

## EVALUATING EFFICACY OF SYSTEMIC ANTIFUNGALS FOR ESOPHAGEAL CANDIDIASIS: A COMPARISON OF CLINICAL TRIAL DESIGNS

Navarro E, Dixon C, Powers JH

Office of Drug Evaluation IV, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, USA

**Purpose of Study:** We reviewed clinical trials in esophageal candidiasis (EC) to ascertain how variations in design and analysis of the trials may impact on interpretation of outcomes. Differences in clinical trial design and analysis may lead to numerically different results for both the study drug and the control, which in turn may impact on the conclusions of a given study.

**Methods:** We assessed the design of pivotal clinical trials for the treatment of EC summarized in publicly available reviews at the U.S. Food and Drug Administration (FDA). We compared the following trial elements in the studies : study populations, comparator drugs, outcome definitions, timing of endpoints, duration of therapy, and statistical parameters such as sample size and non-inferiority margins. We examined differences in the numerical outcomes and their possible relationship to variations in the clinical design and analysis of the trials.

**Results:** The patient populations with esophageal candidiasis generally consisted of HIV positive patients with low CD4 counts. However, the populations were more variable in terms of proportions of patients with prior antifungal or antiretroviral therapy. The comparator for most trials was oral fluconazole. However, the dose of fluconazole varied from 100mg to 400mg qd. Duration of treatment varied widely in the clinical trials of EC, from fixed duration (2-8 weeks) schedules to duration based on recovery of symptoms. Treatment duration impacts the timing of assessment of outcomes. The timing of assessment for primary efficacy varied, from fixed time point analyses to variable time point evaluations (time to event). Additionally, studies that relied on a fixed time point varied in the timing of the outcome measurement, using either an on-therapy, an end-of-therapy or late post-end-of-therapy assessment. Relapse or recurrence of esophageal candidiasis was assessed as a separate outcome in a few studies. The definition of a primary outcome also varied, from symptom relief, endoscopic resolution or microbiologic eradication.

**Conclusions.** The study of EC would benefit from standardization of clinical trial design. Variation in the numerical outcomes of a given trial may be related to variability in factors such as the definition of the primary endpoint, the timing of outcome assessment, and the population studied. Such numerical variations in outcomes may impact on the interpretation of the results of the trial. An examination of the durability of response may add valuable information about the impact of therapy on clinical disease.

<b>Antifungal Efficacy in the Esophageal Candidiasis</b>									
Study Drug	FLUCONAZOLE		VORICONAZOLE		ITRACONAZOLE		CASPOFUNGIN		
Dosing Regimen	100-200mg X 3-8wks		300mg BID x 2 wks		100-200 mg 3-8wks		50-mg, 72 hours post resolution		
Comparator	Ketoconazole 200-400mg X 3-8wks		Fluconazole 200-400mg QD		Fluconazole 100-200 mg QD		IV Fluconazole 200 mg QD.		
Population	85% AIDS		88% AIDS, 47% ART		93% AIDS				
Power and delta	Not stated		80%, 15%		Not stated in review		80%, 20%		
Primary Endpoint Population	Clinical ITT		Endoscopy PP		Clinical		Clinical MITT		
Timing of Outcome assessment	last on therapy		Variable up to day 43 or end of therapy		Not stated		5-7d post therapy		
Other analyses	2, 4 wk relapse		N/A		Need for Dose escalation 4 wk relapse		End of treatment 2, 4 wk relapse		
Clinical Efficacy	Flu	Comparator	Vori	Comparator	Itra	Comparator	CASPO	Comparator	
Cure (%)	61	46	N/A	N/A	N/A	N/A	Symptom resolution		
Improved(%)	24	38	N/A	N/A	N/A	N/A	93	96	
Total	85	85	N/A	N/A	86	86	Symptom+endoscopy		
							82	85	
Endoscopic cure	87	53	95	90	N/A	N/A	Endoscopy		
							85	86	