Introduction and Review of Clinical Safety and Efficacy

New Drug Application (NDA) 209128

Sufentanil Sublingual Tablet (SST) 30 mcg

Anesthetic and Analgesic Drug Products

Advisory Committee Meeting

October 12, 2018

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Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA

Overview of FDA Presentations

- **Introduction and Review of Clinical Safety and Efficacy**
  - Ning Hu, MD, MS
    Clinical Reviewer
    DAAAP, ODE-II, OND, CDER, FDA
- **Human Factors Evaluation**
  - James Schlick, MBA, RPh
    Reviewer
    Division of Medication Error Prevention and Analysis (DMEPA)
    Office of Medication Error Prevention and Risk Management (OMEPRM)
    Office of Surveillance and Epidemiology (OSE), CDER, FDA
- **Risk Evaluation and Mitigation Strategies (REMS) Considerations**
  - LaShaun Washington-Batts, PharmD
    Reviewer
    Division of Risk Management (DRISK), OMEPRM, OSE, CDER, FDA
- **Benefit/Risk Considerations**
  - Ning Hu, MD, MS

Presentation Overview

- Introduction
- Efficacy
- Safety

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Overview

- **Drug name, class, and dosage form:**
  - Sufentanil sublingual tablet (SST), 30 mcg (proposed trade name Dsuvia)
  - Opioid analgesic, Schedule II

- **Combination drug/device**
  - Small tablet (3 mm in diameter and 0.85 mm in thickness) in a single-dose applicator (SDA)

Applicant's Proposed Indication and Dosing

- **Applicant's proposed indication:**
  - Management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting

- **Dosing:**
  - 30 mcg sublingually as needed with a minimum interval of one hour between doses
  - Do not exceed 12 tablets in 24 hours
  - Given by a healthcare provider in a certified medically supervised setting

Issues for Consideration

- Efficacy of SST 30 mcg for the management of acute pain
- Safety profile of SST 30 mcg
- Risk of misplaced tablets and risk of accidental exposure
- Overall benefit/risk considerations for SST 30 mcg

Key Regulatory Interactions: SST 30 mcg

- **October 4, 2011:** IND 113059 submission
- **December 12, 2016:** Original NDA submission
- **October 11, 2017:** Complete Response letter issued
  - The letter outlined two deficiencies:
    - Inadequate number of patients dosed at the maximum dosing proposed for labeling
    - Risk of misplaced tablets
- **January 26, 2018:** Post-action meeting to discuss the deficiencies and the Applicant's proposal to address them
- **May 3, 2018:** NDA resubmission

IND=Investigational New Drug

SST 15 mcg program

- SST 15 mcg is a different sufentanil-device combination (proposed trade name Zalviso)
- NDA received a complete response in 2014 primarily due to device-related issues
- Key differences between SST 15 mcg and 30 mcg:
  - Different devices
  - SST 30 mcg is administered by a health care provider while SST 15 mcg is administered by a patient
  - Different doses (30 mcg vs. 15 mcg)
- The Applicant used selected safety data from the SST 15 mcg program to support the SST 30 mcg program
  - Bioequivalence established between two doses of SST 15 mcg administered within 20 to 25 minutes and a single dose of SST 30 mcg

Overview of Data Supporting the SST 30 mcg Application

- 505(b)(2) NDA
  - References listed drug: Sufenta (sufentanil citrate for injection; NDA 19050)
- SST 30 mcg program
- Selected safety data from SST 15 mcg program

SST 30 mcg Clinical Studies

- Studies included in FDA's analysis
  - SAP 101: Phase 1 pharmacokinetic study
  - SAP 301: Phase 3 multicenter, randomized, placebo-controlled study
  - SAP 302: Phase 3 multicenter, open-label study
  - SAP 303: Phase 3 multicenter, open-label study

- Data from SAP 202 were not used to support the efficacy and safety of SST 30 mcg
  - SAP 202 used a different formulation and the in vitro data were not sufficient to bridge it to the final to-be-marketed formulation

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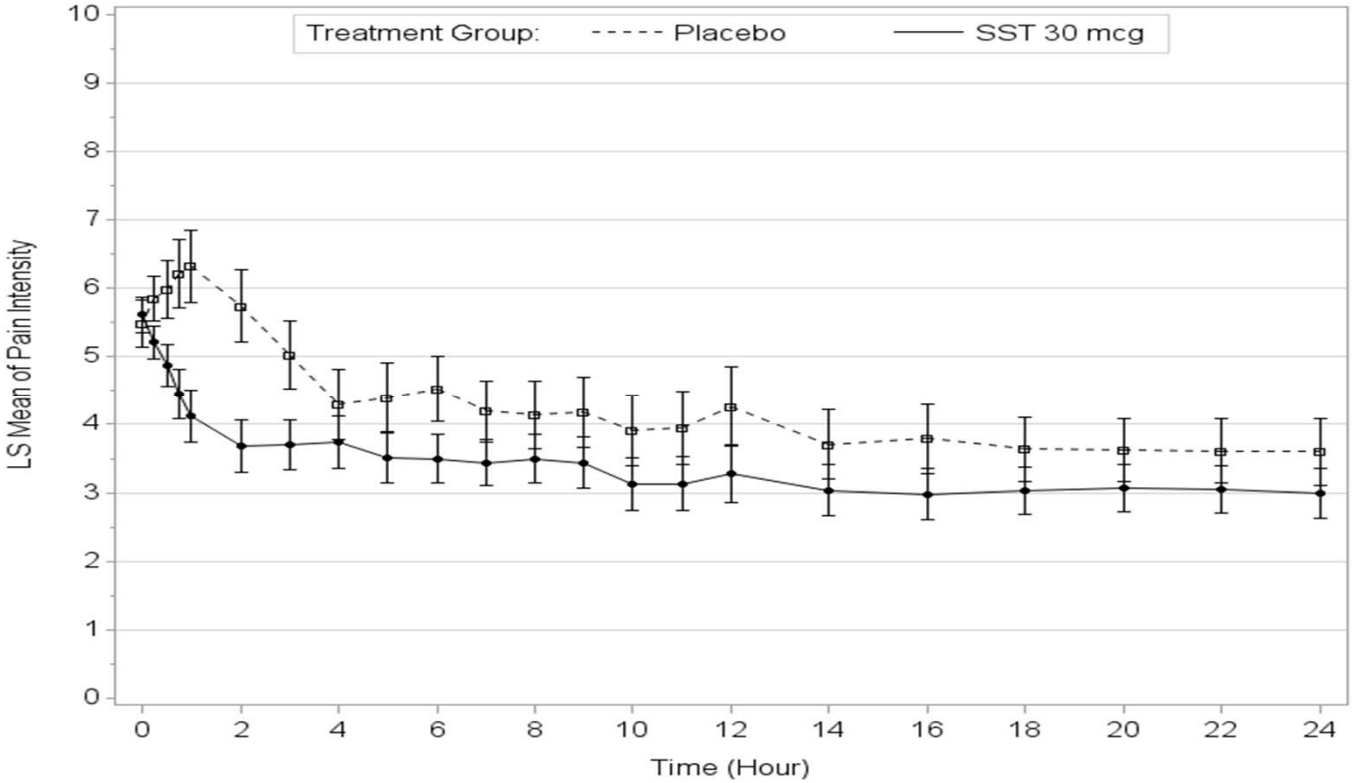
Overview of Study SAP 301

Characteristics	SAP 301
Design	• Multicenter, randomized, placebo-controlled
Treatment groups (# of patients)	• Sufentanil sublingual tablet 30 mcg (107) • Placebo (54)
Dosing regimen	• As needed per request with a minimum of 60 minutes between doses
Rescue analgesia	• Morphine IV 1 mg
Study duration	• Up to 48 hours
Study population	• Post-surgical adult patients pain intensity of ≥4 following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery
Efficacy measurement	• 11-point numerical pain rating scale (NPRS)
Primary efficacy endpoint	• Time-weighted summed pain intensity difference from baseline over 12 hours (SPID12)
Selected secondary efficacy endpoints	• Total number of study medication and rescue medication doses used over 12-hour study period • Time to onset of meaningful pain relief

Pain Intensity Scores Over 24 Hours: SAP 301 (ITT Population)



SPID12

Mean Difference (95% CI)	P-value
12.7 (7.2, 18.2)	< 0.001

Number of Rescue Medication Doses Used Over the First 12-Hours: SAP 301 (ITT population)

Number of Doses Used over 12 Hours	SST 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	0.4 (1.0)	1.6 (1.8)	
Median	0	1	
Range	(0, 7)	(0, 8)	
LS Mean Difference (vs placebo)	-1.2 (-1.6, -0.8)		< 0.001

- 22% (SST 30 mcg) vs 65% (placebo) of patients used rescue medication in the first 12 hours

Time to Onset of Meaningful Pain Relief: SAP 301 (ITT population)

Time to Onset (minutes)	SST 30 mcg (n = 107)	Placebo (n = 54)
Median (95% CI)	54 (42, 72)	84 (56, 250)
Range	4, 2400	6, 606

Efficacy Summary and Conclusions

- The primary and secondary endpoints in SAP 301 support the efficacy of SST 30 mcg for the management of acute pain
- The efficacy of SST 30 mcg was compared to placebo

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Overview of Safety

- Evaluation of SST 30 mcg
  - Safety database included data from three SST 30 mcg studies and selected data from six SST 15 mcg studies

- Evaluation of device/misplaced tablet risk
  - Human factors studies
  - Risk assessment following accidental exposure to SST 30 mcg

Review of Safety: Original NDA

- **Sufentanil Exposure**
  - Total of 646 patients exposed to SSTs
    - 323 patients exposed to SST 30 mcg
      - 86% used fewer than six doses in the first 12 hours, and the remaining 14% used between 6 to 12 doses (SAP 301)
    - 323 patients exposed to SST 15 mcg
  - The overall size of the safety database was adequate for the 505 (b)(2) application. However, the number of patient exposed to multiple doses was not adequate.
- **Misplaced tablets**
  - Three events of dropped tablets in SST 30 mcg Phase 3 trials
  - Errors occurred in the first human factors validation study

Safety Review of SAP 301

- No deaths occurred
- **SAEs:** Two occurred in the placebo group
- **Discontinuations due to AEs:** Higher in the placebo group (3.7%) compared to the SST 30 mcg group (0.9%)
- **Common AEs:** The events in the SST 30 mcg treatment group were consistent with an opioid's safety profile
- **Respiratory:**
  - More patients had oxygen saturation < 93% in the SST 30 mcg group than in the placebo group (7.5% vs. 0% for SST and placebo, respectively)
  - Two patients in the SST 30 mcg group had oxygen saturations less than 92%

Deficiencies in Original NDA Review (1)

- **Inadequate number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of SST 30 mcg**
  - Important as there is a nearly 4-fold increase in exposure and a more than 2-fold increase in the maximum concentration when dosed at steady state
  - To address the deficiency: collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety following the maximum dosing proposed

Applicant's proposal to address this deficiency:

- Decreased the maximum daily dose from 24 to 12 tablets and submitted new pooled safety analyses

Deficiencies in Original NDA Review (2)

- **The possibility of misplaced tablets poses a potential risk for accidental exposure and improper dosing**

  – To address the deficiency: develop mitigation strategies to address the risk of dropped tablets and conduct another human factors validation study

  Applicant's proposal to address this deficiency:

  – Performed a second human factors study after incorporating the FDA's recommendations
  – Submitted a risk assessment following accidental exposure to SST 30 mcg

Applicant's Pooled Safety Analysis to Support Proposed Maximum Dose

- Pooled data from one SST 30 mcg study (up to 48 hours) and three SST 15 mcg studies (up to 72 hours)
- Analyses were based on total sufentanil dose received (<300 mcg or ≥300 mcg)
  - There are limitations to these safety analyses, such as:
    - Differences in the SST 15 and 30 mcg clinical programs
    - A variety of factors influence total dose received
  - Despite these limitation, there was no clear relationship between higher total sufentanil dose received and adverse events

Safety Concern Associated with Dropped/Misplaced Tablets

- **Significant safety concern of accidental exposure, overdose, and death, particularly in children**
  - Sufentanil is a Schedule II opioid
  - Small tablet size
- **To address this safety concern:**
  - Risk assessment following accidental exposure to SST 30 mcg
  - Two human factors validation studies
  - Risk Evaluation and Mitigation Strategies (REMS)

Risk Analysis Following Accidental Exposure to SST 30 mcg

- **Applicant predicted the sufentanil plasma concentration following accidental exposure**
  - FDA agrees with the Applicant's methodology
- **Applicant considered clinical implications of the predicted plasma concentration**
  - There are limitations in using the published literature to evaluate the risks associated with accidental exposure
  - While definitive conclusions are not possible, there is a risk of respiratory depression and death associated with accidental exposure

Summary

- SST 30 mcg was effective in reducing pain intensity in one placebo, controlled trial
- Safety profile of SST 30 mcg was consistent with an opioid agonist
  - However, given the small size of the sufentanil tablet, there is concern for risks associated with misplaced tablets, such as accidental exposure and respiratory depression

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