Unique Study Considerations for Assessing BE of Intraoral Dosage Forms

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Outline

• Drivers for developing intraoral (IO) dosage forms
• Highlights of current regulatory guidance on clinical evaluations of intraoral dosage forms
• Various scenarios of pharmacokinetic (PK) outcome of IO dosage forms as compared to oral immediate release (IR) references
• Unique factors in protocol designs and their implications on Bioavailability/Bioequivalence (BA/BE) outcome
• Assessment of intraoral absorption and its impact on BE
• Summary
Drivers for developing intraoral dosage forms

For patients
- Pediatric
- Geriatric
- Patients with dysphagia
- Convenience
- Compliance

For innovators
- Effective product life-cycle management (LCM) option
- Unique PK/efficacy profiles
- Enabling delivery of drugs with significant 1st pass metabolism

First approved ODT in 1996

Mucoadhesive buccal film of buprenorphine/naloxone approved by FDA in Jun-2014

First approved Rx ODF in 2010
Common Intraoral Dosage Forms and Development Strategy

• Variety of presentations
  – ODT (Orally Disintegrating Tablet)
  – ODF (Orally Disintegrating Film)
  – Sublingual tablet/film
  – Buccal tablet/film
  – Chewable tablet
  – Oral spray
  – Others

• Common development strategy is 505(b)(2) via BE to existing approved conventional tablet/capsule
  – but.....
Similarity and difference in regulatory guidance on BE study design for ODT/ODF

- **FDA (US)**
  - Typically 3-way crossover fasted
    - Reference IR formulation w/water
    - ODT w/o water – intended label
    - ODT w/water – accidental swallowing of intact tablet
  - 240 mL of water

- **PMDA (Japan)**
  - No specific details on ODT administration
  - 100-200 mL, normally 150 mL of water

- **EMEA (EU)**
  - 3-way crossover (ref formulation w/water, ODT w/ and w/o water)
  - 2-way if ODT w/o water and ref formulation w/water is BE
  - =>150 mL of water
  - 20 mL water pre-wet mouth cavity to minimize variability (dry mouth issue)

- **CFDA (China)**
  - No specific details on ODT administration
  - Published data showing 2-way crossover with both ref and ODT w/water
  - 200-250 mL of water
Various scenarios of PK outcome of IO dosage forms as compared to film-coated tablet (FCT)

- Bioequivalent & Bioenhanced
- Bioequivalent
- Bioinequivalent

Test

IO

Reference

FCT
Typical outcome for IO presentations as LCM
- Case of Sildenafil ODT

- Sildenafil is the API of Viagra for treatment of ED
- Patient convenience and discreetness are highly desirable
- Sildenafil ODT (50 mg) was developed
- BE demonstrated for ODT w/o water, ruling out IO absorption

PK profiles for sildenafil (solid lines) and its metabolite (dashed lines), after administration of a 50-mg dose of sildenafil FCT and sildenafil ODT given with or without water in the BE study (N=36)

*B. Damle et al, Clinical Therapeutics, 2014, 36(2), 236
Desirable outcome between IO dosage forms
- Case of Ondansetron oral soluble film (OSF)

• Zuplenz (Ondansetron) OSF was developed under 505(b)(2) provision using Zofran ODT 8 mg as reference product

• The sponsor demonstrated no effect of water intake on PK for OSF

• Followed by pivotal BE between Zofran ODT and Zuplenz OSF under fasted and fed conditions with water intake

* Zuplenz FDA NDA review 2010
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022524Orig1s000ClinPharmR.pdf
Ideal outcome for IO dosage forms
- Case of Intermezzo sublingual tablet (SL)

- Low doses of zolpidem tartrate SL tablet (1.75 mg and 3.5 mg), Intermezzo, approved by FDA in 2011
- Unique product labels - for the treatment of middle-of-the-night awakening followed by difficulty returning to sleep
- BE and bioenhancement (AUC$_{0-20\text{min}}$ increased 3-fold)
- Contribution of IO absorption drives PK profile change but high intestinal absorption dominate overall PK leading to BE outcome

PK profiles of zolpidem after Intermezzo SL tablet vs Ambien IR FCT at a dose of 3.5 mg in human (N=35)

*FDA 2011. Intermezzo NDA file
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000ClinPharmR.pdf
Bioequivalence to FCT can be a great outcome
- Case of Asenapine sublingual tablet

- Asenapine IR tablet is NOT orally bioavailable (F=3%) due to rapid and extensive 1st pass metabolism
- SL tablet developed with >10x increase in BA
- IO absorption primarily contributed to the increased BA
- SL delivery enabled the development of Asenapine
- Saphris SL tablet was approved by FDA in 2009

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route/Dosage/Dose</th>
<th>$C_{\text{max}}$ (µg/L)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{AUC}_{0-\text{inf}}$ (µg*h/L)</th>
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<tr>
<td>Asenapine</td>
<td>PO/Tablet/5 mg</td>
<td>0.204</td>
<td>2.0</td>
<td>1.87</td>
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<tr>
<td></td>
<td>Sublingual/Tablet/5 mg</td>
<td>3.02</td>
<td>1.0</td>
<td>21.3</td>
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*FDA Saphris NDA file 2008
Unique factors in protocol designs vs BA/BE outcome

- Resting saliva volume vs pre-wet mouth with a fixed water volume
- Water volume for co-dosing with the IO dosage form and ref
- Holding/residence time in oral cavity vs swallowing (esp. for sublingual/buccal tablet/film)
- Site of administration within oral cavity
- Study power – inherent high inter-subject variability

- Often lead to failed BE for $C_{\text{max}}$
- Could lead to failed BE for both $C_{\text{max}}$ and AUC
Why study design matters so much?
- Effect of dosing conditions on PK of Rizatriptan ODT

- ODT w/water has a greater mean AUC\(_{0-2h}\) than ODT w/o water
- ODT w/water has a slightly greater mean AUC\(_{0-1h}\) than tablet w/water
- Median T\(_{\text{max}}\) of 0.67 hr for ODT w/water & tablet, and 1.33 hr for ODT w/o water
  - Implication of PK difference on efficacy requires clinical evaluations

PK profiles of rizatriptan (BCS class I) following administration of 10-mg single oral doses to healthy subjects (n = 24). ODTc = ODT w/ water (closed circles); ODTs = ODT w/o water (open circles)

Effect of dosing site on PK of Olanzapine

- Zyprexa (Olanzapine) ODT is a Zydis-based ODT
- BE achieved among 3 dosing regimens
- BUT >2x greater AUC$_{0-1hr}$ for ODT w/o water on and under the tongue
- Olanzapine exhibits extensive 1$^{st}$ pass metabolism

- Zyprexa ODT can be taken w/o restrictions to site of dosing

Effect of dosing site on PK of Asenapine

- Saphris (Asenapine) SL tablet is a Zydis-based fast dissolving tablet
- BE was not achieved among 3 dosing sites
- Differences in exposure associated with variable placement in the oral cavity did not compromise safety

Product labels:
Saphris SL tablets should be placed under the tongue and left to dissolve completely within seconds in saliva.

Effect of post-dosing drinking and residence time in oral cavity on PK of Asenapine

• Typically no water intake is allowed 1-hr after dosing for BA/BE study
• To facilitate Saphris SL tablet product labeling, the effect of drinking close to the time of SL administration was assessed

➢ Product labels: Eating and drinking should be avoided for 10 minutes after administration.

Conducting pilot BA study for IO dosage forms

• Potential high inter- and/or intra-subject variability due to the unique nature of IO dosage form designs
  – Understand key parameters in protocols most impacting PK outcome

• Benefits for conducting pilot BA study prior to pivotal BE study
  – Assess variability (especially $C_{\text{max}}$) and location of point estimates
  – Inform required sample size for pivotal BE study
  – Evaluate palatability and mouth feel
Impact of pilot PK study on pivotal BE study design
- Case study with MK-X ODT

• Pilot PK and general palatability were assessed in 12 subjects
  – Treatment A – ODT w/o water (but mouth pre-wetted w/20 mL of water)
  – Treatment B - ODT w/ 150 mL of water
  – Treatment C – FCT w/ 150 mL of water

• High inter-subject and moderate intra-subject variability observed with $C_{\text{max}}$

• Pivotal BE study should be adequately powered (N=120)

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Treatment A/C</th>
<th>Treatment B/C</th>
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<tbody>
<tr>
<td></td>
<td>GMR</td>
<td>90% CI</td>
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<tr>
<td>$AUC_{0-t}$ (ng·hr/mL)</td>
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<td>(1.05, 1.15)</td>
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<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
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<td>(1.10, 1.24)</td>
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<td>$AUC_{0-\infty}$ (ng·hr/mL)</td>
<td>1.11</td>
<td>(1.07, 1.15)</td>
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IO absorption contributions and their impact on BA/BE

- For drugs with high oral(intestinal) BA, measurable IO absorption may not affect overall BA/BE outcome
  - Zolpidem, Olanzapine

- For drugs with low oral(intestinal) BA, measurable IO absorption could significantly affect overall BA/BE outcome
  - Asenapine, Vardenafil, Buprenorphine

- Common approaches for investigating IO absorption contributions
  - Dosing w/ and w/o water
  - Dosing with a range of holding time in oral cavity
  - Hold-then-spit/mass balance study
  - Dosing w/ and w/o charcoal block
Suprabioavailability of vardenafil ODT

- Vardenafil is the API of Levitra for treatment of ED
- Levitra has oral BA of 15% due to extensive 1st pass metabolism
- Vardenafil ODT (10 mg) was developed to better patient convenience and discreetness
- ODT w/o water was 21-44% more bioavailable than FCT, indicating IO absorption

Levitra FCT and Staxyn ODT is not interchangeable

PK profiles for vardenafil after administration of a 10-mg dose of Levitra FCT w/180 mL water and vardenafil ODT w/o water (N=22)

*R. Heinig et al, Clin Drug Investig 2011, 31 (1), 27-41
Absorption of vardenafil in oral cavity

• A crossover study was conducted using a solution of 10 mg vardenafil HCl salt
  – Treatment A - Swallowed with water
  – Treatment B – Hold in mouth for 15 min w/o swallowing; followed by emptying the mouth and rinsed with 5 x 20 mL water; all recovered liquids were assayed for mass balance

• 0.7 mg (out of 10 mg) of drug was absorbed intraorally

• Dose normalized BA (AUC/Dose) for IO absorption is 3x higher than intestinal absorption
  – Exposure from IO absorption contributes to 25% of the total exposure

*CHMP assessment report 2010
Summary

• Compared to conventional oral tablets/capsules, more variable/factors for IO dosage forms require additional attentions in designing BA/BE studies

• Insufficient details and/or lack of harmonization of global regulatory guidance further increase the complexity in BE assessment for IO dosage forms

• Unique nature of IO dosage forms often leads to high PK variability (especially when IO absorption is significant)

• Identifying key factors impacting PK of IO presentations is essential for optimal study designs