

**AN ECONOMIC EVALUATION OF  
POSACONAZOLE  
IN THE TREATMENT OF  
INVASIVE ASPERGILLOSIS WITH  
REFRACTORY DISEASE IN KOREA**

by

**C. Jo, SJ Lee, S Jun, YH Kim,  
and DG Lee**

# Basic Issues

## 1. Targeted Patient Group

Patients of confirmed infection of invasive aspergillosis with refractory disease

## 2. Selected Comparators

Posaconazole, Voriconazole (IV and oral)

Caspofungin, Liposomal Amphotericin-B (L-AMB)

## 3. Primary and Secondary Outcomes

Global Response and Overall Survival after 90 days of Tx.

# Based On the Prelim Study..

## 4. Methodology

Cost–Minimization Analysis (CMA) in case the outcomes are identical or very similar between the selected comparators.

## 5. Literature Review

No head–to–head comparison b/w POS and VOR.

**P00041**: Phase III, open, multinational study of salvage therapy with Posaconazole 800mg/day

**P02387**: Retrospective, External Clinical study for P00041. Partially solves bias and ethical problems  
Find the preceding studies of Voriconazole in a salvage therapy with similar patient group of P00041 or P02387.

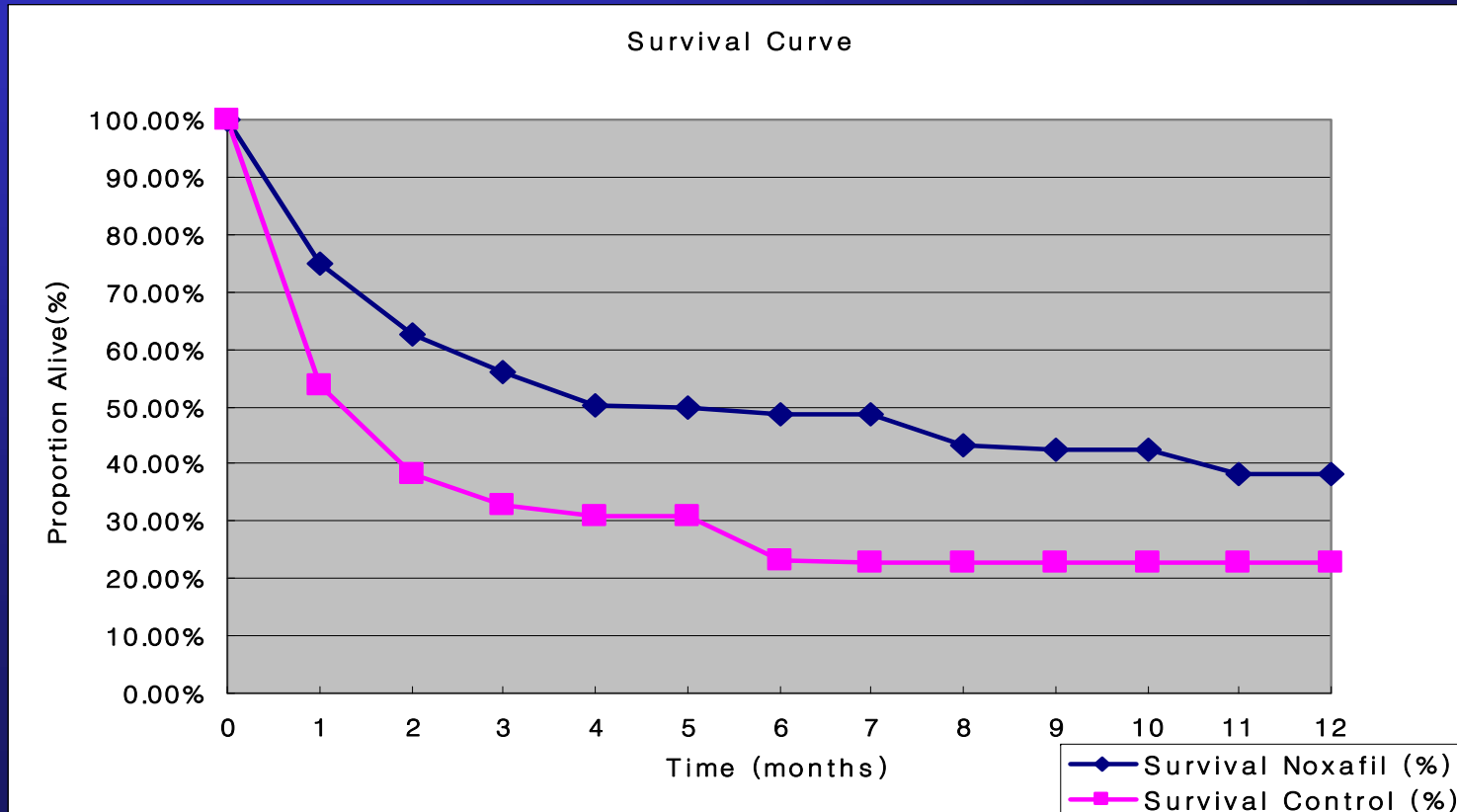
# From Clinical Trials (1)

- Global response: responders for Posaconazole versus control (other salvage therapies): MITT

	P00041	P02387	OR	
	Posaconazole	Control	[95% CI]	<i>P</i>
Primary pathogen group	n/N (%)	n/N (%)		
<i>Adjusted results</i>				
All patients	119/238 (50.0)	96/218 (44.0)	1.75 (1.01, 3.02)	0.046
Aspergillus	<b>45/107 (42.1)</b>	22/86 (25.6)	4.06 (1.50, 11.04)	0.006
<i>Unadjusted results</i>				
All patients	119/238 (50.0)	96/218 (44.0)	1.27 (0.92, 1.76)	0.149
Aspergillus	<b>45/107 (42.1)</b>	22/86 (25.6)	2.11 (1.14, 3.92)	0.018

# From Clinical Trials (2)

Survival: proportion alive at 90 days (Kaplan Meier):  
MITT.



# From Literature Review (1)

- Global response: responders for voriconazole salvage therapy: MITT

Study	Perfect et al.		Denning et al.	
	N	n (%)	N	n (%)
All pathogens	301	151 (50.2)	116	NA
Aspergillus	142	<b>62 (43.7)</b>	116	<b>56 (48.3)</b>
First line therapy	NA	NA	60	35 (58.3)
Salvage therapy	142	<b>62 (43.7)</b>	56	<b>21 (37.5)</b>

# From Literature Review (2)

- Survival: proportion alive at 90 days (Kaplan Meier): MITT.

Study	Perfect	Denning <sup>a</sup>	Marr <sup>a</sup>	P0041
Treatment	Voriconazole			Posaconazole
	%, [95% CI]	% [95% CI] <sup>b</sup>	% [95% CI] <sup>b</sup>	% [95% CI] <sup>b</sup>
Aspergillus	<b>56</b> , (48, 65)	<b>60.8</b> (52, 70)	31.0 (15, 47)	<b>56</b> (61, 71)

Abbreviations: MITT, modified intention to treat. <sup>a</sup>Values estimated from the graph of Kaplan Meier survival proportions over time. <sup>b</sup> calculated confidence intervals.

Study	Design	Follow-up	Patient population
<i>Posaconazole</i>			
P00041	Open-label, non-comparative, multi-center	30 days after end of treatment	Patients with IFIs that were resistant or refractory to standard antifungal therapies, for which there was no effective therapy available or when the patient was intolerant of these therapies due to the potential for severe toxic reactions
P02387	Retrospective	Reviewed for end of treatment evaluation (372 days)	Patients with IFIs that were refractory, resistant or intolerant of standard therapies and who were administered salvage antifungal therapy other than NOXAFIL
<i>Voriconazole</i>			
Perfect et al. (2003)	Open-label, non-comparative, multicenter	End of treatment ( $\geq$ week 16). Safety was evaluated at weeks 0, 8, 12 and 16	Patients with documented IFIs and evidence of failure of, resistant to, or toxicity related to standard antifungal Treatments
Denning et al. (2002)	Open-label, non-comparative, multicenter	30 days after end of treatment (16 weeks + 30 days)	Patients with definite or probable aspergillosis that had previously been treated with AmB or itraconazole
Marr et al. (2004)	Retrospective, comparative single-center	Not Reported	Patients with definite or probable aspergillosis that were refractory or intolerant to AmB-d or LFABs and went on to receive voriconazole or voriconazole plus caspofungin as salvage therapy



# Dose Regimens

Study	Treatment	Route	Duration	Treatment regimen
P00041	Posaconazole	oral	From 1–609 days.	200mg * 4 times/day oral therapy in hospital then 400mg * 2 times/day (oral therapy). Outpatients 400mg * 2 times/day (oral therapy)
Perfect	Voriconazole	IV and oral	From 1–326 days	6 mg/kg IV every 12 hrs for the first 24h then 4 mg/kg IV every 12 hrs for $\geq 3$ days. Patients were then given oral therapy 200mg * 2 times/day. If no response after $\geq 3$ days the dose was increased to 300 mg * 2 times/day.
Denning	Voriconazole	IV and oral	IV: 6–27 days oral: 168 days	6 mg/kg IV * 2 times/day and 3 mg/kg * 2 times/day for 6–27 days followed by 200 mg * 2 times/day orally for 24 weeks
Marr	Voriconazole	IV	Not Reported	6 mg/kg * 2 times/day followed by 4 mg/kg * 2 times/day
	Voriconazole + Caspofungin	IV	Not Reported	Caspofungin 70mg on day 1 followed by 50mg in combination with voriconazole dose as above

# Cost Calculation

Drug	Brand Name	Daily Dose	<u>Exchange rate 1</u> (Jan. 01,08 ~Nov. 26,08)		<u>Exchange rate 2</u> (year of 2007)		<u>Exchange rate 3</u> (Sep.01,08 ~Nov.26,08)	
			Unit Cost	Daily Cost	Unit Cost	Daily Cost	Unit Cost	Daily Cost
Posaconazole	Noxafil	800mg(20mL)	97,848†	195,696	78,787	157,575	106,113	212,226
Voriconazole	Vfend**	1st day 6mg/kg*2 2nd day 4mg/kg*2	130,927		-		-	
		Change to oral 200mg	29,240	58,480	-	-	-	-
Caspofungin	Cancidas	70mg(loading) for 1st day	474,090	474,090	-	-	-	-
		50mg(maintenance) for remaining days	374,000	374,000	-	-	-	-
LAB*	AmBisome	300mg daily	179,473	1,076,838	-	-	-	-

\*: liposomal Amphotericin B, \*\*: assumed weight of 70kg, †: For example, we can get the unit cost of posaconazole 400mg.  
 $((650 * 1,580.62) / 4,200) * 400 = \text{KRW } 97,848$

Exchange Rate 1: KRW 1,580.62  
 Exchange Rate 2: KRW 1,272.72  
 Exchange Rate 3: KRW 1,714.13

# Strategy for Cost–Minimization Analysis

- Market share input (from IMS)

	4 <sup>th</sup> Quarter, 2007 (Total, KRW)	Candida market (KRW)	Aspergillosis market (KRW)	Aspergillosis Market share
Caspofungin	1,413,420,002	1,060,065,002	353,355,000	
Cancidas	1,413,420,002	1,060,065,002	353,355,000	12.52%
Voriconazole	1,856,324,368	122,964,726	1,733,359,642	
VFend	1,856,324,368	122,964,726	1,733,359,642	61.42%
Amphotericin	3,147,794,857	2,203,253,622	944,541,235	
Ambisome	2,451,750,983	1,716,225,688	735,525,295	26.06%
Total	6,417,539,227	3,386,283,350	2,822,239,937	100.00%

# Result of CMA (1)

			Ex Rate 1		Ex Rate 2		Ex Rate 3		
Product	Median Duration of Treatment (days)		Total Dose (mg)	Total Cost per therapy	Incremental Cost	Total Cost per therapy	Incremental Cost	Total Cost per therapy	Incremental Cost
	IV (days)	Oral (days)							
Posaconazole	N/A	56	44,800	<b>10,958,965</b>		<b>8,824,192</b>		<b>11,884,635</b>	
Voriconazole IV followed by oral	18	69	34,800	8,748,492	<b>2,210,473</b>	8,748,492	<b>75,700</b>	8,748,492	<b>3,136,143</b>

10% price reduction			Ex Rate 1		Ex Rate 2		Ex Rate 3		
Product	Median Duration of Treatment (days)		Total Dose (mg)	Total Cost per therapy	Incremental Cost	Total Cost per therapy	Incremental Cost	Total Cost per therapy	Incremental Cost
	IV (days)	Oral (days)							
Posaconazole	N/A	56	44,800	<b>7,863,069</b>		<b>7,941,773</b>		<b>10,696,171</b>	
Voriconazole IV followed by oral	18	69	34,800	8,748,492	<b>1,114,577</b>	8,748,492	<b>-806,719</b>	8,748,492	<b>1,947,676</b>

Reasonable price which can guarantee cost-saving Posaconazole would be KRW 78,110/400mg. Posaconazole will be more cost-saving than Voriconazole if price is equal to or lower than KRW 78,110, which also means that it is possible if the KRW-EURO Ex rate is stabilized lower than KRW 1,491/EURO.

# Result of CMA (2)

Antifungal Agent	Median of treatment period (days)		Total dose (mg)	Total cost per Patient (KRW)	Market Share	Weighted Average Drug Cost (KRW)
	IV	Oral				
Posaconazole	N/A	56	44,800	10,958,965 (A)	N/A	N/A
Voriconazole IV	18	N/A	7,200	4,713,372	31.61%	1,489,897
Voriconazole Oral	N/A	69	27,600	4,035,120	29.81%	1,202,869
L-AMB	48.5	N/A	14,550	52,226,643	26.06%	13,610,263
Caspofungin	33.7	N/A	1,705	12,703,890	12.52%	1,590,527
Total Cost per Patient (current practice)					100.00%	17,893,556 (B)
Incremental Cost = (A) - (B)						-6,934,591

# Sensitivity Analysis (1)

## 1. Ex rate and market share

Ex Rate 1	Total Drug Cost per Patient (KRW)	Market share (Base Value)	Weighted Average Cost (KRW)	Market share (Case I)	Weighted Average Cost (KRW)	Market share (Case II)	Weighted Average Cost (KRW)
Posaconazole	10,958,965	N/A	N/A	N/A	N/A	N/A	N/A
Voriconazole IV	4,713,372	31.61%	1,489,897	35%	1,649,680	28%	1,319,744
Voriconazole Oral	4,035,120	29.81%	1,202,869	33%	1,331,590	40%	1,614,048
L-AMB	52,226,643	26.06%	13,610,263	12%	6,267,197	12%	6,267,197
Caspofungin	12,703,890	12.52%	1,590,527	20%	2,540,778	20%	2,540,778
Total Cost per Patient		100.00%	17,893,556	100%	11,789,245	100%	11,741,767
Incremental-Cost			<b>-6,934,591</b>		<b>-830,280</b>		<b>-782,802</b>

Ex Rate 2	Total Drug Cost per Patient (KRW)	Market share (Base Value)	Weighted Average Cost (KRW)	Market share (Case I)	Weighted Average Cost (KRW)	Market share (Case II)	Weighted Average Cost (KRW)
Posaconazole	8,824,192	N/A	N/A	N/A	N/A	N/A	N/A
Voriconazole IV	4,713,372	31.61%	1,489,897	35%	1,649,680	28%	1,319,744
Voriconazole Oral	4,035,120	29.81%	1,202,869	33%	1,331,590	40%	1,614,048
L-AMB	52,226,643	26.06%	13,610,263	12%	6,267,197	12%	6,267,197
Caspofungin	12,703,890	12.52%	1,590,527	20%	2,540,778	20%	2,540,778
Total Cost per Patient		100.00%	17,893,556	100%	11,789,245	100%	11,741,767
Incremental-Cost			<b>-9,069,364</b>		<b>-2,965,053</b>		<b>-2,917,575</b>

# Sensitivity Analysis (2)

<b>Ex Rate 3</b>	Total Drug Cost per Patient (KRW)	Market share (Base Value)	Weighted Average Cost (KRW)	Market share (Case I)	Weighted Average Cost (KRW)	Market share (Case II)	Weighted Average Cost (KRW)
Posaconazole	11,884,635	N/A	N/A	N/A	N/A	N/A	N/A
Voriconazole IV	4,713,372	31.61%	1,489,897	35%	1,649,680	28%	1,319,744
Voriconazole Oral	4,035,120	29.81%	1,202,869	33%	1,331,590	40%	1,614,048
L-AMB	52,226,643	26.06%	13,610,263	12%	6,267,197	12%	6,267,197
Caspofungin	12,703,890	12.52%	1,590,527	20%	2,540,778	20%	2,540,778
Total Cost per Patient		100.00%	17,893,556	100%	11,789,245	100%	11,741,767
Incremental Cost			<b>-6,008,922</b>		<b>95,390</b>		<b>142,867</b>

# Sensitivity Analysis (3)

## 2. IV period of Voriconazole

Voriconazole IV Treatment Period (days)	Market share	Ex rate 1 (KRW 1,580.62)	Ex rate 2 (KRW 1,272.72)	Ex rate 3 (KRW 1,714.13)
10	Base Value	-6,411,878	-8,546,651	-5,486,208
	Case 1	-251,476	-2,386,249	<b>674,194</b>
	Case 2	-383,385	-2,518,158	<b>542,284</b>
14	Base Value	-6,673,234	-8,808,008	-5,747,565
	Case 1	-540,878	-2,675,651	<b>384,792</b>
	Case 2	-583,094	-2,717,867	<b>342,576</b>
18 (Base Value)	Base Value	-6,934,591	-9,069,364	-6,008,922
	Case 1	-830,280	-2,965,053	<b>95,390</b>
	Case 2	-782,802	-2,917,575	<b>142,867</b>



# Sensitivity Analysis (4)

## 3. Price of Posaconazole

Price of Posaconazole	Market share	Ex rate 1 (KRW 1,580.62)	Ex rate 2 (KRW 1,272.72)	Ex rate 3 (KRW 1,714.13)
10% Reduction	Base Value	-8,030,488	-9,951,784	-7,197,385
	Case 1	-1,926,176	-3,847,472	<b>-1,093,074</b>
	Case 2	-1,878,699	-3,799,995	<b>-1,045,596</b>
Base Value	Base Value	-6,934,591	-9,069,364	-6,008,922
	Case 1	-830,280	-2,965,053	<b>95,390</b>
	Case 2	-782,802	-2,917,575	<b>142,867</b>
10% Hike	Base Value	-5,838,694	-8,186,945	-4,820,458
	Case 1	265,617	-2,082,634	<b>1,283,853</b>
	Case 2	313,095	-2,035,156	<b>1,331,331</b>

**Q & A**  
**Comments**