Effect of Dosing Interval on Pharmacokinetics and Safety of Lazanda® (Fentanyl Pectin Nasal Spray)
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Purpose
To evaluate the effect of dosing interval on pharmacokinetics and safety of fentanyl pectin nasal spray.

Methods
This was an open-label, randomized study in healthy volunteers. Five treatments were administered to the right nostril of each subject, with a ≥3-day washout period: 1X100 µg; 2X100 µg, 4-hr interval; 2X100 µg, 2-hr interval; 2X100 µg, 1-hr interval; and 8X100 µg, consecutively. Each treatment was administered under naltrexone blockade. Blood samples were collected and analyzed for plasma fentanyl concentrations. Pharmacokinetic parameters were derived using non-compartmental model method.

Results
13 subjects were enrolled and 10 (77%) completed the study.
For the two-dose regimens, maximum concentration (Cmax) was higher after the second dose than after the first. The increase was statistically significant for the 1-hr and 2-hr intervals, but not for the 4-hr dosing interval. There were no statistically significant differences in area-under-concentration (AUC) values. After 8 consecutive 100-µg doses, the average Cmax was 5.2-fold greater and the AUC0-24 5.4-fold greater than those attained after a single 100-µg dose, suggesting that the increase in exposure was less than dose proportional. Time to peak concentration (tmax) was approximately 15 min and this was consistent across all dosing groups.
No new adverse events or safety signals were observed. Fifty-three percent of patients reported ≥1 adverse event (AE), with dizziness (11.9%) and somnolence (4.9%) most common; 12.9% of patients discontinued due to AEs. Rates of all AEs rapidly decreased to sustained low levels after 4-5 weeks of treatment.

Conclusion
Single- and multiple-doses of nasal fentanyl under naltrexone blockade were well tolerated. When intervals between two doses were shorter, the Cmax of the second dose was higher compared with the first dose. AUC values appeared to be independent of dosing interval. Cmax and AUC reached a plateau after 8 consecutive doses into the same nostril.