

Pharmacokinetics and Dose Proportionality of Sublingual Sufentanil NanoTab™ in Healthy Volunteers

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Sufentanil: A Superior Opioid

- Approved for intravenous (IV) and epidural administration¹
- High therapeutic index²
- No active metabolites³
- Rapid transmucosal uptake

Opioid	Therapeutic index ²
Methadone	12
Meperidine	28
Morphine	70
Hydromorphone	232
Fentanyl	300
Sufentanil	25,000

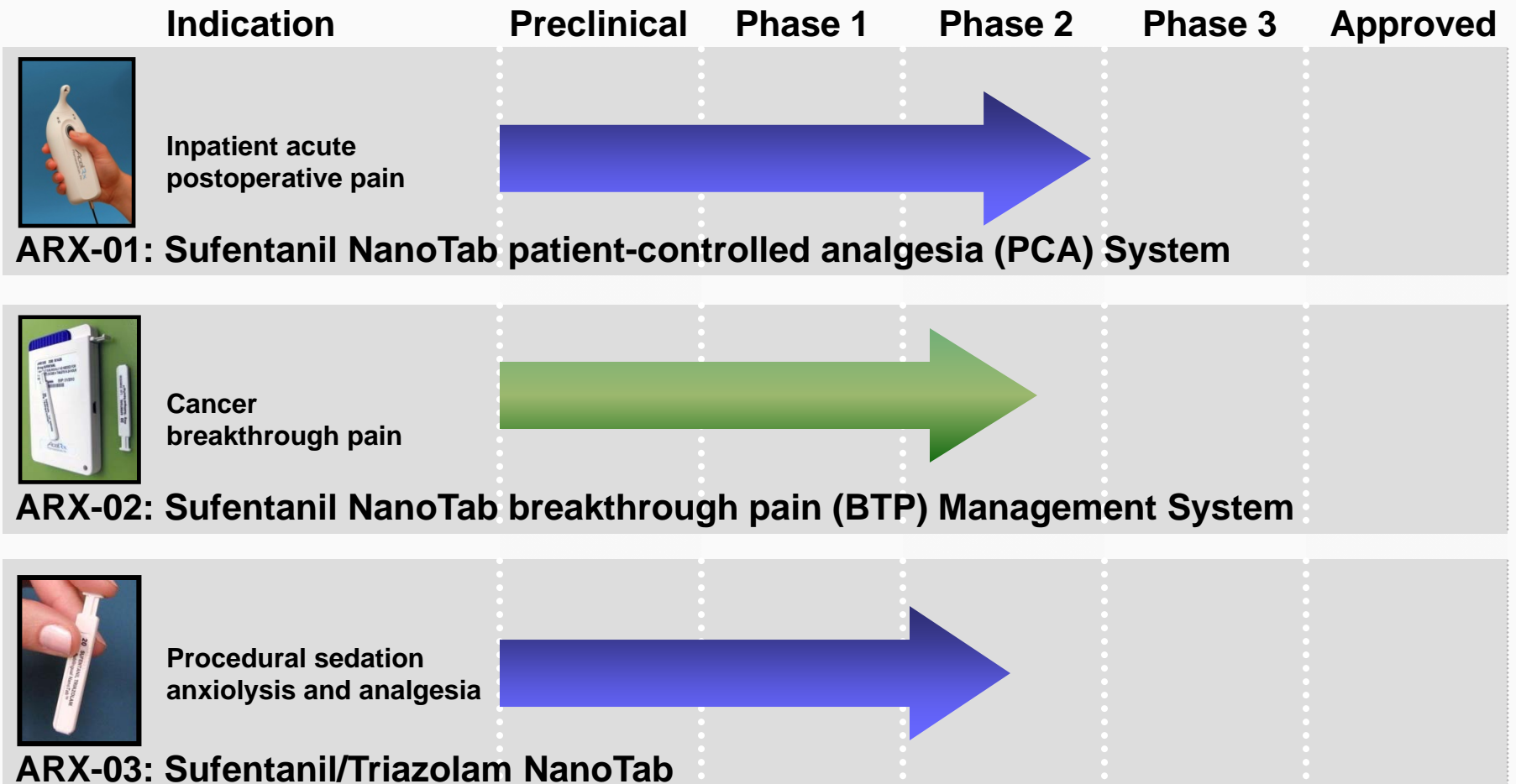
Therapeutic index = median lethal dose (LD₅₀) / lowest median effective dose (ED₅₀)

NanoTab: Efficient Transmucosal Delivery

- NanoTab: a novel oral transmucosal dosage form
- Key attributes:
 - Bioadhesive
 - Low saliva response
 - Minimal swallowed drug
 - Enhanced transmucosal uptake
 - Consistent pharmacokinetics
 - High bioavailability



AcelRx Development Programs



Study Objective and Methods

Objective:

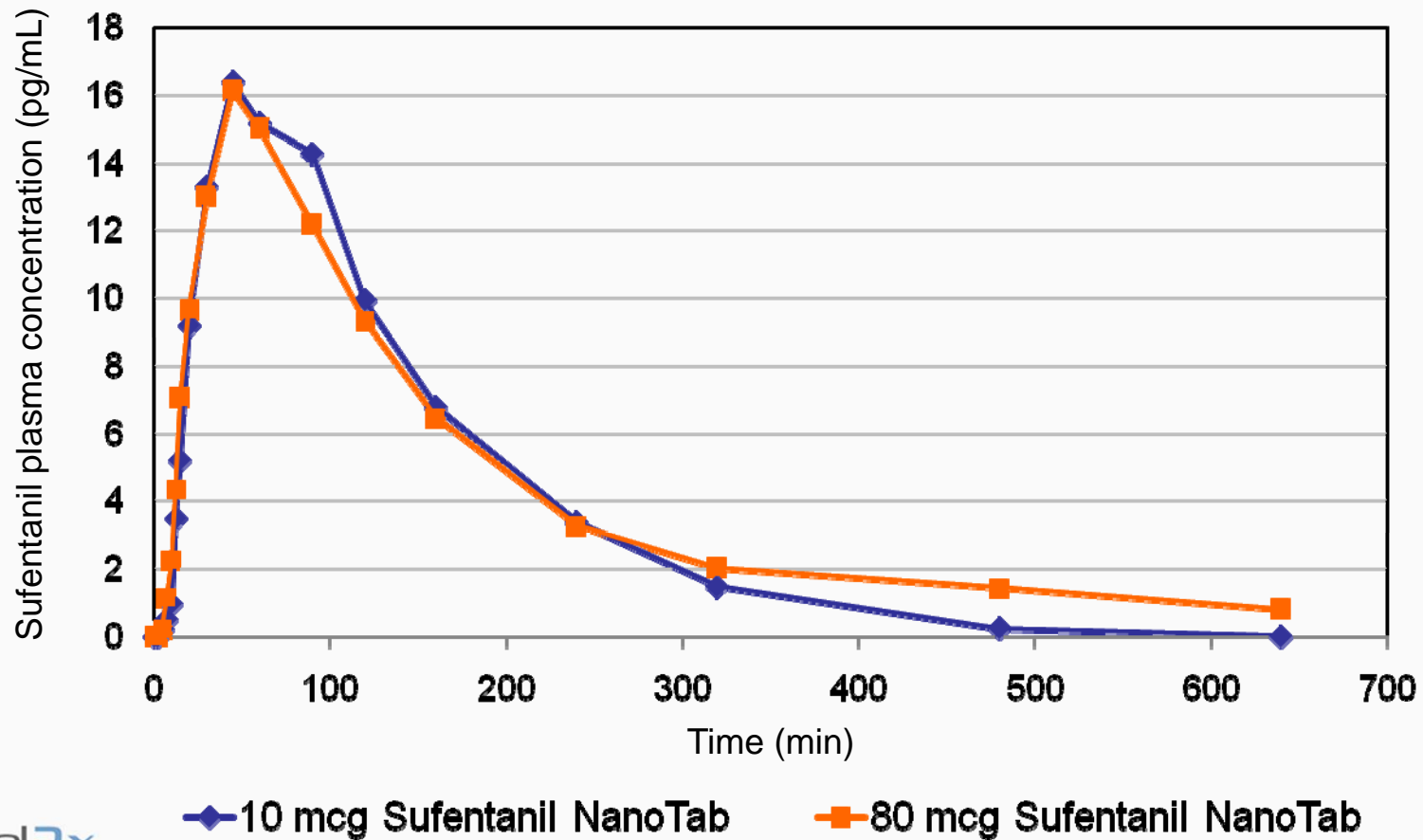
- To determine the pharmacokinetics and dose proportionality of varying strengths of sublingual Sufentanil NanoTabs

Methods:

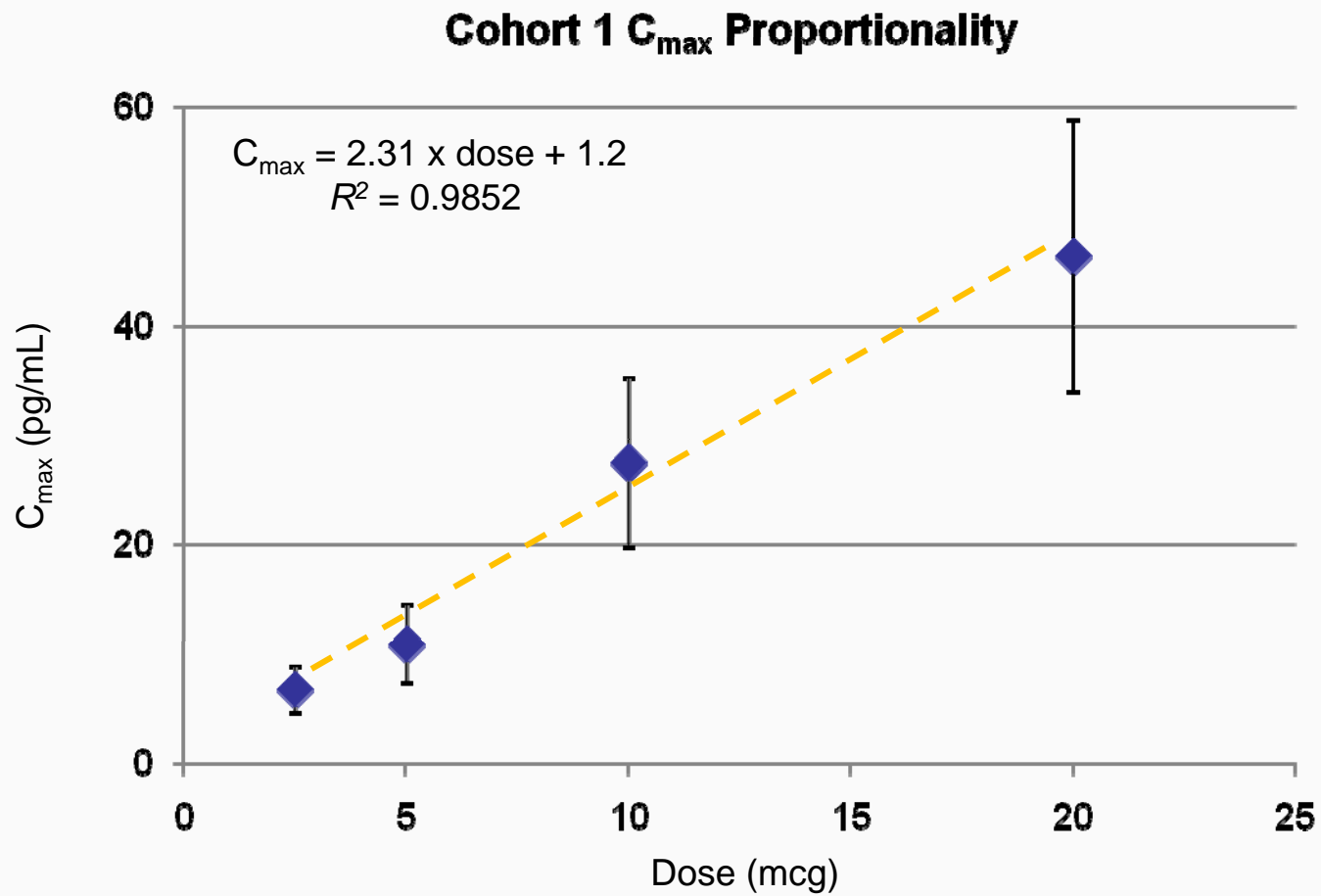
- Design: open-label, single-dose, crossover design
- 24 healthy volunteers (12 males, 12 females, 18-45 years of age) in 2 cohorts
- Treatments:
 - Cohort 1 (n = 12) received lower dosage strengths (2.5, 5, and 10 mcg)
 - Cohort 2 (n = 12) received higher strengths (10 and 80 mcg)
 - All subjects received IV sufentanil 5 mcg
 - All subjects were blocked with oral naltrexone 50 mg bid
- Plasma sufentanil concentrations were determined for 640 minutes following Sufentanil NanoTab dosing

Linear Dose Proportionality

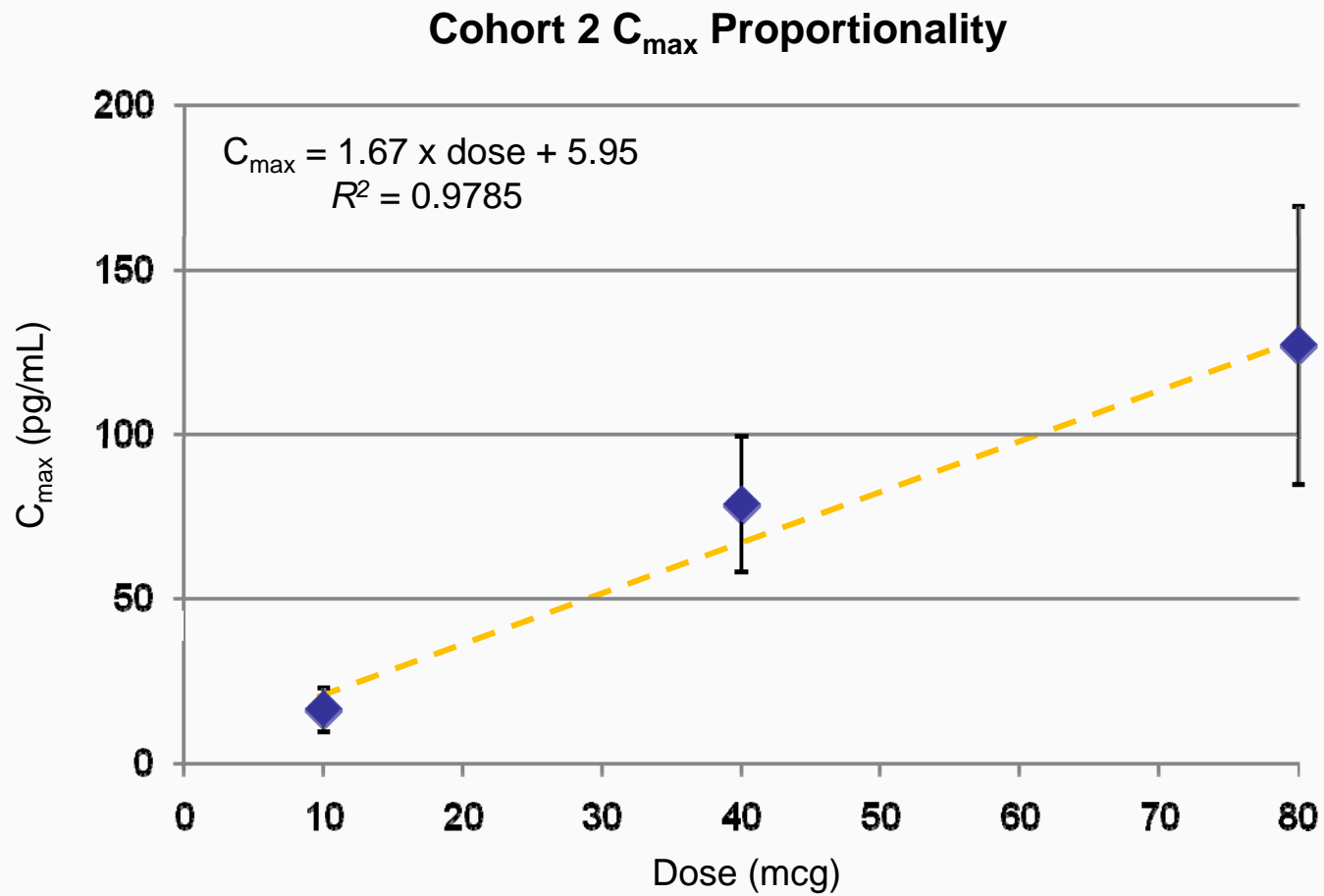
10 mcg vs 80 mcg (80 mcg dose normalized to 10 mcg)



Mean (\pm SD) C_{\max} of Sufentanil versus Dose



Mean (\pm SD) C_{\max} of Sufentanil versus Dose



Oral Transmucosal Products: Sufentanil vs Fentanyl

	ARX-02 80 mcg	Actiq 400 mcg	Fentora 400 mcg	Onsolis 800 mcg
Active ingredient	Sufentanil	Fentanyl	Fentanyl	Fentanyl
Bioavailability	79%	47% ^{1,*}	65% ¹	71% ³
T _{max} (range)	53 min (30-90)	91 min ^{1,*} (35-240)	47 min ¹ (20-240)	60 min ³ (45-240)
t _{1/2} (range) (%CV)	4.23 h (2.89-5.79) (21%)	6.43 h ² (NA) (115%)	11.09 h ¹ (4.63-20.59) (NA)	14 h ³ (NA) (NA)

T_{max}, time to maximum concentration; t_{1/2}, half-life;
CV, coefficient of variation; NA, not available.
*Dose adjusted (800 mcg to 400 mcg).

1. Fentora (fentanyl citrate) [package insert]. Frazer, PA: Cephalon; 2006.
2. Actiq (fentanyl citrate) [package insert]. Salt Lake City, UT: Cephalon; 2007.
3. Onsolis (fentanyl citrate) [package insert]. Somerset, NJ: Meda Pharmaceuticals; 2009.

Sufentanil NanoTab BTP Management System

- First transmucosal formulation of sufentanil
 - Allows opioid rotation
- Highly consistent C_{max} and T_{max}
 - Avoids dose stacking
- Shorter half-life than fentanyl products
 - More closely matches BTP episode
- Compact smart dispenser to monitor dosing in an outpatient setting



Thank You