

Bioavailability of four different sublingual formulations of fentanyl in healthy male volunteers: Phase I, randomised, open-label, crossover study

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Background

- Breakthrough cancer pain (BTcP) is a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy.¹ It is characterised by sudden onset, reaching maximal intensity within as little as 3 minutes, and lasts for an average of 30 minutes.²
- Sublingual fentanyl (SLF) is a new sublingual formulation of fentanyl citrate, indicated for the management of BTcP in patients already receiving maintenance opioid therapy for chronic cancer pain.³
- Available as a transmucosal delivery formulation, SLF is administered as a rapidly disintegrating tablet of fast-acting fentanyl citrate.⁴
- SLF works by exploiting the positive conditions of the sublingual environment, which favour rapid absorption of fentanyl across the oral mucosa into the systemic circulation.^{3,4} This combined with the rapid onset and short duration of action of the drug molecule³ makes SLF well suited to the time course of rapid-onset BTcP.
- In order to further improve the treatment of BTcP, a number of pharmaceutical formulations of SLF, each varying in their proportion of inactive ingredients, were developed to further optimise the pharmacokinetic (PK) profile of SLF.

Objectives

- The objective of this study in healthy volunteers was to:
 - characterise and compare three optimised formulations of SLF (A, B and C) with a previously developed reference formulation of SLF (D).

Methods

- This was a Phase I, Sweden-based, randomised, single-centre, open-label crossover study consisting of four treatment periods (Figure 1).

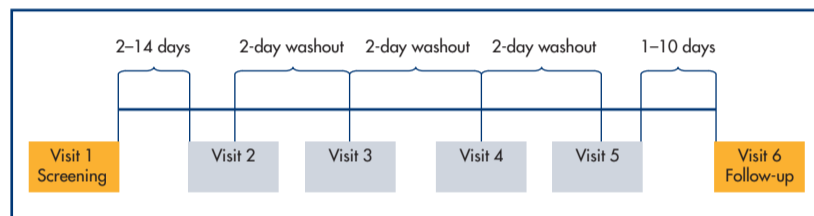


Figure 1: Study design

Study population

- 16 healthy male Caucasian volunteers were recruited.
- Key inclusion criteria included:
 - subjects aged 18–45 years
 - body mass index of 18–28 kg/m²
 - non-smokers.
- Key exclusion criteria included:
 - any clinically significant abnormality at screening that could interfere with study evaluations
 - use of any prescription medication within 14 days of study start
 - no prior investigational drugs within 8 weeks of the pre-entry examination
 - history of fentanyl intolerance or severe allergic disease.

Treatment

- Following a 2–14-day screening phase, subjects received a single dose (400 µg) of the four formulations of SLF in random order at four separate treatment visits (Visits 2–5).
- Each treatment visit lasted 2 days, and was separated by a ≥2-day washout period.
- All subjects were treated with naltrexone hydrochloride 12 hours prior to treatment administration in order to block the opioid effects of fentanyl.
- At each treatment period, blood samples were collected just prior to treatment administration and at regular interval for 10 hours thereafter.

Assessments

- The PK parameters assessed for fentanyl included the:
 - maximum plasma concentration (C_{max})
 - time to C_{max} (t_{max})
 - time to first measurable plasma concentration (t_{first})
 - area under the plasma concentration versus time curve from time 0 to the last quantifiable sampling point (AUC_{0–t})
 - area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{0–∞})
 - terminal half-life of the drug (t_{1/2}).
- Subjects were monitored continuously throughout the study for signs of adverse events (AEs).

Statistical analysis

- The study was designed to include 16 subjects in order to have ≥12 subjects for PK and safety evaluation.
- Individual PK parameters were compared between treatments using SAS statistical programme; sequence, subject nested within sequence, period and treatment were considered as class variables.
- All patients were to be included in the safety analysis.
- The three optimised formulations of SLF were deemed to be bioequivalent to the reference formulation (D) if the test/reference geometric mean ratios for AUC and C_{max} were within the pre-specified range 0.80–1.25.

Results

Baseline demographics and characteristics

- All 16 enrolled subjects completed all four treatment visits.
- All subjects were male and Caucasian, and had a mean age of 24.6±4.4 years and a mean BMI of 23.8±2.6 kg/m².

Mean plasma concentration–time curves

- The mean plasma concentration–time curves for all four formulations, A, B, C and D, showed rapid absorption of fentanyl (Figure 2).
- The time curve for formulation A was superimposable on that for formulation D, suggesting that formulation A was a close match to the reference formulation.
- The single peak observed in the time curves of all four formulations indicates that sublingual fentanyl is absorbed primarily through the oral mucosa.

Fentanyl pharmacokinetics

- The summary measures of the PK parameters for each formulation are presented in Table 1.
- Fentanyl was first quantifiable in plasma approximately 10–15 minutes after treatment administration (t_{first}), with formulation D showing the fastest absorption rate (9.45 mins post-dose).

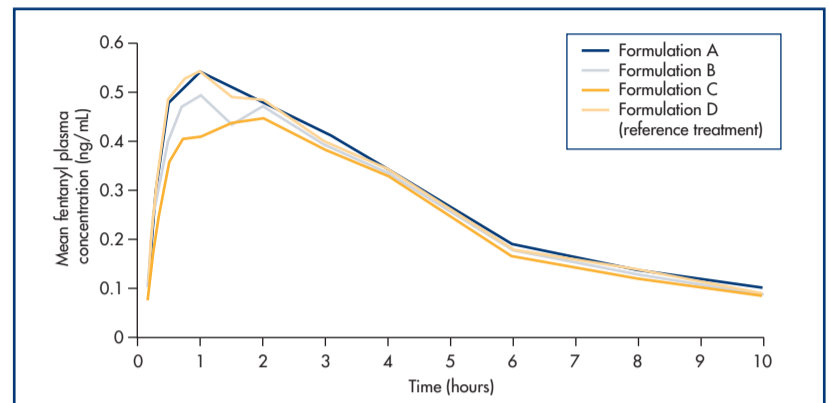


Figure 2: Mean plasma fentanyl concentration versus time in healthy male Caucasian subjects following administration of one single 400 µg dose of four sublingual fentanyl citrate formulations (A, B, C and D)

Pharmacokinetic variable	Mean±SD Range	SLF formulation			
		A	B	C	D
AUC _{0–t} (min.ng/mL)	167.66±42.07 107.8–234.7	156.72±34.79 110.9–222.9	148.09±40.46 94.4–235.4	164.73±41.66 116.9–242.7	
AUC _{0–∞} (min.ng/mL)	204.03±57.39 125.3–318.2	187.75±44.72 127.2–294.7	182.01±60.53 123.4–317.1	198.31±60.07 135.0–326.5	
C _{max} (ng/mL)	0.63±0.19 0.34–1.03	0.61±0.19 0.31–1.01	0.55±0.16 0.29–0.95	0.62±0.14 0.41–0.81	
t _{max} (minutes)	66.00±41.76 15.00–121.20	62.55±39.60 15.00–121.20	78.23±43.73 15.00–181.80	55.16±38.41 19.80–180.00	
t _{first} (minutes)	10.69±4.41 4.80–19.80	10.65±3.71 4.20–15.00	14.74±7.12 4.80–30.00	9.45±3.71 4.80–15.00	
t _{1/2} (hours)	4.15±0.80 2.99–5.95	4.01±0.91 2.91–6.04	4.27±1.10 2.84–6.26	4.04±0.75 2.93–5.49	

SD: standard deviation; SLF: sublingual fentanyl citrate

Table 1: Overview of the sublingual fentanyl pharmacokinetic data (mean±SD) for healthy male Caucasian subjects

- Reflecting the fentanyl plasma concentration–time curves, C_{max} was rapidly attained with all three optimised formulations, although mean t_{max} was longer with formulation C.
- Mean C_{max} was comparable between formulations A, B and D, but was lower with formulation C.
- Total systemic exposure (AUC_{0–t} and AUC_{0–∞}) was greatest with formulation A and lowest with formulation C.
- For formulations A and B, the geometric mean ratios for AUC_{0–t} and C_{max} were within the pre-specified range. However, for formulation C the C_{max} ratio fell just outside the pre-specified range of 0.80–1.25 (Table 2).

Pharmacokinetic variable	Ratio for SLF formulation	90% CI	
		Lower	Upper
AUC _{0–t} (min.ng/mL)	A/D	0.9456	1.0895
	B/D	0.8916	1.0273
	C/D	0.8338	0.9607
AUC _{0–∞} (min.ng/mL)	A/D	0.9579	1.1052
	B/D	0.8940	1.0315
	C/D	0.8491	0.9796
C _{max} (ng/mL)	A/D	0.8917	1.1473
	B/D	0.8613	1.1082
	C/D	0.7714	0.9925

CI: confidence interval; SLF: sublingual fentanyl citrate

Table 2: 90% confidence intervals of the geometric mean ratios for AUC_{0–t}, AUC_{0–∞} and C_{max}

Tolerability profile for sublingual fentanyl

- Thirty-one AEs were reported by eight subjects.
- More AEs were reported with formulation B than with formulations A, C and D (12 versus 5, 6 and 8, respectively).
- Headache was the most frequently reported AE and was observed with all four formulations.
- All but three AEs (headache, moderate) were mild in severity; the majority of AEs were considered possibly or probably treatment-related.

Conclusions

- Fast uptake of fentanyl from the oral mucosa is a highly desired property for drugs used in the treatment of BTcP as it allows for rapid onset of action and rapid relief of the pain episode. Fentanyl was rapidly absorbed, being first quantifiable in plasma (t_{first}) approximately 10 minutes post-dose with formulations A, B and D.
- All formulations were well tolerated by healthy volunteers, with the majority of AEs being mild in severity.
- Optimised SLF formulations A and B were bioequivalent to the reference formulation D.
- Overall, formulation A presented the most favourable PK profile, in terms of the rate and extent of fentanyl absorption, and was selected for commercialisation.

References

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