A novel funding model for drug development in global health: using the priority review voucher for moxidectin.

ECTMIH 2015

Mark Sullivan
Outline of Presentation

- Rationale for moxidectin
- Priority review voucher
- Furthering our goals with voucher proceeds
Moxidectin
A Veterinary Mainstay in Filarial and Ectoparasitic Diseases

- Fermentation product of *Streptomyces cyaneogriseus*
- Discovered in 1982
  - 2nd generation pentacyclic lactone
  - Milbemycin class (not an avermectin)
- Potent ectoparasiticide and microfilaricide
  - glutamate-gated chloride channel
- Veterinary commercialization in 1989
  - Licensed in >80 countries
  - Indicated for most domestic species
  - Manufactured in tonne quantities for use in food producing animals
  - >400 moxidectin-based products
  - Pharmaceutically stable
Key Differences between Ivermectin and Moxidectin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ivermectin</th>
<th>Moxidectin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Avermectin</td>
<td>Milbemycin</td>
</tr>
<tr>
<td><strong>$T_{\text{max}}$</strong></td>
<td>~ 4 hours</td>
<td>~3.2 hours</td>
</tr>
<tr>
<td><strong>$T_{\frac{1}{2}}$</strong></td>
<td>12 hours</td>
<td>432-1032 hours (18-43 days)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP450 (10 metabolites)</td>
<td>Not metabolised</td>
</tr>
<tr>
<td><strong>P-glycoprotein substrate</strong></td>
<td>✔✔✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Collie Dogs neurotoxicosis$^1$</strong></td>
<td>✔✔✔ (at 0.2 mg/kg)</td>
<td>✗ (at 32.5 mg/kg)</td>
</tr>
<tr>
<td><strong>Activity in ivermectin resistant strains$^2$</strong></td>
<td>✗</td>
<td>✔</td>
</tr>
</tbody>
</table>

Differing binding sites to glutamate-gated chloride channel

Moxidectin (maroon) superimposed over ivermectin (black).

Solid red circle sites where interactions will be different for moxidectin compared with IVM

Dashed red circle – possible additional MOX binding moiety

From Prichard et. al., Int J Parasitol Drugs Drug Resist 2012. 2:134-53
SAR is different between ivermectin and moxidectin

Sugar moiety at C13 position

Cut 1 = ivermectin monosaccharide: 1/3rd the activity of parent compound

Cut 2 = aglycone has 1/30th the activity against worms

Summary Non Clinical Studies

At least 72 preclinical safety and pharmacology studies conducted relevant to human use:

- **Wide therapeutic index**
  - Not genotoxic or mutagenic
  - No liability in cardiovascular ion channel and dog telemetry studies
  - Well tolerated in single and long term repeat-dose studies in rats, mice and dogs
  - Negative in 2 year carcinogenicity rats and mice
  - Not a selective developmental toxicant nor a teratogen (rat and rabbit)

- **Minimal metabolism overall**
  - same pattern in rat and human
  - excreted mainly in faeces
  - no/weak inhibition 7 CYP enzymes
    - inducer of CYP3A4 but not clinically relevant (midazolam clinical drug drug interaction study conducted)
## Onchocerciasis - Clinical Safety & Efficacy Program

### Phase I

- Single **ascending dose** of moxidectin liquid in healthy adults (n = 37)  
  3110A1-100-EU

- Relative **bioavailability** (tablet or liquid) moxidectin in healthy males (n = 58)  
  3110A1-101-EU

- Open label, 3-period, sequential, midazolam **drug-drug interaction** study in healthy adults (n = 39)  
  3110A1-1004-EU

- Single dose, parallel group **food-effect** study in healthy adults (n = 54)  
  3110A1-1005-EU

- Single-dose study in **lactating women** (n = 12)  
  3110A1-1002-EU

### Phase II

- Randomized, ivermectin controlled, double-blind, single ascending dose study in adults with onchocerciasis (n = 172)  
  3110A1-200-GH

### Phase III

- Multi-country, randomized, ivermectin controlled, double-blind study in adults & adolescents ≥ 12 Years with onchocerciasis (n = 1472)  
  3110A1-3000-AF
Clinical Safety

- 1,299 subjects (in 7 studies) received a single moxidectin dose ranging from 3 mg to 36 mg.
- 1105 patients in Phases II and III with *O. volvulus* infection.
- 194 healthy subjects in 5 clinical pharmacokinetic studies received moxidectin, 188 at doses at least 8 mg

Well tolerated:
- No drug-related serious adverse events in any study
- Adverse event profile similar to placebo in Phase I
- Profile of Mazzotti events similar to ivermectin and not treatment limiting
Phase III Multicentre Clinical Study Design (n = 1472)

A randomized single dose, ivermectin-controlled, double-blind, efficacy study of orally administered moxidectin in subjects infected with *Onchocerca volvulus*.

**Adults and adolescents ≥ 12 years infected with *O. volvulus*.**

- Randomized (2 MOX : 1 IVM), double-blind trial.
- Stratified by skin microfilaria level and gender.
- Multicentre study: Liberia, Ghana and DRC sites.

**Moxidectin 8 mg, once, per oral (n = 978)**

**Ivermectin 150 µg/kg, once, per oral (n = 494)**

**On-study period (months):**
- 0, 1, 6, 12, 18

**Primary Endpoint:** Microfilaria count
Moxidectin’s Significantly Superior Efficacy
Pre-defined Primary Endpoint

Microfilarial (mf) skin density end-point – mf reduction used for ivermectin FDA approval for onchocerciasis.

### Microfilarial Skin Density
Time course following single treatment

**Primary Endpoint**
Anti-parasitic efficacy of MOX compared with IVM at 12 months

* *p <0.0001

<table>
<thead>
<tr>
<th>Months</th>
<th>MOX (n =)</th>
<th>IVM (n =)</th>
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<tbody>
<tr>
<td>0</td>
<td>41.2</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3.7</td>
<td>*0</td>
</tr>
<tr>
<td>9</td>
<td>*9.9</td>
<td>1.3</td>
</tr>
<tr>
<td>12</td>
<td>15.3</td>
<td>*4.3</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td></td>
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<tr>
<td>0</td>
<td>978</td>
<td>494</td>
</tr>
<tr>
<td>3</td>
<td>973</td>
<td>492</td>
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<tr>
<td>6</td>
<td>946</td>
<td>481</td>
</tr>
<tr>
<td>9</td>
<td>758</td>
<td>384</td>
</tr>
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Microfilaria Counts
Suboptimal Response to Ivermectin, Rapid Return to Pre-Treatment

Individual patients microfilariae counts relative to Baseline.

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
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<tr>
<td><strong>IVM</strong></td>
<td>n = 494</td>
<td>n = 492</td>
<td>n = 481</td>
<td>n = 384</td>
</tr>
<tr>
<td><strong>MOX</strong></td>
<td>n = 973</td>
<td>n = 946</td>
<td>n = 758</td>
<td></td>
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Red line: 5 mf/mg skin
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The voucher entitles the bearer to FDA priority review of any new drug, speeding registration by at least 4 months.

- **incentive** for developers of drugs and vaccines for
  - 16 neglected diseases (including onchocerciasis) (2007)
  - rare paediatric diseases (2012)
  - Ebola (2014)
  - Chagas disease and neurocysticercosis (2015)
To be eligible for a priority review voucher:

1. The application must be for a listed tropical disease;
2. The application must be submitted either as a 505(b)(1) NDA or a 505(b)(2) application;
3. The drug that is the subject of the application must not contain a previously-approved active moiety; and
4. The application must qualify for a 6-month priority review under FDA’s policies.
Other diseases

FDA can include “any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations.”

- Will use “a flexible approach” to tropical disease designations based on “scientifically informed, qualitative assessment of disease candidates.”
- Have a “public docket” to receive future suggestions for tropical disease designations.
Sanofi Successfully Uses its PRV

- August 19, 2015: Sanofi-Aventis redeemed a Pediatric PRV for its Praluent (alirocumab) NDA.

- July 24, 2015: Praluent became first US approved PCSK9 cholesterol therapy: projected to be billions of dollars per year.
  - Amgen’s PCSK9 beat Sanofi’s to market in Europe but the PRV allowed Sanofi to beat Amgen in the US.
Voucher value

Published August 30, 2015
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Medicines Development for Global Health
Corporate Overview

Purpose: developing and delivering life changing medicines for neglected diseases

- Public Company, not-for-profit, registered charity
- Formed October 2005
- Purpose embedded in company Constitution
- Independent, self-funded
- Collaboration is core
GHIF News

US$10 Million Investment into the Registration of Moxidectin

US$10 Million investment into the Registration of Moxidectin, an important new drug, was awarded to Novartis International, Ltd. (Novartis). The Global Health Investment Fund (GHIF) announced today that the investment will support the development and registration of Moxidectin, a drug that combats neglected tropical diseases.

June 14, 2014 - 1 Comment

US$7.5M Investment into EuBiologics

South Korean biopharmaceutical company, Europe Biopharmaceuticals (EuBiologics), is pleased to announce today that it has entered into a collaborative funding agreement with The Global Health Investment Fund (GHIF). Under the terms of the agreement, EuBiologics will receive a $7.5 million USD investment to support the development of its pipeline.

June 14, 2014 - 1 Comment

Funding Agreement with Epistem PLC

The Global Health Investment Fund (GHIF) is pleased to announce today that it has entered into a collaborative funding agreement with Epistem PLC, a UK-based technology company that specializes in the development of advanced medical and biotechnology.

June 14, 2014 - 1 Comment

Financial Times Award

Lilab, led by Global Pharma and J.P. Morgan, was honored as a winner in the 2014 FT Innovation Awards. The Financial Times recognized Lilab's innovative and transformative work in the field of infectious disease research.

June 14, 2014 - 1 Comment

New Investment Fund

J.P. Morgan Chase, the global finance leader, and Global Health Investment Fund announced today a new investment fund to support the development and registration of new medicines.

June 14, 2014 - 1 Comment
Use of Funds

If moxidectin is approved by FDA and a voucher is awarded:

- Proceeds stay within global health sector
- Pre-commitment by both GHIF and Medicines Development to co-invest in further development of moxidectin
- Financial foundation for further programs

Corporate objective is to:

- Be a self sustained, independent global health biotechnology company
- Be a key new collaborator in global health
- Have substantial impact for patients