E1224 - PROOF OF CONCEPT FOR A SAFE, EFFECTIVE AND AFFORDABLE NEW THERAPY FOR CHAGAS DISEASE

ISABELA RIBEIRO, HEAD DNDI CLINICAL PROGRAMME

DNDi

Drugs for Neglected Diseases *initiative*
Iniciativa "Medicamentos para Doenças Negligenciadas"

ASTMH, Philadelphia, 6 December 2011

A New Model for Drug Development: DNDi

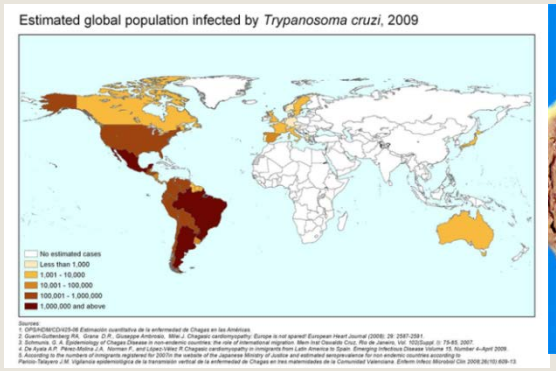
- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

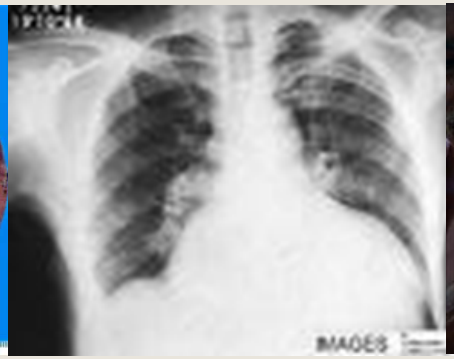
7 Founding Partners

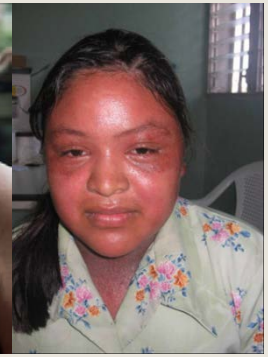
- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation Brazil
- Medecins Sans Frontieres (MSF)
- Institut Pasteur France
- WHO/TDR (permanent observer)

Chagas Disease: an unmet medical need

- Parasitic disease with greater disease burden in the New World
- Leading cause of infectious myocarditis worldwide





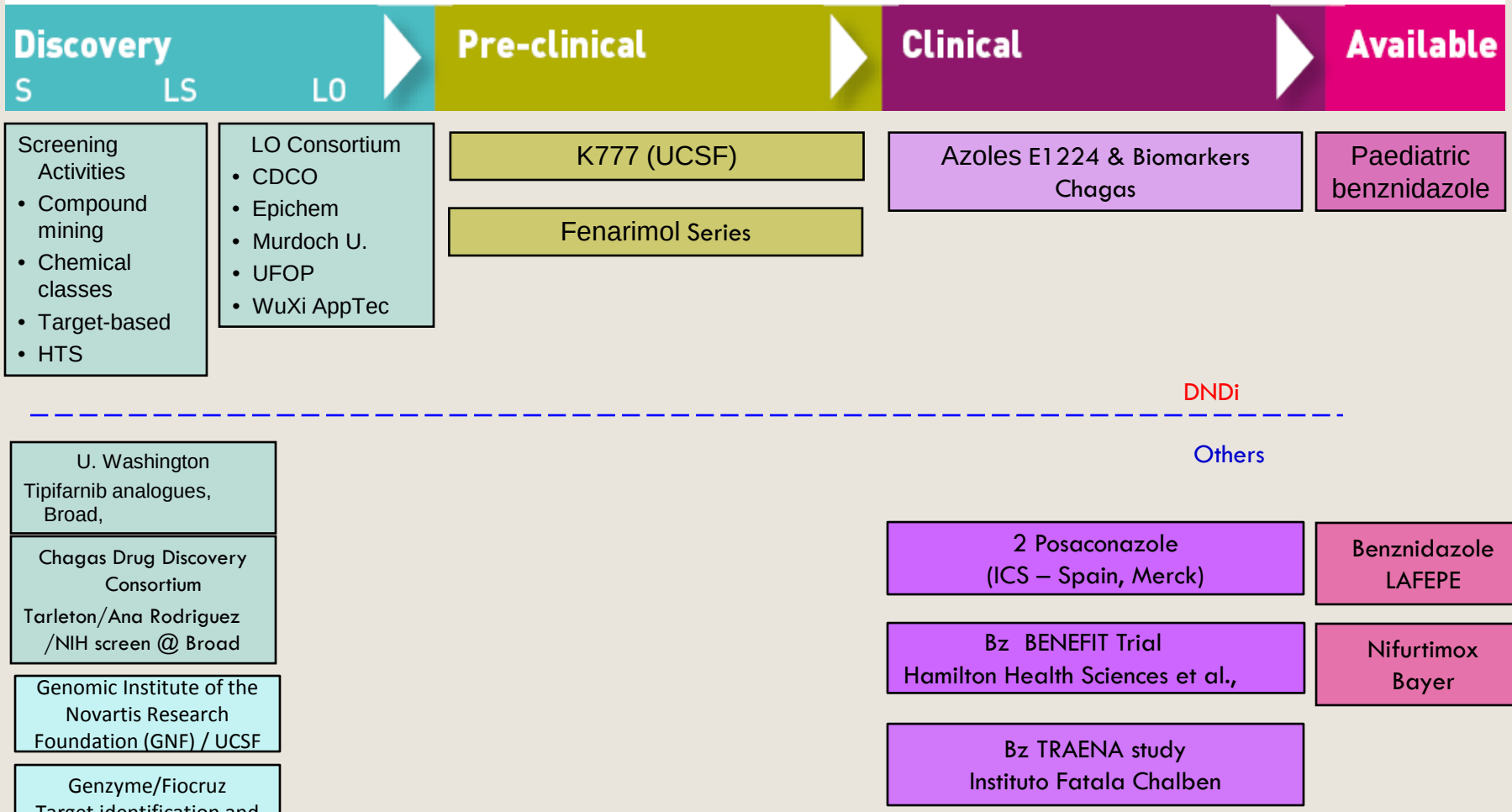


- Only two drugs available: nifurtimox and benznidazole
  - Safety and tolerability issues
  - Long treatment period (1-2 months)

Chagas Disease: knowledge gaps

- PK/PD relationship for Chagas disease largely unknown
- Limited knowledge on the relevance of animal models
- Limited information on the importance of the different parasite strains to human disease, coexistence of infection and mechanisms of resistance
- No general consensus on reference treatment
- Lack of early test of cure in Chagas disease
- Limited sensitivity of PCR

Chagas Landscape - 2012 projections



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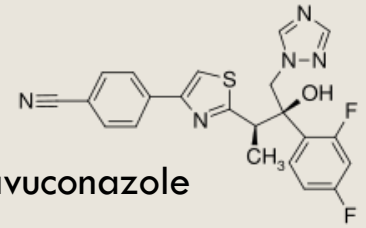
E1224: A Drug Candidate in a Promising Class



Ravuconazole

License signed with the Japanese pharma Eisai for clinical development of **E1224** for treatment of Chagas disease, sponsored by DNDi (Sept 29, 2009)

Pharmacological characteristics

- **Water-soluble monolysine salt of a phosphonoxymethyl ether of ravuconazole**
- **Rapid conversion to ravuconazole**
- **Good bioavailability and long terminal half-life**
- **Completed preclinical studies and Phase I studies**
- **Encouraging safety and tolerability profile**

Rationale for Chagas disease

- **Ergosterol synthesis inhibitor**
- **Ravuconazole: extremely potent *in vitro* inhibitor of *T. cruzi* growth**
- **Activity of ravuconazole documented in all *T. cruzi* species tested**
- **Differences in performance ascribed to PK parameters in animal models (AUC, T1/2 and Vd)**

E1224 - Phase II trial

- Target population: Adult patients (18-50y) with chronic indeterminate CD

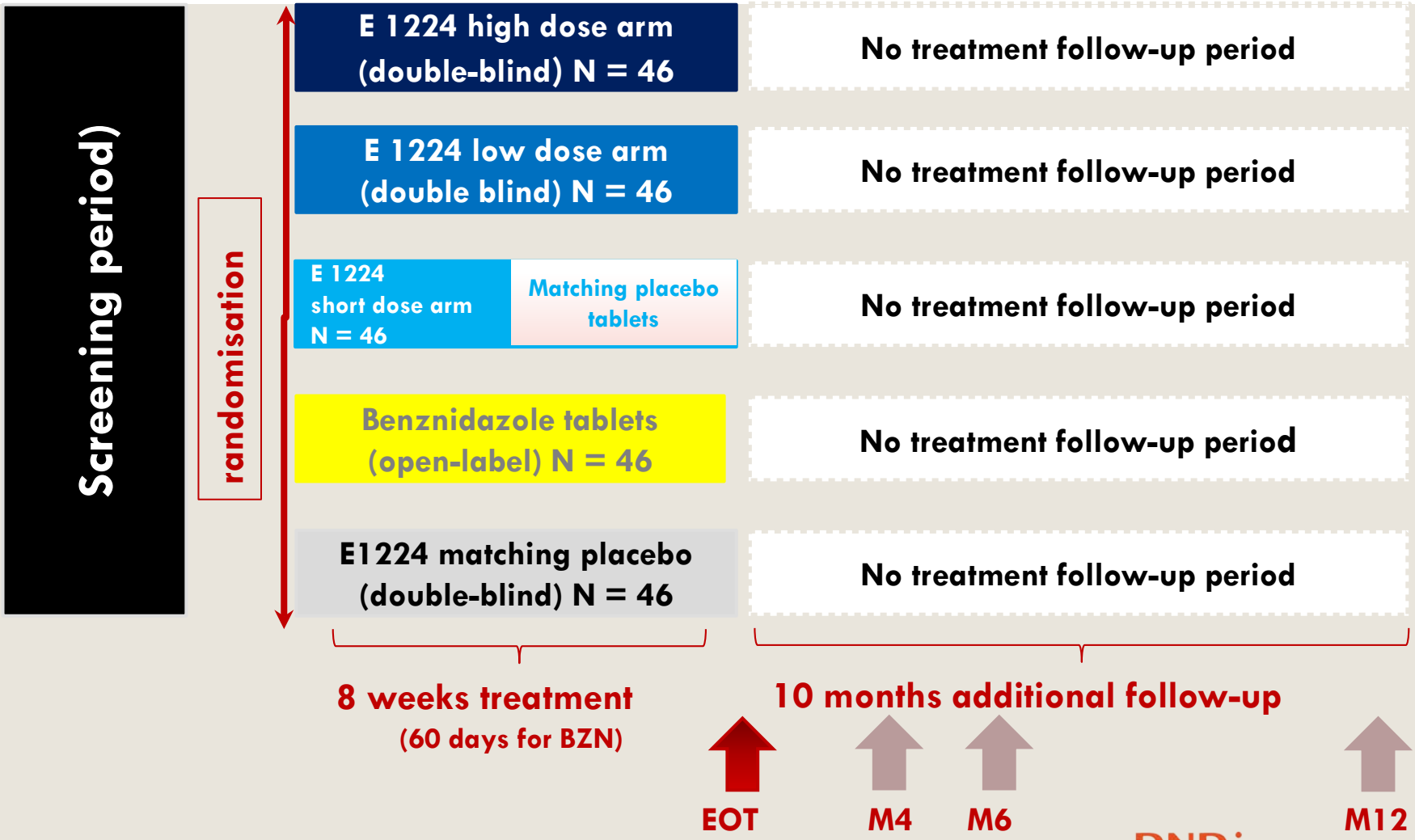
- General Objective: To determine whether each of three different dosing regimens of E1224 are **efficacious and safe** in eradicating *T. cruzi* parasitemia in individuals with the chronic indeterminate form of CD, in comparison to placebo
- Study sites: "Plataforma de Atención al Paciente con Enfermedad de Chagas", a collaborative program between 'Facultad de Medicina de la Universidad Mayor de San Simon", Universidad Autónoma Juan Misael Saracho, CEADES Salud y Medio ambiente and 'Centre de Recerca en Salut Internacional de Barcelona" (CRESIB)

- PI: Drs. Faustino Torrico and Joaquim Gascón

Scope of current assessment:

Early development, proof-of-concept evaluation

Phase II Study - design



Efficacy based on repeated PCR and candidate biomarkers + PK

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Phase II Study - endpoints

Primary endpoint:

Clearance of parasitaemia in serial, qualitative RT-PCR tests (3 negative PCR results) at end of treatment

Secondary endpoints:

- Sustained parasitological response over one year by RT-PCR
- Evaluation of t biomarkers of treatment response
  - Parasite load over time, conventional and nonconventional serology, brain natriuretic peptide, troponin, prothrombotic factors, lytic antibodies, apolipoprotein A1 and multiplex serodiagnostic assay.
  - Changes in the levels of biomarkers will be correlated with parasite eradication and population-PK parameters of BZN or E1224.
- Safety and tolerability of E1224 and Benznidazole
- Population-pharmacokinetics of Ravuconazole and Benznidazole

E1224 Phase II Study - status

- Study initiated in July 2011
- Total number of patients offered study participation: 294
- Total number of patients screened: 186 (52% in Cbba; 77% in Tarija)
- Total number of patients included: 59 (Nov 24th)
- Pending evaluation for inclusion: 11
- Causes of screening failure: 57 (49%) biochemical alterations; 34 (29%) PCR negative; 26 (22%) other (EKG, >15d screening period, haematological abnormalities)
- No SAEs identified

Balancing knowledge gaps and the urgent medical need

- Decision to proceed with clinical development and generation of scientific information that would help fill existing gaps and inform future drug development
- PCR - selected primary endpoint for clinical trials following extensive expert consultation
  - Standardised PCR technique – TDR multicentre evaluation
  - Use of serial examination for increased sensitivity
  - Sequential parasite examination for a total of 12 months
  - Inclusion of placebo control arm
  - Evaluation of reference compound
- Early regulatory consultation and agreement on endpoints, trial design and development strategy
- Generation of PK/PD data in humans (with different markers and parasite genotyping) for E1224 and benznidazole

Balancing knowledge gaps and the urgent medical need

- Generation of data in support of PCR and other biomarkers
- Harmonisation of clinical trial protocols and success measurements for development in CD in preparation for Phase III trials
- Continued regulatory and expert consultation through development process
- Plans for integration of results with data from other clinical trials on Chagas disease

Conclusions

- The E1224 Phase 2 study is in line with current «State of the Art» for the development of a treatment for the chronic indeterminate form of Chagas Disease
- This project will generate data that will be useful for future development in Chagas with any potential drug candidate
- DNDi aims to promote the integration of all new scientific data to advance knowledge and support the development of new tools in Chagas Disease

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Thank you for all the partners!

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