ORIGINAL RESEARCH

# Cost-effectiveness analysis of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis in Spain

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**Objective:** According to a recent randomized, double-blind clinical trial comparing the combination of voriconazole and anidulafungin (VOR+ANI) with VOR monotherapy for invasive aspergillosis (IA) in patients with hematologic disease or with hematopoietic stem cell transplant, mortality was lower after 6 weeks with VOR+ANI than with VOR monotherapy in a post hoc analysis of patients with galactomannan-based IA. The objective of this study was to compare the cost-effectiveness of VOR+ANI with VOR, from the perspective of hospitals in the Spanish National Health System.

**Methods:** An economic model with deterministic and probabilistic analyses was used to determine costs per life-year gained (LYG) for VOR+ANI versus VOR in patients with galactomannan-based IA. Mortality, adverse event rates, and life expectancy were obtained from clinical trial data. The costs (in 2015 euros [€]) of the drugs and the adverse event-related costs were obtained from Spanish sources. A Tornado plot and a Monte Carlo simulation (1,000 iterations) were used to assess uncertainty of all model variables.

**Results:** According to the deterministic analysis, for each patient treated with VOR+ANI compared with VOR monotherapy, there would be a total of 0.348 LYG (2.529 vs 2.181 years, respectively) at an incremental cost of €5,493 (€17,902 vs €12,409, respectively). Consequently, the additional cost per LYG with VOR+ANI compared with VOR would be €15,785. Deterministic sensitivity analyses confirmed the robustness of these findings. In the probabilistic analysis, the cost per LYG with VOR+ANI was €15,774 (95% confidence interval: €15,763–16,692). The probability of VOR+ANI being cost-effective compared with VOR was estimated at 82.5% and 91.9%, based on local cost-effectiveness thresholds of €30,000 and €45,000, respectively.

**Conclusion:** According to the present economic study, combination therapy with VOR+ANI is cost-effective as primary therapy of IA in galactomannan-positive patients in Spain who have hematologic disease or hematopoietic stem cell transplant, compared with VOR monotherapy.

**Keywords:** anidulafungin, cost-effectiveness, galactomannan, invasive aspergillosis, voriconazole

## Introduction

Invasive aspergillosis (IA) is a life-threatening infection, particularly in patients with hematologic disease or who have received hematopoietic stem cell transplantation (HSCT).[1] Although survival has increased in recent years due to advances in diagnosis and new antifungal drugs,[2] prognosis of IA continues to be suboptimal,

with an attributable mortality of 42%–64%.[3,4] Combination therapies may improve antifungal efficacy but do so at increased cost.

The public price of treating diagnosis-related group number 580 (systemic infections and parasitic disorders except septicemia with major complications), which includes aspergillosis, has been reported to be €7,173 in Madrid[5] and €9,072 in Navarra, Spain.[6] In a German study published in 2014, which looked at Spanish hospital data on the cost of antifungal therapy of IA, voriconazole (VOR) had a lower total treatment cost compared with liposomal amphotericin B (€8,032 and €10,516, respectively).[7] Given the significant health and economic impact of IA, it is extremely important to select the most appropriate IA therapy strategy.

Accurate diagnosis of IA is difficult, because the health status of the patient often precludes invasive procedures and biopsy sampling. Given that early diagnosis is fundamental for improving therapeutic outcomes, rapid detection of galactomannan antigen in serum or bronchoalveolar lavage is useful in the early diagnosis and monitoring of IA.[8]

According to a recent clinical trial in patients with hematologic disease or HSCT, mortality at 6 weeks of IA therapy was lower with a combination of voriconazole and anidulafungin (VOR+ANI) than with VOR monotherapy and was lower in the subgroup of patients receiving combination therapy who had probable IA based on positive galactomannan antigen testing than in the overall population of patients receiving combination therapy.[9] The objective of our study was to compare the cost-effectiveness of both therapies, from the perspective of hospitals in the Spanish National Health System.

# Methods
## Economic model

Using an economic model, the efficacy of VOR+ANI combination therapy was compared with VOR monotherapy for the treatment of IA in a hypothetical cohort of 1,000 galactomannan-positive patients. The model consisted of a decision tree (Figure 1) predicting outcomes after 6 weeks of therapy. The analysis considered the following variables: mortality or survival rate of the patient; probability of adverse events (AEs) occurring or not; probability of any AEs occurring being serious or mild-to-moderate; costs of antifungal therapy, AE-related costs, and costs of hospital stays (ward and intensive care unit [ICU]); and life expectancy in patients with HSCT who respond satisfactorily to antifungal therapy for IA. Efficacy and toxicity data were obtained from a clinical trial reporting on VOR+ANI combination therapy in 108 patients and VOR monotherapy in 110 patients (NCT00531479).[9]
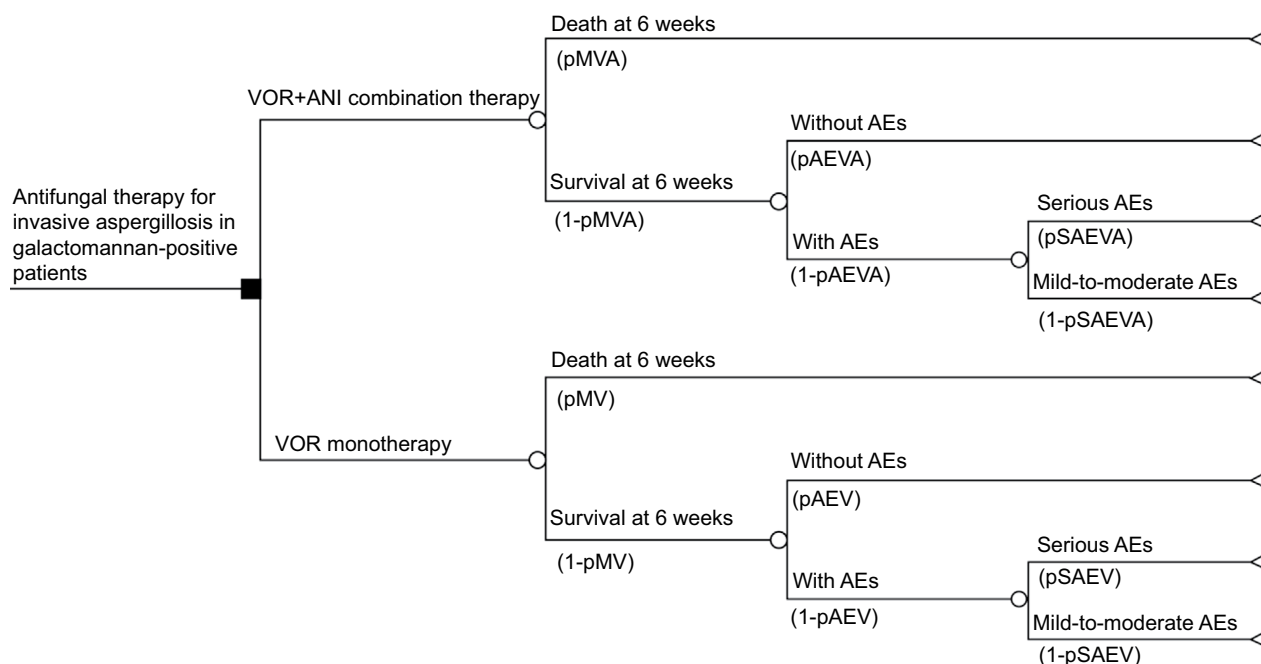


**Figure 1** Decision tree model.
**Note:** 1- Represents the complementary probability.
**Abbreviations:** AE, adverse event; ANI, anidulafungin; pAEV, probability of AEs occurring with VOR monotherapy; pAEVA, probability of AEs occurring with VOR+ANI combination therapy; pMV, probability of mortality with VOR monotherapy; pMVA, probability of mortality with VOR+ANI combination therapy; pSAEV, probability of serious AEs occurring with VOR monotherapy; pSAEVA, probability of serious AEs occurring with VOR+ANI combination therapy; VOR, voriconazole.

The main model inputs are presented in Table 1. Deterministic and probabilistic analyses were conducted. The base-case deterministic analysis was constructed using mean values for each variable; sensitivity analyses modifying each parameter were also performed for all of the variables presented in Table 1. Specifically, the sensitivity of the result to variation in the following parameters was assessed (for VOR+ANI or VOR): probability of mortality, duration of hospital stay, life expectancy, drug acquisition cost; probability of occurrence of mild-to-moderate or serious AEs, and costs related to mild-to-moderate or serious AEs. Variation in the duration of antifungal therapy (base-case ±7 days) was also considered. Probabilistic analysis was conducted using second-order Monte Carlo simulations[10] (1,000 iterations), with the objective of assessing the uncertainty of all variables, which is indicated in Table 1. Monte Carlo simulations use computerized statistical sampling techniques to obtain a probabilistic approximation of the solution of an equation or mathematical model.[11] The rates were adjusted to beta distributions and the costs to gamma distributions.[10]

The economic model was applied using the TreeAge Pro 2014 program (TreeAge Software, Inc., Williamstown, MA, USA). All prices and costs in the model were expressed in 2015 euros (€), with the exception of the 7.5% reduction of the price of ANI (Ecalta®; Pfizer Inc., NY, USA) in Spain that was authorized in early 2016.

## Mortality

As shown in Table 1, according to the clinical trial of Marr et al,[9] mortality after 6 weeks of IA therapy was significantly lower with VOR+ANI than with VOR monotherapy in galactomannan-positive patients (15.7% and 27.3%, respectively; *p*=0.037).

## Adverse events

A serious AE was defined as an event for which the patient outcome is death, life-threatening, hospitalization, or permanent disabilities or damage, in accordance with guidance issued by the US Food and Drug Administration.[12] The overall AE rate in the galactomannan-positive patient group was

**Table 1** Economic model assumptions

| Item | Average | Interval[a] | SD | Distribution | Alpha | Beta | References |
|---|---|---|---|---|---|---|---|
| **Mortality rates, %** | | | | | | | |
| VOR+ANI | 15.74 | 10.07–23.77 | 3.50 | Beta | 16.93 | 90.62 | Marr et al[9] |
| VOR | 27.27 | 19.82–36.26 | 4.19 | | 30.51 | 81.35 | |
| **Treatment-related AEs, %** | | | | | | | |
| VOR+ANI | 69.74 | 63.49–75.33 | 3.02 | Beta | 160.49 | 69.65 | Marr et al[9] |
| VOR | 62.39 | 55.92–68.45 | 3.20 | | 142.62 | 85.98 | |
| **Serious treatment-related AEs, %** | | | | | | | |
| VOR+ANI | 19.50 | 14.09–26.34 | 3.13 | Beta | 31.12 | 128.48 | Marr et al[9] |
| VOR | 14.18 | 9.37–20.90 | 2.94 | | 19.85 | 120.06 | |
| **Antifungal treatment cost[b] €** | | | | | | | |
| VOR+ANI | 10,899.89 | 10,817.01–11,126.86 | 79.04 | Gamma | 19,015.61 | 0.57 | Ministerio de Sanidad Servicios Sociales e |
| VOR | 6,054.74 | 5,971.86–6,281.71 | 79.04 | | 5,867.56 | 1.03 | Igualdad;[16] Consejo General de Colegios Oficiales de Farmacéuticos[13] |
| **Mild to moderate AE unit cost[c] €** | | | | | | | |
| Both | 457.04 | 365.64–548.45 | 46.64 | Gamma | 96.04 | 4.76 | Ojeda et al;[17] Martin-Iglesias;[18] Llibre-Codina et al;[19] Presidente de la Gerencia Regional de Salud;[20] Servicio Madrileño de Salud;[5] Marr et al[9] |
| **Serious AE unit cost[c] €** | | | | | | | |
| Both | 1,859.57 | 1,487.66–2,231.49 | 189.75 | Gamma | 96.04 | 19.36 | Ojeda et al;[17] Ministerio de Sanidad Servicios Sociales e Igualdad;[21] Holstenson et al;[22] Isla et al;[23] Servicio Madrileño de Salud;[5] Marr et al[9] |
| **Hospital stay cost[d] €** | | | | | | | |
| VOR+ANI | 6,815.59 | 5,126.41–8,728.69 | 918.95 | Gamma | 55.01 | 123.90 | Peiró et al;[38] Asensio et al;[24] Marr et al[9] |
| VOR | 6,274.84 | 4,645.32–8,127.05 | 888.20 | | 49.91 | 125.72 | |
| **Life expectancy[e] years** | | | | | | | |
| Both | 3.00 | 2.70–3.30 | 0.15 | Gamma | 384.16 | 0.01 | Jansen et al;[25] Jansen et al;[26] Ament et al;[27] Krueger and Nelson[28] |

**Notes:** [a]Interval is given as 95% CI unless otherwise indicated; [b]body weight in Spanish adults (70.0 kg; 95% CI: 67.76–76.13 kg) obtained from Spanish official figures[16]; [c]calculated on the basis of AE with significant cost (NCT00531479); [d]calculated from clinical trial data,[9] 32% of total hospital costs were subtracted as the cost of drugs to avoid double-counting;[38] [e]life expectancy of recipients of a hematopoietic stem cell transplant who survive after invasive aspergillosis treatment is ~3 years.[25–28] Interval: ±10%.
**Abbreviations:** AE, adverse event; ANI, anidulafungin; CI, confidence interval; SD, standard deviation; VOR, voriconazole.

higher with VOR+ANI (69.7%) than with VOR monotherapy (62.4%); the rate of serious AEs was also higher (19.5% and 14.2%, respectively; Table 1).[9]

## Drug acquisition costs

The acquisition costs of VOR (Vfend®; Pfizer Inc.) and ANI (Ecalta®) were obtained from the official manufacturer's sales prices in Spain, including the recently authorized mandatory discount of 7.5% for ANI (Table 2).[13] We also considered the dosage schedules recommended in the Summary of Product Characteristics of both drugs[14,15] and, in the case of VOR, the average body weight of adults in Spain (70.0 kg; 95% confidence interval [CI]: 67.8–76.1 kg), obtained from Ministry of Health databases (Table 2).[16] Patients were assumed to receive treatment with ANI (200 mg on day 1, followed by 100 mg every subsequent day of treatment) for at least 2 weeks and no more than 4 weeks.

## AE-related costs

The costs of serious and mild-to-moderate AEs were calculated from the rates described by Marr et al[9] and from the unit costs of handling the AE, obtained from Spanish sources (Table 1).[5,17–23]

## Hospitalization costs

The frequencies of hospitalization (within a timeframe of 6 weeks) with VOR (31.7%) and VOR+ANI (30.4%) on the ward and in the ICU were obtained from data reported by Marr et al;[9] length of hospital stay for VOR+ANI and VOR alone in the general ward (36.0 and 34.4 days, respectively)

and the ICU (14.2 and 13.7 days, respectively) were also taken from this clinical trial. Unit costs of a 1-day stay on the general ward (€457; 95% CI: €366–548) and ICU (€1,860; 95% CI: €1,488–2,231) were obtained from a previously published Spanish study (Table 1).[24]

## Life expectancy (time horizon)

The life expectancy of patients with HSCT who survive after antifungal therapy for IA is ~3 years.[25–28] Therefore, the time horizon (the duration of monitoring of the hypothetical patients of the model) of the presented model was 3.0 years (95% CI: 2.7–3.3 years; Table 1).

## Presentation of results

The results are presented as average cost per life-year gained (LYG) by galactomannan-positive patients with IA treated with VOR+ANI and VOR monotherapy and as differences in costs and life-years between the two therapy strategies. Cost per LYG for VOR+ANI compared with VOR monotherapy was calculated. For the probabilistic analysis, cost-effectiveness planes were calculated and probability of cost-effectiveness estimated relative to local willingness-to-pay thresholds of €30,000 and €45,000 as previously reported.[29,30]

## Results
### Deterministic analysis

In each hypothetical cohort of 1,000 patients receiving either VOR+ANI combination therapy or VOR alone, 157 and 273 deaths were expected to occur, respectively. In surviving patients, 256 and 274 AEs were predicted in patients

**Table 2** Drug acquisition cost calculation

| Body weight[a] (kg) | Item | Day 1 | Days 2–7 | Days 2–14 | Days 8–42 | Total cost (€) |
|---|---|---|---|---|---|---|
| **Voriconazole** | | | | | | |
| 70.0 | Dose (mg/kg)[b] | 840 | 560 | – | 600 | – |
| | Administration[c] | IV | IV | – | Oral | – |
| | Cost (€)[d] | 517.95 | 2,071.79 | – | 3,465.00 | 6,054.74 |
| 67.8 | Dose (mg/kg)[b] | 813 | 542 | – | 600 | – |
| | Administration[c] | IV | IV | – | Oral | – |
| | Cost (€)[d] | 501.37 | 2,005.48 | – | 3,465.00 | 5,971.86 |
| 76.1 | Dose (mg/kg)[b] | 914 | 609 | – | 600 | – |
| | Administration[c] | IV | IV | – | Oral | – |
| | Cost (€)[d] | 563.34 | – | 2,253.36 | 3,465.00 | 6,281.71 |
| **Anidulafungin** | | | | | | |
| Any | Dose (mg)[b] | 200 | – | 100 | – | – |
| | Administration[c] | IV | IV | IV | – | – |
| | Cost (€) | 646.02 | – | 4,199.13 | – | 4,845.15 |

**Notes:** [a]Body weight in Spanish adults (70.0 kg; 95% CI: 67.76–76.13 kg) obtained from Spanish official figures[16,39]; [b]doses calculated from Marr et al[9]; [c]obtained from Summary of Product Characteristics[13]; [d]drug acquisition costs were obtained from the approved ex-factory prices in Spain with official 7.5% discount rate as of early 2016.[13]
**Abbreviations:** CI, confidence interval; IV, intravenous.

receiving either VOR+ANI combination therapy or VOR alone, respectively. More serious AEs were expected with VOR+ANI (n=50) than with VOR monotherapy (n=39).

The median duration of VOR+ANI combination therapy was 14 days (range: 1–29 days); the median duration of VOR monotherapy was 42 days (range: 1–48 days).[9] As shown in Table 3, the average life expectancy per patient was 2.5 years with VOR+ANI and 2.2 years with VOR monotherapy (an increase of 0.348 LYG with VOR+ANI). The average cost per patient of antifungal therapy for IA was €17,902 with VOR+ANI and €12,409 with VOR monotherapy (an additional cost of €5,493 with VOR+ANI). Consequently, the incremental cost per LYG was €15,785 with VOR+ANI versus VOR.

The results of the univariate sensitivity analyses are represented in the Tornado plot (Figure 2). The variables that most influenced the results were mortality probabilities for each of the compared therapy strategies. The variation in the mortality probability with VOR+ANI (0.10–0.24) would lead to a cost per LYG with VOR+ANI versus VOR monotherapy from €10,669 to €52,144. The variation in the mortality probability with VOR monotherapy (0.20–0.36) would lead to a cost per LYG with combination from €8,924 to €44,509 (Figure 2). When the duration of antifungal therapy was varied by ±7 days relative to the base-case analysis, the cost per LYG was €9,287 with VOR+ANI versus €22,282 with VOR monotherapy.

## Probabilistic analysis

In the probabilistic analysis, the cost per LYG with VOR+ANI was €15,774 (95% CI: €15,763–16,692; Table 4). The probability that VOR+ANI would be considered cost-effective compared with VOR was estimated at 82.5% and 91.9% at locally established willingness-to-pay thresholds of €30,000 and €45,000, respectively (Figure 3). The cost-effectiveness acceptability curves for both therapy options are presented in Figure 4.

## Discussion

The pharmacoeconomic model used in this study suggests an increase of 0.348 LYG with VOR+ANI compared with VOR monotherapy for galactomannan test-based IA in each patient with hematologic disease or HSCT. According to the study by

Rodriguez-Tudela et al, there were 419 such patients across Spain in 2010.[31] Therefore, widespread VOR+ANI combination therapy in patients with hematologic disease or HSCT in Spain could provide an annual gain of ~146 years compared with VOR monotherapy. Similarly, our findings suggest that the probability that VOR+ANI combination therapy of IA is cost-effective compared with VOR monotherapy is 82.5% at a previously established local willingness-to-pay threshold of €30,000 per LYG (91.9% at a threshold of €45,000 per LYG).[29,30]

Certain limitations and inconsistencies of this study must be taken into account when considering these results. This was a theoretical model, which, by definition, was a simulation of real-world clinical practice. Additionally, efficacy and AE data were obtained from an explanatory double-blind, randomized clinical trial (NCT00531479),[9] as no data from pragmatic clinical trials were available.[32] Consequently, the results of the economic analysis are applicable only to patients with similar characteristics to those included in that clinical trial. Also, the lower mortality of the subgroup of patients who received VOR+ANI combination therapy for IA indicated by galactomannan testing in the trial reported by Marr et al[9] was determined by means of a post hoc analysis, with associated methodological limitations.[33] As noted by Marr et al,[9] further work is required to confirm the results obtained in the combination therapy subgroup; our economic model was, therefore, also dependent on such limitations. The highest mortality probabilities used in the deterministic sensitivity analyses with VOR+ANI and VOR monotherapy lead to costs per LYG with the combination above €30,000 per LYG.

Reliability of the presented findings were assessed by Monte Carlo simulation.[34] In clinicoeconomic research, this statistical approach is used to predict individual clinical outcomes for a hypothetical cohort of patients using theoretical sampling of random variables, the behavior of which is described by means of given sampling distributions.[35] Therefore, the Monte Carlo simulation shows the effect of the random changes conducted on different parameters and consequently imitates the actual clinical development of the patients. The reliability of the result obtained was effectively confirmed by the sensitivity analyses conducted. According to our probabilistic sensitivity analysis, the probability of VOR+ANI being cost-effective compared with VOR

**Table 3** Deterministic analysis results: base-case

| Treatment | Costs (€) | Cost differences (€) | Life-years | LYG | Cost per LYG[a] (€) |
|---|---|---|---|---|---|
| VOR+ANI | 17,902 | 5,493 | 2.529 | 0.348 | 15,785 |
| VOR | 12,409 | | 2.181 | | |

**Notes:** [a]Incremental cost-effectiveness ratio (cost per LYG with VOR+ANI versus VOR monotherapy).
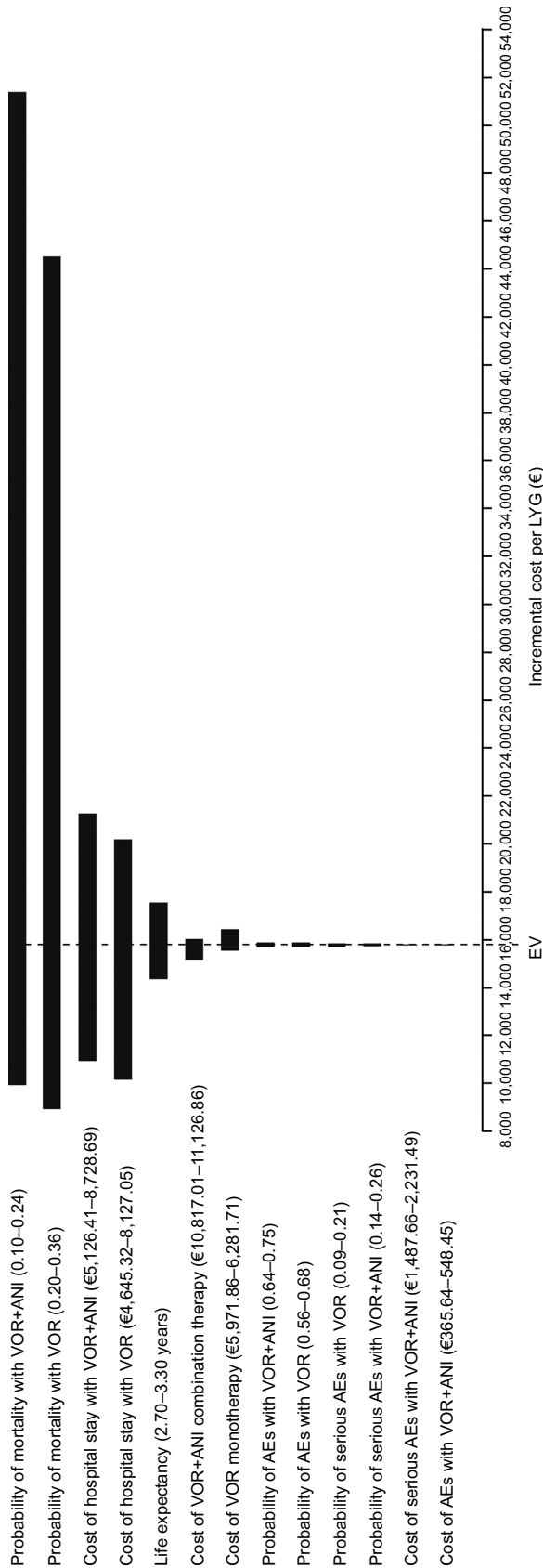**Abbreviations:** ANI, anidulafungin; LYG, life-year gained; VOR, voriconazole.

**Table 4** Probabilistic analysis results

| | Cost, € (95% CI) | LYG (95% CI) | Cost per LYG[a] (95% CI) |
|---|---|---|---|
| VOR+ANI | 18,063 (16,431–20,020) | 2.534 (2.224–2.843) | 15,774 (15,763–16,692) |
| VOR | 12,385 (10,720–14,206) | 2.174 (1.862–2.495) | |

**Notes:** [a]Incremental cost-effectiveness ratio (cost per LYG with VOR+ANI combination therapy vs VOR monotherapy).
**Abbreviations:** ANI, anidulafungin; CI, confidence interval; LYG, life-year gained; VOR, voriconazole.

monotherapy was 82.5% versus 91.9%, at local willingness-to-pay thresholds of €30,000 and €45,000 per LYG, respectively.[29,30] All costs used in the model were taken from Spanish sources, to ensure that the results accurately reflected routine clinical practice in the Spanish healthcare system.

It was not possible to compare the results and procedures of this study with those from another country, as no similar economic analyses comparing VOR+ANI combination therapy with VOR monotherapy for IA in galactomannan-positive patients were identified. Nor were any studies found that compared the efficacy of other antifungal therapy strategies in IA or in other indications in galactomannan-positive patients. In published studies, only the unit cost of the galactomannan test was assessed, and not its diagnostic role as a possible determinant of the cost-effectiveness of IA therapy.[36,37] No costs were considered for additional diagnostic tests given as part of a full diagnostic workup or as follow-up to galactomannan antigen testing, under the assumption that these costs would not be substantial.

## Conclusion

On the basis of the findings of our economic model and probabilistic sensitivity analysis, combination therapy with VOR+ANI may be cost-effective as the primary therapy for IA in galactomannan-positive patients in Spain, compared with VOR monotherapy.

## Acknowledgments

## Authors contribution

CRT and DRR developed the economic model. CP, JAB, and FJM reviewed the economic model. All authors had full access to the data, and contributed heavily to the analysis and
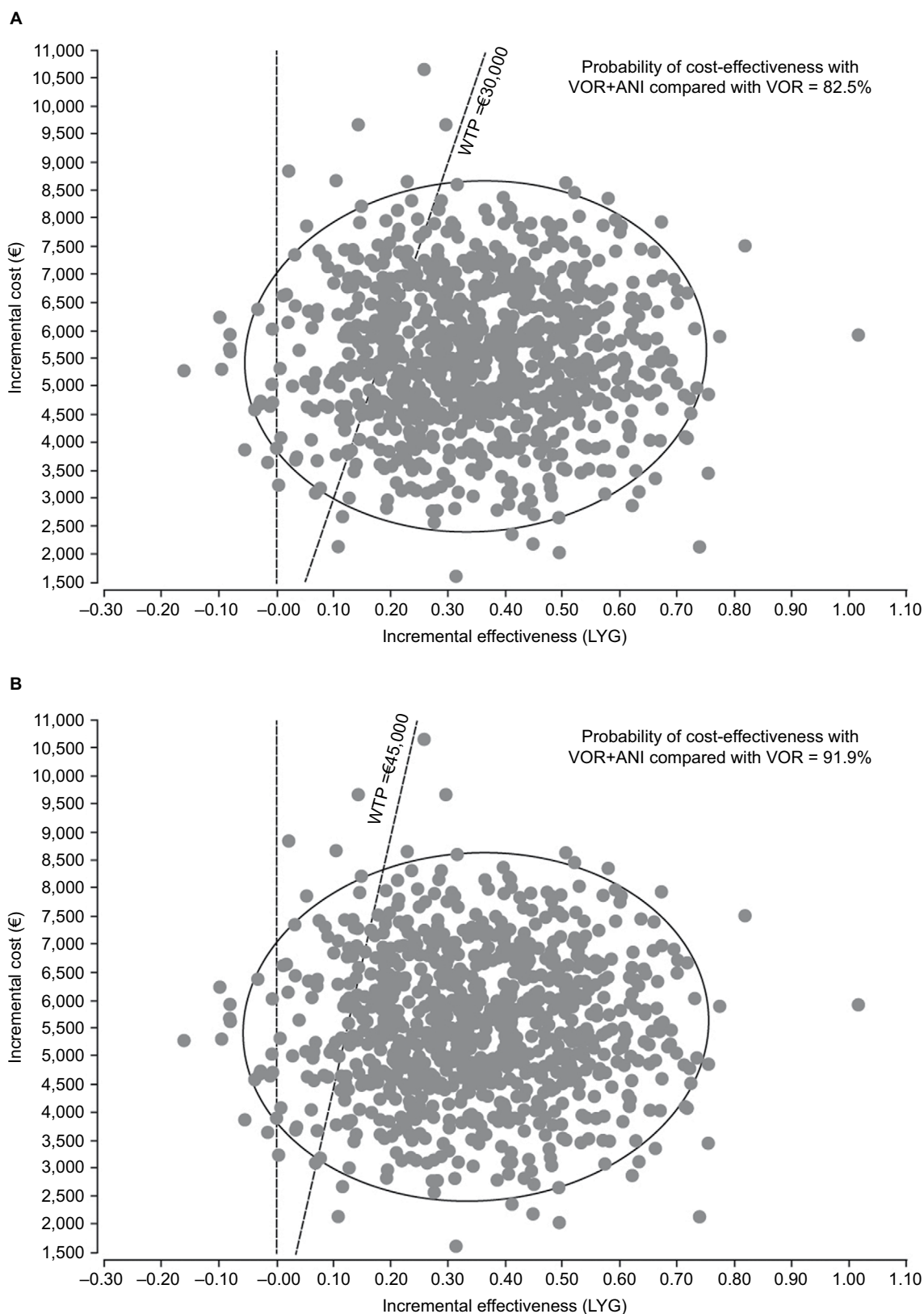


**Figure 2** Tornado plot (deterministic sensitivity analysis).
**Abbreviations:** AE, adverse event; ANI, anidulafungin; EV, expected value; LYG, life-year gained; VOR, voriconazole.

**A**



**B**



**Figure 3** Cost-effectiveness plane (Monte Carlo simulation) at: **(A)** a willingness-to-pay threshold of €30,000; and **(B)** a willingness-to-pay threshold of €45,000.
**Abbreviations:** ANI, anidulafungin; LYG, life-year gained; VOR, voriconazole; WTP, willingness-to-pay threshold.

interpretation of the results. All authors contributed to the drafting of the manuscript and to the subsequent revisions at each stage of the manuscript development. All authors have approved the final version for publication and agreed to remain accountable for the accuracy and integrity of this work. CRT is the guarantor for the overall content of the paper.
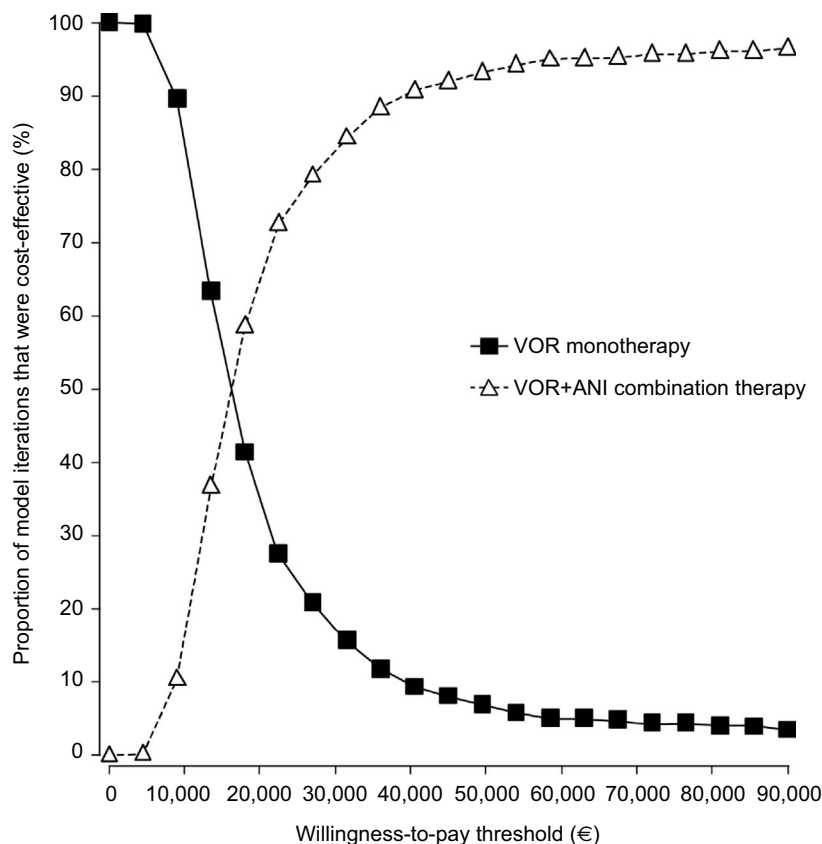
**Figure 4** Cost-effectiveness acceptability curve.
**Abbreviations:** ANI, anidulafungin; VOR, voriconazole.

# Disclosure

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