Cost-Effectiveness of Once-Weekly Rezafungin for the Treatment of Candidemia and Invasive Candidiasis in the UK

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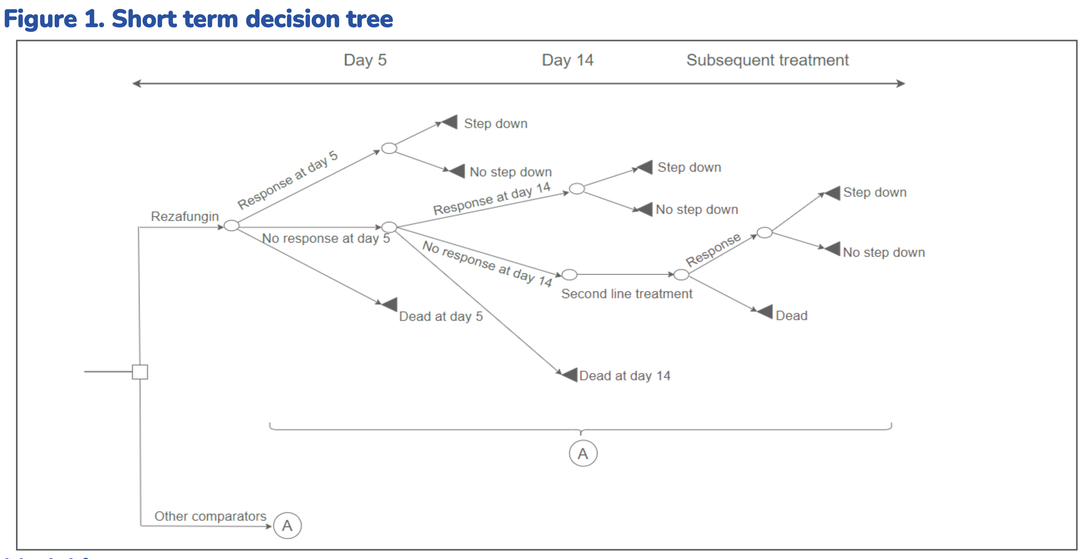
INTRODUCTION AND OBJECTIVES

- Invasive candidiasis (IC) is a serious, life-threatening fungal infection with high economic burden due to lengthy hospitalisations and long ICU stay (1).
- International clinical guidelines recommend daily intravenous (IV) echinocandins (e.g., caspofungin, anidulafungin and micafungin) as first line therapy (2, 3, 4).
- A new once weekly echinocandin, rezafungin when compared to once daily caspofungin, demonstrated safety, tolerability, and efficacy in the phase II STRIVE trial and non-inferior treatment efficacy in the phase III ReSTORE trial (5, 6).
- As the trials were double-dummy double-blind, the potential implications of the different dosing schedules could not be assessed. However, in a survey of investigators in the ReSTORE trial, they indicated if they had been able to administer once weekly IV rezafungin instead of daily treatment, they would have considered discharging 16% of the patients from the hospital on an average of 5.9 days earlier than their actual discharge date. This was in line with the findings of the ECMM Candida III Multinational European Observational Cohort Study, which reported 16% of patients with candidaemia had their hospital stay extended only to complete daily parenteral antifungal treatment (7).
- This study aims to assess the cost-effectiveness of the once weekly rezafungin versus daily caspofungin,

METHODS

- A hybrid model was developed including a short-term decision tree (capturing treatment duration of ≤30 days) and a long-term Markov model (capturing lifetime outcomes) (Figure 1).
- Trial data (5, 6), network meta-analyses (8, 9, 10), and clinical experts suggested similar efficacy for all echinocandins, therefore cost-minimisation analysis (CMA) was performed as base case and cost-utility analysis (CUA) as scenario analysis.
- As in the case of all acute fungal infection, costs are incurred only in the short-term, the time horizon for the CMA base case was the treatment duration, while for the CUA lifetime horizon was required to take into account the consequences on mortality.
- Treatment response was assessed at days 5 and 14 (Figure 1).
  - 90% of non-responders were assumed to switch to second-line IV fluconazole and 10% of non-responders were assumed to switch to liposomal amphotericin B. Patients with negative repeat blood cultures could step down to oral fluconazole (24% and 35% of patients for rezafungin and daily echinocandins respectively).
  - Weekly rezafungin could allow early discharge for 16% of all patients. The model assumed that 17% of these patients were discharged to outpatient parenteral antimicrobial therapy (OPAT), and 83% to home. Risk of death was included.
- To be able to assess the long-term consequences of the disease, patients who survived IC were moved to a Markov model consisting of two health states : alive and dead. The model used a cycle length of 1 year and an annual discount rate of 3.5%.
  - General population mortality rates and utilities, adjusted to commonly observed underlying comorbidities in the ReSTORE trial were used to estimate health consequences.

Figure 1. Short term decision tree



Model inputs

- Efficacy and resource use estimates were from pooled trial data (5, 6, 11), assuming equal efficacy/resource use for daily echinocandins (Table 2, Table 3). In line with UK clinical practice, response was defined as:
  - Mycological response at day 5; negative blood culture or negative culture from normally sterile site and no change needed in initial antifungal therapy and global response at day 14; composite outcome including clinical response, radiological cure, and mycological response.
- Grade 3-4 treatment emergent adverse events (TEAEs) observed in at least 5% of the patients in the ReSTORE trial (5) were assumed to have important cost consequences for the patient population
  - Due to limited published information, varying reporting and the substantial heterogeneity, anidulafungin and micafungin were assumed to have the same safety profile as caspofungin in the ReSTORE trial (5).
- Costs included drug costs (Table 1), aseptic reconstitution, drug administration costs, laboratory testing costs, hospitalisation costs, OPAT costs and TEAE costs.
- Unit costs, utilities, long-term mortality were from published literature and public UK databases. Due to lack of data, utility value reported for sepsis (0.5) was used as a proxy based on prior published cost-effectiveness studies for treatments of IC and clinical expert input. Detailed inputs are available at request.
- Conceptual/technical validation, probabilistic and deterministic sensitivity analyses were conducted.

Table 1. Drug costs

	Pack size	Price (£)	Dosing	Source
Rezafungin (IV)*	1 x 200mg	1,999.95	Loading: 400 mg Maintenance: 200 mg weekly	Mundipharma ReSTORE trial(5)
Caspofungin (IV)	1 x 70mg	27.25	Loading: 70mg daily Maintenance: 70mg daily (>80kg) or 50mg daily (<80kg)	eMIT (2023)(12), SmPC(13)
Caspofungin (IV)	1 x 50mg	21.19		
Micafungin (IV)	1 x 100mg	49.83	100mg daily	eMIT (2023)(12), SmPC(13)
Anidulafungin (IV)	1 x 100mg	38.85	Loading: 200mg daily Maintenance: 100mg daily	eMIT (2023)(12), SmPC(13)
Fluconazole (oral)	7 x 200mg	1.02	400mg daily	eMIT (2023)(12), SmPC(13)
Amphotericin B	10 x 50mg	821.87	3mg kg^{-1} daily	BNF (2022), BNF(14)
Fluconazole (IV)	20 x 200mg	47.20	Loading: 800mg daily Maintenance: 400mg daily	eMIT (2023)(12), SmPC(13)

*Indicative price

Table 2. Efficacy inputs

Treatments	Day 5			Day 14			Second line	
	Response (SE)	No response (SE)	Death (SE)	Response (SE)	No response (SE)	Death (SE)	Response (SE)	Death (SE)
Rezafungin	0.73 (0.04)	0.22 (0.02)	0.04 (0.02)	0.59 (0.05)	0.32 (0.03)	0.09 (0.03)	0.81 (0.03)	0.19 (0.03)
Daily echinocandins	0.65 (0.04)	0.32 (0.03)	0.04 (0.02)	0.61 (0.05)	0.30 (0.03)	0.09 (0.03)	0.81 (0.03)	0.19 (0.03)

Table 3. Inpatient stay

	Rezafungin		Daily echinocandins		Cost/day (£)*
	% of patients	LoS	% of patients	LoS	
ICU	40%	17.3	46%	21.4	3,066.78
General ward	83%	20.8	81%	23.1	424.14

Values were adjusted for the imbalance in the proportion of patients receiving ventilation in the two treatment arms.
SE: Standard error, IV: Intravenous, ICU: Intensive care unit, LoS: length of stay. Source: Pooled analyses of the STRIVE and ReSTORE trials (5, 6), NIHR 2020/21(15)
* costs were inflated to 2022 GBP using the NHS cost inflation index(16)

RESULTS

- Rezafungin was cost-saving compared to daily echinocandins with discounted incremental costs of -£3,863, -£4,209 and -£4,586 vs. caspofungin, micafungin and anidulafungin respectively (Table 4). Costs were driven by differences in inpatient stay between the treatments.
- In the lifetime CUA, quality-adjusted life-years (QALYs) were similar across all comparators, with an incremental QALY of just -0.03 compared to all daily echinocandins (Table 5), as the results were driven by very small non-significant differences in the point estimates.
- As both the incremental costs and incremental QALYs were negative, the ICERs show the cost-effectiveness of the daily echinocandin compared to rezafungin, not the cost-effectiveness of rezafungin.
  - Daily echinocandins were not cost-effective compared to rezafungin with ICERs between £121,644.25/QALY - £144,399.56/QALY.
- As ICERs can be misleading when the incremental QALYs and/or incremental costs are negative, net monetary benefit (NMB) was estimated. Using the £20,000/QALY threshold, the NMB for rezafungin compared to daily echinocandins was positive (£3,228 to £3,951 vs. daily echinocandins), resulting in rezafungin being cost-effective.
- Results were most sensitive to ICU length of stay and treatment response (day 14) (Figure 2).
- A threshold analysis further emphasised the importance of ICU length of stay. As long as the ICU length of stay did not increase for rezafungin by more than 18% (from the 17.3 days in the pooled analysis to 20.5 days), rezafungin remained cost-saving. Meanwhile, the general ward stay has to increase by 55% (from 19.7 in the pooled analysis to 30.6 days), for rezafungin to be no longer cost saving.
- At willingness to pay threshold of £20,000/ QALY, the probability of rezafungin being cost-effective was 42% (Figure 3).

Table 4. Cost-minimisation analysis results

Description	Rezafungin	Caspofungin	Micafungin	Anidulafungin
Deterministic results				
Drug costs (£)	6,166.24	462.39	808.29	704.40
Disease management costs (£)	40,112.64	49,714.80	49,714.80	50,195.47
TEAE costs (£)	432.77	397.75	397.75	397.75
Total costs (£)	46,711.65	50,574.94	50,920.84	51,297.62
Incremental costs (£): Rezafungin (IV) vs.	-	-3,863.29	-4,209.18	-4,585.97
Probabilistic results				
Incremental costs (£): Rezafungin (IV) vs. [95% CI]	-	-3,883.41 [-12,442.44, 4,176.88]	-4,140.59 [-12,863.61, 4,540.90]	-4,426.43 [-12,814.53, 3,547.29]

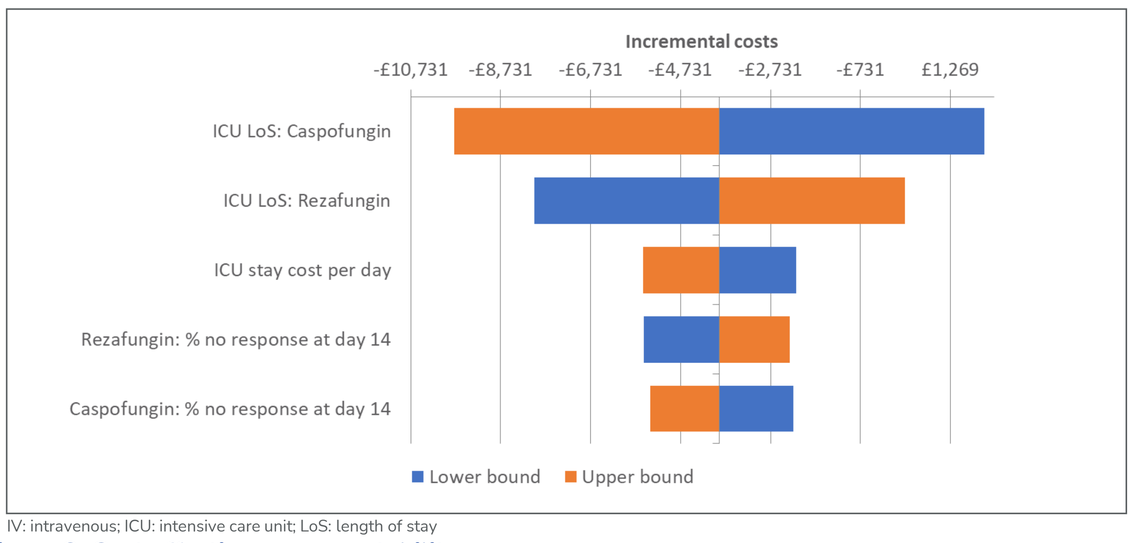
IV: Intravenous; TEAE: treatment-emergent adverse event; CI: confidence interval

Table 5. Cost-utility analysis results (discounted)

Rezafungin vs.	Caspofungin	Micafungin*	Anidulafungin*
Incremental costs (£)	-3,863.29	-4,209.18	-4,585.97
Incremental LYs	-0.04	-0.04	-0.04
Incremental QALYs	-0.03	-0.03	-0.03
ICER (£/QALY)	Caspofungin vs. rezafungin: £121,644.25 / QALY**	Micafungin vs. rezafungin: £132,535.64 / QALY**	Anidulafungin vs. rezafungin: £144,399.56 / QALY**
NMB (£)	3,228.11	3,574.01	3,950.79

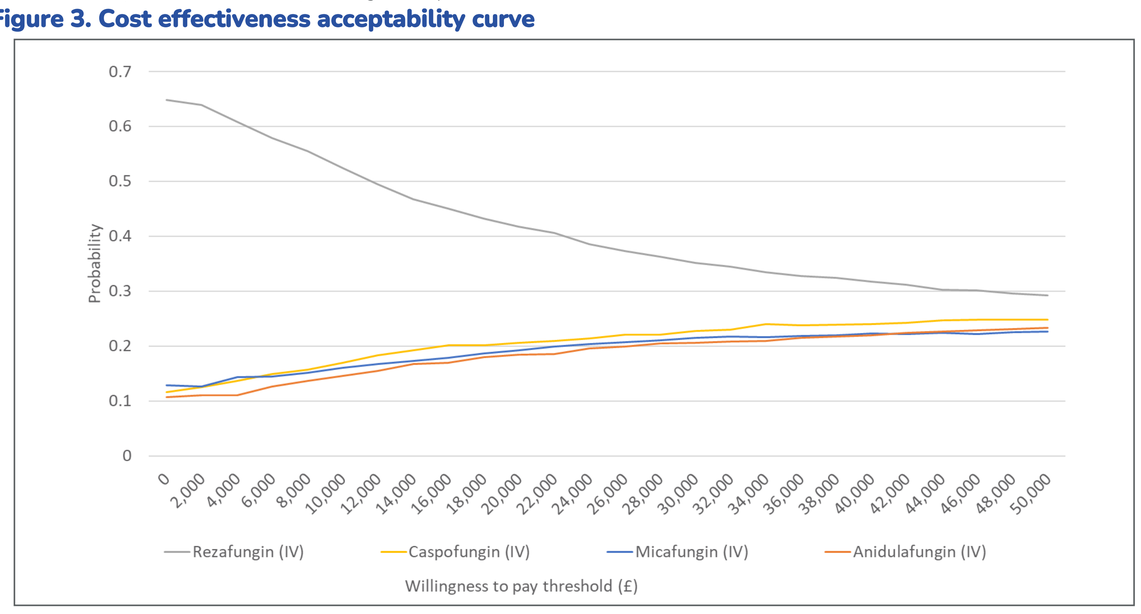
IV: Intravenous, LY: Life years, QALY: Quality adjusted life years, ICER: incremental cost-effectiveness ratio, NMB: Net monetary benefits
*Treatment efficacy is assumed same as for caspofungin.
** As rezafungin results in lower QALYs and lower costs, the ICER shows the cost-effectiveness of the daily echinocandin compared to rezafungin, not the cost-effectiveness of rezafungin

Figure 2. Deterministic sensitivity analysis (rezafungin vs caspofungin)



IV: intravenous; ICU: intensive care unit; LoS: length of stay

Figure 3. Cost effectiveness acceptability curve



IV: intravenous

LIMITATIONS

- The model assumes the same efficacy/safety for micafungin/ anidulafungin as for caspofungin based on NMA due to lack of head-to-head trial data. This was in line with prior NMAs and was validated by clinical experts.
- Due to the lack of published cost estimates, the unit cost of ICU and general ward stay used in the model are not specific for invasive candidiasis.

CONCLUSIONS

- Once weekly rezafungin is a cost-saving and cost-effective treatment option in IC from the UK healthcare perspective compared to the daily echinocandins caspofungin, anidulafungin and micafungin.
- Further research on healthcare resource use associated with IC in the UK, and the effect of weekly administration could further strengthen the analysis.

References

1.Candidemia and Invasive Candidiasis: A Systematic Review. Value Health Reg Issues. 2020;21:53-8.
2.Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.
3.Martin-Loeches I, Antonelli M, Cuenca-Estrella M, Dimopoulos G, Einav S, De Waele JJ, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med. 2019;45(6):789-805.
4.Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19-37.
5.Thompson GR, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2023;401(10370):49-59.
6.Thompson GR, Soriano A, Skoutelis A, Vazquez JA, Honore PM, Horcajada JP, et al. Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial. Clin Infect Dis. 2021;73(11):e3647-e55.
7.Hoenigl M, Salmanton-García J, Egger M, Gangneux J-P, Bicanic T, Arikan-Akdagli S, et al. Guideline adherence and survival of patients with candidaemia in Europe: results from the ECMM Candida III multinational European observational cohort study. The Lancet Infectious Diseases. 2023.
8.Demir KK, Butler-Laporte G, Del Corpo O, Ekmekjian T, Sheppard DC, Lee TC, et al. Comparative effectiveness of amphotericin B, azoles and echinocandins in the treatment of candidemia and invasive candidiasis: A systematic review and network meta-analysis. Mycoses. 2021;64(9):1098-110.
9.Domingos EL, Vilhena RO, Santos J, Fachi MM, Böger B, Adam LM, et al. Comparative efficacy and safety of systemic antifungal agents for candidemia: a systematic review with network meta-analysis and multicriteria acceptability analyses. Int J Antimicrob Agents. 2022;60(2):106614.
10.Visible Analytics. Network Meta-Analysis for the treatment of patients with candidemia and/or invasive candidiasis. Data of file. 2022.
11.I Bielicka SD, N Manamley, A Das, T Sandison. Integrated Analysis of Efficacy and ICU Length of Stay Data from Phase 2 and Phase 3 Trials of Rezafungin for the Treatment
of Invasive Candidiasis and/or Candidemia. Value in Health. 2022;25(12):s35.
12.Drugs and pharmaceutical electronic market information tool (eMIT) [Internet]. 2023. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
13.Summary of Product Characteristics (SmPC) [Internet]. 2022. Available from: https://www.medicines.org.uk/emc.
14.British National Formulary (BNF) [Internet]. 2022. Available from: https://bnf.nice.org.uk/.
15.National Institute for Health Research (NIHR). Investigation and intervention tariff 2020/21.2020. Available from: https://www.leedsth.nhs.uk/assets/71432c14fa/NIHR-2020-Investigation-and-Intervention-Tariff-1-v2.2-1.pdf.
16.Jones K, C. Weatherly, H. Birch, S Castelli, A. Chalkey, M. Dargan, A. Forder, J. Gao, M. Hinde, S. Markham, S. Ogunleye, D. Premji, S. Roland, D. Unit Costs of Health and Social Care 2022 Manual. Kent: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2023

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