Fumaric Acid Microenvironment Tablet Formulation and Process Development for Crystalline Cenicriviroc Mesylate, a BCS IV Compound

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Presentation Outline

• Properties of Cenicriviroc Mesylate (CVC)
• Formulation and Process Background
• Challenges and Objectives
• Microenvironment pH Modification
• Formulation Screening Study
• Dog PK Evaluation
• FBRM Application in Formulation Selection
• Characterization of Scale-up Batches
Physicochemical Properties of CVC

- CCR5 and CCR2 dual chemokine receptor antagonist
- BCS IV
- Solubility
  - Intrinsic (pH 6.3): <0.002 mg/mL
  - 0.01 N HCl (pH 2): >100 mg/mL
- Papp: $< 1 \times 10^{-6}$ cm/sec
- Non-hygroscopic
- $pK_{a1}$: 4.3 $pK_{a2}$: 6.2
- log P: >3
- Melting point: 153°C
- Milled API
CVC as CCR5 Antagonist in HIV Infection Treatment

- CCR5 chemokine receptor is a validated HIV target (entry inhibitors)
- CCR5 and CCR2 receptor antagonist
  - IC\textsubscript{50} CCR2 = 3.1 nM
  - IC\textsubscript{50} CCR5 = 5.9 nM
- Once-daily dosing
  - Plasma T\textsubscript{1/2} = 30-40 hours

Photo source: NIAID
## Historical Drug Product: Phase 1 and Phase 2a, pH Modified Tablet Formulation

<table>
<thead>
<tr>
<th>Components</th>
<th>Conc. (% w/w)</th>
<th>Unit Formula (mg/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cenicriviroc Mesylate</td>
<td>4.74</td>
<td>28.45</td>
</tr>
<tr>
<td>Mannitol</td>
<td>56.93</td>
<td>341.55</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>13.33</td>
<td>80.00</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td><strong>Citric Acid</strong></td>
<td>12.50</td>
<td>75.00</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>5.00</td>
<td>30.00</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td>Talc</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.50</td>
<td>9.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100.0%</td>
<td>600.0 mg</td>
</tr>
</tbody>
</table>
Dissolution Decrease of Phase 1 and 2a Citric Acid Formulation

Accelerated Stability at 40 °C/ 75% RH

![Graph showing the decrease of CVC released at 60 minutes over time (weeks).]
## Historical Drug Product:
### Phase 2b, Spray-Dried Dispersion Tablet Formulation

<table>
<thead>
<tr>
<th>Components</th>
<th>Conc. (% w/w)</th>
<th>Unit Formula (mg/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cenicriviroc Mesylate</td>
<td>8.33</td>
<td>50.00</td>
</tr>
<tr>
<td>Hypromellose Acetate Succinate</td>
<td>25.00</td>
<td>150.00</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>6.00</td>
<td>36.00</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>27.83</td>
<td>167.00</td>
</tr>
<tr>
<td>Mannitol</td>
<td>27.83</td>
<td>167.00</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>1.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>600.0 mg</strong></td>
</tr>
</tbody>
</table>
Inclusion criteria, included:

- Tx-naive adults
- CCR5-tropic only
- Viral load ≥1000 c/mL
- CD4 cell count ≥200 cells/mm³

Primary endpoint: Subjects (%) with HIV RNA <50 copies/mL at Week 24 (Snapshot)

Study regimen: 6 tablets daily with split dosing schedule

- CVC/placebo (4 tablets) taken with breakfast
- EFV/placebo (1 tablets) taken at bedtime, plus
- Truvada® (1 tablets)

Primary Analysis
Week 24

Final Analysis
Week 48

CVC 100 mg + TDF/FTC + EFV placebo

CVC 200 mg + TDF/FTC + EFV placebo

EFV 600 mg + TDF/FTC + CVC placebo

- Tropism determined by both Quest genotypic and Monogram Trofile® phenotypic tropism assays
- Stratified by baseline viral load (< or ≥100,000 c/mL)
A total of 6 tablets/day with split dosing schedule

**DOSING INSTRUCTIONS**

- **Cenicriviroc/Placebo**
  - Take 2 tablets from each bottle in the morning with breakfast and 8 oz. (240 mL) of water.

- **Truvada**
  - Take 1 tablet with 8 oz. of water, with or without food and at any time.

- **Efavirenz/Placebo**
  - Take 1 capsule on an empty stomach with 8 oz. of water, at bedtime.
Historical Drug Product Formulation Challenges for CVC

• Poor Chemical Stability
  – Lipid formulation
  – Wet granulation formulations

• Poor Physical Stability
  – Citric acid-containing formulation
  – Wet granulation formulations
  – Increase in moisture content

• Tablet Size/API Concentration
  – Phase 2b formulation 8.3% CVC
  – Multiple tablet burden for 100 mg and 200 mg dose
  – Requires formulation with higher API load and/or bioavailability to enable combination with other antiretroviral agents in a single tablet
Tablet Reformulation Objectives

- Develop a single, once daily, oral tablet formulation suitable for CVC dose adjustment up to 200 mg
- Maximize CVC concentration to maintain core tablet weight below 900 mg
- Use as a common formulation for various fixed-dose combination products
- Demonstrate acceptable chemical and physical stability
- Bioavailability comparable to or exceeding the spray-dried dispersion formulation
- Reduce sensitivity to gastric pH variability
- Develop a robust and scalable manufacturing process
Screening Study with Pharmaceutically Acceptable Acids

<table>
<thead>
<tr>
<th>Components</th>
<th>Citric Acid</th>
<th>Fumaric Acid</th>
<th>Maleic Acid</th>
<th>Sodium Bisulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cenicriviroc Mesylate</td>
<td>28.45^a</td>
<td>28.45^a</td>
<td>28.45^a</td>
<td>28.45^a</td>
</tr>
<tr>
<td>Mannitol</td>
<td>7.88</td>
<td>7.88</td>
<td>7.88</td>
<td>7.88</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>2.62</td>
<td>2.62</td>
<td>2.62</td>
<td>2.62</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>3.50</td>
<td>3.50</td>
<td>3.50</td>
<td>3.50</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>43.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fumaric Acid</td>
<td>-</td>
<td>43.75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maleic Acid</td>
<td>-</td>
<td>-</td>
<td>43.75</td>
<td>-</td>
</tr>
<tr>
<td>Sodium Bisulfate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>43.75</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.88</td>
<td>0.88</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>Total</td>
<td>87.5</td>
<td>87.5</td>
<td>87.5</td>
<td>87.5</td>
</tr>
</tbody>
</table>

^a equivalent to 25 mg cenicriviroc
Dog PK Results of Acid Screening Study

N=5 dogs, fasted, no pretreatment

<table>
<thead>
<tr>
<th>Formulation Acidulant</th>
<th>Absolute Bioavailability in Dogs (%F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumaric Acid</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>25 ± 6</td>
</tr>
<tr>
<td>Maleic Acid</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Sodium Bisulfate</td>
<td>5 ± 1</td>
</tr>
</tbody>
</table>
Lab Equipment Setup

- Mettler Toledo EasyMax
- G400 FBRM probe
- 2 m/s scan speed
- 90 mL purified water
- 250 rpm impeller speed
- Upward pumping, 4 blade impeller
- Macro mode
- Length weighting for granular systems
FBRM Application: Dissolution Kinetics of Acidic Excipients

Method
- 200 mg acid
- 90 mL purified water
- 200 rpm impeller speed
- Upward pumping, 4 blade impeller

Results
- Fumaric acid had slowest dissolution rate
- Increased contact time during dissolution
- Other acids dissolve too rapidly (regardless of pKa)
  - Correlates with increased absorption in dog pK study

<table>
<thead>
<tr>
<th>Acid</th>
<th>Dissolution time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipic</td>
<td>68  32</td>
</tr>
<tr>
<td>Citric</td>
<td>6   &lt;2</td>
</tr>
<tr>
<td><strong>Fumaric</strong></td>
<td><strong>312</strong>  <strong>152</strong></td>
</tr>
<tr>
<td>Maleic</td>
<td>4   &lt;2</td>
</tr>
<tr>
<td>Sodium Bisulfate</td>
<td>26  &lt;2</td>
</tr>
<tr>
<td>Succinic</td>
<td>46  8</td>
</tr>
<tr>
<td>Tartaric</td>
<td>6   &lt;2</td>
</tr>
</tbody>
</table>
Formulation Optimization

- Dry Granulation Process (Vector TFC-Lab Micro)
- 500 psi roll pressure
- 400 g batch size

<table>
<thead>
<tr>
<th>Components</th>
<th>Unit Formula (mg/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DG1</td>
</tr>
<tr>
<td>Cenicriviroc Mesylate</td>
<td>170.69(^a)</td>
</tr>
<tr>
<td>Fumaric Acid</td>
<td>160.00</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>252.68</td>
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<tr>
<td>Crospovidone</td>
<td>-</td>
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<tr>
<td>Croscarmellose Sodium</td>
<td><strong>58.50</strong></td>
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<tr>
<td>Magnesium Stearate</td>
<td>8.13</td>
</tr>
<tr>
<td>Total</td>
<td>650.0</td>
</tr>
</tbody>
</table>

\(^a\) equivalent to 150 mg cenicriviroc
\(^b\) added extragranularly
CVC Tablet Prototypes

Spray-Dried Dispersion
50 mg

Dry Granulation
25 mg & 150 mg
Dog PK of Fumaric Acid Prototype Formulations

- DG2 formulation had similar exposure as an oral solution
- Fumaric acid prototypes had increased bioavailability as compared to the SDD or PIC prototypes
- N=5 dogs, fasted, no pretreatment
In vitro Dissolution

- USP Type II, 0.1 N HCl + 0.1% CTAB
- 50 rpm paddle speed
- N=3
- No correlation between dissolution and dog PK

![Graph showing in vitro dissolution data for DG1, DG2, DG3, and DG4.](chart)
DG1 high disintegrant and DG3 extragranular fumaric acid had high counts upon disintegration.

DG2 disintegrated rapidly but had lower counts.

DG4 disintegrated by slow erosion.
Total Length Weighted Counts, 1-1000 micron

- Average of 5 samples
- Demonstrates good method reproducibility
Length Weighted Mean

- Length weighted means show a similar trend and converge to a similar mean chord length corresponding to the insoluble excipients.
Rank order of particle counts are consistent over the binned size ranges.
Length Weighted Counts, 150-300 micron

- **DG1**
- **DG2**
- **DG3**
- **DG4**

The graph shows the length weighted counts (#/sec) over time (min) for different groups labeled DG1 to DG4. The y-axis represents the length weighted counts, ranging from 0 to 1800, and the x-axis represents time in minutes, ranging from 0 to 14.
Length Weighted Counts, 50-150 micron

![Graph showing length weighted counts over time for DG1, DG2, DG3, and DG4]
Length Weighted Counts, <50 micron
Peak and Final Distributions

Dashed lines correspond to plateau

Solid lines correspond to peak

- DG1
- DG2
- DG3
- DG4

length weighted counts (#/sec)

chord length (micron)
Low counts (at peak) correlate with granules remaining intact and prolonged low microenvironment pH via slow dissolving fumaric acid.

DG1 and DG3 fast disintegration circumvented optimal interaction with fumaric acid.
Dog PK Normalized by Maximum Counts and Tablet Weight
Effect of Gastric pH on Dog PK

N=5 dogs, fasted
Physical and Chemical Stability

- **Weight Change (% w/w)** vs. **Relative Humidity (%) at 25 °C**
  - Graphs show weight change for different conditions.

- **Total Impurities (%)** vs. **Time (weeks)**
  - Graphs illustrate impurity growth over time for various conditions.

**Samples**:
- WG CA
- DG2
- CVC Mesylate
- WG FA
- SDD
Dissolution Stability

- Time (weeks): 0, 2, 4, 6, 8, 10, 12
- CVC Released at 60 minutes (%): 0, 20, 40, 60, 80, 100
- WG FA
- DG2
- SDD

Graph showing the dissolution stability over time for different samples.
Scale-up and Transfer of Process

- Process scale-up to approximately 5 kg batch size
- Qualify 2 different models of roller compactors

Vector TF-220

Gerteis Minipactor
Tablet Disintegration Total Length Weighted Counts
Peak and Final Distributions

Dashed lines correspond to plateau

Solid lines correspond to peak
Granule Distribution in Silicon Oil

- Added 1 g of granules to 50 mL silicon fluid to characterize granule distribution.

Gerteis Minipactor produces coarser granules with less fines than the TF-220.
Conclusions

- New single tablet formulation at 150 mg CVC (650 mg total weight) performed as well as 4 x 50 mg CVC (2,520 mg total weight) spray-dried dispersion formulation.
- Tablet disintegration characterization by FBRM supported formulation selection.
- FBRM detected and quantified distinct disintegration regimes between the formulations.
- Formulation disintegration characteristics were maintained during scale-up and between 2 roller compactor designs.
- FBRM is a useful drug product performance characterization tool applicable for formulation screening, process optimization, scale-up, equipment and site transfers.
Acknowledgments

- Mettler-Toledo AutoChem
- WuXi AppTech
- APC Ltd