Coccidioidomycosis (Valley Fever): Considerations for Development of Antifungal Drugs

Nikkomycin Z

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Disclosure: Employee and Shareholder of VFS
Early reported cases

First report: Posada, Argentina, ~1890

Coccidioidomycosis

Joas Furtado Silverra, an ambitious young man of 33 years, came to the San Joaquin Valley from his home in the Azores in 1886. Within a year or so he noticed a tender spot on the back of his neck, where his collar rubbed the skin. Similar patches appeared on the forehead. Although he was able to work for several years, his fellow laborers were so afraid of his ugly skin lesion that he had to room by himself. In 1893, when his strength had long since failed, he entered the San Francisco City and County Hospital to remain until he died in January, 1895. Fungating skin lesions spread over most of his face and invaded the eyes, destroying his vision. The eruption was so sensitive that the slightest touch caused him to cry out in pain. Regional lymph nodes became swollen and fluctuant. Cough and purulent sputum increased. Rales filled the lungs. Abscesses appeared on the legs and in the testes. Despite frequent surgical...
Nikkomycin Z (NikZ) - Novel Antifungal Fungicidal against Cocci

First in class, NCE (New Chemical Entity), novel Mechanism of Action
- Novel Mechanism of Action targets fungi
  Blocks chitin-synthase – prevents “armor plate”
- Strong safety profile helps new acute profile
- Flexible formulation (oral, IV)

Good preclinical results
- Fungicidal in mouse,
  Acute resolution of disseminated disease
- Positive results in several very sick pet dogs
- More reports in preparation
Fungicidal: cures new infection, (similar with flare-ups, growth)

Antimicrob Agents Chemother, 1990:34(4)587-593

Brain (meningocerebral) very tough, 80% after 300 mg/kg BID (recent studies pending)
Addresses established Disease
Fungicidal

Relief of symptoms will be welcome continuing relief will be apparent, “Cure” is hard to prove – watch lack of relapse

Short Communications

Efficacy of Nikkomycin Z for respiratory coccidioidomycosis in naturally infected dogs

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Nikkomycin Z (NikZ) is a chitin synthase inhibitor with antifungal efficacy against Coccidioides spp. and other endemic fungi. Dogs suffer a rate and range of natural coccidioidomycosis similar to humans and were considered an excellent model for initially testing NikZ against naturally acquired disease. Twelve dogs with coccidioidal pneumonia that had been present for an average of three months were treated with 250 mg (5–15 kg) or 500 mg (>15–30 kg) twice daily for 60 days. Nine dogs completed the course of treatment and seven dogs had improvement in disease based on radiographs, clinicopathological parameters, physical examination findings, and subjective assessment by owners; three dogs had resolution or near resolution of disease. Based on this small study, NikZ shows efficacy to treat naturally acquired coccidioidomycosis and merits further development for trials in humans.

SOC: 3-6 months, extend if needed (years, even life)

This trial: NikZ: 2 month, Limited drug

33% near resolution
Trial Strategy Considerations

- Target Indication (strategy around drug candidate choice)
  - Indication of interest (intractable, rare)
  - Trial Design opportunities (clinical, regulatory)
  - Superior endpoints? (such as biomarker)
  - Enrollment candidates
  - Impact against large indication is a benefit

- Drug Attributes
  - Safety (Side effects, DDI)
  - Tolerability (Mode – oral/IV, frequency, dosage format)
  - Drug supply limitations
  - Manufacturability, stability
Drugs in Development

VT-1129, VT-1161, VT-1598

Candida albicans
Candida tropicalis
Candida parapsilosis
Candida krusei
Candida glabrata
Candida kefyr
Candida auris
Trichosporon asahii
Malassezia furfur
Saccharomyces cerevisiae
Cryptococcus neoformans
Cryptococcus gattii
Pneumocystis jirovecii

Aspergillus fumigatus
Aspergillus terreus
Aspergillus flavus
Aspergillus nidulans
Aspergillus niger
Rhizopus spp
Mucor spp
Fusarium spp
Scedosporium spp
Lomentospora prolificans
Trichophyton spp

Histoplasma capsulatum
Blastomyces dermatitidis
Coccidioides immitis
Talaromyces marneffei

Olorofim

NikZ

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Rauseo AM et al., Open Forum Infect. Dis., 2020:7(2):ofaa016
Fungal Cell Wall Components

Cortés JCG et al., Biotechnology Adv., 2019:37(6) 107352
Fungal Cell Wall Drug Action

Many useful combinations

Inhibit chitin synthase

Cortés JCG et al., Biotechnology Adv., 2019:37(6) 107352

NikZ
Market / Business Considerations

- Business motivation
  - 3T's: Team, Technology, Target (addressable market)
    - Team can be reinforced/replaced
    - Technology (drug) may have formulation opportunities (AmB)
    - Target has to be credible and attractive to investor
  - Market size, time to revenue, duration of revenue
  - Competing / alternative opportunities
## Anti-infectives Success Rates

<table>
<thead>
<tr>
<th>Phase Success</th>
<th>Phase I to Phase II</th>
<th>Phase II to Phase III</th>
<th>Phase III to NDA/BLA</th>
<th>NDA/BLA to Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced or Suspended</td>
<td>Phase Success</td>
<td>Advanced or Suspended</td>
<td>Phase Success</td>
<td>Advanced or Suspended</td>
</tr>
<tr>
<td>Hematology</td>
<td>86</td>
<td>73.3%</td>
<td>83</td>
<td>56.6%</td>
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<tr>
<td>Infectious disease</td>
<td>329</td>
<td>69.5%</td>
<td>286</td>
<td>47.7%</td>
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<tr>
<td>Ophthalmology</td>
<td>22</td>
<td>84.8%</td>
<td>46</td>
<td>39.7%</td>
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<tr>
<td>Other</td>
<td>96</td>
<td>66.7%</td>
<td>116</td>
<td>39.7%</td>
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<tr>
<td>Metabolic</td>
<td>95</td>
<td>61.1%</td>
<td>84</td>
<td>45.2%</td>
</tr>
<tr>
<td>Gastroenterology*</td>
<td>41</td>
<td>75.6%</td>
<td>36</td>
<td>35.3%</td>
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<tr>
<td>Allergy</td>
<td>37</td>
<td>67.6%</td>
<td>40</td>
<td>32.5%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>295</td>
<td>52.9%</td>
<td>242</td>
<td>40.1%</td>
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<tr>
<td>Respiratory</td>
<td>150</td>
<td>65.3%</td>
<td>196</td>
<td>29.1%</td>
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<tr>
<td>Urology</td>
<td>21</td>
<td>57.1%</td>
<td>52</td>
<td>32.7%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>297</td>
<td>65.9%</td>
<td>319</td>
<td>31.7%</td>
</tr>
<tr>
<td>All Indications</td>
<td>3582</td>
<td>63.2%</td>
<td>3862</td>
<td>30.7%</td>
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<tr>
<td>Neurology</td>
<td>462</td>
<td>59.1%</td>
<td>465</td>
<td>29.7%</td>
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<tr>
<td>Cardiovascular</td>
<td>209</td>
<td>58.9%</td>
<td>237</td>
<td>24.1%</td>
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<tr>
<td>Psychiatry</td>
<td>154</td>
<td>53.9%</td>
<td>169</td>
<td>23.7%</td>
</tr>
<tr>
<td>Oncology</td>
<td>1222</td>
<td>62.0%</td>
<td>1416</td>
<td>24.6%</td>
</tr>
</tbody>
</table>


- **Phase 1>2**: 69.5% (18%)
- **Phase 2>3**: 42.7% (26%)
- **Phase 3>NDA**: 72.7% (60%)
- **NDA > Approve**: 88.7% (89%)
Rare Disease Success Rates

(Anti-Infectives)
Phase 1>2
69.5% (18%)
Phase 2>3
42.7% (26%)
Phase 3>NDA
72.7% (60%)
NDA > Approve 88.7% (89%)

Development Costs

- Capitalized cost $1.3-1.8 B ($2.3B, $5.5B for large pharma, Phase IV)
- Out of Pocket costs $870 M ($350M for single drug company) (Tufts, see Wikipedia)

![Figure 3: Clinical Trial Costs (in $ Millions) by Phase and Therapeutic Area](chart)
Years of High Risk, expense

Figure 2: Drug Development Decision Tree Depicting Net Present Value (NPV) of Returns at Each Node

- 1 year
- 2 years
- 4 years
- 1 year

Success: $973
Failure: -$181
Success: $777
Failure: -$180
Success: $346
Failure: -$180
Success: $103
Failure: -$67
Success: $59
Failure: -$30
Abandon: $0

EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT
ERG, July 25, 2014
2019E: New drugs: $500-800K in 5 year peak
Main drugs used for VF: $1.8B (to $2.8B)
Thank You!
Valley Fever Solutions: Nikkomycin-Z

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