Chagas Disease Portfolio

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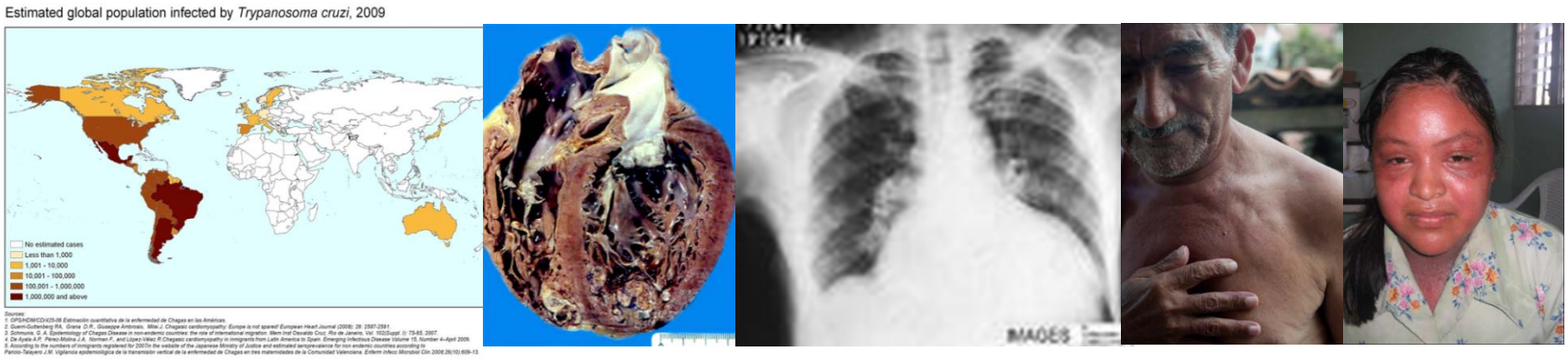
Chagas Disease: an unmet medical need

- 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)
  - No pediatric formulations available

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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 lineages to human disease, coexistence of infection and mechanisms of resistance
- Lack of early test of cure in Chagas disease
- Limited sensitivity of parasitological methods, PCR

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DNDi's Chagas Strategy

Short-term objectives:

Better use of existing treatments through new formulations, therapeutic switching, and combinations

- Pediatric dosage form of benznidazole
- Azoles
- Combination treatment

Long-term objectives:

New drugs and improved R & D capacity

- Nitroimidazoles, fenarimol series, K777
- Improved screening methodologies
- Lead optimisation consortium
- Biological markers of treatment response: validated and qualified

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Target Product Profile 2011

	Acceptable	Ideal
Target population	Chronic	Chronic and Acute (Reactivations)
Strains	TcI, TcII, TcV and TcVI (according to new 2009 classification)	All according to new classification (2009)*
Distribution	All areas	All areas
Adult/children	Adult	All
Clinical efficacy	Non inferior to benznidazole in all endemic regions (parasitological)	Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)
Safety	Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment	Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment
Activity against resistant strains	Not necessary	Active against nitrofuran- and nitroimidazole-resistant *T. cruzi* strains
Contraindications	Pregnancy/lactation	None
Precautions	No genotoxicity; No prolongation of QTc interval	No genotoxicity; No teratogenicity; No negative inotropic effect; No prolongation of QTc interval
Interactions	No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs	None
Presentation	Oral	Oral
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regimen	Comparable to systemic antifungal treatments	Once daily/ 30days

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Balancing knowledge gaps and the urgent medical need

- 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
- Early regulatory consultation and agreement on endpoints, trial design and development strategy
- Generation of data in support of PCR (*T.cruzi* DNA) and other biological markers of therapeutic response
- Generation of PK/PD data in humans (with different markers and parasite genotyping) for E1224 and benznidazole

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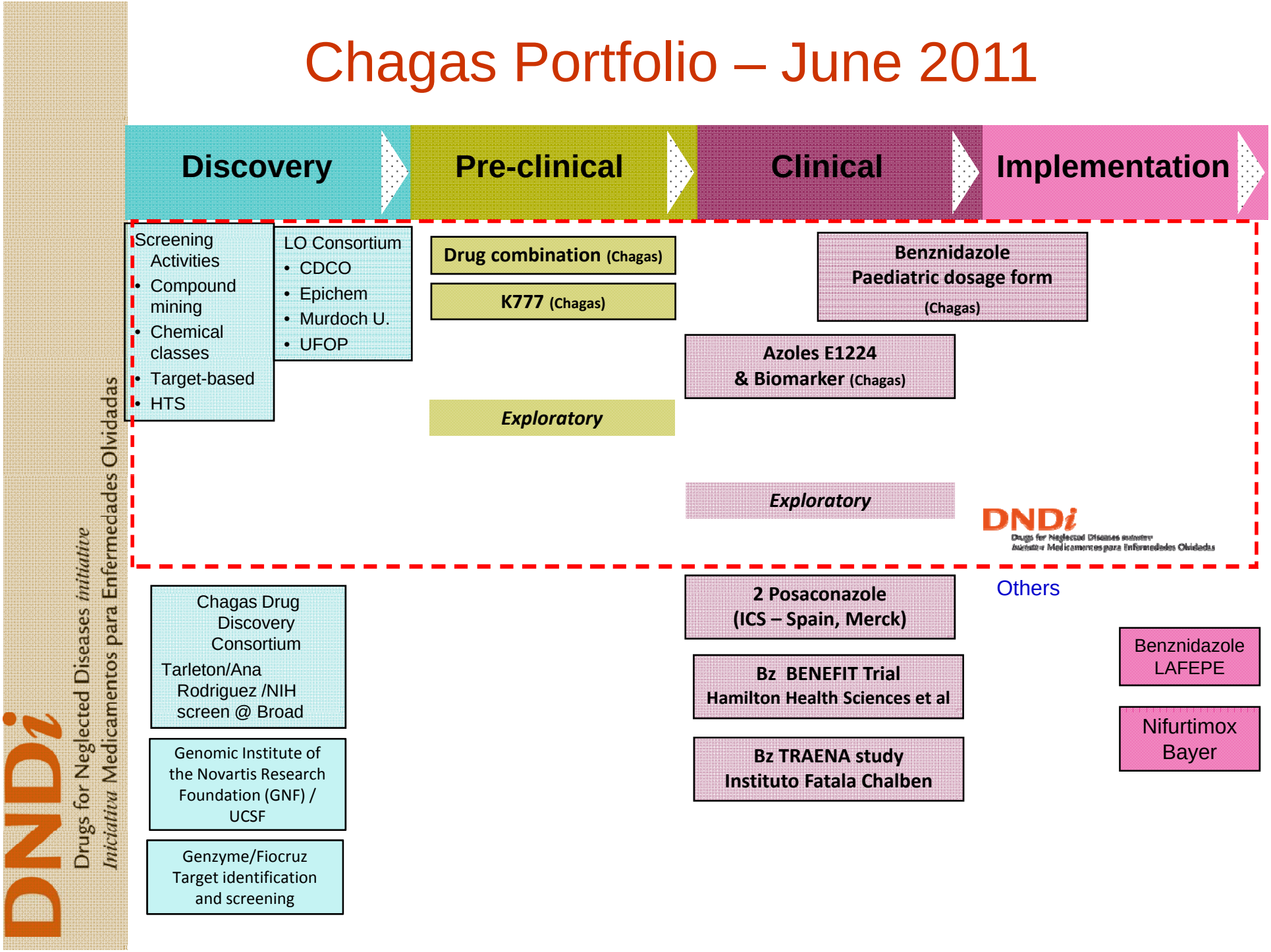
Chagas Portfolio – June 2011



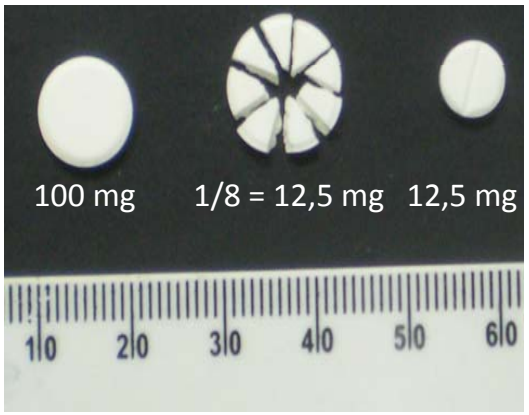
Pediatric Benznidazole

Overall Objective:

An affordable, age-adapted, easy to use, pediatric dosage form for Chagas disease

Definition of Tablet Strength and Formulation:

12.5 mg dispersible tablets for <20 kg children



Partner: LAFEPE (sole Bz producer)
DNDi-LAFEPE signed agreement in 2008 for the development of a Bz peadiatric formulation

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SIPEL
Scout

Chagas

Pediatric Benznidazole 2011-2012

- Submission to Brazil DRA: March 2011
  - Feedback awaited 10/2011
- Implementation of access plan: interaction with different stakeholders to ensure the product availability, affordability, and adoption in key endemic countries
- Population PK study of Pediatric Benznidazole in children with Chagas disease (Argentina, PI: Jayme Altcheh)
  - Recruitment initiated in May 2011 – 30 children recruited, so far
- Comparative Bioavailability Study of Pediatric Benznidazole in Healthy Normal Volunteers (Brazil, CRO: NUDFAC).

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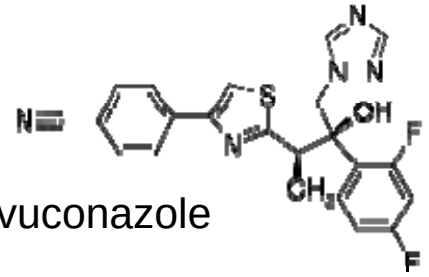
E1224:
A Drug Candidate in a Promising Class



Ravuconazole

Eisai

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* lineages tested**
- **Differences in performance ascribed to PK parameters in animal models (AUC, T1/2 and Vd)**

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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" in Cochabamba and Tarija, Bolivia
- PI: Drs. Faustino Torrico and Joaquim Gascón

Study initiated in July 2011

Scope of current assessment:

Early development, proof-of-concept evaluation

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PCR Study

Optimization of sampling procedure for PCR technique to assess parasitological response for patients with Chronic Chagas Disease treated with benznidazole in Aiquile, Bolivia

- PCR - selected primary endpoint for clinical trials following extensive expert consultation
- Improvements in PCR sensitivity through sampling procedures vs logistics and feasibility for implementation in the field
- Collaboration with MSF Spain, Bolivia Mission (MSF-OCBA) and UMSS

Primary objective: To estimate the gain in sensitivity of several multiple-sample strategies of PCR with respect to the current standard (single sample of 10 ml) to detect Chagas chronic stage at baseline assessment.

Study Design

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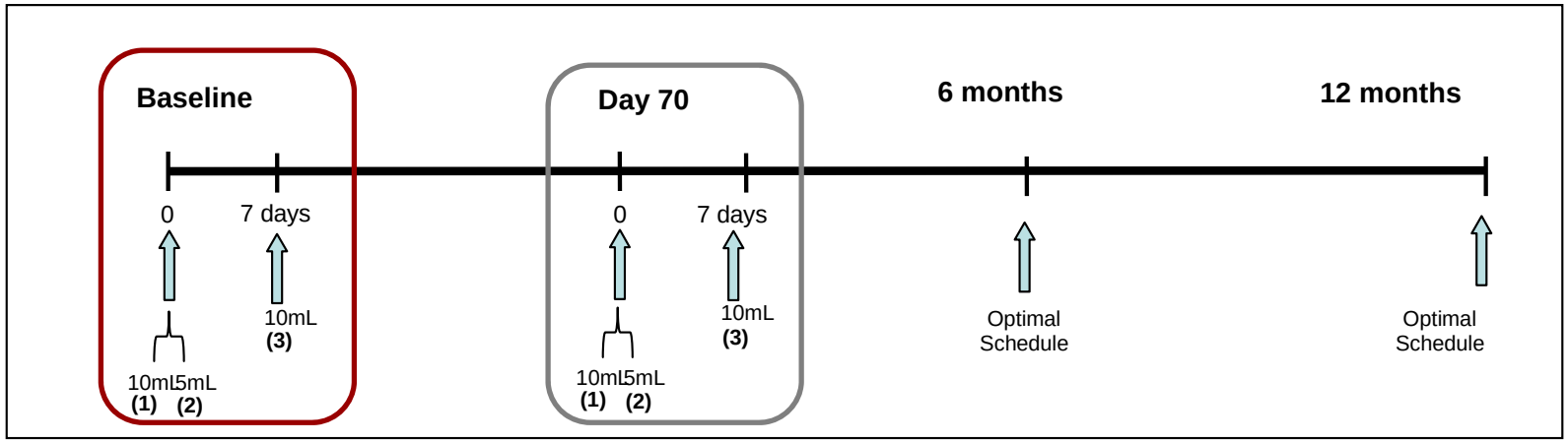
Benznidazole 5mg/kg/d during 60 days

Target recruitment n=220
Study initiation – April 13th (185 patients recruited)



Primary endpoint:
+ or – PCR
in sero+ patients

Secondary endpoint
Definition of optimal sampling
+ or – PCR
in PCR +(10 or 5+10 ml)

Secondary endpoint

Secondary endpoint

Current Strategy = 1 sample of 10 ml
Reinforcement Strategy = adding other sample: RS1: 10+5; RS2: 10+10 at D7; RS3: 10+5+10 at D7
Substitution Strategy = SS1: 5 ml; SS2: 5+10 at D7

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Biomarkers in Chagas

- RT-PCR lab optimization and validation for clinical studies
- NHEPACHA network for long term evaluation of candidate biomarkers
- Proteomic platforms: collaboration with HUG and McGill University
- Non-human primate study: collaboration with Univ. of Georgia and TBRI
- TRAENA – qualification of *T. cruzi* DNA and selected markers
- Coordination of activities with different partners
  - Work towards the integration of data on candidate markers
  - Collaboration in PAHO/TDR PCR
  - CRESIB

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Chagas Clinical Research Platform

Objectives:

- Facilitate effective and efficient trials to deliver improved treatment for Chagas disease
- Strengthen institutional research capacity
- Support an environment conducive to quality research
- Develop a critical mass of expertise
- Define priority areas for clinical evaluation of new treatments in Chagas disease
- Conduct periodic review and update of Target Product Profile in Chagas Disease
- Facilitate access to new tools
- Articulate with other initiatives

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