Best Science for the Most Neglected

DNDi
Drugs for Neglected Diseases initiative

Doença de Chagas: Estudos Clínicos com Novos Compostos

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DNDi: an innovative R&D model

- 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)

2010: DNDi established as Brazilian entity. The objective is to play a strategic role in the field of ND in Brazil and LA, to advocate for ND and to look for local funding

DNDi Drugs for Neglected Diseases initiative

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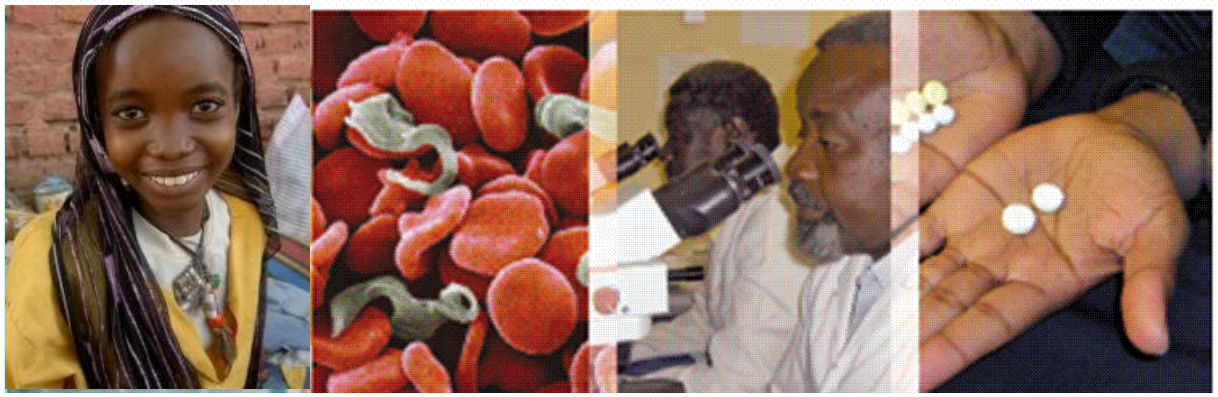
DNDi's Main Objectives

- Deliver **6 - 8 new treatments by 2014** for sleeping sickness, Chagas disease, leishmaniasis and malaria
- Establish a **robust pipeline** for future needs
- Use and strengthen existing **capacity in disease-endemic countries**
- Raise awareness and advocate for increased **public responsibility**



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Scope of Activities for DNDi

Major focus on kinetoplastids
(HAT /Leishmaniases /Chagas)

3 Core Diseases

3 Core Diseases

+ malaria: complete the 2 FDC

DNDi Portfolio-Building Model

- **Existing chemical libraries**
- **New lead compounds**

Long-term projects

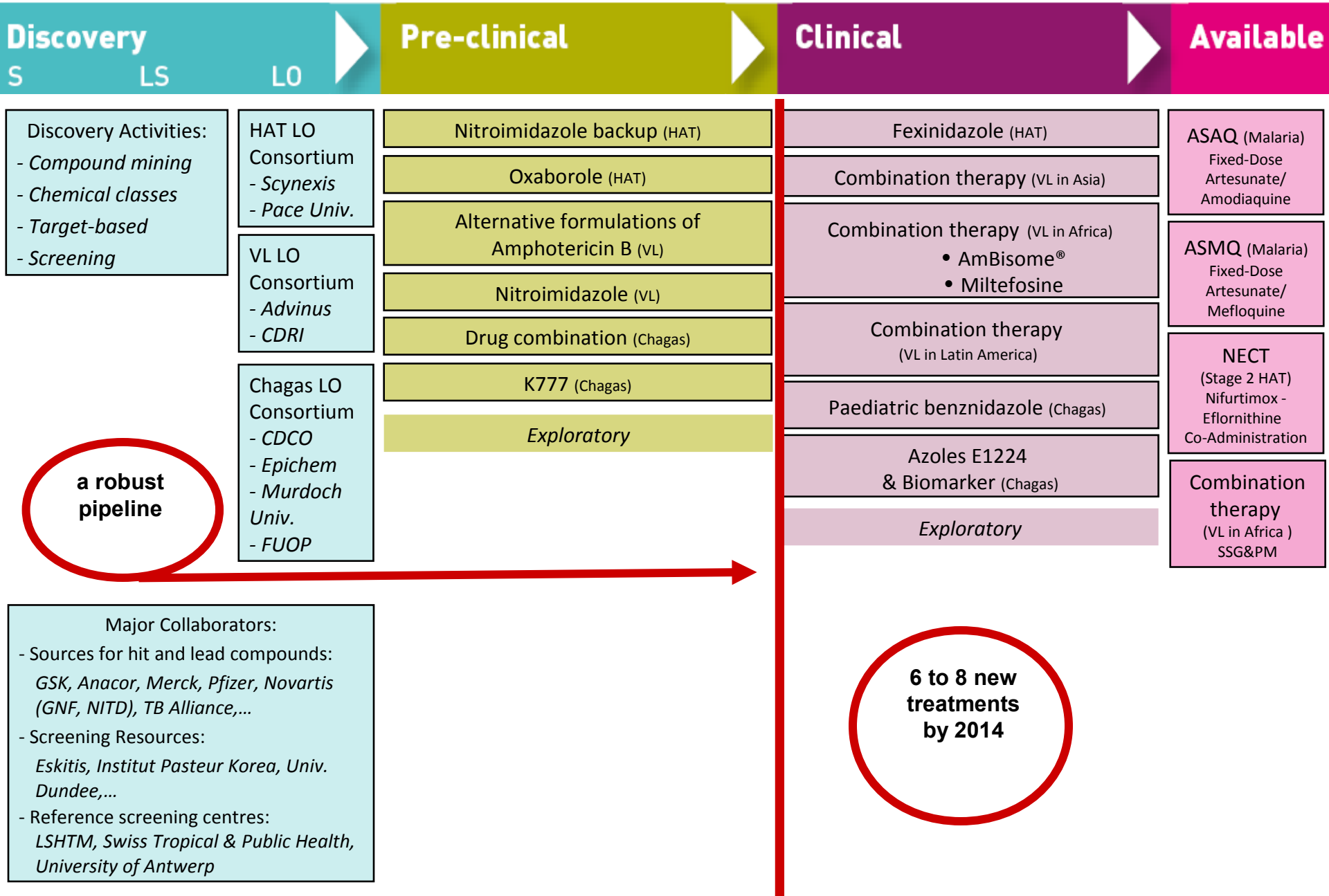
- **New formulations (fixed-dose combinations)**
- **New indications of existing drugs**

Medium-term projects

- **Completing registration dossier**
- **Geographical extension**

Short-term projects

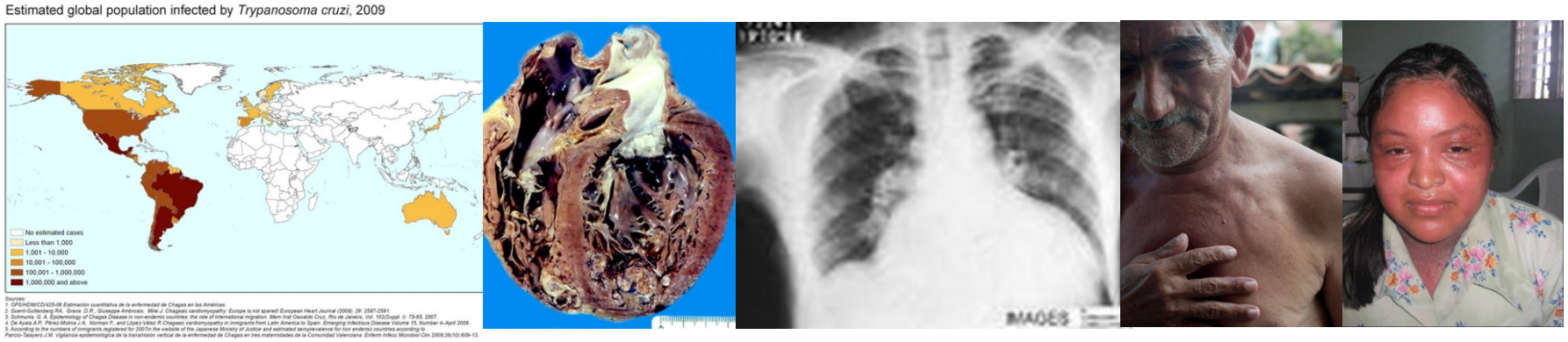
Project Portfolio – 2011



Chagas Disease Strategy: Clinical development

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
  - Poor efficacy in chronic patients

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Chagas Portfolio & Landscape

Discovery Activities
- Compound mining
- Chemical classes
- Target-based
- Screening

IPK
- High content screening

University Washington
- Tipifarnib analogs (JK36)
- Disubstituted Imidazoles

Chagas LO Consortium
- CDCO
- Epichem
- Murdoch University
- UFOP/IPK

ANACOR
- Oxaboroles
- AN4169

Merck Frost
- Cysteine protease inhibitors

Drug combination

K777 Sandler/UCSF

Azole /E1224 (Eisai) & Biomarkers

Benznidazole Pediatric Formulation LAFEPE

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Ana Rodriguez
Broad Institute

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Target identification and screening

Others

2 Posaconazole (ICS Spain) (Merck)

BENZNIDAZOLE LAFEPE

Bz BENEFIT Trial
Hamilton Health Sciences
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NIFURTIMOX Bayer

Bz TRAENA study – Instituto Fatala Chalben

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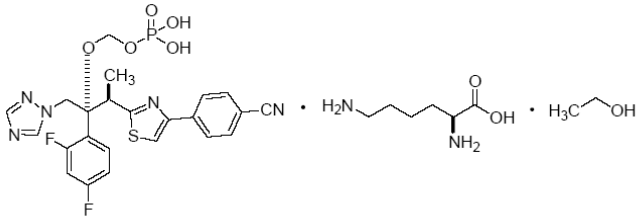
E1224:
A Drug Candidate in a Promising Class



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

Pharmacological characteristics

- Water-soluble monolysine salt form of ravuconazole
- Rapid conversion to ravuconazole
- Good bioavailability and long terminal half-life (7.7 – 10.5 days)
- 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* tested
- Differences in performance ascribed to PK parameters in animal models (AUC, $T_{1/2}$ and Vd)

E1224 - Phase II trial

- Target population: Adult patients (18-50y) with chronic indeterminate form of Chagas Disease
- 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
- Primary Objective: To determine whether at least one of three dosing regimens of orally administered E1224 is more efficacious than placebo in individuals with chronic indeterminate CD, by determining the number of patients who convert from positive to negative in serial, qualitative PCR test results (3 negative PCR results) at end of treatment (EOT)

Scope of current assessment:

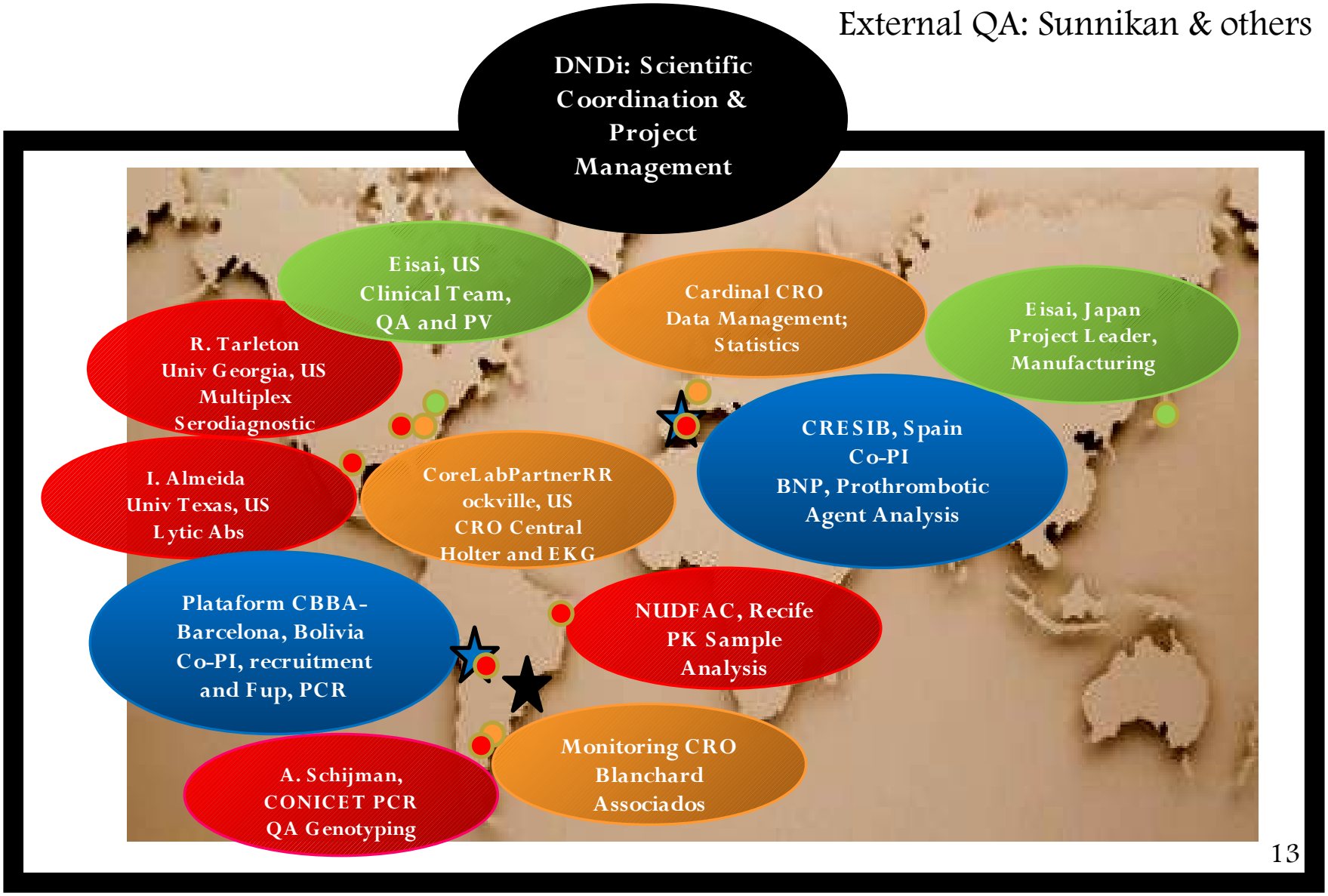
Early development, proof-of-concept evaluation

E1224 - Phase II trial

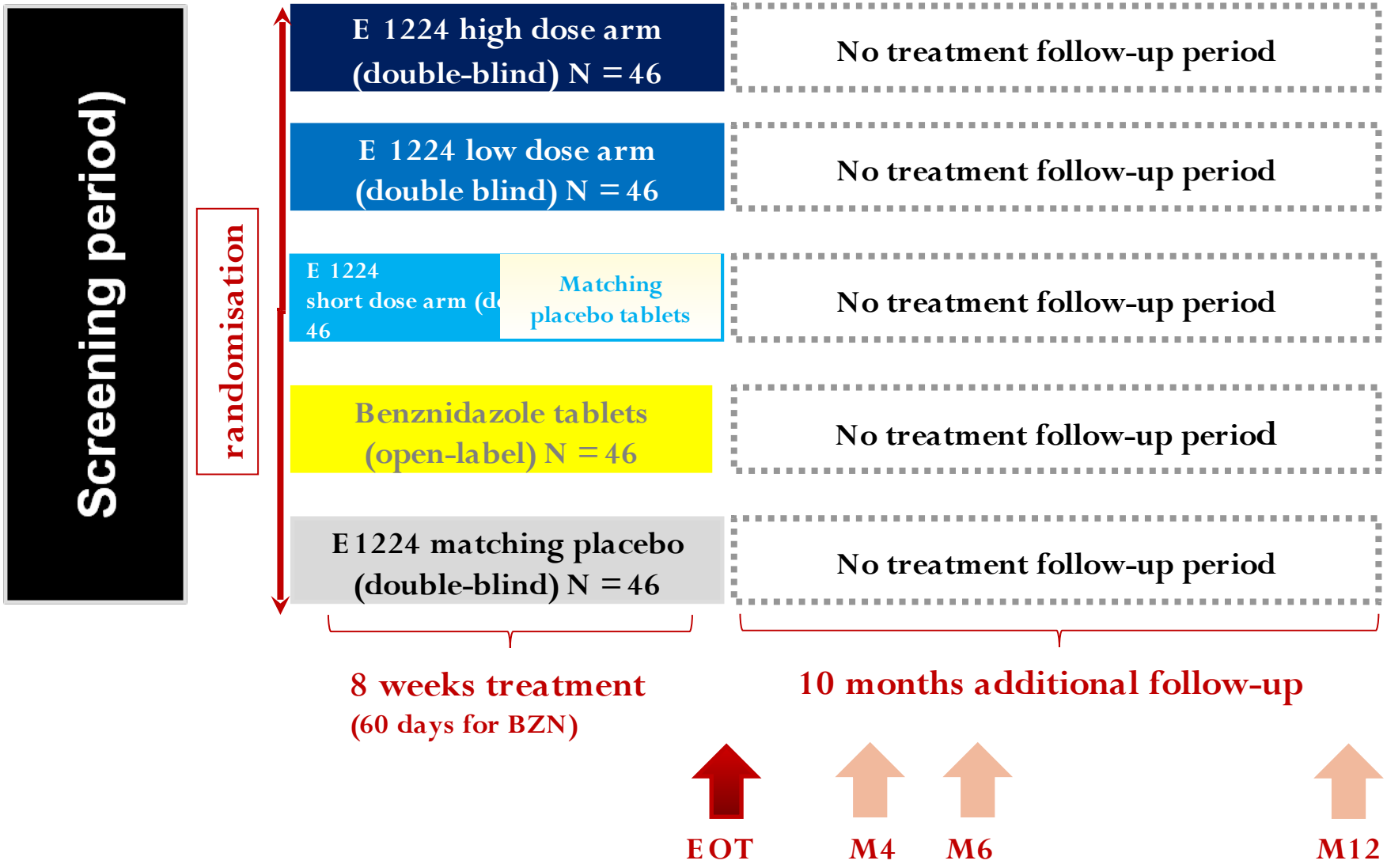
- Study sites: "Plataforma de Atención al Paciente con Enfermedad de Chagas", a collaborative program between 'Facultad de Medicina de la Universidad Mayor de San Simon' and 'Centre de Recerca en Salut Internacional de Barcelona' (CRESIB)
- PIs: Dr. Faustino Torrico and Dr. Joaquim Gascón

E1224 – Project Organisation

External QA: Sunnikan & others



Phase II Study design



Efficacy based on repeated PCR and candidate biomarkers

Key Decision Points for E-1224 development

Decision point 1 (EOT): Preliminary analysis of primary efficacy and safety will be performed to determine the continuation of the Phase II trial and initiation of Phase III clinical trial preparations.

Go decision: if at least one dose of E1224 shows superior efficacy in comparison to placebo and no significant safety concerns are identified.

No go: if no doses of E1224 are superior to placebo and/or significant safety concerns are identified.

Decision point 2 (12 months f-up): Analysis of sustained response and safety performed to determine the dose selection, initiation of Phase III clinical trial and decisions regarding paediatric evaluation and combination.

- Results to be integrated with available information from other clinical trials on azole compounds.

Go decision: if at least one dose of E1224 shows sustained treatment response in comparison to placebo and no significant safety concerns are identified.

No go: if no doses of E1224 are superior to placebo and/or significant safety concerns are identified.

'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

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.

PCR study

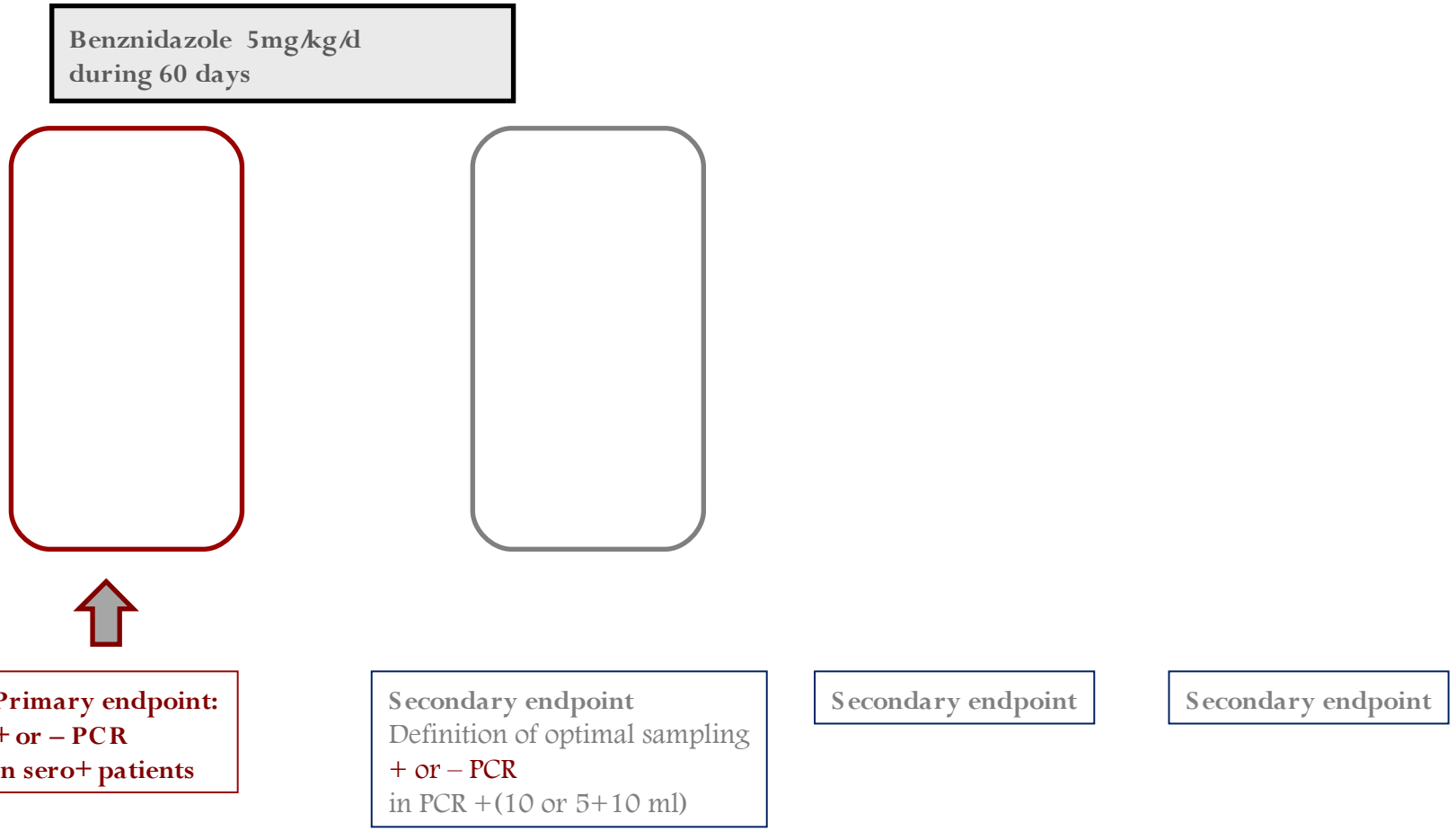
- **Co-sponsorship with MSF Spain and implementation with MSF Bolivia Mission (MSF-OCBA) and UMSS**
- **Location: Aiquile, Dept Cochabamba**
- **Status:**
  - Protocol finalization (English and Spanish)
  - Submission and approval by 2 ECs (MSF-OCBA and CEADES)
  - National control programme clearance

- **Study materials preparation (Spanish and English):**
  - CRF (collaboration FIOCRUZ platform) – printed and available for use
  - Study manual of operations
  - Study forms (adaptation of MSF forms to study context and DNDi SOPs)

- **Field visits:**
  - initial training of MSF team GCP and study procedures

- **Milestones:**
  - First patient in: April 2011
  - Study end : Q2 2012

Study Design



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

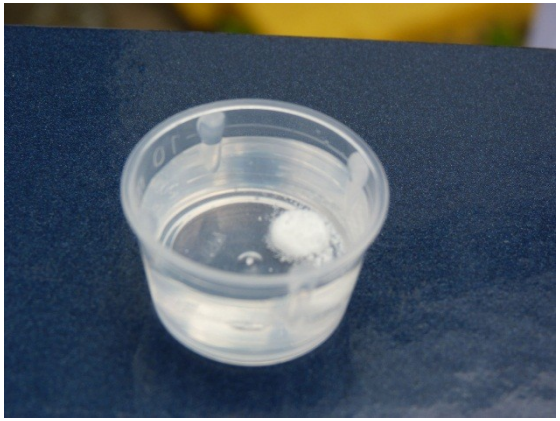
Pediatric Benznidazole

Overall Objective:

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

Definition of Tablet Strength and Formulation:

12.5 mg dispersible tablets for <20 kg children

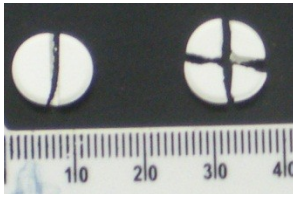


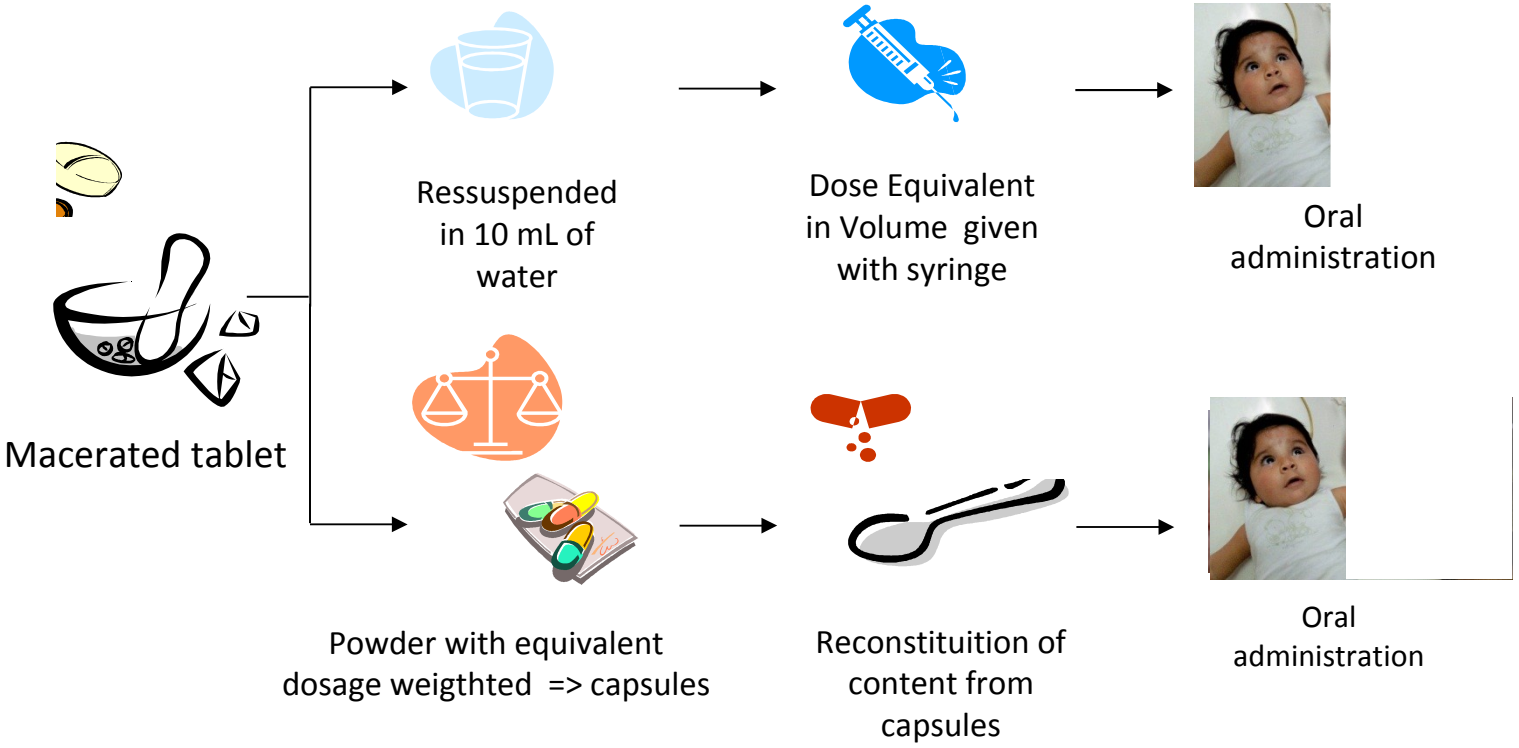
Partner: LAFEPE (sole Bz producer)
DNDi-LAFEPE signed agreement in 2008 for the development of a Bz peadiatric formulation

Pediatric Benznidazole - The need

Current ways to administer Benznidazole

. 100 mg tablet fractionation in ½ (50mg), ¼ (25mg), etc






SIPEL
Scout

Pediatric Benznidazole
"Population Pharmacokinetics of Benznidazole in Children with CD"

Principal Investigator: Dr. Jaime Altcheh
Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina

Study sites: Buenos Aires, Santiago del Estero, Salta and Jujuy

Primary objective: To describe the population pharmacokinetic parameters of benznidazole in children with acute or early chronic indeterminate form of Chagas Disease.

Study status:

- Ethical approval of study protocol – concluded
- Submission to ANMAT for national clearance and import license - technical approval Dec 2010; legal approval received Feb 2011
- All study specific materials finalised, printing of CRF ordered
- Finalisation of development of microsample method, NUDFAC – report awaited Mar 2011
- Supplies ordered to LAFEPE and available for shipment
- Contract with different study sites in preparation
- Expected FPFV: April 2011

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Muito Obrigada!

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