E1224 FOR CHAGAS DISEASE

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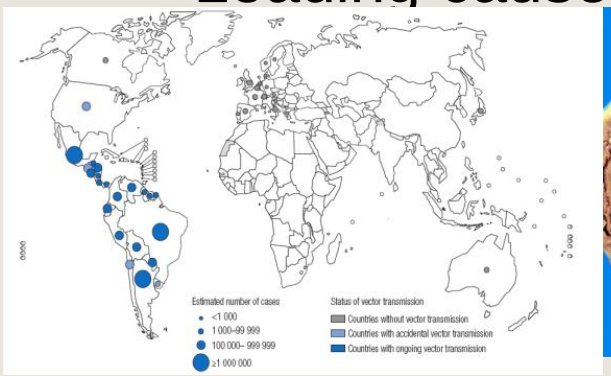
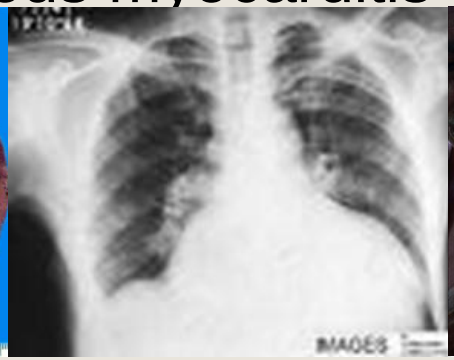
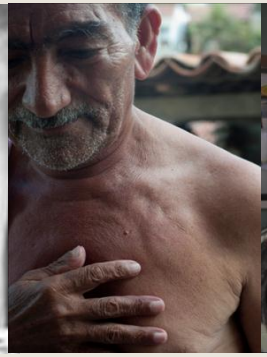
September 2012

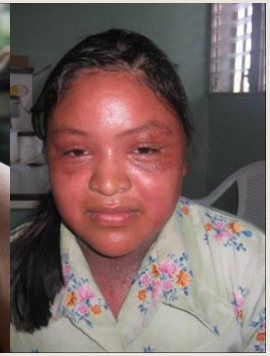
Chagas Disease: an unmet medical need

- Parasitic disease with greatest 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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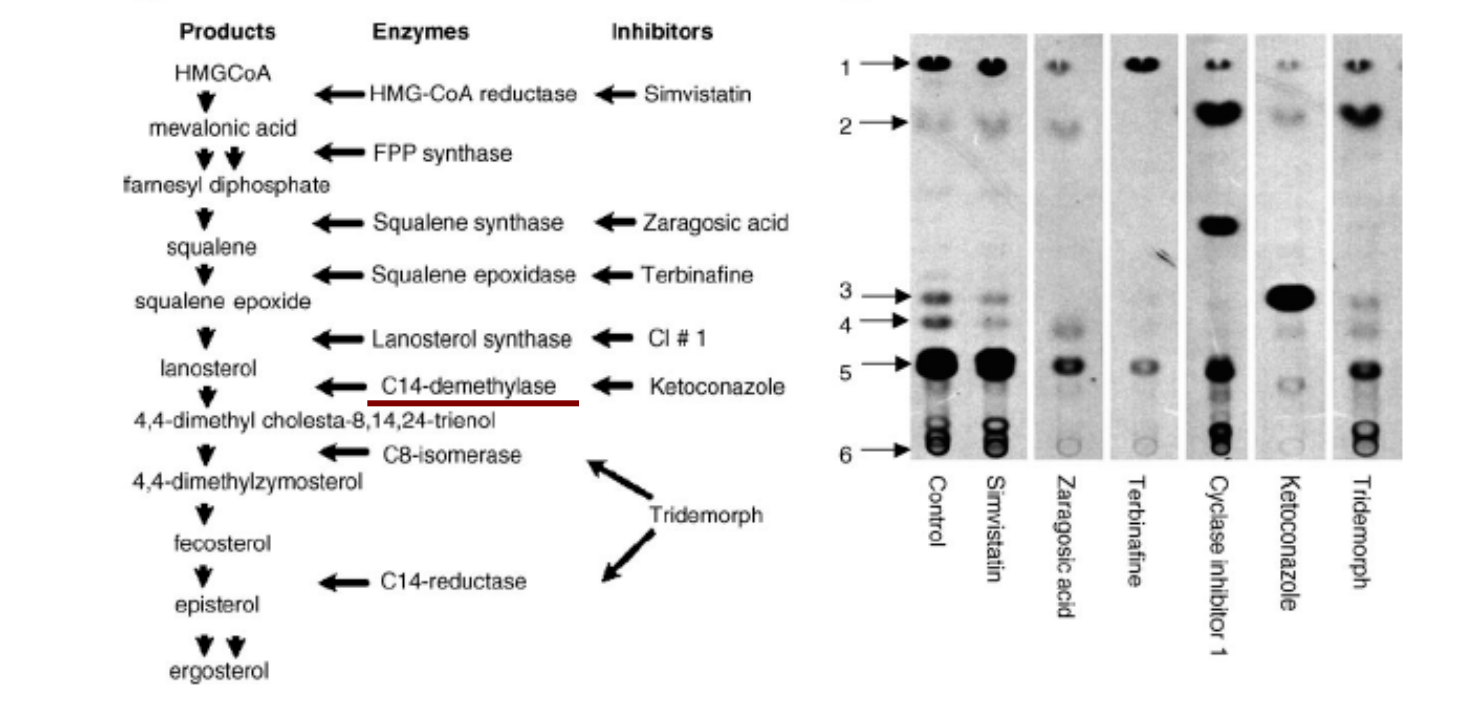
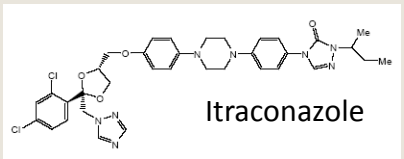
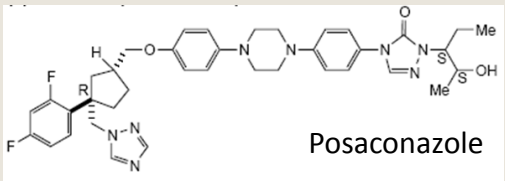
Azoles and Chagas disease

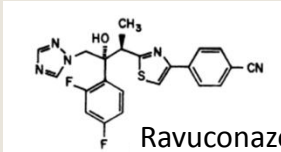


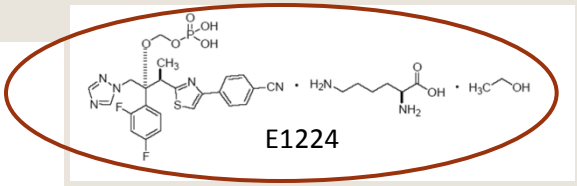
Azole class of compounds: Itraconazole, Posaconazole, Ravuconazole/E1224, others

Mechanism of action: C14-demethylase inhibition


Itraconazole


Posaconazole


Ravuconazole


E1224

E.G. Hankins et al. / Molecular & Biochemical Parasitology 144 (2005) 68–75

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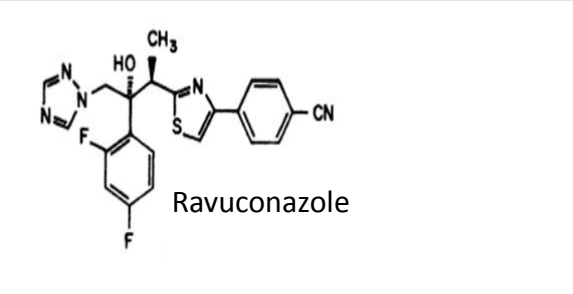
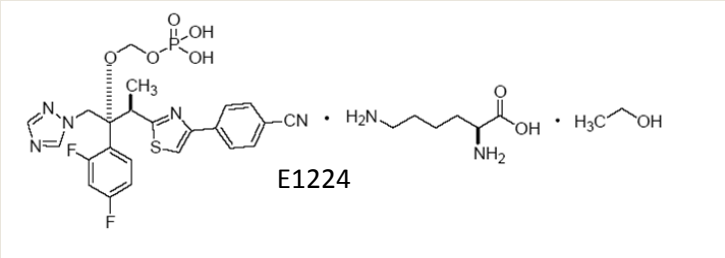
E1224 (ravuconazole prodrug) Product Profile





- Water-soluble monolysine salt of a phosphonoxymethyl ether of ravuconazole
- Rapid conversion to ravuconazole (within seconds)
- Ravuconazole is the active moiety
- Broad-spectrum triazole antifungal
- Available in parenteral and oral formulations (50 and 100 mg tablets, now capsules)
- Stable product, 5 years shelf-life for tablet formulation

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E1224 (ravuconazole prodrug) Product Profile

- Phase 2 trials of ravuconazole showed efficacy in treating mucosal *Candida* infections and onychomycosis in humans
  - Proof of concept for invasive aspergillosis and systemic candidiasis demonstrated in animal models
- Available in both IV and PO formulations
- Linear dose proportional increase in ravuconazole C_{max} and AUC following E1224 IV and PO administration
- Little effect of food intake on ravuconazole PK parameters after E1224 PO administration
- Long plasma half life of ravuconazole (about 7 to 10 days)
- Once weekly dosing after a 3-day loading dose regimen
- Good safety profile: consistent with azole class; no visual disturbances or hallucinations

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Phase 1 Key Findings
Safety

- **Safety profile of oral E1224 consistent with azole class**
  - **Liver enzyme elevations**
    - Dose-related
    - Most elevations less than 3X upper limit of normal
    - Onset after Day 7 of treatment, typically between Days 10-14
    - Reversible: Resolution began upon discontinuation of drug
    - At the target dose for IFI (400 mg bid X 3 d, then 200 mg qd), elevation incidence is comparable to other triazoles

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Phase I Key Findings
Safety

- **QT**
  - No QTc prolongation
  - No arrhythmias or significant, clinically relevant adverse events reported during thorough QT study
- **Other**
  - Only minor adverse events (mild or moderate in severity) occurred in all Phase 1 studies (pruritus, headache, nausea, etc.). Frequency was similar to that seen with other azoles

Liver Enzymes: E1224 versus Placebo

	PLACEBO	**E1224**	400 mg BID X 3 days then 200 mg QD X **6-11** days	200 mg QD X 14 days	400 mg X 14 days or >400 mg for >3 days
N	19	105	46	8	51
AST/ALT/ BILIRUBIN:					
>ULN	5 (26.3%)	40 (38.1%)			
>1.5 X ULN	4 (**21%**)	20 (19%)	8 (**17%**)	0	12 (**24%**)
AST/ALT:					
>2 X ULN	1 (**5%**)	15 (14%)	5 (**11%**)	0	10 (**20%**)
>3 X ULN	1 (**5%**)	7 (7%)	1 (**2%**)	0	6 (**12%**)
>5 X ULN	0	0	0	0	0

→Highest incidence of ALT elevations seen only with 400 mg maintenance dose – lower doses were planned for subsequent studies

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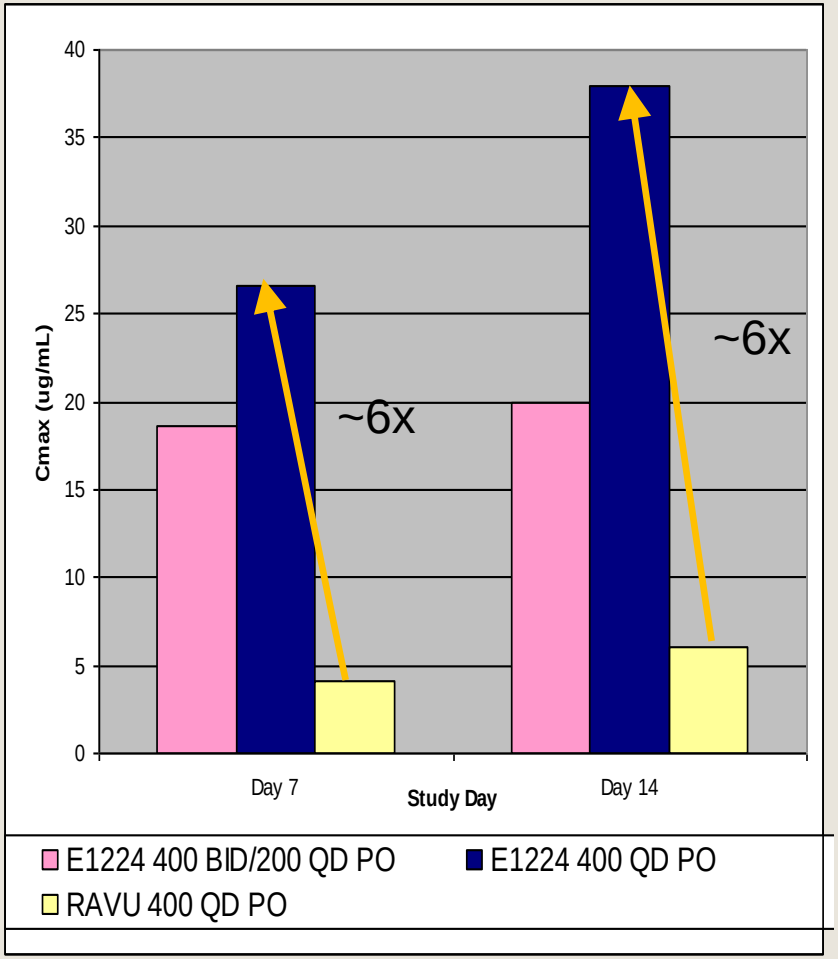
Phase 1 Key Findings
Pharmacokinetics

- E1224 PO formulation
  - High Bioavailability
  - No food effect
  - No effect on cytochrome P450 isoenzymes
- Both PO E1224 C_{max} and AUC are several-fold higher than PO RAVU
- PO loading dose strategy is feasible
- Steady state reached in 3 days



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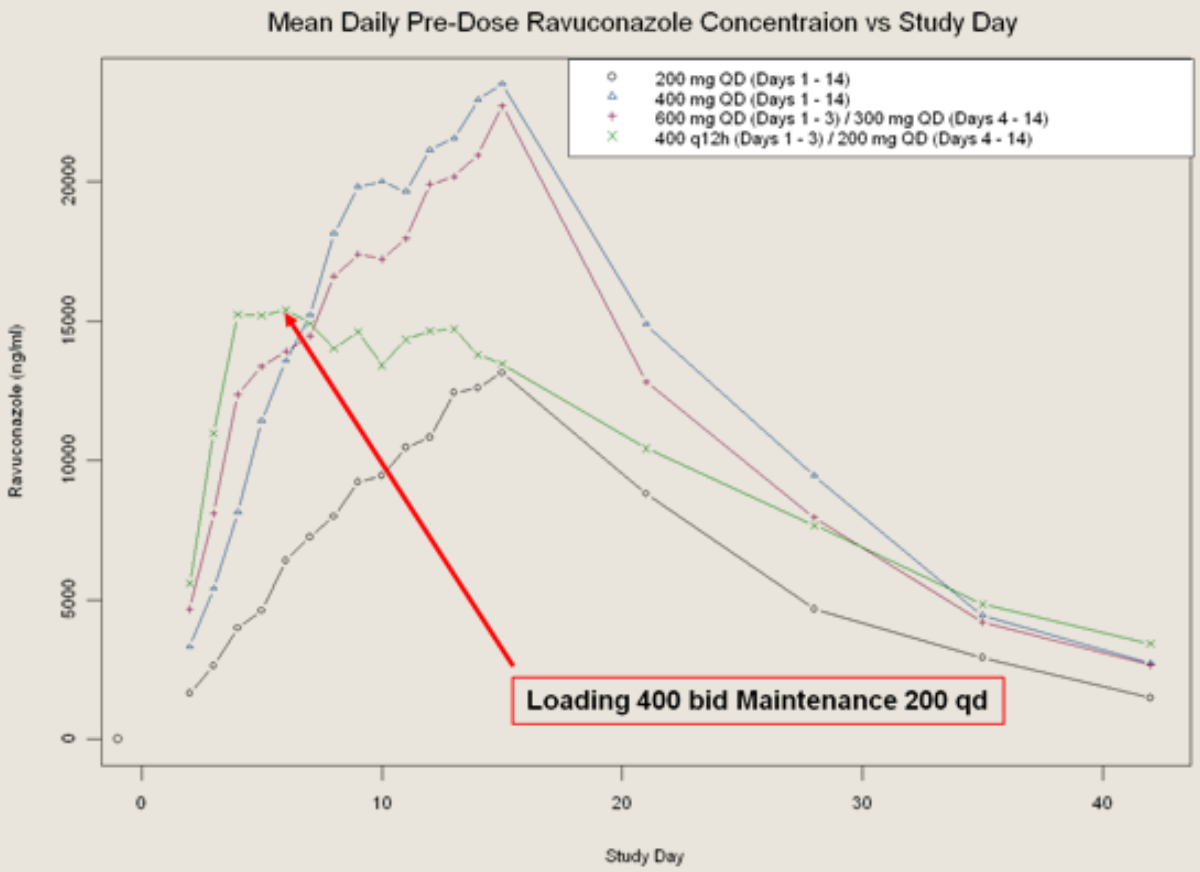
Phase 1 Key Findings
Pharmacokinetics

- PO loading dose strategy is feasible
- 3-day, daily loading dose
- Steady state reached in 3 days



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Effect of Food on Ravuconazole PK

		E1224 600mg N=9	E1224 600mg N=8
		Fasted	**Fed**
C_{max} (µg/mL)	Mean (SD)	8.83 (3.31)	8.70 (2.57)
AUC_{0-t} (µg.hr/mL)	Mean (SD)	976 (305)	949 (308)
$T_{1/2}$ (hr)	Mean (SD)	215 (72)	209 (57)
T_{max} (hr)	Mean (SD)	3.11 (0.60)	6.00 (1.07)

- Standard FDA Meal comprised of 500-600 calories from fats
- No change in C_{max} or AUC
- Two-fold increase in T_{max} with food

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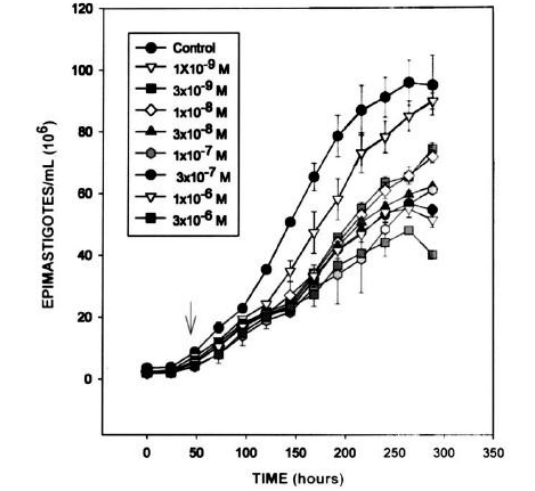
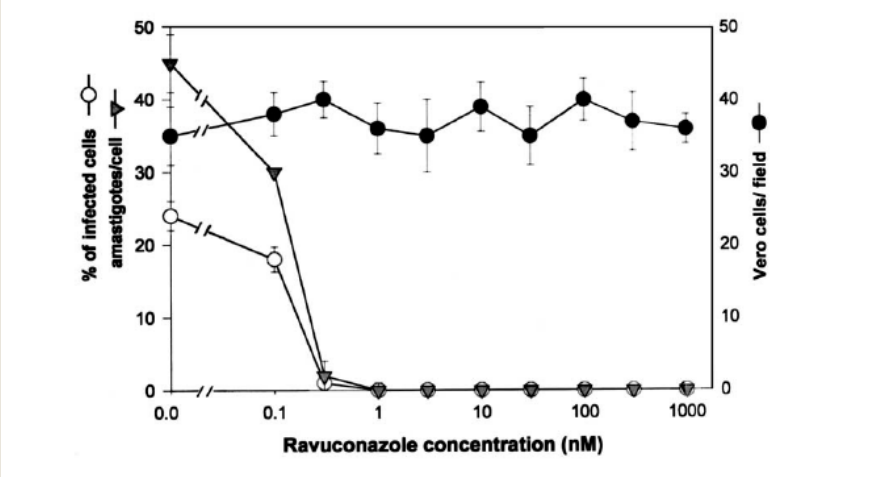
Anti-protozoal activity

- **Ravuconazole**
  - MIC 300 nM (221 ng/ml) for epimastigote form
  - MIC 1 nM (7.4 ng/ml) IC_{50} = 0.1 nM for amastigote form
  - No effect on cell viability and proliferation at concentrations 1000-fold higher than MIC
  - Parasite strain not specified (EP and Y strains mentioned in the cited ref.)





Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

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In vitro IC_{50} Ravuconazole - IPK

Strain	TC serotype	IC 50	N
Dm28c	I	0.9	3
Y	II	0.9	4
ERA	IV	1.4	3
92.80	V	1.9	3

In general, IC_{50}s for Ravuconazole are around 2-10 times lower than those obtained with Posaconazole

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Background
In vivo Activity – 20-d Acute Murine Model

Effects of ravuconazole and benznidazole in murine models of acute Chagas disease with different strains of *T. (Schizotrypanum) cruzi*[a]

Strain	Control (untreated)	Benznidazole 100 mg/kg, daily[b]	Ravuconazole 15 mg/kg, b.i.d.[c]
CL	S: 3/12 C: 0/3	S: 12/12 C: 12/12	S: 12/12 C: 12/12
Y	S: 2/11 C: 0/2	S: 12/12 C: 9/12	S: 12/12 C: 7/12
Colombiana	S:1/11 C: 0/1	S: 12/12 C: 4/12	S: 10/10 C: 0/10

Survival (S, survivors/total number of animals) and parasitological cures (C, negative tests/survivors), 60 days p.i.

[a] Female Swiss albino mice (10–12 animals/group; 18–20 g/animal) were inoculated with 10^4 bloodstream trypomastigotes of the indicated strain and treatment started 4 days p.i. The drugs were given orally by gavage, suspended in aqueous 2% methyl-cellulose+0.5% Tween 80, for 20 days. Parasitological cure was evaluated by haemoculture and xenodiagnosis.

[b] Total of 20 doses.

[c] Twice a day, total of 40 doses.

Molina et al. Antimicrobial Agents and Chemotherapy, Jan. 2000, p. 150–155
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

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Efficacy of E1224 treatment for 20 days in *Trypanosoma cruzi* murine model[1]

Experimental groups[2]	Number of surviving/ total number of animals	Number of negative FBE[3]/ number of mice	Number of negative blood PCR[4] sample/number of mice	Total of negative assays/number of mice
Uninfected	7/7 (100%)	7/7	7/7	7/7 (100%)
Untreated	0/7 (0%)	0/7	-[5]	0/7 (0%)
Bz 100 mg/kg/day	7/7 (100%)	6/7	6/6	6/7 (85.7%)
E1224 10mg/kg	7/7 (100%)	7/7	7/7	7/7 (100%)
E1224 20mg/kg	7/7 (100%)	6/7	5/6	5/7 (71.5%)
E1224 30mg/kg	7/7 (100%)	7/7	6/7	6/7 (85.7%)
E1224 40mg/kg	7/7 (100%)	7/7	5/7	5/7 (71.5%)
E1224 50mg/kg	7/7 (100%)	6/7	6/6	6/7 (85.7%)

[1]Swiss female (7 /group) weight 20 to 24 g were inoculated with $5x10^3$ trypomastigotes (Y strain)
[2]Treatment was initiated at 4 days after inoculation followed by 20 days and it was administered per oral route.
[3] FEB - fresh blood examination performed before and after cyclophosphamide immunosuppression
[4] PCR assay was performed in the 1st and 6th month after treatment
[5] All mice died before 30 days of infection

Rationale for E1224 Dose Selection for Chagas Disease

- Focus on dosing regimens that would maximize the probability of parasite eradication while also being optimally safe for the subjects.
- Phase 1 data: Liver enzyme elevations were not seen with total loading doses of less than 2400 mg or given as 400mg per week for 12 weeks.
- Achieving high C_{max} concentrations and reaching steady state rapidly leads to rapid killing and sustained parasite eradication.
- Duration of treatment was based on the standard of care for chronic indeterminate Chagas disease treatment of eight weeks of benznidazole therapy.

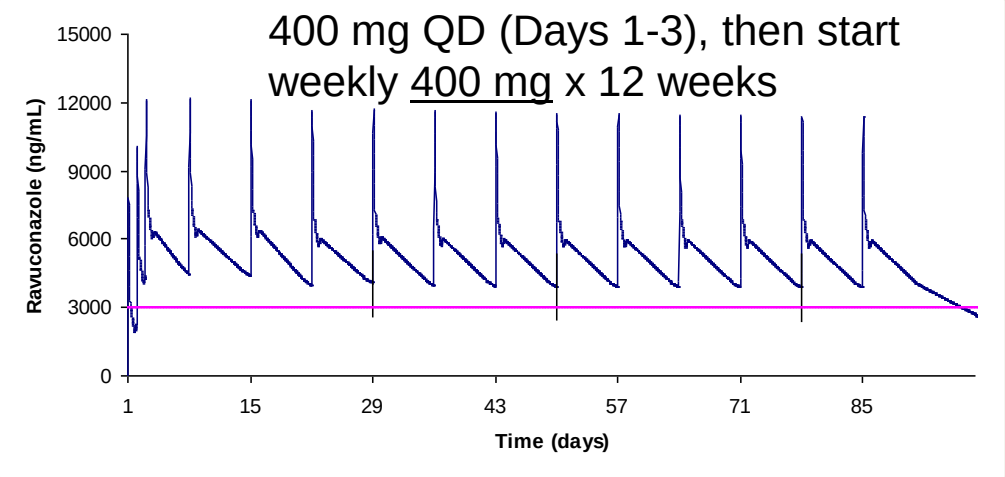
Rationale for E1224 Dose Selection for Chagas Disease

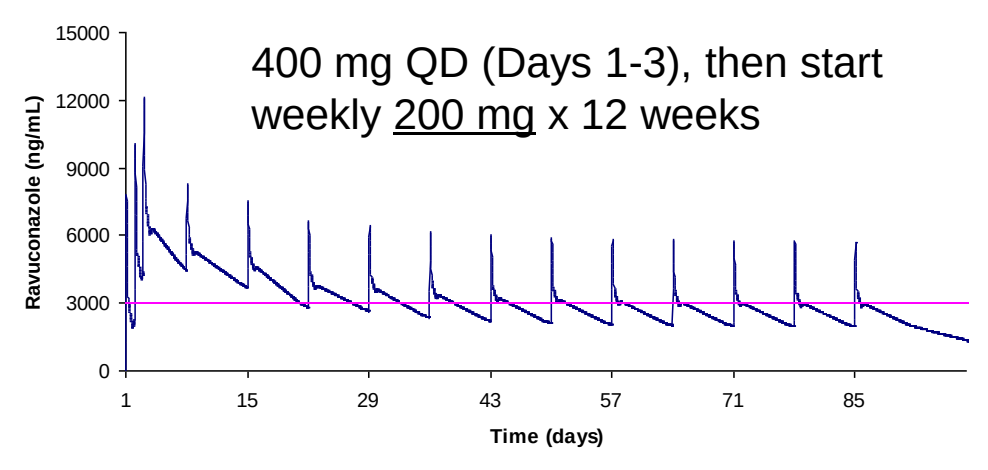
E1224's long half-life permits novel dosing regimens:

- •PK models show that a 3-day loading dose followed by doses given 1 day per week **(weekly therapy)** provides favorable PK

CD PK/PD Driver Assumption:
-Free AUC/MIC is the key PD parameter

- •Y strain amastigote Dose: 400 BID LD then 200 mg QD MD
- AUC/MIC =1,045,793
- MIC = 7.4 ng/mL
- Free AUC/MIC = 31,372





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E1224 - Phase 2 trial

Early development, proof-of-concept evaluation

- 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 Integral al Paciente de Chagas, Instituto de Investigaciones Biomédicas, Facultad de Medicina, Universidad Mayor San Simón CEADES, Cochabamba; Universidad Autonoma Juan Misael Saracho, Tarija, Bolivia
- PI: Drs. Faustino Torrico and Joaquim Gascón

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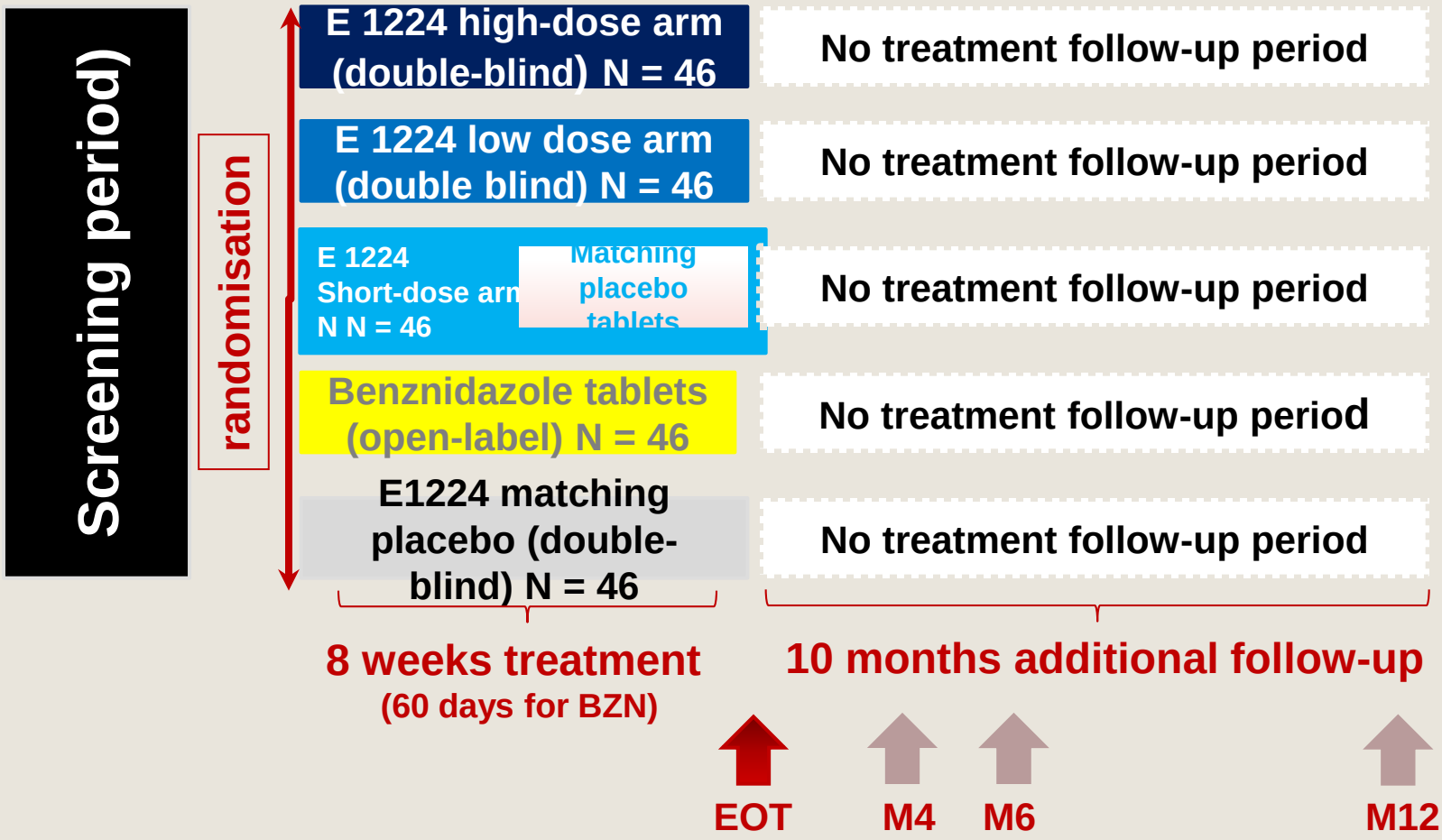
Phase 2 Study Design



- **Efficacy based on repeated PCR and candidate biomarkers**
- **Population PK Analysis included**

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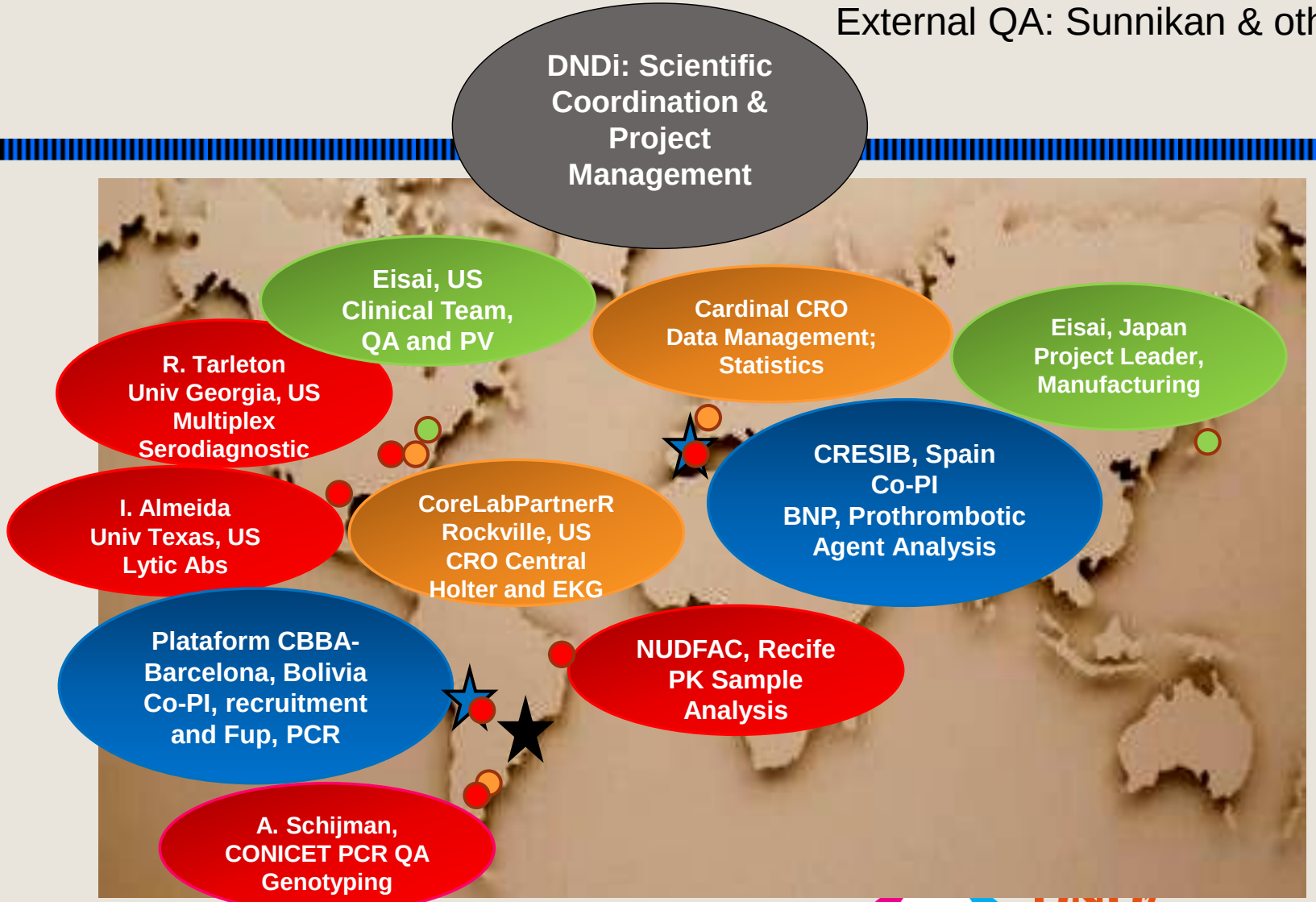
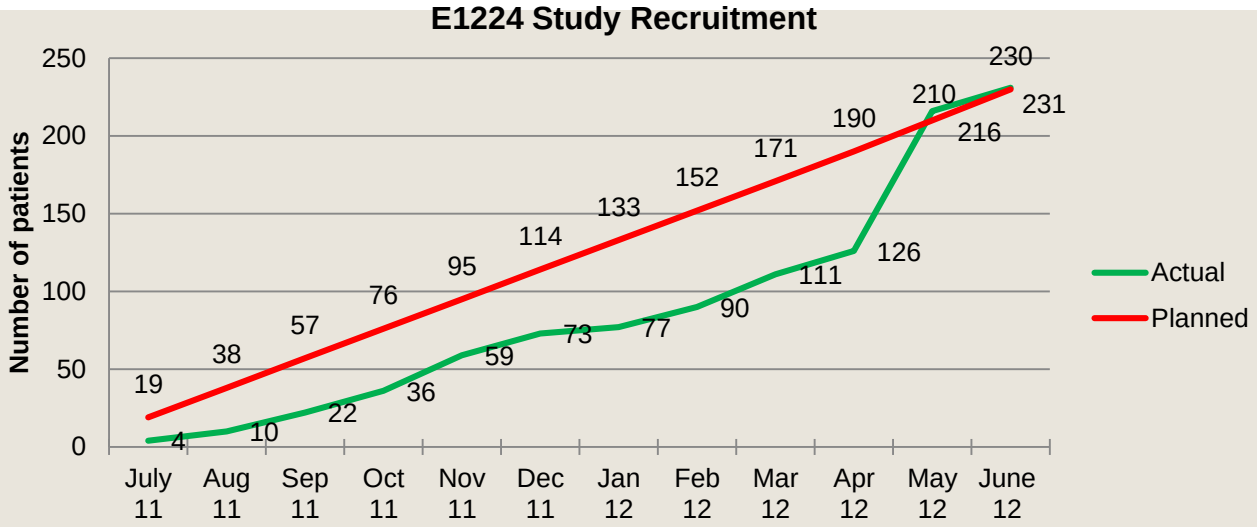
E1224 - Project Organisation

External QA: Sunnikan & others



Study Status



- Number of patients offered study participation: 820
- Number of patients screened: 560 (53% in Cbba; 47% in Tarija)
- Number of patients included: 231 (June 26th LPI)
- Causes of screening failure: 20% biochemical alterations; 20% PCR negative; 16% other (EKG, positive pregnancy tests, abnormal labs).

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Key Project Milestones

Milestone 1

- Completion of 50% Phase 2 POC study recruitment – total of 115 patients

Milestone 2

- Evaluation of primary efficacy and safety endpoint of Phase 2 POC clinical study (EOT) – Q4 2012
- Initiate preparatory activities for Phase 3 clinical trial – Q4 2012

Decision point: Preliminary analysis of primary efficacy and safety will be performed to determine the initiation of Phase 3 clinical trial preparations.

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

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

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Key Project Milestones

Milestone 3

- End of 12 months follow-up in Phase 2 clinical trial – Q2 2013

Decision point:

- Analysis of sustained response and safety to determine the initiation of Phase 3 clinical trial, dose selection, and decisions regarding pediatric investigations and/or combination therapy.
- Results to be integrated with available information from other clinical trials on azole compounds.
- **Go decision:** if at least one regimen of E1224 shows a favorable sustained treatment response in comparison to placebo and no significant safety concerns are identified.
- **No go:** if no regimen of E1224 is superior to placebo and/or significant safety concerns are identified.
- Decision matrix adjusted based on availability of results of other azole clinical trials and success measurements developed in the context of this project.

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Obrigada a todos os colaboradores, doadores e pacientes!

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