)	1 (3.3)	2 (6.7)	0 (0.0)	2 (7.1)
Primary reason for study discontinuation:								
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	2 (5.4)	0 (0.0)	1 (6.7)	2 (12.5)	1 (3.3)	2 (6.7)	0 (0.0)	2 (7.1)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

Table 11-2 Baseline demographic characteristics

Category	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28	Total N=203
Age (years)									
n	37	31	15	16	30	30	16	28	203
Missing	0	0	0	0	0	0	0	0	0
Mean (SD)	19.4 (2.07)	19.0 (1.52)	18.7 (1.10)	19.6 (1.90)	20.0 (3.59)	19.6 (2.55)	19.5 (3.08)	19.9 (3.24)	19.5 (2.55)
Minimum	18	18	18	18	18	18	18	18	18
Median	19.0	18.0	18.0	19.0	18.0	18.0	18.0	19.0	18.0
Maximum	26	24	21	24	32	27	28	34	34
Weight (kg)									
n	37	31	15	16	30	30	16	28	203
Missing	0	0	0	0	0	0	0	0	0
Mean (SD)	74.54 (9.099)	74.86 (9.261)	69.65 (9.573)	70.88 (9.935)	77.43 (9.813)	76.12 (9.992)	71.97 (7.356)	75.94 (9.870)	74.59 (9.572)
Minimum	59.5	59.1	56.8	56.4	60.9	58.2	62.0	62.3	56.4
Median	72.70	72.30	65.00	70.40	76.40	76.40	72.05	73.65	73.60
Maximum	97.3	92.3	85.3	90.9	99.5	100.5	87.7	97.1	100.5
Height (cm)									
n	37	31	15	16	30	30	16	28	203
Missing	0	0	0	0	0	0	0	0	0
Mean (SD)	177.7 (7.66)	177.8 (6.40)	171.1 (6.25)	175.0 (4.93)	179.3 (4.64)	178.5 (6.82)	178.4 (5.06)	178.9 (8.61)	177.6 (6.87)
Minimum	166	167	162	168	171	165	173	165	162
Median	178.0	178.0	173.0	175.0	180.0	178.5	177.5	178.0	178.0
Maximum	200	193	180	183	189	196	188	196	200

Note: BMI [kg/m2] = weight[kg]/(height[m]**2)

Table 11-2 Baseline demographic characteristics

Category	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28	Total N=203
BMI (kg/m2)									
n	37	31	15	16	30	30	16	28	203
Missing	0	0	0	0	0	0	0	0	0
Mean (SD)	23.61 (2.523)	23.71 (2.853)	23.79 (2.918)	23.10 (2.692)	24.05 (2.651)	23.85 (2.499)	22.64 (2.350)	23.82 (3.345)	23.65 (2.725)
Minimum	19.1	18.7	20.5	19.7	20.0	18.0	19.7	18.5	18.0
Median	23.52	22.96	23.03	23.96	23.77	23.95	22.31	22.86	23.31
Maximum	29.2	29.7	29.2	27.1	30.3	29.4	28.1	30.3	30.3
Sex, n (%)									
Male	37 (100.0)	31 (100.0)	15 (100.0)	16 (100.0)	30 (100.0)	30 (100.0)	16 (100.0)	28 (100.0)	203 (100.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Predominant race, n (%)									
Caucasian	33 (89.2)	30 (96.8)	13 (86.7)	15 (93.8)	28 (93.3)	27 (90.0)	16 (100.0)	25 (89.3)	187 (92.1)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	2 (7.1)	3 (1.5)
Asian	2 (5.4)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	4 (2.0)
Native american	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	1 (0.5)
Pacific islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Other	2 (5.4)	1 (3.2)	1 (6.7)	1 (6.3)	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.6)	7 (3.4)

Note: BMI [kg/m2] = weight[kg]/(height[m]**2)

Table 11-2 Baseline demographic characteristics

Category	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28	Total N=203
Ethnicity, n (%)									
Hispanic/Latino	5 (13.5)	2 (6.5)	2 (13.3)	1 (6.3)	1 (3.3)	1 (3.3)	0 (0.0)	1 (3.6)	13 (6.4)
Chinese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Indian (Indian subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	1 (2.7)	1 (3.2)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
Mixed Ethnicity	2 (5.4)	3 (9.7)	0 (0.0)	1 (6.3)	0 (0.0)	1 (3.3)	0 (0.0)	1 (3.6)	8 (3.9)
Other	29 (78.4)	25 (80.6)	12 (80.0)	14 (87.5)	29 (96.7)	28 (93.3)	16 (100.0)	26 (92.9)	179 (88.2)
Pain intensity, n (%)									
None/absent/not present	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate	22 (59.5)	15 (48.4)	8 (53.3)	4 (25.0)	21 (70.0)	24 (80.0)	8 (50.0)	17 (60.7)	119 (58.6)
Severe	15 (40.5)	16 (51.6)	7 (46.7)	12 (75.0)	9 (30.0)	6 (20.0)	8 (50.0)	11 (39.3)	84 (41.4)

Note: BMI [kg/m2] = weight[kg]/(height[m]**2)

Outcome measures

Primary Outcome Results

Table 11-4 Summary of SPID(0-6)[1]

Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
n	37	31	15	16	30	30	16	28
Mean (SD)	0.23 (0.558)	0.39 (0.717)	0.72 (0.758)	0.67 (0.690)	0.56 (0.671)	0.50 (0.522)	0.76 (0.637)	1.36 (0.729)
Minimum	-0.9	-0.9	-0.9	0.0	-0.9	-0.9	0.0	0.0
Median	0.00	0.10	0.81	0.65	0.71	0.59	0.85	1.34
Maximum	1.4	2.1	2.4	2.0	1.8	1.9	1.9	2.7
95% CI [2]		(-0.152, 0.463)	(0.076, 0.837)	(-0.084, 0.674)	(0.057, 0.671)	(0.022, 0.637)	(0.109, 0.853)	(0.826, 1.448)
P-value[2]		0.319	0.019	0.127	0.020	0.036	0.011	<0.001

For subjects that drop out or take the rescue medication (including Tylenol) after the first 90 minutes of treatment, the last observation was carried forward (LOCF).
[1] SPID(0-6): time-weighted sum of the PID (pain intensity difference)-categorical scores from 0 to 6 hours
[2] P-values for the difference to placebo are from ANCOVA model including treatment/dose and number of removed teeth as factors, and the baseline PI value as a covariate, comparing each treatment/dose against placebo. 95% confidence intervals are based on the least-squared differences from the ANCOVA between each treatment/dose and placebo.

Table 11-5 Estimated response SPID(0-6) based on the selected model

Dose levels	Mean of SPID(0-6)	Estimated response	S.E.	90% CI
0 mg (Placebo)	0.234	0.229	0.1052	(0.056, 0.402)
7.5 mg	0.391	0.474	0.0978	(0.313, 0.635)
15 mg	0.719	0.530	0.0703	(0.415, 0.646)
25 mg	0.669	0.561	0.0573	(0.467, 0.656)
50 mg	0.558	0.589	0.0596	(0.491, 0.687)
200 mg	0.497	0.613	0.0773	(0.486, 0.740)
600 mg	0.758	0.619	0.0834	(0.482, 0.756)

1. Time-weighted sum of the PID (pain intensity difference)-categorical scores from 0 to 6 hours, SPID(0-6), was considered as response.
2. For subjects that drop out or take the rescue medication (including Tylenol) after the first 90 minutes of treatment, the last observation was carried forward (LOCF).
3. The R package DoseFinding was used to obtain the estimated response of the selected model Emax.

Secondary Outcome Results

PID based on categorical scale / Summary of categorical time-specific pain intensity differences (PID)[1] at each time point

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.25hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)	1 (6.3)	0 (0.0)
	0	36 (97.3)	27 (87.1)	12 (80.0)	13 (81.3)	27 (90.0)	27 (90.0)	15 (93.8)	27 (96.4)
	1	1 (2.7)	3 (9.7)	3 (20.0)	3 (18.8)	1 (3.3)	2 (6.7)	0 (0.0)	1 (3.6)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	P-value [2]		0.446	0.029	0.067	0.322	0.438	0.252	0.855
TP/0.5hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	2 (5.4)	1 (3.2)	0 (0.0)	0 (0.0)	3 (10.0)	1 (3.3)	1 (6.3)	0 (0.0)
	0	31 (83.8)	26 (83.9)	10 (66.7)	10 (62.5)	20 (66.7)	20 (66.7)	9 (56.3)	20 (71.4)
	1	4 (10.8)	3 (9.7)	5 (33.3)	6 (37.5)	5 (16.7)	8 (26.7)	4 (25.0)	8 (28.6)
	2	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)	2 (12.5)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	P-value [2]		0.650	0.097	0.087	0.355	0.236	0.066	0.110

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.75hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	2 (5.4)	1 (3.2)	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)
	0	30 (81.1)	21 (67.7)	9 (60.0)	10 (62.5)	15 (50.0)	16 (53.3)	7 (43.8)	10 (35.7)
	1	5 (13.5)	8 (25.8)	5 (33.3)	6 (37.5)	10 (33.3)	12 (40.0)	6 (37.5)	12 (42.9)
	2	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	3 (10.0)	1 (3.3)	3 (18.8)	5 (17.9)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
	P-value [2]		0.509	0.087	0.148	0.053	0.059	0.004	<0.001
TP/1hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	1 (3.2)	1 (6.7)	0 (0.0)	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)
	0	27 (73.0)	19 (61.3)	5 (33.3)	10 (62.5)	16 (53.3)	14 (46.7)	4 (25.0)	6 (21.4)
	1	7 (18.9)	9 (29.0)	8 (53.3)	4 (25.0)	9 (30.0)	13 (43.3)	10 (62.5)	15 (53.6)
	2	0 (0.0)	2 (6.5)	0 (0.0)	2 (12.5)	3 (10.0)	2 (6.7)	2 (12.5)	6 (21.4)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
	P-value [2]		0.337	0.020	0.197	0.148	0.051	<0.001	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/1.5hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	2 (6.7)	1 (6.7)	0 (0.0)	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)
	0	27 (73.0)	18 (60.0)	3 (20.0)	9 (56.3)	11 (36.7)	11 (36.7)	5 (31.3)	2 (7.1)
	1	7 (18.9)	9 (30.0)	9 (60.0)	3 (18.8)	13 (43.3)	17 (56.7)	8 (50.0)	14 (50.0)
	2	0 (0.0)	1 (3.3)	1 (6.7)	4 (25.0)	4 (13.3)	1 (3.3)	3 (18.8)	7 (25.0)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.9)
	P-value [2]		0.595	0.003	0.035	0.008	0.010	0.002	<0.001
TP/2hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	2 (6.5)	1 (6.7)	0 (0.0)	3 (10.0)	1 (3.3)	0 (0.0)	0 (0.0)
	0	24 (64.9)	19 (61.3)	3 (20.0)	7 (43.8)	9 (30.0)	13 (43.3)	5 (31.3)	1 (3.6)
	1	9 (24.3)	6 (19.4)	8 (53.3)	4 (25.0)	16 (53.3)	14 (46.7)	8 (50.0)	12 (42.9)
	2	1 (2.7)	4 (12.9)	2 (13.3)	5 (31.3)	2 (6.7)	2 (6.7)	3 (18.8)	11 (39.3)
	3	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.3)
	P-value [2]		0.486	0.020	0.039	0.041	0.226	0.022	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/3hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	2 (6.5)	1 (6.7)	0 (0.0)	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)
	0	25 (67.6)	18 (58.1)	3 (20.0)	8 (50.0)	10 (33.3)	14 (46.7)	6 (37.5)	3 (10.7)
	1	8 (21.6)	8 (25.8)	9 (60.0)	5 (31.3)	14 (46.7)	14 (46.7)	7 (43.8)	8 (28.6)
	2	1 (2.7)	2 (6.5)	2 (13.3)	3 (18.8)	4 (13.3)	1 (3.3)	3 (18.8)	13 (46.4)
	3	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.3)
	P-value [2]		0.663	0.011	0.211	0.014	0.209	0.045	<0.001
TP/4hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
	0	21 (56.8)	15 (48.4)	5 (33.3)	7 (43.8)	10 (33.3)	13 (43.3)	6 (40.0)	3 (10.7)
	1	10 (27.0)	9 (29.0)	7 (46.7)	6 (37.5)	15 (50.0)	14 (46.7)	6 (40.0)	10 (35.7)
	2	3 (8.1)	3 (9.7)	2 (13.3)	3 (18.8)	3 (10.0)	1 (3.3)	3 (20.0)	11 (39.3)
	3	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.3)
	P-value [2]		0.805	0.455	0.485	0.290	0.384	0.333	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/5hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.9)	0 (0.0)	0 (0.0)
	0	21 (56.8)	16 (51.6)	4 (26.7)	8 (50.0)	10 (33.3)	10 (34.5)	6 (37.5)	5 (17.9)
	1	9 (24.3)	7 (22.6)	8 (53.3)	4 (25.0)	15 (50.0)	15 (51.7)	7 (43.8)	8 (28.6)
	2	4 (10.8)	4 (12.9)	1 (6.7)	3 (18.8)	2 (6.7)	2 (6.9)	3 (18.8)	10 (35.7)
	3	0 (0.0)	1 (3.2)	1 (6.7)	1 (6.3)	1 (3.3)	0 (0.0)	0 (0.0)	5 (17.9)
	P-value [2]		0.773	0.112	0.601	0.266	0.157	0.281	<0.001
TP/6hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
	0	21 (56.8)	17 (54.8)	4 (26.7)	9 (56.3)	11 (36.7)	10 (33.3)	6 (40.0)	7 (25.0)
	1	9 (24.3)	5 (16.1)	7 (46.7)	4 (25.0)	14 (46.7)	16 (53.3)	6 (40.0)	8 (28.6)
	2	4 (10.8)	5 (16.1)	3 (20.0)	2 (12.5)	2 (6.7)	2 (6.7)	3 (20.0)	8 (28.6)
	3	0 (0.0)	1 (3.2)	0 (0.0)	1 (6.3)	1 (3.3)	0 (0.0)	0 (0.0)	5 (17.9)
	P-value [2]		0.504	0.238	0.692	0.382	0.119	0.366	0.004

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/8hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
	0	20 (54.1)	16 (51.6)	4 (26.7)	9 (56.3)	9 (30.0)	10 (33.3)	6 (37.5)	7 (25.0)
	1	10 (27.0)	6 (19.4)	8 (53.3)	4 (25.0)	15 (50.0)	15 (50.0)	7 (43.8)	10 (35.7)
	2	4 (10.8)	5 (16.1)	2 (13.3)	3 (18.8)	3 (10.0)	3 (10.0)	3 (18.8)	5 (17.9)
	3	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	6 (21.4)
	P-value [2]		0.564	0.275	0.700	0.315	0.289	0.356	0.007
TP/10hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
	0	21 (56.8)	16 (51.6)	5 (33.3)	9 (56.3)	11 (36.7)	11 (36.7)	7 (43.8)	11 (39.3)
	1	10 (27.0)	6 (19.4)	7 (46.7)	3 (18.8)	12 (40.0)	14 (46.7)	6 (37.5)	9 (32.1)
	2	2 (5.4)	5 (16.1)	2 (13.3)	3 (18.8)	4 (13.3)	3 (10.0)	2 (12.5)	4 (14.3)
	3	1 (2.7)	1 (3.2)	0 (0.0)	1 (6.3)	1 (3.3)	0 (0.0)	1 (6.3)	4 (14.3)
	P-value [2]		0.540	0.287	0.422	0.440	0.322	0.565	0.092

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/12hr	Categorical PID, n(%)								
	-3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	-1	3 (8.1)	3 (9.7)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
	0	22 (59.5)	17 (54.8)	4 (26.7)	9 (56.3)	10 (33.3)	11 (36.7)	6 (37.5)	12 (42.9)
	1	9 (24.3)	5 (16.1)	8 (53.3)	4 (25.0)	12 (40.0)	13 (43.3)	7 (43.8)	8 (28.6)
	2	2 (5.4)	5 (16.1)	2 (13.3)	2 (12.5)	5 (16.7)	4 (13.3)	2 (12.5)	4 (14.3)
	3	1 (2.7)	1 (3.2)	0 (0.0)	1 (6.3)	1 (3.3)	0 (0.0)	1 (6.3)	4 (14.3)
	P-value [2]		0.544	0.149	0.716	0.216	0.228	0.337	0.098

PID based on the visual analog scale

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/0.25hr	n	37	31	15	16
	Mean (SD)	-0.1 (6.12)	1.3 (8.13)	5.4 (8.80)	3.0 (10.05)
	Minimum	-21	-15	-2	-11
	Median	0.0	-1.0	2.0	1.0
	Maximum	12	28	32	33
	95% CI [2]		(-2.08, 5.18)	(1.10, 10.06)	(-1.54, 7.31)
	P-value [2]		0.401	0.015	0.201
TP/0.5hr	n	37	31	15	16
	Mean (SD)	3.0 (14.43)	3.0 (12.56)	8.8 (14.17)	7.1 (13.07)
	Minimum	-23	-18	-10	-8
	Median	1.0	1.0	8.0	2.0
	Maximum	45	44	49	40
	95% CI [2]		(-7.04, 8.59)	(-3.72, 15.58)	(-6.10, 12.96)
	P-value [2]		0.846	0.227	0.479

Note: For subjects that drop out or take the rescue medication (including Tylenol) after the first 90 minutes of treatment, the last observation was carried forward (LOCF).
[1] VAS pain intensity (PI) scale: 0-100 (No pain - Worst imaginable pain). PID at a certain time point is defined as the PI at predose minus the PI at this timepoint.
[2] P-values for the difference to placebo are from ANCOVA model including treatment/dose and number of removed teeth as factors, and the baseline PI value as a covariate, comparing each treatment/dose against placebo. 95% confidence intervals are based on the least-squared differences from the ANCOVA between each treatment/dose and placebo.

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.25hr	n	30	30	16	28
	Mean (SD)	-0.2 (7.19)	0.5 (8.84)	-1.1 (5.48)	0.6 (4.42)
	Minimum	-21	-20	-12	-8
	Median	0.0	2.0	-1.0	1.0
	Maximum	21	29	10	12
	95% CI [2]	(-3.69, 3.52)	(-2.86, 4.37)	(-5.45, 3.31)	(-2.97, 4.36)
	P-value [2]	0.963	0.681	0.630	0.709
TP/0.5hr	n	30	30	16	28
	Mean (SD)	9.4 (19.71)	9.5 (17.42)	16.1 (25.31)	7.4 (10.01)
	Minimum	-21	-17	-10	-7
	Median	5.5	5.0	13.5	4.5
	Maximum	70	58	80	28
	95% CI [2]	(-1.34, 14.20)	(-1.03, 14.53)	(3.51, 22.37)	(-3.40, 12.39)
	P-value [2]	0.104	0.089	0.007	0.263

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/0.75hr	n	37	31	15	16
	Mean (SD)	3.9 (16.58)	9.8 (16.40)	18.6 (22.00)	9.9 (16.38)
	Minimum	-23	-15	-4	-13
	Median	1.0	6.0	15.0	5.5
	Maximum	51	65	75	48
	95% CI [2]		(-3.36, 15.92)	(2.97, 26.79)	(-6.58, 16.95)
	P-value [2]		0.201	0.015	0.386
TP/1hr	n	37	31	15	16
	Mean (SD)	5.4 (19.79)	13.1 (19.58)	19.9 (21.41)	17.1 (25.45)
	Minimum	-28	-15	-14	-11
	Median	1.0	9.0	20.0	8.5
	Maximum	71	70	75	67
	95% CI [2]		(-2.28, 19.13)	(1.31, 27.75)	(-2.43, 23.69)
	P-value [2]		0.122	0.031	0.110

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.75hr	n	30	30	16	28
	Mean (SD)	15.6 (21.32)	14.9 (18.65)	24.2 (25.27)	29.6 (22.74)
	Minimum	-23	-24	-11	-2
	Median	13.5	12.5	22.0	26.0
	Maximum	69	58	89	90
	95% CI [2]	(2.14, 21.32)	(1.77, 20.98)	(8.43, 31.70)	(15.90, 35.38)
	P-value [2]	0.017	0.020	<0.001	<0.001
TP/1hr	n	30	30	16	28
	Mean (SD)	19.3 (21.05)	18.2 (20.49)	29.4 (25.28)	40.6 (24.87)
	Minimum	-24	-22	0	0
	Median	16.5	14.0	28.0	39.5
	Maximum	57	66	90	91
	95% CI [2]	(3.38, 24.68)	(2.31, 23.63)	(10.77, 36.61)	(24.47, 46.11)
	P-value [2]	0.010	0.017	<0.001	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/1.5hr	n	37	30	15	16
	Mean (SD)	7.9 (21.70)	10.9 (17.99)	24.3 (21.95)	23.1 (30.81)
	Minimum	-28	-15	-15	-14
	Median	2.0	9.5	27.0	10.0
	Maximum	76	60	74	85
	95% CI [2]		(-7.09, 16.06)	(1.99, 30.27)	(-0.20, 27.74)
	P-value [2]		0.446	0.026	0.053
TP/2hr	n	37	31	15	16
	Mean (SD)	10.1 (22.93)	14.6 (23.88)	27.9 (25.03)	26.8 (30.92)
	Minimum	-28	-16	-15	-19
	Median	5.0	6.0	32.0	20.0
	Maximum	81	66	76	83
	95% CI [2]		(-6.55, 17.94)	(2.45, 32.69)	(0.08, 29.96)
	P-value [2]		0.360	0.023	0.049

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/1.5hr	n	30	30	16	28
	Mean (SD)	24.0 (23.97)	22.2 (20.70)	31.1 (27.54)	53.5 (26.46)
	Minimum	-24	-19	-8	-3
	Median	22.0	25.5	30.5	60.0
	Maximum	58	58	86	99
	95% CI [2]	(5.23, 28.00)	(2.88, 25.69)	(8.88, 36.51)	(34.38, 57.52)
	P-value [2]	0.004	0.014	0.001	<0.001
TP/2hr	n	30	30	16	28
	Mean (SD)	24.0 (28.08)	21.1 (23.64)	29.1 (25.05)	59.3 (23.31)
	Minimum	-24	-20	-10	-8
	Median	26.0	20.5	29.5	65.5
	Maximum	64	67	72	99
	95% CI [2]	(2.29, 26.65)	(-1.08, 23.31)	(3.64, 33.19)	(37.10, 61.85)
	P-value [2]	0.020	0.074	0.015	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/3hr	n	37	31	15	16
	Mean (SD)	10.1 (23.66)	16.6 (26.08)	24.1 (22.02)	22.7 (27.50)
	Minimum	-28	-14	-15	-19
	Median	5.0	6.0	27.0	17.0
	Maximum	69	81	68	85
	95% CI [2]		(-5.04, 19.60)	(-1.21, 29.22)	(-4.56, 25.50)
	P-value [2]		0.245	0.071	0.171
TP/4hr	n	37	31	15	16
	Mean (SD)	12.7 (26.42)	17.7 (28.75)	21.7 (21.81)	22.8 (28.11)
	Minimum	-28	-30	-15	-19
	Median	5.0	6.0	20.0	17.5
	Maximum	73	81	58	85
	95% CI [2]		(-7.33, 18.90)	(-6.98, 25.39)	(-7.72, 24.27)
	P-value [2]		0.385	0.263	0.309

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/3hr	n	30	30	16	28
	Mean (SD)	26.3 (26.93)	19.3 (25.89)	28.7 (24.90)	58.1 (24.71)
	Minimum	-24	-20	-10	-23
	Median	25.0	23.5	27.5	61.0
	Maximum	67	68	72	100
	95% CI [2]	(4.50, 29.01)	(-2.45, 22.09)	(3.10, 32.84)	(35.75, 60.65)
	P-value [2]	0.008	0.116	0.018	<0.001
TP/4hr	n	30	30	15	28
	Mean (SD)	24.6 (26.91)	18.5 (27.45)	28.3 (26.00)	54.9 (27.00)
	Minimum	-24	-31	-10	-23
	Median	26.0	24.5	29.0	56.5
	Maximum	68	71	73	99
	95% CI [2]	(-0.97, 25.11)	(-6.70, 19.42)	(-1.20, 31.19)	(28.96, 55.46)
	P-value [2]	0.069	0.338	0.069	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/5hr	n	37	31	15	16
	Mean (SD)	15.1 (29.41)	19.6 (31.53)	26.0 (24.91)	22.8 (31.27)
	Minimum	-28	-29	-15	-19
	Median	5.0	7.0	24.0	12.0
	Maximum	76	81	74	95
	95% CI [2]		(-8.73, 19.76)	(-6.41, 28.76)	(-11.79, 22.96)
	P-value [2]		0.446	0.212	0.527
TP/6hr	n	37	31	15	16
	Mean (SD)	15.2 (29.66)	18.5 (30.75)	25.1 (23.37)	22.2 (31.39)
	Minimum	-28	-29	-15	-19
	Median	5.0	6.0	31.0	7.0
	Maximum	78	82	65	94
	95% CI [2]		(-10.37, 18.76)	(-7.87, 28.10)	(-12.38, 23.15)
	P-value [2]		0.571	0.269	0.551

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/5hr	n	30	29	16	28
	Mean (SD)	25.8 (27.88)	21.0 (30.23)	30.1 (27.02)	54.5 (29.41)
	Minimum	-24	-31	-10	-23
	Median	26.0	24.0	31.5	59.0
	Maximum	84	77	74	100
	95% CI [2]	(-3.27, 25.06)	(-7.70, 20.93)	(-2.72, 31.65)	(25.03, 53.81)
	P-value [2]	0.131	0.363	0.099	<0.001
TP/6hr	n	30	30	15	28
	Mean (SD)	25.6 (28.49)	22.3 (30.31)	30.3 (27.21)	49.6 (32.84)
	Minimum	-24	-31	-10	-23
	Median	25.0	26.0	41.0	55.0
	Maximum	83	75	71	99
	95% CI [2]	(-3.95, 25.02)	(-6.90, 22.11)	(-3.36, 32.61)	(19.75, 49.19)
	P-value [2]	0.153	0.302	0.110	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/8hr	n	37	31	15	16
	Mean (SD)	17.3 (31.52)	17.8 (30.15)	27.1 (24.74)	19.5 (27.62)
	Minimum	-28	-29	-15	-19
	Median	5.0	5.0	36.0	6.5
	Maximum	84	79	67	75
	95% CI [2]		(-13.77, 16.20)	(-8.38, 28.62)	(-17.71, 18.85)
	P-value [2]		0.873	0.282	0.951
TP/10hr	n	37	31	15	16
	Mean (SD)	16.2 (30.79)	20.1 (31.06)	26.1 (24.68)	20.5 (30.63)
	Minimum	-28	-29	-15	-19
	Median	5.0	6.0	21.0	8.0
	Maximum	81	77	63	94
	95% CI [2]		(-10.39, 20.21)	(-8.90, 28.88)	(-15.18, 22.14)
	P-value [2]		0.527	0.298	0.713

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/8hr	n	30	30	16	28
	Mean (SD)	28.6 (30.02)	21.8 (30.61)	30.9 (27.52)	45.2 (36.42)
	Minimum	-24	-31	-10	-23
	Median	31.5	24.5	30.5	51.0
	Maximum	83	73	70	99
	95% CI [2]	(-3.42, 26.38)	(-9.65, 20.20)	(-4.83, 31.33)	(12.75, 43.03)
	P-value [2]	0.130	0.487	0.150	<0.001
TP/10hr	n	30	30	16	28
	Mean (SD)	28.8 (31.08)	21.8 (31.67)	31.3 (28.50)	33.6 (35.64)
	Minimum	-24	-31	-10	-25
	Median	27.0	24.5	31.5	34.0
	Maximum	83	75	82	99
	95% CI [2]	(-2.66, 27.77)	(-9.51, 20.96)	(-3.61, 33.31)	(2.02, 32.94)
	P-value [2]	0.105	0.460	0.114	0.027

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
TP/12hr	n	37	31	15	16
	Mean (SD)	16.1 (31.12)	19.3 (31.95)	27.3 (24.94)	19.4 (29.94)
	Minimum	-28	-29	-15	-19
	Median	5.0	6.0	32.0	8.0
	Maximum	80	80	69	95
	95% CI [2]		(-10.87, 19.98)	(-7.93, 30.17)	(-16.50, 21.13)
	P-value [2]		0.561	0.251	0.809
TP/24hr	n	37	31	15	16
	Mean (SD)	17.6 (33.54)	19.4 (32.96)	32.1 (30.25)	20.9 (31.81)
	Minimum	-28	-29	-15	-19
	Median	3.0	5.0	34.0	8.0
	Maximum	83	81	78	94
	95% CI [2]		(-12.61, 20.79)	(-6.32, 34.92)	(-18.07, 22.68)
	P-value [2]		0.630	0.173	0.824

Timepoint	Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/12hr	n	30	30	16	28
	Mean (SD)	30.4 (31.79)	22.3 (31.88)	33.8 (29.85)	30.6 (34.98)
	Minimum	-24	-31	-10	-25
	Median	33.5	24.5	38.0	34.0
	Maximum	83	71	82	99
	95% CI [2]	(-1.04, 29.64)	(-9.15, 21.58)	(-1.29, 35.94)	(-0.92, 30.26)
	P-value [2]	0.068	0.426	0.068	0.065
TP/24hr	n	30	30	16	28
	Mean (SD)	32.2 (32.98)	25.0 (35.24)	42.1 (32.95)	29.6 (39.50)
	Minimum	-24	-31	-10	-27
	Median	36.5	24.5	54.0	26.0
	Maximum	83	84	82	99
	95% CI [2]	(-1.83, 31.39)	(-9.64, 23.63)	(3.90, 44.21)	(-4.48, 29.28)
	P-value [2]	0.081	0.408	0.020	0.149

Summary of categorical time-specific pain relief (PR) at each timepoint

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.25hr	Categorical								
	PR scale, n(%)								
	None	32 (86.5)	26 (83.9)	8 (53.3)	12 (75.0)	27 (90.0)	26 (86.7)	15 (93.8)	25 (89.3)
	A little	4 (10.8)	5 (16.1)	7 (46.7)	3 (18.8)	3 (10.0)	4 (13.3)	1 (6.3)	3 (10.7)
	Moderate	1 (2.7)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	A lot	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	P-value [1]		0.640	0.010	0.593	0.619	0.646	0.706	0.676
TP/0.5hr	Categorical								
	PR scale, n(%)								
	None	26 (70.3)	20 (64.5)	7 (46.7)	8 (50.0)	16 (53.3)	13 (43.3)	6 (37.5)	12 (42.9)
	A little	8 (21.6)	9 (29.0)	5 (33.3)	7 (43.8)	10 (33.3)	13 (43.3)	7 (43.8)	15 (53.6)
	Moderate	3 (8.1)	2 (6.5)	2 (13.3)	0 (0.0)	1 (3.3)	3 (10.0)	2 (12.5)	1 (3.6)
	A lot	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.3)	2 (6.7)	0 (0.0)	1 (6.3)	0 (0.0)
	Complete	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)
	P-value [1]		0.815	0.205	0.176	0.280	0.143	0.079	0.033

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/0.75hr	Categorical								
	PR scale, n(%)								
	None	23 (62.2)	14 (45.2)	6 (40.0)	9 (56.3)	10 (33.3)	8 (26.7)	3 (18.8)	2 (7.1)
	A little	10 (27.0)	11 (35.5)	5 (33.3)	6 (37.5)	9 (30.0)	14 (46.7)	6 (37.5)	10 (35.7)
	Moderate	2 (5.4)	6 (19.4)	2 (13.3)	0 (0.0)	7 (23.3)	5 (16.7)	5 (31.3)	11 (39.3)
	A lot	2 (5.4)	0 (0.0)	1 (6.7)	1 (6.3)	3 (10.0)	2 (6.7)	2 (12.5)	5 (17.9)
	Complete	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)
	P-value [1]		0.187	0.293	0.717	0.143	0.057	0.008	<0.001
TP/1hr	Categorical								
	PR scale, n(%)								
	None	20 (54.1)	11 (35.5)	4 (26.7)	8 (50.0)	7 (23.3)	6 (20.0)	1 (6.3)	1 (3.6)
	A little	13 (35.1)	14 (45.2)	5 (33.3)	3 (18.8)	11 (36.7)	12 (40.0)	7 (43.8)	6 (21.4)
	Moderate	2 (5.4)	3 (9.7)	4 (26.7)	4 (25.0)	7 (23.3)	7 (23.3)	4 (25.0)	7 (25.0)
	A lot	2 (5.4)	3 (9.7)	1 (6.7)	1 (6.3)	3 (10.0)	3 (10.0)	4 (25.0)	13 (46.4)
	Complete	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	2 (6.7)	2 (6.7)	0 (0.0)	1 (3.6)
	P-value [1]		0.435	0.055	0.237	0.055	0.027	0.003	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/1.5hr	Categorical								
	PR scale, n(%)								
	None	20 (54.1)	11 (36.7)	4 (26.7)	8 (50.0)	7 (23.3)	6 (20.0)	4 (25.0)	1 (3.6)
	A little	12 (32.4)	14 (46.7)	2 (13.3)	2 (12.5)	6 (20.0)	9 (30.0)	3 (18.8)	3 (10.7)
	Moderate	3 (8.1)	4 (13.3)	6 (40.0)	2 (12.5)	11 (36.7)	9 (30.0)	4 (25.0)	5 (17.9)
	A lot	2 (5.4)	1 (3.3)	2 (13.3)	3 (18.8)	4 (13.3)	5 (16.7)	5 (31.3)	11 (39.3)
	Complete	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.3)	2 (6.7)	1 (3.3)	0 (0.0)	8 (28.6)
	P-value [1]		0.265	0.013	0.317	0.012	0.021	0.011	<0.001
TP/2hr	Categorical								
	PR scale, n(%)								
	None	16 (43.2)	14 (45.2)	4 (26.7)	6 (37.5)	10 (33.3)	7 (23.3)	4 (25.0)	1 (3.6)
	A little	13 (35.1)	9 (29.0)	2 (13.3)	3 (18.8)	3 (10.0)	9 (30.0)	3 (18.8)	0 (0.0)
	Moderate	6 (16.2)	4 (12.9)	5 (33.3)	3 (18.8)	8 (26.7)	9 (30.0)	5 (31.3)	6 (21.4)
	A lot	1 (2.7)	4 (12.9)	3 (20.0)	3 (18.8)	9 (30.0)	4 (13.3)	4 (25.0)	11 (39.3)
	Complete	1 (2.7)	0 (0.0)	1 (6.7)	1 (6.3)	0 (0.0)	1 (3.3)	0 (0.0)	10 (35.7)
	P-value [1]		0.539	0.076	0.376	0.006	0.273	0.053	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/3hr	Categorical								
	PR scale, n(%)								
	None	19 (51.4)	14 (45.2)	5 (33.3)	6 (37.5)	8 (26.7)	9 (30.0)	4 (25.0)	1 (3.6)
	A little	13 (35.1)	7 (22.6)	3 (20.0)	4 (25.0)	6 (20.0)	7 (23.3)	3 (18.8)	1 (3.6)
	Moderate	1 (2.7)	6 (19.4)	2 (13.3)	3 (18.8)	7 (23.3)	8 (26.7)	6 (37.5)	3 (10.7)
	A lot	4 (10.8)	3 (9.7)	5 (33.3)	3 (18.8)	8 (26.7)	5 (16.7)	3 (18.8)	13 (46.4)
	Complete	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	10 (35.7)
	P-value [1]		0.187	0.101	0.170	0.012	0.035	0.006	<0.001
TP/4hr	Categorical								
	PR scale, n(%)								
	None	18 (48.6)	14 (45.2)	6 (40.0)	6 (37.5)	8 (26.7)	11 (36.7)	4 (26.7)	1 (3.6)
	A little	8 (21.6)	7 (22.6)	3 (20.0)	3 (18.8)	6 (20.0)	4 (13.3)	5 (33.3)	2 (7.1)
	Moderate	5 (13.5)	6 (19.4)	3 (20.0)	5 (31.3)	7 (23.3)	10 (33.3)	3 (20.0)	5 (17.9)
	A lot	6 (16.2)	3 (9.7)	3 (20.0)	2 (12.5)	9 (30.0)	4 (13.3)	3 (20.0)	9 (32.1)
	Complete	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	11 (39.3)
	P-value [1]		0.817	0.898	0.500	0.258	0.252	0.497	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/5hr	Categorical								
	PR scale, n(%)								
	None	18 (48.6)	14 (45.2)	5 (33.3)	7 (43.8)	8 (26.7)	11 (37.9)	4 (25.0)	2 (7.1)
	A little	6 (16.2)	7 (22.6)	2 (13.3)	2 (12.5)	6 (20.0)	3 (10.3)	2 (12.5)	1 (3.6)
	Moderate	6 (16.2)	4 (12.9)	4 (26.7)	4 (25.0)	7 (23.3)	7 (24.1)	4 (25.0)	6 (21.4)
	A lot	7 (18.9)	5 (16.1)	3 (20.0)	1 (6.3)	8 (26.7)	7 (24.1)	6 (37.5)	7 (25.0)
	Complete	0 (0.0)	1 (3.2)	1 (6.7)	2 (12.5)	1 (3.3)	1 (3.4)	0 (0.0)	12 (42.9)
	P-value [1]		0.654	0.414	0.309	0.456	0.606	0.317	<0.001
TP/6hr	Categorical								
	PR scale, n(%)								
	None	18 (48.6)	15 (48.4)	5 (33.3)	7 (43.8)	8 (26.7)	11 (36.7)	4 (26.7)	3 (10.7)
	A little	7 (18.9)	7 (22.6)	1 (6.7)	2 (12.5)	6 (20.0)	4 (13.3)	2 (13.3)	2 (7.1)
	Moderate	3 (8.1)	3 (9.7)	5 (33.3)	3 (18.8)	7 (23.3)	6 (20.0)	4 (26.7)	7 (25.0)
	A lot	9 (24.3)	3 (9.7)	3 (20.0)	3 (18.8)	8 (26.7)	8 (26.7)	5 (33.3)	4 (14.3)
	Complete	0 (0.0)	3 (9.7)	1 (6.7)	1 (6.3)	1 (3.3)	1 (3.3)	0 (0.0)	12 (42.9)
	P-value [1]		0.176	0.059	0.669	0.293	0.453	0.245	<0.001

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/8hr	Categorical								
	PR scale, n(%)								
	None	18 (48.6)	15 (48.4)	5 (33.3)	8 (50.0)	8 (26.7)	11 (36.7)	4 (25.0)	4 (14.3)
	A little	6 (16.2)	6 (19.4)	1 (6.7)	2 (12.5)	4 (13.3)	3 (10.0)	2 (12.5)	3 (10.7)
	Moderate	3 (8.1)	4 (12.9)	4 (26.7)	3 (18.8)	8 (26.7)	6 (20.0)	5 (31.3)	5 (17.9)
	A lot	10 (27.0)	3 (9.7)	5 (33.3)	2 (12.5)	8 (26.7)	8 (26.7)	5 (31.3)	6 (21.4)
	Complete	0 (0.0)	3 (9.7)	0 (0.0)	1 (6.3)	2 (6.7)	2 (6.7)	0 (0.0)	10 (35.7)
	P-value [1]		0.138	0.232	0.220	0.140	0.284	0.151	<0.001
TP/10hr	Categorical								
	PR scale, n(%)								
	None	18 (48.6)	15 (48.4)	5 (33.3)	8 (50.0)	8 (26.7)	12 (40.0)	4 (25.0)	5 (17.9)
	A little	7 (18.9)	5 (16.1)	2 (13.3)	3 (18.8)	5 (16.7)	3 (10.0)	2 (12.5)	6 (21.4)
	Moderate	2 (5.4)	3 (9.7)	2 (13.3)	2 (12.5)	7 (23.3)	6 (20.0)	5 (31.3)	4 (14.3)
	A lot	9 (24.3)	5 (16.1)	6 (40.0)	1 (6.3)	7 (23.3)	7 (23.3)	4 (25.0)	8 (28.6)
	Complete	1 (2.7)	3 (9.7)	0 (0.0)	2 (12.5)	3 (10.0)	2 (6.7)	1 (6.3)	5 (17.9)
	P-value [1]		0.453	0.405	0.476	0.074	0.361	0.131	0.049

Timepoint	Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
TP/12hr	Categorical PR scale, n(%)								
	None	18 (48.6)	15 (48.4)	5 (33.3)	8 (50.0)	8 (26.7)	12 (40.0)	4 (25.0)	7 (25.0)
	A little	7 (18.9)	6 (19.4)	1 (6.7)	3 (18.8)	5 (16.7)	2 (6.7)	2 (12.5)	5 (17.9)
	Moderate	3 (8.1)	2 (6.5)	4 (26.7)	2 (12.5)	4 (13.3)	6 (20.0)	4 (25.0)	4 (14.3)
	A lot	8 (21.6)	5 (16.1)	5 (33.3)	2 (12.5)	9 (30.0)	8 (26.7)	5 (31.3)	7 (25.0)
	Complete	1 (2.7)	3 (9.7)	0 (0.0)	1 (6.3)	4 (13.3)	2 (6.7)	1 (6.3)	5 (17.9)
	P-value [1]		0.507	0.260	0.932	0.150	0.361	0.336	0.132
TP/24hr	Categorical PR scale, n(%)								
	None	20 (54.1)	16 (51.6)	5 (33.3)	8 (50.0)	8 (26.7)	12 (40.0)	4 (25.0)	9 (32.1)
	A little	6 (16.2)	5 (16.1)	1 (6.7)	3 (18.8)	6 (20.0)	3 (10.0)	2 (12.5)	4 (14.3)
	Moderate	3 (8.1)	1 (3.2)	2 (13.3)	1 (6.3)	4 (13.3)	4 (13.3)	1 (6.3)	4 (14.3)
	A lot	1 (2.7)	4 (12.9)	4 (26.7)	1 (6.3)	6 (20.0)	6 (20.0)	4 (25.0)	4 (14.3)
	Complete	7 (18.9)	5 (16.1)	3 (20.0)	3 (18.8)	6 (20.0)	5 (16.7)	5 (31.3)	7 (25.0)
	P-value [1]		0.575	0.110	0.942	0.131	0.189	0.091	0.266

Total pain relief (TOTPAR) based on categorical scale / Safety analysis set - Part A and B

Statistics	Placebo N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	Ibuprofen 400 mg N=28
n	16	30	30	28
Mean (SD)	0.96 (1.298)	1.72 (1.284)	1.49 (1.288)	2.17 (1.198)
Minimum	0.0	0.0	0.0	0.0
Median	0.03	1.78	1.91	2.20
Maximum	3.4	3.7	3.9	3.9
95% CI [2]		(0.039, 1.629)	(-0.226, 1.337)	(0.480, 2.087)
P-value[2]		0.040	0.162	0.002

Time to onset of analgesia / Median time to onset of analgesia (in Mins) using Kaplan-Meier method

Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16
n	37	31	15	16
Number of event	25	22	11	12
Number of censored	12	9	4	4
Percent censored (%)	32.4	29.0	26.7	25.0
50% survival time				
Point estimate	65.0	44.0	26.0	44.5
95% CI	(30.00,104.00)	(33.00, 68.00)	(15.00, 56.00)	(20.00, 122.00)
P-value [1]		0.569	0.218	0.423

Statistics	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
n	30	30	16	28
Number of event	25	27	14	28
Number of censored	5	3	2	0
Percent censored (%)	16.7	10.0	12.5	0.0
50% survival time				
Point estimate	39.5	31.0	26.0	31.0
95% CI	(28.00, 58.00)	(27.00, 45.00)	(22.00, 39.00)	(27.00, 39.00)
P-value [1]	0.083	0.014	0.029	<0.001

Patient global evaluation

Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
Categorical patient global evaluation scale, n(%)								
Poor	23 (62.2)	19 (61.3)	5 (33.3)	7 (43.8)	6 (20.7)	7 (23.3)	4 (25.0)	1 (3.6)
Fair	4 (10.8)	0 (0.0)	0 (0.0)	4 (25.0)	7 (24.1)	11 (36.7)	2 (12.5)	3 (10.7)
Good	5 (13.5)	9 (29.0)	7 (46.7)	2 (12.5)	9 (31.0)	8 (26.7)	7 (43.8)	12 (42.9)
Excellent	5 (13.5)	3 (9.7)	3 (20.0)	3 (18.8)	7 (24.1)	4 (13.3)	3 (18.8)	12 (42.9)
P-value [1]		0.215	0.043	0.484	0.015	0.009	0.061	<0.001

Summary of pharmacokinetic variables

Variable	Statistics	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=15	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16
AUCinf	n	20	10	10	27	13	6
(hr*ug/mL)	Mean (SD)	0.2120 (0.0455)	0.4445 (0.107)	0.6892 (0.147)	1.762 (0.487)	7.370 (1.70)	15.97 (3.39)
	CV (%)	21.48	23.99	21.30	27.64	23.06	21.26
	Geo. mean	0.2072	0.4341	0.6761	1.701	7.192	15.71
	Geo. CV (%)	22.58	22.79	20.63	27.64	23.33	18.91
	Median	0.2132	0.3970	0.6584	1.659	7.090	14.86
	Min, Max	0.131, 0.288	0.348, 0.642	0.513, 0.984	1.05, 2.94	5.46, 10.1	13.8, 22.7
AUClast	n	31	15	15	30	30	16
(hr*ug/mL)	Mean (SD)	0.1868 (0.0391)	0.3872 (0.0817)	0.6555 (0.242)	1.493 (0.414)	6.272 (1.50)	13.99 (3.59)
	CV (%)	20.93	21.11	36.90	27.75	24.03	25.66
	Geo. mean	0.1828	0.3799	0.6196	1.441	6.096	13.59
	Geo. CV (%)	21.71	19.79	35.24	27.43	24.94	24.85
	Median	0.1849	0.3671	0.6176	1.416	6.132	13.15
	Min, Max	0.113, 0.271	0.299, 0.571	0.312, 1.33	0.924, 2.51	3.14, 10.0	9.07, 21.6

Variable	Statistics	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=15	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16
Cmax	n	31	15	15	30	30	16
(ng/mL)	Mean (SD)	25.56 (4.57)	66.61 (18.6)	96.35 (26.3)	189.4 (57.4)	734.2 (195)	1580 (631)
	CV (%)	17.87	27.86	27.33	30.29	26.53	39.94
	Geo. mean	25.15	64.28	93.37	181.4	707.6	1474
	Geo. CV (%)	18.49	28.00	25.76	30.61	28.97	39.20
	Median	25.40	66.10	87.30	176.5	730.0	1325
	Min, Max	17.0, 35.3	44.2, 97.9	62.4, 162	97.2, 347	349, 1090	825, 2950
Tmax (hr)	n	31	15	15	30	30	16
	Mean (SD)	1.664 (0.792)	1.726 (0.715)	1.858 (0.661)	2.044 (0.786)	2.440 (0.817)	2.604 (0.820)
	CV (%)	47.60	41.44	35.58	38.47	33.49	31.51
	Geo. mean	1.486	1.595	1.743	1.902	2.313	2.474
	Geo. CV (%)	52.46	42.79	39.21	40.71	34.42	35.42
	Median	1.083	2.033	2.050	2.050	2.050	2.534
	Min, Max	0.533, 3.07	1.05, 3.05	1.07, 3.03	0.967, 4.05	1.00, 4.10	1.03, 4.07
T1/2 (hr)	n	28	13	13	30	26	15
	Mean (SD)	9.972 (2.51)	9.140 (2.85)	10.22 (5.035)	9.487 (6.01)	12.46 (7.28)	15.44 (10.9)
	CV (%)	25.13	31.22	49.28	63.29	58.44	70.34
	Geo. mean	9.679	8.744	9.361	8.633	11.04	12.75
	Geo. CV (%)	25.21	31.68	42.79	39.17	50.24	69.06
	Median	9.270	8.485	7.618	8.212	9.976	11.77
	Min, Max	6.43, 15.2	5.24, 14.6	5.94, 22.3	5.38, 38.4	5.30, 39.1	4.29, 45.8

1. CV: coefficient of variation=sd/mean*100; Geo. CV(%): sqrt(exp(variance for log transformed data)-1)*100
2. PK evaluation: Non-compartmental analysis using WinNonlin Pro (Version 5.02)
3. Concentrations below the Limit of Quantification are treated as zero. They are not considered for calculation of PK variables (with the exception of the pre-dose samples).
4. Note: AUClast was the same as AUC0-24hr for all subjects treated.

Time to rescue medication intake

Table 11-6 Subjects receiving rescue medication (including Tylenol) up to 24 hrs after dose

	Time to intake(hrs)			Number of patients
	N	Mean*	SD*	n (%)
Placebo	37	2.81	2.636	26 (70.3)
SAF312 7.5 mg	31	3.87	4.545	21 (67.7)
SAF312 15 mg	15	2.45	1.088	7 (46.7)
SAF312 25 mg	16	4.43	3.183	12 (75.0)
SAF312 50 mg	30	3.38	2.872	15 (50.0)
SAF312 200 mg	30	3.76	3.178	19 (63.3)
SAF312 600 mg	16	2.48	1.324	6 (37.5)
Ibuprofen 400 mg	28	9.65	4.381	16 (57.1)

* Mean and SD are calculated based on the number (n) of patients who took rescue medication (including Tylenol).

Proportion of patients requiring rescue medication in the first six (6) hours:

Table 11-7 Comparisons of proportions of subjects requiring rescue medication in the first 6 hours

Statistics	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28
Use of rescue medication, n(%)								
Yes	24 (64.9)	18 (58.1)	7 (46.7)	9 (56.3)	13 (43.3)	17 (56.7)	6 (37.5)	2 (7.1)
No	13 (35.1)	13 (41.9)	8 (53.3)	7 (43.8)	17 (56.7)	13 (43.3)	10 (62.5)	26 (92.9)
P-value [1]		0.680	0.241	0.726	0.097	0.546	0.073	<0.001

Note: Tylenol is considered as a rescue medication.
[1] P-values are from Cochran-Mantel-Haenszel tests, adjusting for the number of teeth removed, comparing active treatment/dose against placebo.

Clinically relevant vital signs (all excluding body temperature):

	SAF312	SAF312	SAF312	SAF312	SAF312	SAF312	Ibuprofen	Placebo
Number (%) of subjects with clinically relevant vital signs findings	7.5 mg	15 mg	25 mg	50 mg	200 mg	600 mg	400 mg	
	N=37	N=31	N=15	N=16	N=30	N=30	N=16	N=28
	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Body temperature:

	Temp	Placebo	SAF312 7.5 mg	SAF312 15 mg	SAF312 25 mg	SAF312 50 mg	SAF312 200 mg	SAF312 600 mg	Ibuprofen 400 mg
		N=28	N=37	N=31	N=15	N=16	N=30	N=30	N=16
% of patients with max. temperature within range	<37.5 °C	73%	42%	0%	25%	0%	0%	0%	91%
	37.5 – 38 °C	22%	42%	80%	18%	23%	7%	13%	6%
	38 – 38.5°C	5%	42%	20%	32%	43%	60%	55%	3%
	≥ 38.5°C	0%	0%	0	25%	33%	33%	32%	0%

Thermal perception (Part C only):

Visit	Thermal perception	Placebo N=21 n (%)	SAF312 7.5 mg N=31 n (%)	SAF312 15 mg N=15 n (%)	SAF312 25 mg N=16 n (%)	SAF312 600 mg N=16 n (%)	Total N=99 n (%)
SCR	Correct	21 (100.0)	31 (100.0)	15 (100.0)	16 (100.0)	16 (100.0)	99 (100.0)
	Not Correct	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TP/24hr	Correct	21 (100.0)	30 (96.8)	15 (100.0)	16 (100.0)	16 (100.0)	98 (99.0)
	Not Correct	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

ECG evaluation:

	SAF312 7.5 mg	SAF312 15 mg	SAF312 25 mg	SAF312 50 mg	SAF312 200 mg	SAF312 600 mg	Ibuprofen 400 mg	Placebo
Number (%) of subjects with clinically relevant ECG findings	N=37	N=31	N=15	N=16	N=30	N=30	N=16	N=28
	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Cardiac Holter monitoring (Part A only)

Treatment	Visit	Statistics	Longest RR (sec)	Maximum heart rate (bpm)	Average heart rate (bpm)	Minimum heart rate (bpm)	Afib (Time%)	Tot SVE pairs	Tot SVE run events
Placebo	TP/Day 1	n	4	4	4	4	4	4	4
		Mean	1.548	124.0	68.5	42.3	0.0	0.0	0.0
		SD	0.1156	4.24	9.26	2.50	0.00	0.00	0.00
		Minimum	1.43	119	56	39	0	0	0
		Median	1.545	124.5	71.0	42.5	0.0	0.0	0.0
		Maximum	1.67	128	76	45	0	0	0
SAF312 50 mg	TP/Day 1	n	6	6	6	6	6	6	6
		Mean	1.517	134.3	71.0	44.8	0.0	2.3	0.5
		SD	0.1089	13.41	7.72	4.36	0.00	4.76	1.22
		Minimum	1.41	125	62	40	0	0	0
		Median	1.490	129.5	71.0	43.5	0.0	0.5	0.0
		Maximum	1.72	161	83	51	0	12	3
SAF312 200 mg	TP/Day 1	n	6	6	6	6	6	6	6
		Mean	1.380	133.2	71.7	50.0	0.0	0.8	0.0
		SD	0.2402	12.62	11.41	9.63	0.00	2.04	0.00
		Minimum	1.11	110	54	36	0	0	0
		Median	1.415	138.0	73.5	48.0	0.0	0.0	0.0
		Maximum	1.75	145	87	62	0	5	0

Note: 1. Cardiac Holter was done only for Part A.
2. Only the measurements taken within 24 hours were used for the calculation of the statistics.

Treatment	Visit	Statistics	Tot single SVEs	Tot SVEs	Tot beats	Tot VE pairs	Tot VE run events	Tot single VEs	Tot VEs
Placebo	TP/Day 1	n	4	4	4	4	4	4	4
		Mean	0.8	0.8	95521.3	0.0	0.0	0.3	0.3
		SD	1.50	1.50	18617.10	0.00	0.00	0.50	0.50
		Minimum	0	0	69040	0	0	0	0
		Median	0.0	0.0	101683.5	0.0	0.0	0.0	0.0
		Maximum	3	3	109678	0	0	1	1
SAF312 50 mg	TP/Day 1	n	6	6	6	6	6	6	6
		Mean	471.0	477.3	85853.2	0.0	0.0	0.0	0.0
		SD	1138.09	1136.18	22875.16	0.00	0.00	0.00	0.00
		Minimum	0	0	40907	0	0	0	0
		Median	1.5	2.5	91662.0	0.0	0.0	0.0	0.0
		Maximum	2794	2796	104562	0	0	0	0
SAF312 200 mg	TP/Day 1	n	6	6	6	6	6	6	6
		Mean	5.2	6.8	100988.5	0.0	0.0	0.3	0.3
		SD	9.52	13.51	16468.99	0.00	0.00	0.52	0.52
		Minimum	0	0	77643	0	0	0	0
		Median	0.5	0.5	102131.0	0.0	0.0	0.0	0.0
		Maximum	24	34	124801	0	0	1	1

Table 14.3-4.3 (Page 3 of 4)
Summary of Cardiac Holter data
Safety analysis set

Treatment	Visit	Statistics	Longest RR (sec)	Maximum heart rate (bpm)	Average heart rate (bpm)	Minimum heart rate (bpm)	Afib (Time%)	Tot SVE pairs	Tot SVE run events
Ibuprofen 400 mg	TP/Day 1	n	3	3	3	3	3	3	3
		Mean	1.533	136.7	63.7	42.0	0.0	0.0	0.0
		SD	0.1888	12.22	5.51	6.56	0.00	0.00	0.00
		Minimum	1.37	126	60	35	0	0	0
		Median	1.490	134.0	61.0	43.0	0.0	0.0	0.0
		Maximum	1.74	150	70	48	0	0	0

Treatment	Visit	Statistics	Tot single SVEs	Tot SVEs	Tot beats	Tot VE pairs	Tot VE run events	Tot single VEs	Tot VEs
Ibuprofen 400 mg	TP/Day 1	n	3	3	3	3	3	3	3
		Mean	3.0	3.0	91622.0	0.0	0.0	1.7	1.7
		SD	1.00	1.00	7566.64	0.00	0.00	1.15	1.15
		Minimum	2	2	86995	0	0	1	1
		Median	3.0	3.0	97517.0	0.0	0.0	1.0	1.0
		Maximum	4	4	100354	0	0	3	3

Safety Results

Adverse Events

Table 12-1 Incidence of AEs by body system and preferred term - n (%) of subjects (all subjects more than 10% in any group) (Safety set)

Body system	Preferred term	Placebo N=37	SAF312 7.5 mg N=31	SAF312 15 mg N=15	SAF312 25 mg N=16	SAF312 50 mg N=30	SAF312 200 mg N=30	SAF312 600 mg N=16	Ibuprofen 400 mg N=28	Total N=203
-Any body system		5 (13.5)	14 (45.2)	7 (46.7)	10 (62.5)	22 (73.3)	24 (80.0)	13 (81.3)	3 (10.7)	98 (48.3)
Gastrointestinal disorders	-Total	1 (2.7)	5 (16.1)	0 (0.0)	2 (12.5)	6 (20.0)	4 (13.3)	3 (18.8)	1 (3.6)	22 (10.8)
	Nausea	1 (2.7)	3 (9.7)	0 (0.0)	1 (6.3)	6 (20.0)	4 (13.3)	3 (18.8)	1 (3.6)	19 (9.4)
	Vomiting	0 (0.0)	1 (3.2)	0 (0.0)	2 (12.5)	0 (0.0)	2 (6.7)	3 (18.8)	0 (0.0)	8 (3.9)
General disorders and administration site conditions	-Total	0 (0.0)	9 (29.0)	7 (46.7)	6 (37.5)	21 (70.0)	23 (76.7)	11 (68.8)	0 (0.0)	77 (37.9)
	Chills	0 (0.0)	6 (19.4)	6 (40.0)	6 (37.5)	14 (46.7)	15 (50.0)	7 (43.8)	0 (0.0)	54 (26.6)
	Hyperthermia	0 (0.0)	0 (0.0)	1 (6.7)	3 (18.8)	11 (36.7)	16 (53.3)	8 (50.0)	0 (0.0)	39 (19.2)
	Feeling cold	0 (0.0)	1 (3.2)	1 (6.7)	0 (0.0)	1 (3.3)	2 (6.7)	2 (12.5)	0 (0.0)	7 (3.4)
Nervous system disorders	-Total	2 (5.4)	3 (9.7)	0 (0.0)	2 (12.5)	4 (13.3)	4 (13.3)	2 (12.5)	0 (0.0)	17 (8.4)
	Dizziness	2 (5.4)	1 (3.2)	0 (0.0)	0 (0.0)	4 (13.3)	2 (6.7)	0 (0.0)	0 (0.0)	9 (4.4)

Serious Adverse Events and Deaths

Number (%) of subjects with serious or other significant events	SAF312 7.5 mg	SAF312 15 mg	SAF312 25 mg	SAF312 50 mg	SAF312 200 mg	SAF312 600 mg	Ibuprofen 400 mg	Placebo
	N=37	N=31	N=15	N=16	N=30	N=30	N=16	N=28
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SAE(s)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued due to SAE(s)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report

18-Apr-2012

Date Inclusion on Novartis Clinical Trial Results Database

30-May-2012

Date of Latest Update

30-May-2012