MOXIDECTIN TO FDA APPROVAL

- **Mark Sullivan (Founder and Managing Director Medicines Development for Global Health)**
- **Annette C. Kuesel (TDR)**

MEDICINES DEVELOPMENT FOR GLOBAL HEALTH (MDGH)

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

Pre-Discovery Research	Discovery	CMC (Drug substance, product development & manufacture)	New Drug application assembly and submission	
		Non-clinical Research		
		Clinical Research		
		Phase 1 n=20-100		
		Phase 2 n=100-500		
		Phase 3 n=1000-5000		Regulatory Agency review
Basic causes of disease – Discover 'targets', which if 'attacked' via a drug can alter the course of the disease	Identify molecules which alter 'target' function but are not 'too' toxic to the 'host' – Drug candidate	Well characterized and stable drug product	All data assembled and analyzed as per regulatory requirements for verification & assessment by RA	
		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?		
		P 1: PK, safety P 2: Initial efficacy, safety (PK) P 3: Large scale efficacy, safety		Label: Prescribing info

WHAT HAPPENED FOR MOXIDECTIN?

Discovery:
FDAH
TDR

CMC (Drug substance, drug product development and manufacture)
FDAH , Wyeth, Medicines Development for Global Health

Non-clinical research FDAH, Wyeth
In vitro (enzymes, cell cultures), *In vivo* (mice, rats, dogs)
Primary pharmacology (efficacy), Secondary pharmacology (safety)
Absorption, distribution, metabolism, excretion (drug interactions)
Single dose, multiple dose toxicity, carcinogenicity, genotoxicity
Reproductive/developmental toxicity (single, multiple generation)
Juvenile toxicity

Wyeth, MDGH: Six Phase 1 studies, including
Food effect, milk excretion, drug interaction, cardiac safety

Wyeth, TDR: Comparative Phase 2 study (Ghana), n=172

Wyeth, TDR: Comparative Phase 3 study (Liberia, Ghana, DRC) n=1472 (to 6 months post enrolment)
TDR: Study completion, data analysis
MDGH: Data analysis and reporting

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 (Tabletting 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 (Tabletting)
Niya Bowers, Advisory
Gerard Cunningham, Advisory
Mike Mitchell (Manufacturing)
Jignesh Patel (Drug Substance)
Tom Cullen (Chemistry)
Michael Putnam (Tabletting)
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
- Allens, 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
- Alcami 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

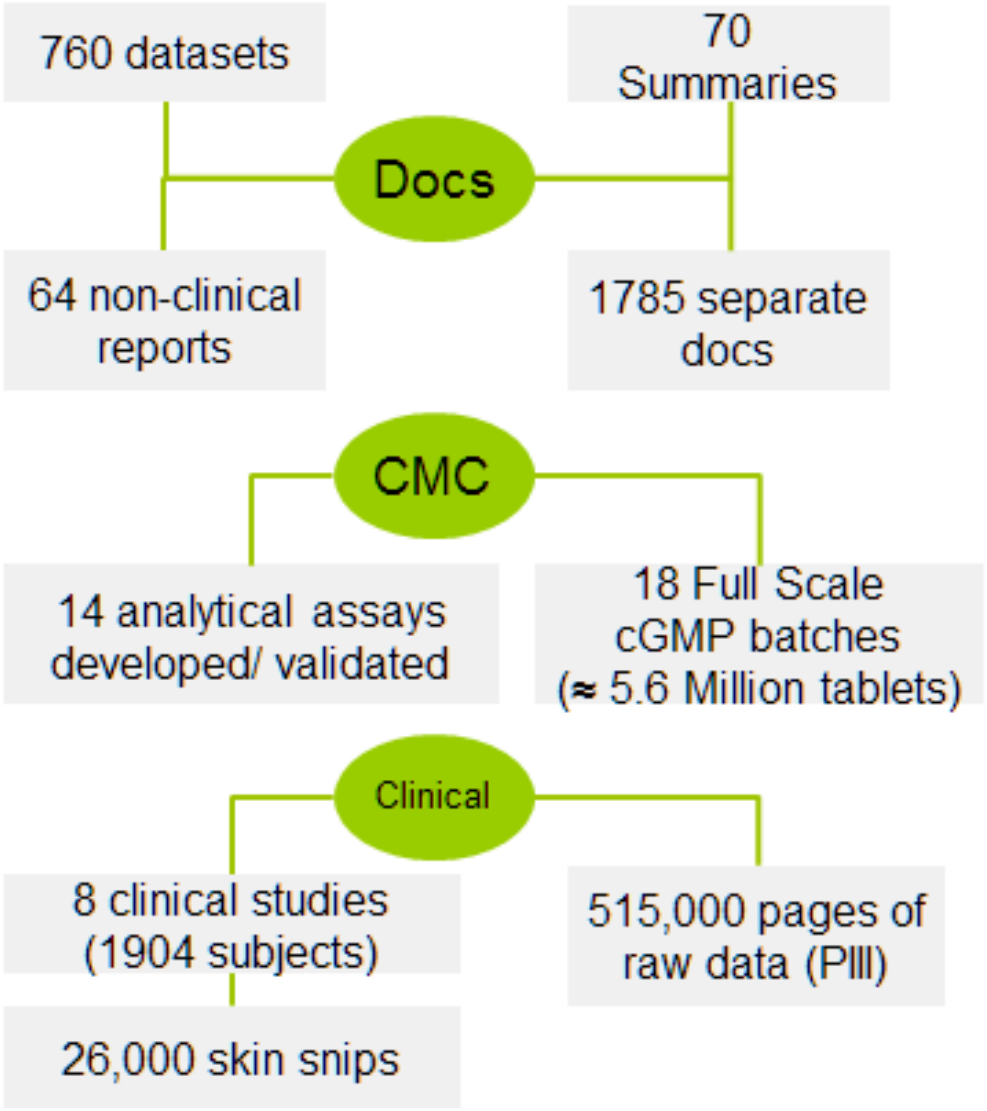
US FDA
- Pre-IND meeting
- Clinical meeting
- CMC meeting
- Pre-NDA meeting
- Mid-cycle review meeting
- Late-cycle review meeting

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



> 400 000 pages

PLUS data sets

submitted to FDA

Reviewed in 6 months by 28 FDA staff

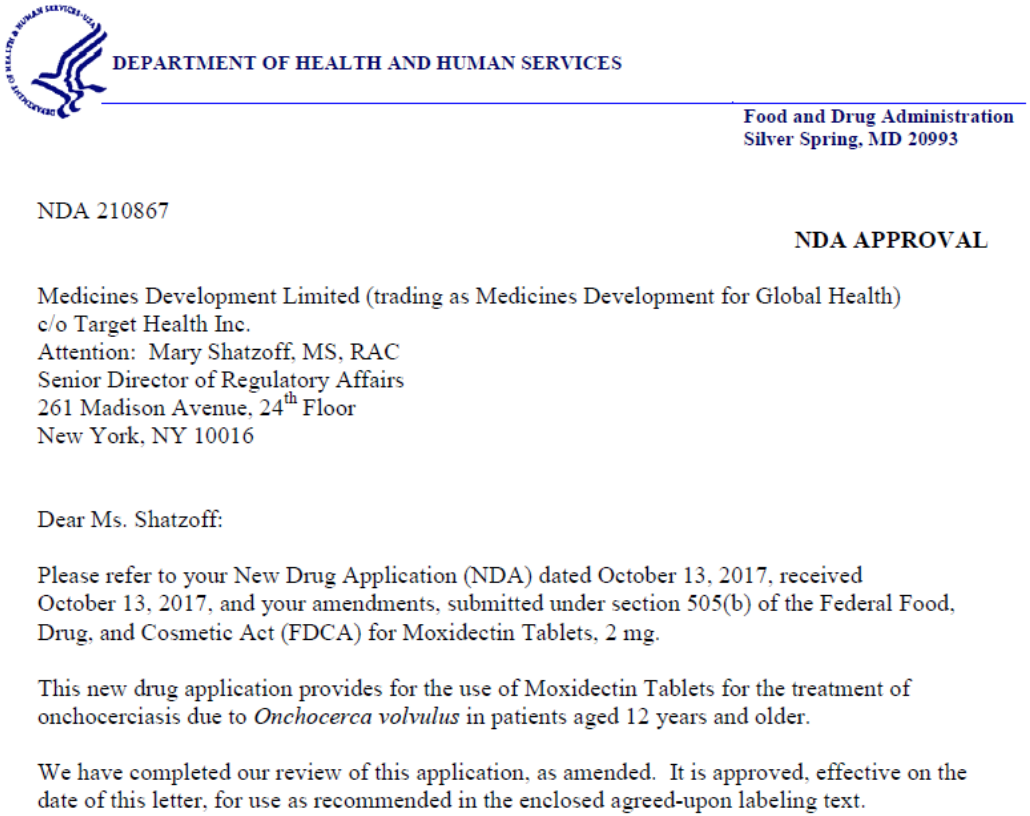
⇒ 525 page summary

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210867

NDA APPROVAL

Medicines Development Limited (trading as Medicines Development for Global Health)
c/o Target Health Inc.
Attention: Mary Shatzoff, MS, RAC
Senior Director of Regulatory Affairs
261 Madison Avenue, 24th Floor
New York, NY 10016

Dear Ms. Shatzoff:

Please refer to your New Drug Application (NDA) dated October 13, 2017, received October 13, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Moxidectin Tablets, 2 mg.

This new drug application provides for the use of Moxidectin Tablets for the treatment of onchocerciasis due to *Onchocerca volvulus* in patients aged 12 years and older.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

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

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

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

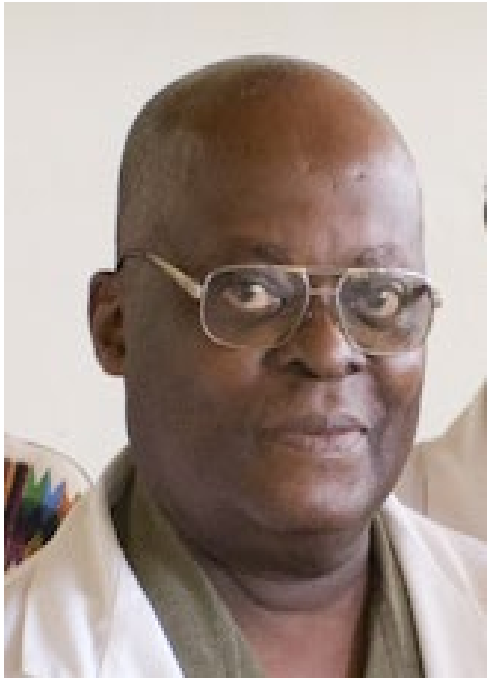
MORE THAN THANKS

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 3 study: Opoku, N.O., Bakajika, D.K., Kanza, E.M., Howard, H., Mambandu, G.L., Nyathirombo, A., Nigo, M.M., Kasonia, K., Masembe, S.L., Mumbere, M., Kataliko, K., Larbelee, J.P., Kpawor, M., Bolay, K.M., Bolay, F., Attah, S.K., Vaillant, M., Halleux, C.M., and Kuesel, A.C., 2018. Single dose moxidectin versus ivermectin for Onchocerca volvulus infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. Lancet (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(17)32844-1.pdf)

Phase 2 study: Awadzi, K., Opoku, N.O., Attah, S.K., Lazdins-Helds, J., and Kuesel, A.C., 2014. A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind Study of Moxidectin in Onchocerca volvulus Infection. PLoS.Negl.Trop.Dis. 8, e2953.(https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002953)

Phase 1 studies:

- Cotreau, M.M. et al., 2003. The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. J.Clin.Pharmacol. 43, 1108-1115.
- Korth-Bradley, J.M. et al. 2012. Relative bioavailability of liquid and tablet formulations of the antiparasitic moxidectin. Clinical Pharmacology in Drug Development 1, 32-37.
- Korth-Bradley, J.M.et al. 2012. The effect of a high-fat breakfast on the pharmacokinetics of moxidectin in healthy male subjects: a randomized phase I trial. Am.J.Trop.Med.Hyg. 86, 122-125.
- Korth-Bradley, J.M., et al. 2011. Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. Antimicrob.Agents Chemother. 55, 5200-5204.
- Korth-Bradley, J.M. et al. 2014. Effect of moxidectin on CYP3A4 activity as evaluated by oral midazolam pharmacokinetics in healthy subjects. Clinical Pharmacology in Drug Development 3, 151-157.
- Kinrade, S.A. et al. 2018. Evaluation of the Cardiac Safety of Long-Acting Endectocide Moxidectin in a Randomized Concentration-QT Study. Clin Transl.Sci. (https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1111/cts.12583)

OTHER REFERENCES

- 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://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_1003_full-version.pdf (page 32f)
  - 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