

Rationale and design of a proof-of-concept Phase II clinical study of E1224, a new drug candidate for chronic Chagas disease

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DNDi

Drugs for Neglected Diseases *initiative*

Iniciativa Medicamentos para Enfermedades Olvidadas

BACKGROUND

There is a dire need for new drugs to treat Chronic Chagas disease (CD):

- In the last 40 years only two anti-*T. cruzi* drugs (benznidazole and nifurtimox) were available and the use was limited to children with recent infection and to children with congenital infections. (**WHO Expert Committee, 1992**)
- At present more or less 8 to 12 millions people are infected with *T. cruzi* and most of them are adult people
- At this time neither of these drugs are available for the treatment of patients with Chagas disease, even if, in 2002, the **WHO Expert Committee**, recommended the specific drug treatment for all patients with positive serology for Chagas.

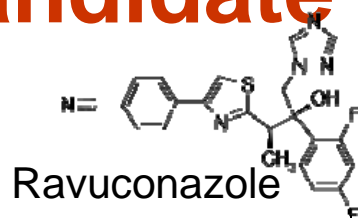
BACKGROUND

The main facts that limits the use of these drugs in Adult Chronic Chagas Disease are:

- ❖ **The lack in the knowledge of the therapeutic efficacy**
- ❖ **The frequency and severity of drug adverse reactions mainly in adults**
- ❖ **Long treatment period (2 months)**
- ❖ **It is difficult to measure the benefit and impact of treatment** (cures can not be readily and rapidly certified)

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

- E1224 is a water-soluble monolysine salt form of the ravuconazole **pro-drug**.
- Rapid conversion to ravuconazole in vivo
- Ravuconazole was **evaluated** extensively in **animal models and in human** trials (Phase 2 **safety** and efficacy trials for treatment of invasive fungal infections). Data from both preclinical and clinical evaluations of ravuconazole are therefore considered relevant to E1224.
- Good bioavailability and long half-life (7.7 – 10.5 days)
- Completed preclinical studies and Phase I studies
- Encouraging safety and tolerability profile

E1224:

A Drug Candidate in a Promising Class

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
- E1224 is available as **parenteral** and **oral** formulations (50 and 100 mg tablets)

E1224

With the benign safety profile and the encouraging results of animal studies and pharmacokinetics, E1224 is considered a priority candidate for clinical development for the treatment of Chagas' disease.

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

Phase II clinical study of E1224

- Total: 230 patients (46 patients/group)
- Two clinical trial sites: Tarija and Cochabamba
- “Plataforma de Atención al Paciente con Enfermedad de Chagas”, a collaborative program between ‘Facultad de Medicina de la Universidad Mayor de San Simon, CEADES Salud y Medio ambiente and ‘Centre de Recerca en Salut Internacional de Barcelona (CRESIB)



E1224



referencias

- CIUDADES CAPITALES
- ZONA ANDINA
- ZONA SUBANDINA
- ZONA DE LLANOS



Phase II clinical study of E1224 Study Design

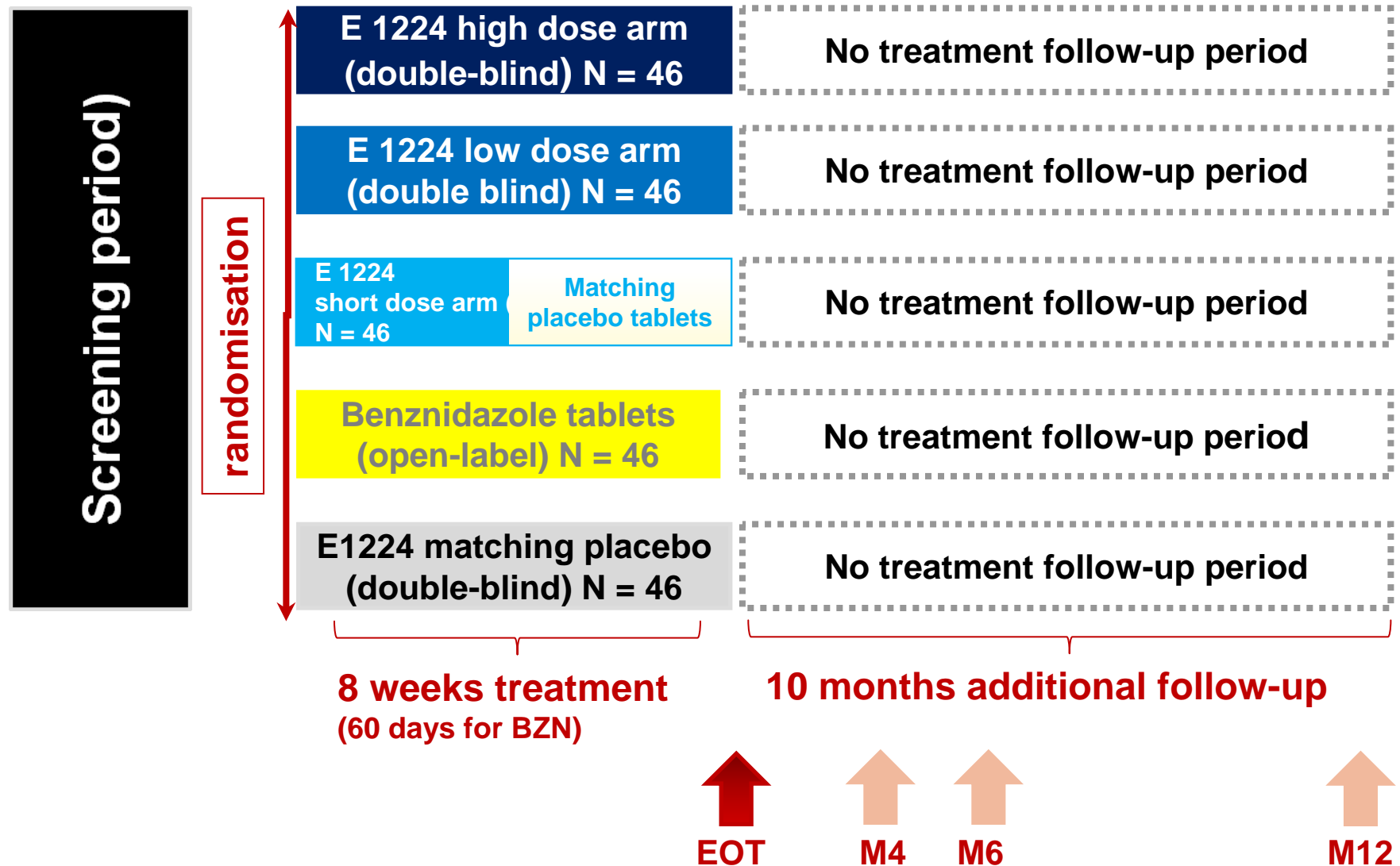
- Randomized,
- Placebo and active-controlled,
- Prospective,
- Assessor blind (E1224 and placebo blinded)
- Comparative
- Dose-finding
- Proof-concept clinical trial

Phase II clinical study of E1224

The study includes five parallel groups:

- three of which will receive one of three different oral E1224 dosing regimens and placebo
- One receiving placebo as the negative control
- One receiving BZN as the positive control for the treatment of CD in adults

Phase II Study design



Efficacy based on repeated PCR and candidate biomarkers

Phase II clinical study of E1224

The primary endpoint:

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

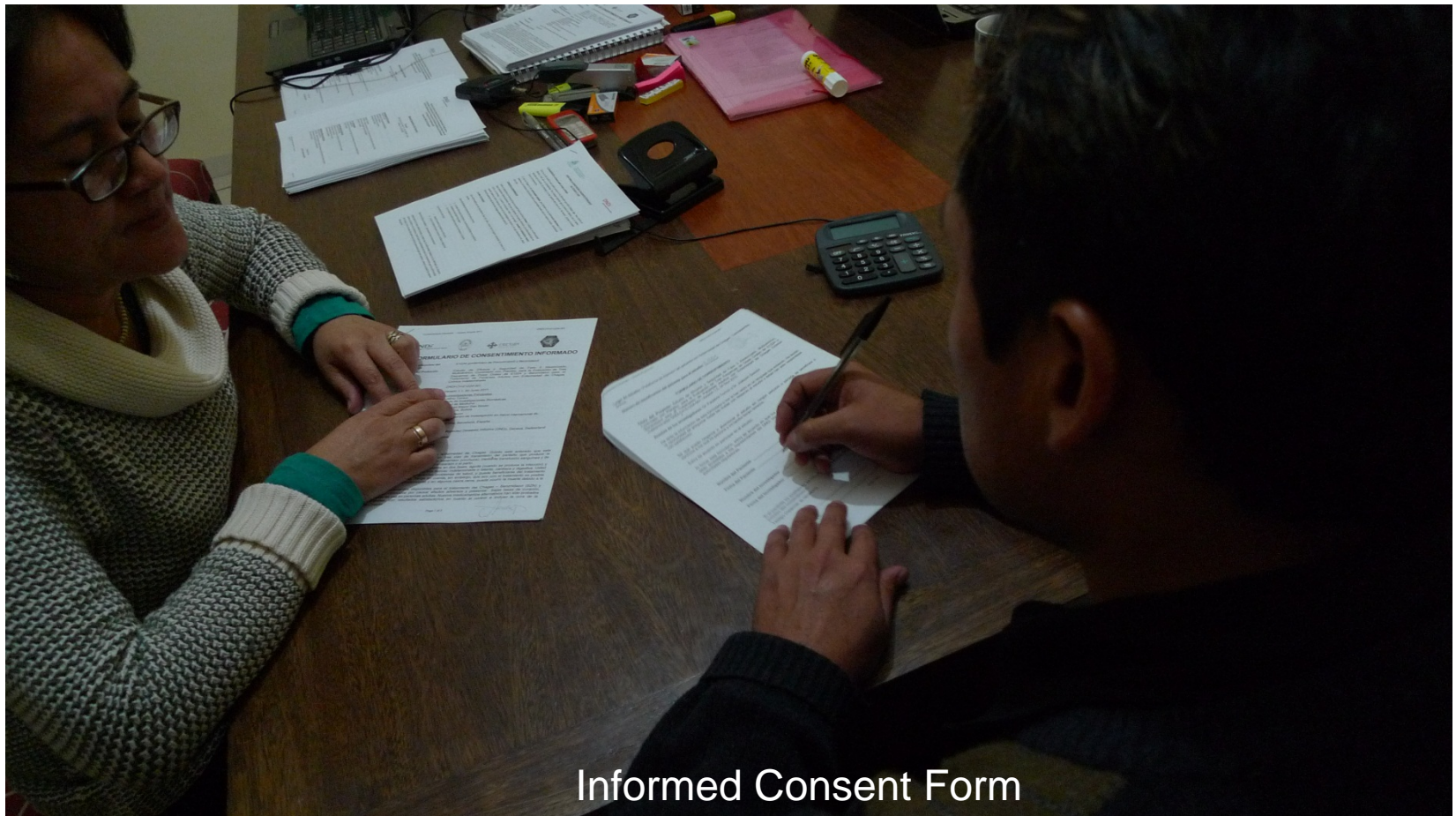
Phase II clinical study of E1224

The secondary endpoints:

- sustained parasitological response over one year by RT-PCR
- different biomarkers of treatment response
 - Parasite load over time, conventional and nonconventional serology, brain natriuretic peptide, troponin, prothrombotic factors, 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 E1224 and Benznidazole

Phase II clinical study of E1224

- Study initiated in July 2011
- Total of 22 patients recruited so far
- Efficacy and safety results from this clinical trial will inform the decision to proceed with a phase III evaluation for Chagas disease



The study began in July 2011



THANKS
MUCHAS
GRACIAS