MOXIDECTIN TO FDA APPROVAL

• Mark Sullivan (Founder and Managing Director Medicines Development for Global Health)
• Annette C. Kuesel (TDR)
Public company, *not for profit Social Enterprise*, registered charity

- **Objective**: Addressing market gap for product development for global health through development to approval and supply of drugs for neglected infectious diseases

- **Funding**: Project income, competitively awarded grants and program investments

- **Approached TDR about moxidectin status in view of MDGH interest to develop it for scabies**

- **Reviewed data available and decided to take on bringing moxidectin to registration**

- **Received license for all data available to TDR**

- **Raised US $12 Million loan to invest with US $3 Million of their own funds to complete development and prepare submission of NDA to US FDA (complementing around US$ 15 Million invested by TDR incl. $$ from APOC)**
**BACKGROUND: WHAT HAPPENS BEFORE A NEW DRUG IS AVAILABLE TO PATIENTS AND PHYSICIANS/HEALTH SYSTEMS**

<table>
<thead>
<tr>
<th>Pre-Discovery Research</th>
<th>Discovery</th>
<th>CMC (Drug substance, product development &amp; manufacture)</th>
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<tbody>
<tr>
<td><strong>Non-clinical Research</strong></td>
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<tr>
<td>Clinical Research</td>
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<tr>
<td>Phase 1 n=20-100</td>
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<tr>
<td>Phase 2 n=100-500</td>
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<td>Phase 3 n=1000-5000</td>
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<tr>
<td><strong>Regulatory Agency review</strong></td>
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**Pre-Discovery Research**
- Basic causes of disease
- Discover 'targets', which if 'attacked' via a drug can alter the course of the disease

**Discovery**
- Identify molecules which alter 'target' function but are not 'too' toxic to the 'host' – Drug candidate

**CMC (Drug substance, product development & manufacture)**
- Well characterized and stable drug product
  - Test candidate in vitro and in animals
  - what does the body do to the drug?
  - safe enough to be tested in adult humans, children, special populations?
  - safe enough to be prescribed to patients – all? subgroups?

**Clinical Research**
- P 1: PK, safety
- P 2: Initial efficacy, safety (PK)
- P 3: Large scale efficacy, safety

**New Drug application assembly and submission**
- All data assembled and analyzed as per regulatory requirements for verification & assessment by RA

**Label: Prescribing info**
**WHAT HAPPENED FOR MOXIDECTIN?**

<table>
<thead>
<tr>
<th>Discovery: FDAH, TDR</th>
<th>CMC (Drug substance, drug product development and manufacture) FDAH, Wyeth, Medicines Development for Global Health</th>
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<tbody>
<tr>
<td><strong>Non-clinical research FDAH, Wyeth</strong></td>
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<tr>
<td><em>In vitro</em> (enzymes, cell cultures), <em>In vivo</em> (mice, rats, dogs)</td>
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<tr>
<td>Primary pharmacology (efficacy), Secondary pharmacology (safety)</td>
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<tr>
<td>Absorption, distribution, metabolism, excretion (drug interactions)</td>
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<tr>
<td>Single dose, multiple dose toxicity, carcinogenicity, genotoxicity</td>
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<td>Reproductive/developmental toxicity (single, multiple generation)</td>
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<td>Juvenile toxicity</td>
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<td><strong>Wyeth, MDGH:</strong> Six Phase 1 studies, including</td>
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<td>Food effect, milk excretion, drug interaction, cardiac safety</td>
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<td><strong>Wyeth, TDR:</strong> Comparative Phase 2 study (Ghana), n=172</td>
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<td><strong>Wyeth, TDR:</strong> Comparative Phase 3 study (Liberia, Ghana, DRC) n=1472 (to 6 months post enrolment)</td>
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<tr>
<td><strong>TDR:</strong> Study completion, data analysis</td>
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<td><strong>MDGH:</strong> Data analysis and reporting</td>
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MOXIDECTIN NDA TEAM

Project Leader
Mark Sullivan

Project Management
Danielle Smith

CMC
John Lambert (Senior Director)
Nicky Konstantopoulos (Project & Drug Development Manager)
Jan Guerrero (Analytical, Regulatory and Quality)
Chris Santos (Tableting and Regulatory)
Andrew Campbell (Quality Assurance)
Martin Hughes (Analytical and Quality)
Magnus Busch/Michela DeCarli (Business & Supply Agreements)
Roger Wang (Chinese Supply representative)
Patricia Kessler (Labelling & Packaging Logistics)
Scott Reynolds (Tableting)
Niya Bowers, Advisory
Gerard Cunningham, Advisory
Mike Mitchell (Manufacturing)
Jignesh Patel (Drug Substance)
Tom Cullen (Chemistry)
Michael Putnam (Tableting)
Mariana Nielsen (Quality)
Grace Furman (Toxicology)
David Browne (Analytical Quality)
Jaclyn Guerrero (Statistics)
Lorraine Webster (medical writer)

Non-clinical Pharmacology
Charlotte Mulder
Rami Cobb (retired FDAH)

Clinical Pharmacology
Craig Rayner
Kris Jamsen
Julie Bullock
Larry Fleckenstein

Clinical
Sally Kinrade
Victoria Ryg-Cornejo
Gill Pearce (Clin ops)
Nic Kruger (clin ops)
Peter Cowey, MD (Consultant Cardiologist)
Thomas Mertenskoetter, MD
George Morstyn, MD
Bruce Burlington, MD (Former FDA)
Catherine Kolonko (Medical Writer)
Anne Norgrove (Medical Writer)
Hugh Taylor, MD (Ophthalmologist)

Non-clinical Safety
Kirk Tarlo
Gerry Fisher (retired Wyeth)

Metabolism
JoAnn Scatina

Data management
Michel Vaillant (LIH)

Biostatistics
Moraye Bear
Alan Forsythe

Business
Curt LaBelle
Charlie Petty
Kabeer Aziz

Previous Sponsors
Catherine Knupp (Zoetis)
Annette Kuesel (TDR)
Christine Halleaux (TDR)

Regulatory
Ralph Smalling
Penny Field
COLLABORATING ORGANISATIONS

**Finance**
- Global Health Investment Fund, New York

**Insurance**
- Avatar Brokers, Melbourne

**Legal**
- Banki Haddock Fiora, Sydney
- Ernst and Young, New York and Melbourne
- Allen, London and Melbourne

**Regulatory Legal**
- Hogan Lovells, New York and Washington DC

**CMC**
- Argenta (Drug Product) Fort Dodge, Iowa, Lawrence, Kansas & Auckland, New Zealand
- JetPharma (Drug Product); Balerna, Switzerland
- Livzon NNR (Drug Substance) Qingyuan City, Guangdong Province, China
- Pharmax (Drug Substance Agent) Diamond Bar, California
- Alcamo Corporation (Analytical); Wilmington, North Carolina & St. Louis, Missouri
- Nelson Laboratories (Analytical); Salt Lake City, Utah
- SSCI, a division of AMRI (Analytical); West Lafayette, Indiana
- Particle Technology Labs (Analytical); Downers Grove, Illinois
- Nitto Avecia Pharma Services (Analytical); Irvine, California
- Whitehouse Laboratories, a division of AMRI (Analytical); Lebanon, New Jersey
- Solid Form Solutions (Analytical); Milton Bridge, Scotland
- Lofton Label & Packaging (Packaging); Inver Grove Hts, Minnesota
- PharmaTOX (In Silico Analysis); Cheyenne, Wyoming
- SafeBridge (Environmental Impact); Mountain View, California
- Jenike & Johanson (Bulk Material Engineering); Tyngsboro, Massachusetts
- The Coghlan Group (Clinical Packaging & Labelling); Bastrop, Texas
- Jeff Yuen & Associates (Quality); Orange, California
- Innovations for Global Health (Quality); Doylestown, Pennsylvania
- SeerPharma (Quality); Melbourne, Australia
- World Courier (Supply Transport); Melbourne, Australia

**Regulatory Affairs**
- Diamond (eCTD Publishing), Washington DC and UK
- Target (US Agent and eCTD submissions), Washington DC
- Data Conversion Laboratory (Labelling SPL)
- EMB Consulting (dataset preparation)

**Non-clinical**
- MPI research (data set), US

**Metabolism**
- Frontage Laboratories (in vitro analytical), US

**Clinical Pharmacology**
- Certara, Melbourne/Princeton NJ
- ProPharma, US

**Clinical**
- Triclinium (site audits), South Africa
- TDR, Clinical advisory, Geneva
- Frontage (assay development and pharmacokinetics on human samples), Philadelphia PA
- Mason Clinical (cardiology assessment)
- Spaulding Healthcare (Phase I Unit), Wisconsin
- Imperial College, London (Modelling)

**Statistics**
- Forsythe and Bear (primary team), California
- Luxemburg Institute of Health (Phase III)
- SQN (Phase III), Diss, UK
- McCloud Consultancy (across program), Sydney
REGULATORY AGENCY SUBMISSIONS/MEETINGS

TDR and Wyeth

UK MCA:
- Development plan

French AFSSAPS:
- Development plan

EMEA:
- Development plan
- Phase 3 plan
- Paediatric population plan
- CMC plan
- Contingency plan

Ghana FDB/FDA:
- Phase 2 study
- Phase 3 study

Liberia MoH:
- Phase 3 study

DRC MdSP:
- Phase 3 study

MDGH

US FDA
- Pre-IND meeting
- Clinical meeting
- CMC meeting
- Pre-NDA meeting
- Mid-cycle review meeting
- Late-cycle review meeting

US FDA audits and inspections during NDA review

cGMP
- Drug manufacturing site
Clinical
- Ghana Phase 2 and 3 study
- TDR
SELECTED STATS ON INFORMATION/DATA MDGH ASSEMBLED FOR THE NEW DRUG APPLICATION AND FDA REVIEWED

- 760 datasets
- 64 non-clinical reports
- 70 Summaries
- 1785 separate docs
- CMC
  - 14 analytical assays developed/ validated
  - 18 Full Scale cGMP batches (~5.6 Million tablets)
- Clinical
  - 8 clinical studies (1904 subjects)
  - 515,000 pages of raw data (PIII)
  - 26,000 skin snips

> 400,000 pages PLUS data sets submitted to FDA

Reviewed in 6 months by 28 FDA staff

⇒ 525 page summary
NDA REVIEW TIME LINES

NDA submitted electronically: 13 October 2017 (NDA210867)

Accepted for priority review: 13 December 2017

Approved and Priority Review Voucher granted: 13 June 2018
PLANS FOR REGISTRATION IN INTERESTED AFRICAN ONCHOCERCIASIS ENDEMIC COUNTRIES

Collaborative Procedure for Accelerated Registration

In many countries with limited regulatory resources, registration of finished pharmaceutical products (FPPs) — be these WHO-prequalified products or products approved by stringent regulatory authorities — can take considerable time. In the worst cases, this time can extend to two or three years, meaning that patients may not receive treatment that could save their lives or improve their state of health.

WHO has responded to this situation:

- secondly by creating a collaborative procedure to accelerate registration of FPPs that have already received approval from a stringent regulatory authority.

WHO facilitation recommended for products of interest to WHO public treatment programmes

Onchocerciasis endemic countries participating in ongoing pilot phase

- Burkina Faso
- Burundi
- Cameroon
- Cote d'Ivoire
- DRC
- Ethiopia
- Ghana
- Malawi
- Mali
- Mozambique
- Nigeria
- Senegal
- Sierra Leone
- Tanzania
- Uganda

Source:
https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras
http://apps.who.int/iris/bitstream/handle/10665/272452/9789241210195-eng.pdf
MORE THAN THANKS

DR. KWABLAH AWADZI

13 JUNE 1939 TO 16 MARCH 2011

DIRECTOR OF THE ONCHOCERCIASIS CHEMOTHERAPY RESEARCH CENTER IN HOHOE, GHANA

HIS EXPERTISE IN ONCHOCERCIASIS AND CLINICAL TRIALS IN O. VOLVULUS INFECTED SUBJECTS IN RURAL AFRICA WAS KEY TO GETTING ONCHOCERCIASIS CONTROL AND MOXI TO WHERE THEY ARE TODAY
REFERENCES: CLINICAL STUDIES OF MOXIDECTIN


Phase 1 studies:


• Collaborative Procedure for SRA approved medicines and recommended WHO facilitation for products needed in public treatment programmes of interest to WHO:
  • https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras
  • http://apps.who.int/iris/bitstream/handle/10665/272452/9789241210195-eng.pdf (p 39 f, page 353 ff WHO guideline)
• Moxidectin prescribing information (label) and US FDA review summaries
  • https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf
  • https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210867Orig1s000TOC.cfm