



## A comparison of the efficacy of posaconazole with fluconazole in the treatment of oropharyngeal candidiasis in HIV infected persons.

### CITATION:

Vazquez JA, Skiest DJ, Nieto L, Rebea Northland, Sanne I, Jagdish G, Greaves W, Isaacs R. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clinical Infectious Diseases* 2006 Apr; 42:1179-86

### RESEARCH QUESTION:

What is the efficacy of posaconazole compared to fluconazole in the treatment of oropharyngeal candidiasis in subjects with HIV?

### THE STUDY

Multicenter, randomized, evaluator-blinded, i.e. single-blind, trial  
Subjects were randomly assigned to 1 of 2 parallel treatment arms.

### STUDY SETTING

47 study sites: 19 in the USA and 28 worldwide, primarily in Europe, Latin America, Canada and South Africa.

Study conducted from 15 December 1998 to 27 October 1999.

Ethics approval was granted by independent ethics committees at each of the study site.  
Each subject signed a written statement of informed consent before receiving study medication.

### PARTICIPANTS

All patients tested for HIV antibodies and hepatitis B surface antigen.  
CD4 lymphocyte counts done by flow cytometry for HIV-infected as soon as possible after randomisation

#### Included:

Older than 18 years if they met the following criteria:

1. Confirmed HIV infection
2. Clinical evidence of pseudomembranous oropharyngeal candidiasis.
  - a.  $\geq 2$  discrete pseudomembranous plaques; or
  - b. single confluent plaque of  $\geq 3$  cm
3. Microbiological evidence of *Candida* species documented by either potassium hydroxide or fungal stain
4. Anticipated survival of  $> 2$  months
5. Ability to swallow study medication
6. Karnofsky performance score of  $\geq 60$

#### Excluded:

1. Any systemic antifungal therapy during week before enrolment.
2. Used topical antifungal treatment within 2 days of enrolment
3. Received other investigational agents in preceding month
4. Intolerant to azole drugs
5. Used protease inhibitors for 1<sup>st</sup> time within 30 days before enrolment
6. Taking medication which could interact with azoles.

#### Additional exclusion criteria:

1. Chemotherapy related oral mucositis
  2. Platelet count  $< 75\ 000$  platelets/mm<sup>3</sup>
  3. QTc interval prolonged by  $> 10\%$  of normal interval
  4. History of failure with fluconazole
  5. Evidence of hepatic or renal disease
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**INTERVENTION**

366 Subjects enrolled and randomised at 47 sites from 15 December 1998 to 27 October 1999  
Sixteen subjects did not receive study drugs. Remaining 350 formed the all-treated subset.  
178 received posaconazole: 200mg oral suspension (40mg/ml) on day 1, followed by 100 mg/day for 13 days  
172 received fluconazole: 200mg oral suspension (40mg/ml) on day 1, followed by 100 mg/day for 13 days

**OUTCOMES**

Primary: Clinical cure: Proportion of patients who were clinically cured or showed improvement after 14 days of treatment

Secondary:

1. Mycological cure: Quantitative yeast culture yielding  $\leq 20$ cfu/ml of *Candida* species. Eradication: 0 cfu/ml
2. Mycological relapse:  $\leq 20$  cfu/ml of *Candida* species on day 14 and  $>20$  cfu/ml on day 42
3. Clinical relapse: recurrence of signs or symptoms after initial improvement on day 14
4. Safety

**Safety Evaluation**

Complete physical at baseline. Evaluations, including assessment of vital signs, monitoring and recording or adverse events and clinical laboratory testing: days 7, 14, 42.  
CD4 cells counted at baseline or within 3 months of study beginning.

**RISK OF BIAS** (Risk Scale: Low – Moderate – High)

**SELECTION BIAS: Moderate**

Allocation concealment unclear. No indication how allocation sequence was generated. Both treatment arms were similar at baseline.

**PERFORMANCE BIAS: Moderate**

No indication whether interventions were identical. Caregiver and patient not blinded

**DETECTION BIAS: Low - Moderate**

Single-blinded study – only evaluators were blinded.

**ATTRITION BIAS: Moderate**

Not all patients randomised were included in the final analysis. Sixteen of Randomised subjects did not receive study drugs and were excluded from analysis.

**STATISTICAL METHODS**

Analysed data sets included data from the following:

1. All treated population: subset from the intention-to-treat (ITT) population i.e. all randomised subjects. Subjects who were randomised and received  $\geq 1$  dose of study drug.
2. Modified ITT population: all subjects randomised and received  $\geq 1$  dose of study drug, and had positive result of *Candida* species at baseline
3. Protocol –evaluable population: modified ITT subjects who received therapy for at least 7 consecutive days and had a clinical response assessment on day 14

**STUDY FINDINGS:**

Primary efficacy analysis was performed on the modified ITT data set. Confirmatory analyses were performed on the protocol-evaluable subset.

Combined cure and improvement:  
Modified ITT population

Outcome	Modified ITT	CER	EER	RR	RRR	ARR	NNT
Clin success 7 days	PCZ: 164/169 FCZ: 155/160	0.901	0.921	1	-2%	-0.020	-50
95% Confidence Interval				0.96 to 1.04	-9% to 4%	-0.080 to 0.040	NNT: 25 to INF NNH:13 to INF
Clin success 14 days	PCZ: 155/169 FCZ: 148/160	0.860	.871	0.99	-1%	-0.011	-91
95% Confidence Interval				0.93 to 1.06	-10% to 7%	-0.083 to 0.061	NNT: 17 to INF NNH: 12 to INF

Protocol –evaluable population:

Outcome	Protocol	CER	EER	RR	RRR	ARR	NNT
Clin success 14 days	PCZ: 139/143 FCZ: 130/135	0.756	0.781	1.01	-3%	-0.025	-40
95% Confidence Interval				0.97 to 1.05	-15% to 8%	-0.113 to 0.063	NNT: 16 to INF NNH: 9 to INF

Mycological cure and eradication at day 42:

Modified ITT population: similar for both treatment arms at days 7 and 14 – 68% in both arms.

Outcome	Time to Outcome	CER	EER	RR	RRR	ARR	NNT
Mycological cure	42 days	0.264	0.406	0.65	-54%	-0.142	-7
95% Confidence Intervals:				0.43 to 0.99	-104% to -4%	-0.274 to -0.010	-98 to -4
Mycological eradication	42 days	0.242	0.356	0.68	-47%	-0.114	-9
95% Confidence Intervals:				0.43 to 1.06	-4% to 68%	-0.014 to 0.242	NNT: 70 to INF NNH: 4 to INF

Relapse:

Clinical relapse: >30%

Mycological relapse: >50% - 59.4% in posaconazole vs 73.6% in fluconazole

#### **ADVERSE EVENTS**

Safety analysis was done on the all-treated subset.

114 of 178 (64%) patients in posaconazole arm reported treatment emergent adverse events opposed to 117 of 172 (68%) in fluconazole arm. See table 4 on page 1184

Treatment related adverse events were 25% in posaconazole vs 24% in fluconazole with most common being gastrointestinal and included nausea (6% vs 5%), vomiting (4% vs 1%), diarrhea (2% vs 3%).

Serious adverse events were reported in 17 of 178 posaconazole recipients (10%) and in 22 of 172 fluconazole recipients (13%). No serious adverse event in posaconazole was seen as related to the study drug. In fluconazole arm 5 events were related to study drug. These were increased serum glutamic-pyruvic transaminase levels in one subject and dehydration, diarrhea, acute gastroenteritis and vomiting in one subject.

#### **COMMENTS**

Posaconazole is as effective in bringing about clinical success as Fluconazole. Mycological efficacy was similar for both interventions, but more patients receiving Posaconazole were able to maintain mycological success at day 42. Need more trials to make a recommendation.

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