Pharmacokinetics of Fentanyl Sublingual Spray in Opioid-Naı ¨ ve Participants: Results of a Phase 1, Multiple Ascending Dose Study

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Abstract

Background and Objectives Fentanyl sublingual spray may be a viable alternative to intravenous (IV) opioids for the treatment of acute pain. As patients with acute pain may include those who have limited prior exposure to opioids, this phase 1, open-label, randomized, multiple ascending-dose study was conducted to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of multiple doses of fentanyl sublingual spray in opioid-naı¨ ve participants. This article primarily reports the pharmacokinetics results.

Methods Study drugs were administered in four dosing cohorts: every 0.5, 1, 2, or 4 h for a maximum of three doses per cohort. Eight fasted individuals per cohort were randomized to either fentanyl sublingual spray (100, 200, or 400 µg) or fentanyl citrate IV 50 µg (6:2 ratio). Blood samples were collected pre-dose through 24 h post first dose.

Results A total of 98 healthy adults were enrolled and 96 completed the study. Mean plasma fentanyl concentrations increased with increasing doses of fentanyl sublingual spray administered every 0.5–4 h. With multiple doses, systemic exposure increased relative to the first dose; shorter dosing intervals resulted in higher concentrations. Analysis of dose proportionality suggested that systemic exposure increased in a linear but slightly greater than dose-proportional manner. Accumulation between the first and last doses of fentanyl sublingual spray was more pronounced with shorter dosing intervals.

Conclusion Dose-dependent fentanyl pharmacokinetics following multiple doses of fentanyl sublingual spray were well characterized in an opioid-naı ¨ ve population. ClinicalTrials.gov identifier NCT02641340.

Key Points

In an opioid-naı ¨ ve population, pharmacokinetics of fentanyl sublingual spray from 100–400 µg administered every 0.5–4 h were characterized with a generally well tolerated safety profile comparable to fentanyl citrate IV 50 µg.

The fentanyl plasma concentration increased with dose after repeated administration of fentanyl sublingual spray.

1 Introduction

Fentanyl is a well-known opioid that was synthesized as a replacement of morphine in 1960. It is approximately 100 times more potent than morphine [1, 2]. Since the approval of fentanyl as an intravenous (IV) injection in 1968 [3],
other delivery forms of fentanyl have been studied and approved for use in patients with a variety of painful conditions [4, 5].

Fentanyl sublingual spray (SUBSYS®; Insys Development Company, Inc.; Chandler, AZ, USA) is a potent, short-acting opioid agonist delivered sublingually as a spray that is indicated for the management of breakthrough pain in opioid-tolerant, adult cancer patients. It has demonstrated its efficacy, showing significant pain relief compared to placebo in as early as 5 min and through 60 min [4], as well as pharmacokinetic parameters similar to those of IV fentanyl, with a rapid increase in plasma concentrations [6].

Because of its pharmacokinetic profile and rapid onset for pain relief, fentanyl sublingual spray may provide a less invasive, viable alternative to IV opioids for the treatment of acute pain such as postoperative pain, burn dressing change, or initial fracture-related pain in the emergency room. As patients in these settings will likely include those who are opioid naïve or who have limited prior exposure to opioids, it is important to understand the pharmacokinetic characteristics of fentanyl sublingual spray and their impact on safety in an opioid-naïve population. Single-dose pharmacokinetics following fentanyl sublingual spray in healthy opioid-naïve volunteers have been reported previously [7]. This study was conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability following multiple doses of fentanyl sublingual spray in an opioid-naïve population. Pharmacodynamics, safety, and tolerability results are reported in a separate publication [8]. Detailed pharmacokinetic results are reported in this article.

2 Methods

This was a phase 1, open-label, randomized, multiple ascending-dose study in opioid-naïve participants. This study included a 28-day screening period and a treatment period, with a follow-up phone contact on Day 7. Study drugs were administered in four dosing cohorts: every 0.5, 1, 2, or 4 h for a maximum of three doses per cohort. Eight fasted individuals per cohort were randomized to either fentanyl sublingual spray (100, 200, or 400 μg) or fentanyl citrate IV 50 μg in a 6:2 ratio. Blood samples were collected pre-dose through 24 h post first dose. Participants fasted for 10 h prior to the first dose and through 4 h post-first dose. To ensure participant safety, participants were closely monitored in an in-clinic setting for up to 24 h post-first dose.

2.3 Pharmacokinetic Analysis

Venous blood samples (6 ml) for the determination of fentanyl plasma concentrations were collected in vacutainer tubes containing K²-EDTA as a preservative, according to the prespecified schedules, dependent on the dosing regimen in each cohort. Human plasma containing fentanyl and the internal standard, fentanyl D₅, was extracted with an organic solvent mixture after the addition of sodium carbonate solution (liquid-liquid extraction). Following centrifugation, the organic layer was transferred and evaporated to dryness. An aliquot of the reconstituted extract was injected onto a Sciex API 4000 LC MS equipped with an HPLC column (AB Sciex, Concord, Ontario, Canada). The peak area of the m/z 337 → 188 fentanyl production was measured against the m/z 342 → 188 fentanyl D₅ internal standard product ion. Quantitation was performed using a weighted linear least-squares regression. The quantification range was validated from 0.0250 to 5.00 ng/ml of plasma fentanyl concentration.

The appropriate pharmacokinetic parameters were derived by noncompartmental analysis using Phoenix® WinNonlin (Version 6.3: Pharsight Corporation, Cary, NC, USA), including maximum plasma concentrations after...
first or last dose, determined directly from individual
collection–time data (Cmax, Cmax); time of the maxi-

mum plasma concentration after first or last dose (Tmax1
and Tmax2); area under the plasma concentration–time
curve from time–zero extrapolated to infinity (AUC0–inf);
area under the plasma concentration–time curve from
time–zero to the time of the last quantifiable
concentration, calculated using the linear-log trapezoidal
rule (AUCt); area under the plasma concentration–time
curve from time–zero extrapolated to infinity (AUC0–inf);
area under the plasma concentration-time curve during the
first and last dosing interval, calculated using the linear-log
trapezoidal rule (AUCt-max1 or AUCt-max2, respectively);
apparent elimination half-life in the terminal phase by non-
compartmental analysis (t1/2); accumulation ratio of Cmax
(ARmax); accumulation ratio of AUCmax (ARmax); total
body clearance of drug (CL); and volume of distribution
during terminal phase (VZ) for fentanyl following IV
administration.

During the pharmacokinetic analysis, plasma drug con-
centrations that were below the limit of quantitation (BLQ)
were treated as zero from time–zero up to the time at which
the first quantifiable concentration was observed; embed-
ded and terminal BLQ were treated as “missing.” Actual
sample times were used in the pharmacokinetic analysis.
The AUC0–inf, VZ, CL, and t1/2 parameters were reported
only for concentration-time profiles that exhibited a clear
terminal log-linear phase and prespecified criteria outline
in the statistical analysis plan.

2.4 Safety and Pharmacodynamic Analyses

Safety variables included physical examinations, vital
signs, pulse-oximetry, capnography, clinical laboratory
testing, electrocardiogram, concomitant medications, and
adverse event (AE) assessments. All AEs were coded using
Medical Dictionary for Regulatory Activities (MedDRA,
version 17.0).

Pharmacodynamic data relevant to respiratory function
from capnography, pulse oximetry, and respiration rate
measurements were further analyzed. The incidence rates
for the primary and additional pharmacodynamic safety
endpoints in each of the fentanyl spray groups were com-
pared, within dosing regimen cohort, to the incidence rates
in the fentanyl IV group. Detailed safety and pharmaco-
dynamic results are presented in a separate publication [8].

2.5 Statistical Analysis

The overall study sample size of 96 participants (eight
participants per cohort) was included in the analysis.

Data processing, tabulation of descriptive statistics, and
calculation of inferential statistics were performed using
SAS® (release 9.2 or higher, SAS Institute Inc.; Cary, NC,
USA) for Windows. Unless otherwise indicated, tabulations
were by the treatment groups, including the three fentanyl
sublingual spray groups and the fentanyl
citrate IV group. The fentanyl citrate IV group consisted of
all participants treated in the fentanyl citrate IV groups
combined over the dosing cohorts. Pharmacokinetic results
for the individual treatment groups were summarized using
descriptive statistics including arithmetic mean and stan-
dard deviation (SD).

The pharmacokinetic parameters Cmax, AUC0–t, and
AUC0–inf for fentanyl after administration of fentanyl
sublingual spray across each sublingual dose level (Cycles
1, 2, and 3) were evaluated for each cohort separately in
order to assess dose proportionality. Statistical analyses
were performed using a power model with mixed effects of
the following general form [9]:

\[
\ln(\text{PK}) = \ln(\beta_0) + \beta_1 \cdot \ln(\text{Dose}) + \varepsilon,
\]

where

PK is the pharmacokinetic parameter tested (e.g. Cmax or
AUC);

\(\ln(\beta_0)\) is the \(y\)-intercept,

\(\beta_1\) is the slope (a value of \(\beta_1\) approximately equal to 1
indicates linearity), and

\(\varepsilon\) is an error term (Subject was used as the random
effects term).

The estimate of \(\beta_1\) was reported along with the p-value
for the deviation of \(\beta_1\) from unity (\(\beta_1 = 1\)).

In addition, natural logarithmic-transformed scatter plots
of Cmax, AUC0–t, and AUC0–inf for fentanyl after admin-
istration of fentanyl sublingual spray by dose were gener-
ated (each cohort separately) and the data analyzed using
linear regression. The intercept and slope describing the
regression line and the goodness of fit (\(R^2\)) were also
reported within each scatter plot.

3 Results

3.1 Participant Demographics

A total of 98 opioid-naïve volunteer participants were
enrolled in the study, and 96 participants completed
treatment.

Overall, the mean (SD) age of study participants was
36.4 (9.87) years and ranged from 20 to 55 years. The
majority of participants were male [72 (75.0%)], white [55
(57.3%)], and non-Hispanic/non-Latino [73 (76.0%)] [8].
There were no remarkable differences in demographic
characteristics among participants treated with fentanyl
sublingual spray 100, 200, and 400 \(\mu\)g, or fentanyl citrate
IV 50 \(\mu\)g.

The demographic and baseline characteristics of the
safety population for participants treated with fentanyl

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sublingual spray 100, 200, and 400 µg, and fentanyl citrate IV 50 µg across the four dosing frequency cohorts are summarized in Supplemental Tables 1, 2, 3, and 4, respectively.

3.2 Pharmacokinetics

The pharmacokinetic analysis population consisted of all randomized participants who received at least one dose of fentanyl and had sufficient plasma data to facilitate the calculation of pharmacokinetic parameters.

Mean plasma fentanyl concentration-time profiles after the administration of multiple doses of fentanyl sublingual spray (100, 200, 400 µg) and fentanyl citrate IV (50 µg) are displayed in Fig. 1. Mean plasma fentanyl concentrations increased with an increase in dose of fentanyl sublingual spray between 100 and 400 µg (Fig. 1a-c). As expected, higher concentrations were observed for the shorter dosing intervals of 1 h (Cohort 3) and 0.5 h (Cohort 4) at each dose level. A similar trend was observed after administration of fentanyl citrate IV 50 µg, with the highest concentrations observed for dosing every 1 h or 0.5 h, as shown in Fig. 1d.

Mean fentanyl pharmacokinetic parameters after the administration of multiple doses of fentanyl sublingual spray (100, 200, 400 µg) and fentanyl citrate IV (50 µg) are summarized by cohort in Tables 1, 2, 3, and 4, respectively.

The mean $C_{\text{max,1}}$ after the first dose of fentanyl sublingual spray 100 µg (Cycle 1, Table 1) was similar across cohorts, ranging from 0.159 ng/ml (Cohort 4) to 0.187 ng/ml (Cohort 2). After the last dose, the mean $C_{\text{max}}$ increased relative to the first dose, ranging from 0.225 ng/ml (Cohort 1) to 0.479 ng/ml (Cohort 4), and shorter dosing intervals resulted in higher concentrations. Similar trends were observed for $AUC_{0-\text{tau}}$ and $AUC_{0-\text{taur}}$, with an increase in exposure between the first and last doses that was most apparent for the shorter dosing intervals of 1 h (Cohort 3) and 0.5 h (Cohort 4). Overall systemic exposure to fentanyl after three consecutive doses of fentanyl sublingual spray 200 µg, based on $AUC_{0-\text{inf}}$, varied across cohorts, ranging from 5.190 h-ng/ml (Cohort 1) to 8.305 h-ng/ml (Cohort 4). The mean $t_{1/2}$ after the last dose of fentanyl sublingual spray 200 µg was relatively consistent across cohorts, ranging from 5.48 h (Cohort 4) to 6.68 h (Cohort 2). The accumulation between the first and last doses of fentanyl sublingual spray 200 µg ranged from 1.22 ($AR_{\text{cum}}$; Cohort 1) to 4.86 ($AR_{AUC_{\text{cum}}}$; Cohort 4), with more pronounced accumulation for shorter dosing intervals (Table 2).

The mean $C_{\text{max,1}}$ after the first dose of fentanyl sublingual spray 400 µg (Cycle 3, Table 3) varied across cohorts, ranging from 0.610 ng/ml (Cohort 2) to 1.14 ng/ml (Cohort 1). After the last dose, the mean $C_{\text{max}}$ increased relative to the first dose, ranging from 1.74 ng/ml (Cohort 1) to 2.77 ng/ml (Cohort 3), and shorter dosing intervals resulted in higher concentrations. Similar trends were observed for $AUC_{0-\text{tau}}$ and $AUC_{0-\text{taur}}$, with an increase in exposure between the first and last doses that was most apparent for the shorter dosing intervals of 1 h (Cohort 3) and 0.5 h (Cohort 4). Overall systemic exposure to fentanyl after three consecutive doses of fentanyl sublingual spray 400 µg, based on $AUC_{0-\text{inf}}$, varied across cohorts, ranging from 13.43 h-ng/ml (Cohort 2) to 17.93 h-ng/ml (Cohort 1). It should be noted, however, that the variability in $AUC_{\text{inf}}$ at the 400-µg dose level was larger than those at the two lower dose levels. The mean $t_{1/2}$ after the last dose of fentanyl sublingual spray 400 µg was relatively consistent across cohorts, ranging from 5.31 h (Cohort 2) to 7.04 h (Cohort 3). The accumulation between the first and last doses of fentanyl sublingual spray 400 µg ranged from 1.64 ($AR_{\text{cum}}$; Cohort 1) to 4.87 ($AR_{AUC_{\text{cum}}}$; Cohort 4), with more pronounced accumulation for shorter dosing intervals (Table 3).

The mean $C_{\text{max,1}}$ after the first dose of fentanyl citrate IV 50 µg (Cycles 1, 2, and 3 combined; Table 4) varied similarly across cohorts, ranging from 0.337 ng/ml (Cohort 1) to 0.549 ng/ml (Cohort 2). This variability is partly due to the difficulty in capturing peak concentrations after IV administration, as illustrated by the intra-participant variability within each cohort, which ranged from 35.25 to 62.84%. After the last dose, the mean $C_{\text{max}}$ increased relative to the first dose, ranging from 0.633 ng/ml (Cohort
| Parameter | Cohort 1 (q4 h) | Cohort 2 (q2 h) | Cohort 3 (q1 h) | Cohort 4 (q0.5 h) |
|-----------|----------------|----------------|----------------|-----------------|
|           | n   | Mean | SD   | CV% | n   | Mean | SD   | CV% | n   | Mean | SD   | CV% | n   | Mean | SD   | CV% |
| C<sub>max1</sub> (ng/ml) | 6   | 0.172 | 0.0337 | 19.62 | 6   | 0.187 | 0.0397 | 21.25 | 6   | 0.160 | 0.0864 | 53.94 | 5   | 0.159 | 0.0971 | 60.91 |
| C<sub>max1</sub>/D (ng/ml/µg) | 6   | 0.00172 | 0.000337 | 19.62 | 6   | 0.00187 | 0.000397 | 21.25 | 6   | 0.00160 | 0.000864 | 53.94 | 5   | 0.00159 | 0.000971 | 60.91 |
| Tmax<sub>1</sub> (h) | 6   | 0.58 | 0.34 | 58.55 | 6   | 0.75 | 0.66 | 87.77 | 6   | 0.66 | 0.19 | 28.59 | 5   | 0.41 | 0.08 | 20.04 |
| C<sub>maxn</sub> (ng/ml) | 6   | 0.225 | 0.0312 | 13.88 | 6   | 0.396 | 0.0994 | 25.11 | 6   | 0.406 | 0.121 | 30.22 | 6   | 0.479 | 0.0971 | 60.91 |
| C<sub>maxn</sub>/D (ng/ml/µg) | 6   | 0.00225 | 0.000312 | 13.88 | 6   | 0.00396 | 0.000994 | 25.11 | 6   | 0.00406 | 0.00121 | 29.79 | 6   | 0.00479 | 0.000971 | 60.91 |
| Tmax<sub>n</sub> (h) | 6   | 0.88 | 0.63 | 71.28 | 6   | 0.63 | 0.30 | 48.57 | 6   | 0.66 | 0.22 | 33.02 | 6   | 0.49 | 0.08 | 20.04 |
| AUC<sub>0–tau1</sub> (h/C<sub>1</sub> ng/ml) | 6   | 0.4177 | 0.05081 | 12.16 | 6   | 0.2487 | 0.04661 | 18.74 | 6   | 0.1119 | 0.07198 | 64.32 | 5   | 0.05979 | 0.04672 | 78.14 |
| AUC<sub>0–tau1</sub>/D (h/C<sub>1</sub> ng/ml/µg) | 6   | 0.00418 | 0.000508 | 12.16 | 6   | 0.00249 | 0.000466 | 18.74 | 6   | 0.00112 | 0.000720 | 64.32 | 5   | 0.000598 | 0.000467 | 78.14 |
| AUC<sub>0–tau</sub> (h/C<sub>1</sub> ng/ml) | 6   | 0.6125 | 0.1972 | 32.20 | 6   | 0.6276 | 0.1897 | 30.22 | 6   | 0.3511 | 0.1122 | 31.95 | 6   | 0.2076 | 0.1121 | 54.00 |
| AUC<sub>0–tau</sub>/D (h/C<sub>1</sub> ng/ml/µg) | 6   | 0.00612 | 0.00197 | 32.20 | 6   | 0.00628 | 0.00190 | 30.22 | 6   | 0.00351 | 0.00112 | 31.95 | 6   | 0.00208 | 0.00112 | 54.00 |
| AUC<sub>0–t</sub> (h/C<sub>1</sub> ng/ml) | 6   | 2.130 | 0.8173 | 38.38 | 6   | 2.736 | 1.032 | 37.74 | 6   | 3.025 | 1.076 | 35.55 | 5   | 2.627 | 0.7565 | 28.80 |
| AUC<sub>0–t</sub>/D (h/C<sub>1</sub> ng/ml/µg) | 6   | 0.00710 | 0.00187 | 38.38 | 6   | 0.00912 | 0.00344 | 37.74 | 6   | 0.0101 | 0.00359 | 35.55 | 5   | 0.00876 | 0.00252 | 28.80 |
| AUC<sub>0–inf</sub> (h/C<sub>1</sub> ng/ml) | 2   | 2.172 | 0.9409 | 43.33 | 3   | 2.419 | 1.147 | 47.40 | 5   | 3.427 | 1.333 | 38.90 | 5   | 3.055 | 0.8191 | 26.81 |
| AUC<sub>0–inf</sub>/D (h/C<sub>1</sub> ng/ml/µg) | 2   | 0.00724 | 0.00314 | 43.33 | 3   | 0.00806 | 0.00382 | 47.40 | 5   | 0.0114 | 0.00444 | 38.90 | 5   | 0.00723 | 0.00273 | 26.81 |
| t<sub>1/2</sub> (h) | 6   | 4.60 | 2.02 | 43.90 | 3   | 4.70 | 2.18 | 46.48 | 5   | 6.06 | 1.94 | 32.03 | 5   | 5.36 | 1.03 | 19.14 |
| AR<sub>C<sub>max</sub></sub> | 6   | 1.35 | 0.33 | 24.22 | 6   | 2.14 | 0.46 | 21.35 | 6   | 3.04 | 1.36 | 44.63 | 5   | 3.62 | 0.77 | 21.27 |
| AR<sub>AUC</sub> | 6   | 1.45 | 0.39 | 26.66 | 6   | 2.51 | 0.52 | 20.65 | 6   | 4.15 | 2.19 | 52.81 | 5   | 4.75 | 1.56 | 32.75 |

q every, SD standard deviation, CV coefficient of variation, C<sub>max1</sub> maximum plasma concentrations after first dose, D dose, T<sub>max1</sub> time of the maximum plasma concentration after first dose, C<sub>maxn</sub> maximum plasma concentrations after last dose, T<sub>maxn</sub> time of the maximum plasma concentration after last dose, AUC<sub>0–tau1</sub> area under the plasma concentration time curve during the first dosing interval, calculated using the linear-log trapezoidal rule, AUC<sub>0–tau</sub>n area under the plasma concentration time curve during the last dosing interval, calculated using the linear-log trapezoidal rule, AUC<sub>0–t</sub>n area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, AUC<sub>0–inf</sub> area under the plasma concentration–time curve from time–zero extrapolated to infinity, t<sub>1/2</sub> apparent elimination half-life in the terminal phase by noncompartmental analysis, AR<sub>C<sub>max</sub></sub> accumulation ratio of C<sub>max</sub>, AR<sub>AUC</sub> accumulation ratio of AUC<sub>tau</sub>.
Table 2  Mean fentanyl pharmacokinetic parameters after administration of fentanyl sublingual spray (200 μg)

| Parameter                          | Cohort 1  | Cohort 2  | Cohort 3  | Cohort 4  |
|------------------------------------|-----------|-----------|-----------|-----------|
|                                    | q4 h      | q2 h      | q1 h      | q0.5 h    |
|                                    | n Mean SD | n Mean SD | n Mean SD | n Mean SD |
| C_{max1} (ng/ml)                   | 6 0.461 0.111 24.17 | 5 0.522 0.256 49.15 | 6 0.458 0.122 26.65 | 6 0.379 0.181 47.83 |
| C_{max1}/D (ng/ml/μg)              | 6 0.00231 0.000557 24.17 | 5 0.00261 0.00128 49.15 | 6 0.00229 0.000610 26.65 | 6 0.00190 0.000907 47.83 |
| T_{max1} (h)                       | 6 0.38 0.14 36.51 | 5 0.40 0.14 34.23 | 6 0.41 0.20 49.02 | 6 0.39 0.11 27.86 |
| C_{max2} (ng/ml)                   | 6 0.548 0.129 23.56 | 6 0.890 0.156 49.15 | 6 0.67 0.30 45.41 | 6 0.54 0.37 67.94 |
| C_{max2}/D (ng/ml/μg)              | 6 0.00274 0.000645 23.56 | 6 0.00445 0.000778 49.15 | 6 0.00532 0.00131 24.68 | 6 0.00190 0.000907 47.83 |
| T_{max2} (h)                       | 6 0.80 0.65 81.94 | 5 0.63 0.30 48.57 | 6 0.67 0.30 45.41 | 5 0.54 0.37 67.94 |
| AUC_{0–tau1} (h-ng/ml/μg)          | 6 0.00480 0.000763 15.91 | 5 0.00327 0.00108 32.97 | 6 0.00168 0.000538 32.06 | 6 0.000599 0.000310 51.72 |
| AUC_{0–tau2} (h-ng/ml/μg)          | 6 1.336 0.1144 8.57 | 6 1.406 0.2473 17.58 | 6 0.9189 0.2537 27.60 | 6 0.5297 0.1987 37.52 |
| AUC_{0–tau3} (h-ng/ml/μg)          | 6 0.00668 0.000572 8.57 | 6 0.00703 0.00124 17.58 | 6 0.00459 0.00127 27.60 | 6 0.00265 0.000994 37.52 |
| AUC_{0–tau4} (h-ng/ml/μg)          | 6 4.820 0.3583 7.34 | 6 5.909 1.329 19.30 | 6 6.911 1.908 27.60 | 6 7.538 1.023 13.57 |
| AUC_{0–tau5} (h-ng/ml/μg)          | 6 5.190 0.5484 10.57 | 6 6.507 1.476 22.49 | 6 7.580 2.143 28.27 | 5 8.305 1.014 12.21 |
| AUC_{0–tau6} (h-ng/ml/μg)          | 4 0.00865 0.000914 10.57 | 6 0.0108 0.00246 22.68 | 6 0.0126 0.00357 28.27 | 5 0.0138 0.00169 12.21 |
| t_{1/2} (h)                        | 4 5.55 0.79 14.17 | 6 6.68 1.07 16.00 | 6 6.61 0.86 13.00 | 5 5.48 0.88 15.99 |
| AR_{C_{max}}                       | 6 1.22 0.27 22.31 | 5 1.87 0.60 32.16 | 6 2.46 0.90 36.51 | 5 3.56 0.81 22.79 |
| AR_{AUC_{tau}}                     | 6 1.43 0.28 19.30 | 5 2.29 0.64 27.92 | 6 3.00 1.40 46.65 | 6 4.86 1.40 28.84 |

q every, SD standard deviation, CV coefficient of variation, C_{max1} maximum plasma concentrations after first dose, D dose, T_{max1} time of the maximum plasma concentration after first dose, C_{max2} maximum plasma concentrations after last dose, T_{max2} time of the maximum plasma concentration after last dose, AUC_{0–tau1} area under the plasma concentration–time curve during the first dosing interval, calculated using the linear-log trapezoidal rule, AUC_{0–tau2} area under the plasma concentration–time curve during the last dosing interval, calculated using the linear-log trapezoidal rule, AUC_{0–tau3} area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, AUC_{0–tau4} area under the plasma concentration–time curve from time–zero extrapolated to infinity, t_{1/2} apparent elimination half-life in the terminal phase by noncompartmental analysis, AR_{C_{max}} accumulation ratio of C_{max}, AR_{AUC_{tau}} accumulation ratio of AUC_{tau}. 
1) to 0.893 ng/ml (Cohort 3), and there was less variability [based on coefficient of variation (CV)% within cohort]; although shorter dosing intervals resulted in higher concentrations, this trend for IV administration was not as apparent as that observed for fentanyl sublingual spray. For AUC0–tau1 and AUC 0–tau apparent as that observed for fentanyl sublingual spray. For concentrations, this trend for IV administration was not as evident as for shorter dosing intervals.

### Table 3: Mean fentanyl pharmacokinetic parameters after administration of fentanyl sublingual spray (400 µg)

| Parameter                      | Cohort 1 q4h | Cohort 2 q2h | Cohort 3 q1h | Cohort 4 q0.5h |
|-------------------------------|--------------|--------------|--------------|---------------|
| n                             | Mean         | CV%          | Mean         | CV%           | Mean         | CV%          | Mean         | CV%           |
| Cmax1 (ng/ml)                 | 6            | 1.14         | 6            | 0.610         | 6            | 0.808        | 6            | 0.704         |
| Cmax1/D (ng/ml/µg)            | 6            | 0.00285      | 6            | 0.00152       | 6            | 0.00202      | 6            | 0.00176       |
| Tmax1 (h)                     | 6            | 0.38         | 6            | 0.54          | 6            | 0.65         | 6            | 0.32          |
| Cmax (ng/ml)                  | 5            | 1.74         | 5            | 1.88          | 6            | 3.77         | 6            | 3.92          |
| Cmax/D (ng/ml/µg)             | 5            | 0.00435      | 5            | 0.00469       | 6            | 0.00693      | 6            | 0.00603       |
| Tmax (h)                      | 5            | 0.51         | 5            | 1.00          | 6            | 0.58         | 6            | 0.71          |
| AUC0–tau1 (h/ng/ml)           | 6            | 2.535        | 6            | 0.8455        | 6            | 0.6263       | 6            | 0.2277        |
| AUC0–tau1/D (ng/ml/µg)        | 6            | 0.00634      | 6            | 0.00211       | 6            | 0.00157      | 6            | 0.000569      |
| AUC0–tau2 (h/ng/ml)           | 5            | 4.259        | 5            | 2.872         | 5            | 3.598        | 6            | 3.232         |
| AUC0–tau2/D (h/ng/ml/µg)      | 5            | 0.0106       | 5            | 0.00718       | 5            | 0.00612      | 5            | 0.00220       |
| AUC0–inf (h/ng/ml)            | 5            | 14.77        | 5            | 12.69         | 6            | 15.55        | 5            | 15.34         |
| AUC0–inf/D (h/ng/ml/µg)       | 6            | 0.0132       | 6            | 0.00945       | 6            | 0.0130       | 6            | 0.0128        |
| AUC0–inf (h/ng/ml)            | 2            | 17.93        | 4            | 13.43         | 5            | 17.22        | 5            | 14.96         |
| AUC0–inf/D (h/ng/ml/µg)       | 3            | 0.0163       | 5            | 0.00979       | 5            | 0.0144       | 5            | 0.0125        |
| t1/2 (h)                      | 3            | 5.67         | 5            | 5.31          | 5            | 7.04         | 5            | 5.68          |
| ARmax                          | 5            | 1.64         | 5            | 3.11          | 6            | 3.54         | 6            | 4.22          |
| ARUACtau                       | 5            | 1.76         | 5            | 3.37          | 6            | 4.08         | 6            | 4.87          |

q every, CV coefficient of variation, Cmax1 maximum plasma concentrations after first dose, D dose, Tmax1 time of the maximum plasma concentration after first dose, Cmax maximum plasma concentrations after last dose, Tmax1 time of the maximum plasma concentration after last dose, AUC0–tau1 area under the plasma concentration time curve during the first dosing interval, calculated using the linear-log trapezoidal rule, AUC0–tau2 area under the plasma concentration time curve during the last dosing interval, calculated using the linear-log trapezoidal rule, AUC0–inf area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, AUC0–inf area under the plasma concentration–time curve from time–zero extrapolated to infinity, t1/2 apparent elimination half-life in the terminal phase by noncompartmental analysis, ARmax accumulation ratio of Cmax, ARUACtau accumulation ratio of AUC0–tau.

In general, pharmacokinetics after three consecutive doses of fentanyl sublingual spray behaved similarly to that after fentanyl citrate IV 50 µg, as follows: (1) after the last dose, the peak and extent of fentanyl exposures increased relative to the first dose and shorter dosing intervals resulted in higher exposures; (2) the mean t1/2 after the last dose of fentanyl was similar across cohorts; (3) the accumulation between the first and last doses of fentanyl was observed for all dosing intervals, with more pronounced accumulation for shorter dosing intervals.

The statistical analysis of dose proportionality of fentanyl sublingual spray (100–400 µg) is summarized in Table 5. The results of the dose proportionality assessments by the power model showed that dose proportionality could not be statistically established over the full dose range of 100–400 µg fentanyl sublingual spray. The slope (β1) estimates for pharmacokinetic exposure parameters were within 0.80 and 1.25 for Cohorts 2 and 4, but greater than 1 (ranging from 1.1764 to 1.4615) for Cohorts 1 and 3, with variable 90% confidence intervals. The dose proportionality results are shown with a linear slope and correlation coefficient by cohort for fentanyl Cmax in Fig. 2a, fentanyl AUC0–inf in Fig. 2b, and fentanyl AUC0–tau in Fig. 2c, showing linear dose-dependent increases of the pharmacokinetic parameters tested. In summary, systemic
exposure following multiple doses of fentanyl sublingual spray appeared to increase in a slightly greater than dose-proportional manner over the range of 100–400 μg.

3.3 Safety and Pharmacodynamics Analyses

There were no deaths or serious AEs reported during the conduct of this clinical trial. Safety results and pharmacodynamic analysis relevant to respiratory function are presented in a separate publication [8].

4 Discussion

Fentanyl sublingual spray was designed to provide rapid onset of analgesia and has demonstrated pharmacokinetic parameters similar to those of IV fentanyl, showing a rapid increase in plasma concentrations after quantifiable mean plasma concentrations of fentanyl observed at the first blood collection timepoint (5 min) after administration [6, 10]. Because of these advantages, it has been postulated that fentanyl sublingual spray might be appropriately used for acute needs (e.g., procedurally or in emergency departments) or for post-operative pain. However, patients likely to receive opioids in these settings will include those who are opioid naïve or who have limited prior exposure to opioids. Consequently, it is important to understand the relationship between systemic exposure of fentanyl following administration of fentanyl sublingual spray and its effects on respiratory function in an opioid-naïve or non-tolerant population. Therefore, a phase 1, single ascending-dose study was conducted in an opioid-naïve population to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of fentanyl sublingual spray prior to entering clinical trials within acute pain and related settings [7]. Overall, a single-dose administration of fentanyl

| Parameter | Cohort 1 q4 h | | Cohort 2 q2 h | | Cohort 3 q1 h | | Cohort 4 q0.5 h |
|-----------|--------------|-----------------|--------------|-----------------|--------------|-----------------|
| n | Mean | CV% | n | Mean | CV% | n | Mean | CV% | n | Mean | CV% |
| Cmax1 (ng/ml) | 6 | 0.337 | 62.84 | 6 | 0.349 | 60.59 | 6 | 0.477 | 35.25 | 6 | 0.369 | 54.09 |
| Cmax1/D (ng/ml/μg) | 6 | 0.00673 | 62.84 | 6 | 0.0110 | 40.59 | 6 | 0.00955 | 35.25 | 6 | 0.00738 | 54.09 |
| Tmax1 (h) | 6 | 0.16 | 101.8 | 6 | 0.08 | 0.00 | 6 | 0.08 | 0.00 | 6 | 0.13 | 50.02 |
| AUC0–tau1 (ng/ml) | 6 | 0.3298 | 25.4 | 6 | 0.3020 | 11.27 | 6 | 0.2182 | 25.41 | 6 | 0.1093 | 34.27 |
| AUC0–tau1/D (ng/ml/μg) | 6 | 0.0660 | 25.4 | 6 | 0.00604 | 11.27 | 6 | 0.00436 | 25.41 | 6 | 0.00219 | 34.27 |
| AUC0–tau2 (h-ng/ml) | 6 | 0.6133 | 21.55 | 6 | 0.6106 | 18.59 | 5 | 0.3964 | 21.95 | 6 | 0.2578 | 10.19 |
| AUC0–tau2/D (h-ng/ml/μg) | 6 | 0.1231 | 21.55 | 6 | 0.1122 | 18.59 | 5 | 0.0793 | 21.95 | 6 | 0.00516 | 10.19 |
| AUC0–t (h-ng/ml) | 6 | 2.139 | 26.38 | 6 | 2.400 | 24.23 | 5 | 2.211 | 34.50 | 6 | 2.286 | 17.34 |
| AUC0–t/D (h-ng/ml/μg) | 6 | 0.0143 | 26.38 | 6 | 0.0160 | 24.23 | 6 | 0.0146 | 31.32 | 6 | 0.0152 | 17.34 |
| AUC0–inf (h-ng/ml) | 6 | 2.882 | 0.00 | 5 | 2.628 | 28.25 | 4 | 2.358 | 40.07 | 6 | 2.517 | 17.65 |
| AUC0–inf/D (h-ng/ml/μg) | 6 | 0.0192 | 0.00 | 5 | 0.0175 | 28.25 | 4 | 0.0157 | 40.07 | 6 | 0.0168 | 17.65 |
| t1/2 (h) | 1 | 6.90 | 0.00 | 5 | 5.13 | 43.75 | 4 | 4.69 | 34.84 | 6 | 5.42 | 17.33 |
| CL (L/h) | 1 | 52.05 | 0.00 | 5 | 61.48 | 32.25 | 4 | 72.29 | 40.05 | 6 | 61.22 | 18.02 |
| Vz (L) | 1 | 518.2 | 0.00 | 5 | 413.3 | 28.35 | 4 | 439.7 | 10.99 | 6 | 468.4 | 11.08 |
| ARmax/Cmax | 6 | 3.08 | 79.40 | 6 | 1.57 | 49.04 | 5 | 2.19 | 57.13 | 6 | 2.72 | 50.85 |
| ARAUCtau | 6 | 1.90 | 18.15 | 6 | 2.04 | 18.10 | 5 | 1.89 | 17.72 | 6 | 2.57 | 33.14 |

IV intravenous, q every, CV coefficient of variation, Cmax maximum plasma concentrations after first dose, D dose, Tmax time of the maximum plasma concentration after first dose, Cmax maximum plasma concentrations after last dose, Tmax time of the maximum plasma concentration after last dose, AUC0–tau area under the plasma concentration time curve during the first dosing interval, calculated using the linear-log trapezoidal rule, AUC0–t area under the plasma concentration time curve during the last dosing interval, calculated using the linear-log trapezoidal rule, AUC0–inf area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, ARCmax accumulation ratio of Cmax, ARAUCtau accumulation ratio of AUCtau, t1/2 apparent elimination half-life in the terminal phase by noncompartmental analysis, ARmax/Cmax accumulation ratio of Cmax, ARAUCtau accumulation ratio of AUCtau.
sublingual spray at doses ranging from 100 to 800 \( \mu \)g was generally well tolerated. Results suggested that doses up to 200 \( \mu \)g may be safely administered to a healthy opioid-naive population with routine monitoring and that doses of 400–800 \( \mu \)g may be administered in a monitored setting where nasal cannula oxygenation is available [7].

**Table 5** Assessment of dose proportionality of fentanyl sublingual spray (100–400 \( \mu \)g)

| Cohort       | Dependent variable | Model variable | Estimate (\( \beta_1 \)) | Lower CL \( ^a \) | Upper CL \( ^a \) | \( p \) value \( ^b \) |
|--------------|--------------------|----------------|--------------------------|-----------------|-----------------|----------------|
| Cohort 1 (q4 h) | ln(C\(_{\text{max}}\)) | ln(Dose)       | 1.4336                   | 1.2382           | 1.6290           | < 0.0001       |
|              | ln(AUC\(_{0-t}\))  | ln(Dose)       | 1.3945                   | 1.1581           | 1.6309           | < 0.0001       |
|              | ln(AUC\(_{0-inf}\))| ln(Dose)       | 1.4615                   | 0.9447           | 1.9783           | 0.0015         |
| Cohort 2 (q2 h) | ln(C\(_{\text{max}}\)) | ln(Dose)       | 1.0993                   | 0.8803           | 1.3183           | < 0.0001       |
|              | ln(AUC\(_{0-t}\))  | ln(Dose)       | 1.0989                   | 0.8057           | 1.3921           | < 0.0001       |
|              | ln(AUC\(_{0-inf}\))| ln(Dose)       | 1.1925                   | 0.7927           | 1.5924           | 0.0002         |
| Cohort 3 (q1 h) | ln(C\(_{\text{max}}\)) | ln(Dose)       | 1.3800                   | 1.1637           | 1.5962           | < 0.0001       |
|              | ln(AUC\(_{0-t}\))  | ln(Dose)       | 1.1932                   | NE               | NE               | NE             |
|              | ln(AUC\(_{0-inf}\))| ln(Dose)       | 1.1764                   | 0.9237           | 1.4291           | < 0.0001       |
| Cohort 4 (q0.5 h) | ln(C\(_{\text{max}}\)) | ln(Dose)       | 1.2031                   | 0.9227           | 1.4836           | < 0.0001       |
|              | ln(AUC\(_{0-t}\))  | ln(Dose)       | 1.2463                   | 1.0037           | 1.4888           | < 0.0001       |
|              | ln(AUC\(_{0-inf}\))| ln(Dose)       | 1.1190                   | 0.8516           | 1.3864           | < 0.0001       |

\( q \) every, \( C_{\text{max}} \) maximum plasma concentrations after last dose, \( AUC_{0-t} \) area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, \( AUC_{0-inf} \) area under the plasma concentration–time curve from time–zero to infinity, \( NE \) not estimable

\( ^a \)90\% confidence intervals (lower and upper)

\( ^b \)Significant difference from unity (1.0000), defined a priori as \( p < 0.05 \)
Furthermore, mean plasma concentrations and mean exposure parameters of fentanyl following fentanyl sublingual spray were comparable to results in previous studies [6, 10] over the dose range from 100 to 800 μg [7].

In the present study, the pharmacokinetics, pharmacodynamics, safety, and tolerability of multiple doses of fentanyl sublingual spray were further investigated in opioid-naïve participants at one clinical site, and compared with those of multiple doses of IV fentanyl citrate.

In general, multiple-dose pharmacokinetics of fentanyl were consistent with previously reported single-dose pharmacokinetic profiles following fentanyl sublingual spray or fentanyl citrate IV. Mean plasma fentanyl concentrations increased with an increase in dose of fentanyl sublingual spray between 100 μg (Cycle 1) and 400 μg (Cycle 3). As expected, higher concentrations were observed for the shortest dosing intervals of 1 h (Cohort 3) and 0.5 h (Cohort 4). A similar trend was observed after administration of fentanyl citrate IV 50 μg, with the highest concentrations observed for more frequent dosing, every 1 h (Cohort 3) or 0.5 h (Cohort 4). The t1/2 was approximately 5–7 h for both fentanyl sublingual spray and fentanyl citrate IV administration. During multiple doses of fentanyl sublingual spray, Cmax increased relative to the first dose, and shorter dosing intervals resulted in higher concentrations. Similar trends were observed for

Fig. 2 Dose proportionality of fentanyl a Cmax, b AUC0–inf, and c AUC0–t after administration of fentanyl sublingual spray 100 μg (Cycle 1), 200 μg (Cycle 2), and 400 μg (Cycle 3) every 4 h (Cohort 1), 2 h (Cohort 2), 1 h (Cohort 3), or 0.5 h (Cohort 4). AUC0–t area under the plasma concentration–time curve from time–zero to the time of the last quantifiable concentration, calculated using the linear-log trapezoidal rule, AUC0–inf area under the plasma concentration–time curve from time–zero extrapolated to infinity, calculated using the linear-log trapezoidal rule, Cmax maximum plasma concentrations after last dose

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AUC\textsubscript{0–\texttau} with an increase in exposure between the first and last doses, which was most apparent for the shorter dosing intervals of 1 h (Cohort 3) and 0.5 h (Cohort 4). The accumulation ratios between the first and last doses of fentanyl sublingual spray ranged from approximately 1.2 to 1.8 (every 4 h), 1.9 to 3.4 (every 2 h), 2.5 to 4.2 (every 1 h), to 3.6 to 4.9 (every 0.5 h), with more pronounced accumulation for shorter dosing intervals. Similarly, accumulation ratios between the first and last doses of fentanyl citrate IV ranged from approximately 1.9 to 3.1 (every 4 h), 1.6 to 2.0 (every 2 h) and 1.9 to 2.2 (every 1 h) to 2.6 to 2.7 (every 0.5 h), with comparable accumulation across all dosing intervals but slightly less than with sublingual sprays.

Analysis of dose proportionality using the power model [9] suggested that maximum fentanyl exposure (C\textsubscript{max}) and total fentanyl exposure (AUC\textsubscript{0–t} and AUC\textsubscript{0–inf}) increased in a linear manner, with an increase in dose following multiple-dose administrations of fentanyl sublingual spray at all dosing intervals ranging from 0.5 to 4 h. From the linear regression through log-transformed parameter values versus log-dose using all dose levels within each dosing interval, the slope of the regression line ranged from 1.099 (AUC\textsubscript{0–t} every 2 h) to 1.462 (AUC\textsubscript{0–inf} every 4 h), suggesting that the increase in exposure was slightly greater than dose proportional. This may be due to some accumulation at the higher dose following short dosing frequency, small number of subjects, and inter-subject variability.

There were no appreciable differences in safety-related pharmacodynamic changes following fentanyl sublingual spray administration for capnography, pulse oximetry, hypoxia, nausea, and vomiting compared with fentanyl citrate IV 50 μg [8].

5 Conclusions

Dose-dependent fentanyl pharmacokinetics following multiple doses of fentanyl sublingual spray were well characterized in healthy opioid-naïve adults. During multiple doses of fentanyl sublingual spray, C\textsubscript{max} increased relative to the first dose, and shorter dosing intervals resulted in higher concentrations. Similar trends were observed for AUC\textsubscript{0–\texttau}, with an increase in exposure between the first and last doses, which was most apparent at shorter dosing intervals. The accumulation ratios between the first and last doses of fentanyl sublingual spray ranged from approximately 1.2 to 4.9, with more pronounced accumulation for shorter dosing intervals. Systemic exposure following multiple doses of fentanyl sublingual spray appeared to increase in a slightly greater than dose-proportional manner over the range of 100–400 μg. Three repeated doses of fentanyl sublingual spray administered at doses of 100, 200, and 400 μg and at dosing intervals ranging from every 0.5 to 4 h were generally well tolerated in a healthy opioid-naïve population.

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Ethics approval All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments). A valid Institutional Review Board (IRB) reviewed and approved the protocol before study initiation.

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Informed consent Written informed consent was obtained prior to study participation.

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