

MAJOR ARTICLE

Treatment Outcomes Among Patients With a Positive *Candida* Culture Close to Randomization Receiving Rezafungin or Caspofungin in the restore Study

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Background: Rezafungin, a novel, once-weekly echinocandin for the treatment of candidemia and/or invasive candidiasis (IC) was non-inferior to caspofungin for Day 30 all-cause mortality (ACM) and Day 14 global cure in the Phase 3 ReSTORE trial (NCT03667690). We conducted pre-planned subgroup analyses for patients with a positive culture close to randomization in ReSTORE.

Methods: ReSTORE was a multicenter, double-blind, double-dummy, randomized trial in patients aged ≥ 18 years with candidemia and/or IC treated with once-weekly intravenous rezafungin (400 mg/200 mg) or once-daily intravenous caspofungin (70 mg/50 mg). This analysis comprised patients with a positive blood culture drawn between 12 hours before and 72 hours after randomization, or a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization. Efficacy endpoints included Day 30 ACM, Day 14 global cure rate, and Day 5 and 14 mycological response. Adverse events were evaluated.

Results: This analysis included 38 patients randomized to rezafungin and 46 to caspofungin. In the rezafungin and caspofungin groups, respectively: Day 30 ACM was 26.3% and 21.7% (between-group difference [95% confidence interval] 4.6% [-13.7, 23.5]); Day 14 global response was 55.3% and 50.0% (between-group difference 5.3% [-16.1, 26.0]); and Day 5 mycological eradication was 71.1% and 50.0% (between-group difference 21.1% [-0.2, 40.2]). Safety was comparable between treatments.

Conclusions: These findings support the efficacy and safety of rezafungin compared with caspofungin for the treatment of candidemia and/or IC in patients with a positive culture close to randomization, with potential early treatment benefits for rezafungin.

Key Words: Candidemia, rezafungin, invasive candidiasis, echinocandin

INTRODUCTION

Candidemia and invasive candidiasis (IC) are common healthcare facility-associated fungal infections that have a substantial impact on patient morbidity and mortality and a high economic burden [1-5]. Echinocandins are recommended as first-line antifungal treatment for candidemia and IC in Europe and the United States (US) [6-8] based on their efficacy and relatively fewer adverse effects and drug-drug interactions compared with polyenes and triazoles. However, emergence of antifungal resistance among *Candida* species mandates the need for novel antifungal drugs [2].

Rezafungin is a novel, US Food and Drug Administration (FDA)- and European Commission-approved echinocandin [9, 10] that is structurally similar to current echinocandins but has

differentiated stability and pharmacokinetics [8, 11-13]. Its low clearance and prolonged half-life versus other echinocandins enables once-weekly intravenous administration resulting in front-loaded exposure that maximizes the drug effect early in therapy [13]. These pharmacokinetic advantages may suppress the development of secondary antifungal resistance [13-15]. The safety and efficacy of rezafungin in treating candidemia and/or IC was demonstrated in the Phase 2, double-blind, randomized STRIVE trial comparing rezafungin and caspofungin [16]. Primary data from the similarly designed Phase 3 ReSTORE trial demonstrated non-inferiority of rezafungin for Day 30 all-cause mortality (ACM) and Day 14 global cure versus caspofungin for the treatment of candidemia and/or IC [17]. Both trials suggested early benefits of rezafungin versus caspofungin, including more rapid clearance of candidemia, and reported similar safety profiles for rezafungin and caspofungin [16, 17].

As with prior randomized trials evaluating echinocandins [18-20], patients in ReSTORE could be randomized for up to 4 days after a positive *Candida* culture [17]. Patients were also allowed a maximum of 48 hours of empiric antifungal treatment before enrollment [17-20]. Culture results obtained closer to initiation of antifungal therapy could theoretically have been negative, either spontaneously or owing to empiric therapy. It is important to understand the potential clinical impact of initiation of study therapy and the timing of blood/tissue cultures because patients with positive cultures closer to antifungal therapy initiation may represent a population with more severe infections.

This pre-planned analysis examined the efficacy and safety of rezafungin versus caspofungin in a subgroup of patients in the ReSTORE trial with a positive culture close to randomization.

METHODS

Study Design and Participants

Full methodological details of the ReSTORE trial (NCT03667690) and primary data have been reported [17]. ReSTORE was a multicenter, prospective, randomized, double-blind, double-dummy, non-inferiority Phase 3 study comparing rezafungin with caspofungin for the treatment of adults ≥ 18 years with candidemia and/or IC. Mycological diagnosis of candidemia and/or IC was from a blood or normally sterile site sample collected ≤ 96 hours before randomization (**Figure 1A**). Patients had ≥ 1 systemic sign attributable to candidemia/IC (eg, fever, hypothermia, tachycardia, tachypnea, local signs of inflammation) appearing from 12 hours before the qualifying positive culture through time of randomization.

This pre-planned analysis examined data for a subgroup of patients in the modified intention-to-treat (mITT) population (mITT2). These patients had either: (1) a positive blood culture drawn between 12 hours before and 72 hours after randomization; or (2) a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization. The

different time cutoffs used for the two sites reflect differences in the relative difficulty of obtaining samples. All patients must have received ≥ 1 dose of study drug (**Figure 1B**).

Patients were randomly assigned (1:1) to receive once-weekly intravenous rezafungin (400 mg on Day 1, 200 mg on Day 8, and optional 200 mg doses on Day 15 and Day 22) or once-daily intravenous caspofungin (70 mg on Day 1, 50 mg on Days 2–28 [with dose adjustment according to hepatic impairment, drug–drug interactions, or patient weight in accordance with the approved labeling and at the investigator’s discretion]) for 14–28 days. Patients in the rezafungin group received intravenous placebo on the other study days to maintain blinding. Patients in both groups who met relevant criteria could step down to oral therapy after ≥ 3 days of intravenous therapy (rezafungin group: placebo; caspofungin group: fluconazole).

Study assessments

Efficacy endpoints included ACM at Day 30 (primary efficacy outcome of ReSTORE as mandated by the FDA) and global response at Days 5 and 14 visits (primary efficacy outcome of ReSTORE as mandated by the European Medicines Agency). The ACM endpoint comprised patients who died on or before Day 30 or whose survival status was unknown. Patients who were alive at Day 28/Day 29 but had unknown survival status at Day 30 were considered alive for the purposes of this assessment. Global response was based on clinical cure as assessed by the investigator, radiological cure (for patients with IC), and mycological eradication, all of which were confirmed by an independent, blinded Data Review Committee (DRC). Outcomes according to the DRC were used for this analysis.

Additional efficacy endpoints included mycological eradication at Days 5 and 14, time to first negative blood culture (TTNBC), and the percentage of negative blood cultures (NBCs) at 24 and 48 hours after the first dose of study drug. For patients with a positive blood culture at baseline, mycological response was defined as eradication if the last blood culture drawn on or prior to the day of assessment was negative with no subsequent positive culture from a sample drawn after the first dose of study drug. For patients with a positive culture at baseline from a normally sterile site other than blood, mycological eradication could be either documented (negative culture from the same normally sterile site on or prior to the day of assessment [ie, Day 5 or Day 14]) or presumed (assessment of clinical and radiological cure [for patients with evidence of disease according to imaging at baseline]) if a culture specimen from the infected site was not available. Mycological failure was defined as documented or presumed fungal persistence, change of antifungal therapy to treat candidemia and/or IC, or death from any cause before or on the day of assessment. Indeterminate mycological response was defined as unavailability of study data for efficacy evaluation for any reason (eg, culture specimen or result not available or patient lost to follow-up). TTNBC (for patients enrolled with a positive blood culture) was calculated as the time from first dose of study drug to the first NBC without subsequent positive culture. Blood cultures were repeated daily or every other day until the first NBC result for *Candida* spp. with no subsequent positive culture.

Safety endpoints included treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events (SAEs), and drug-related SAEs. A TEAE was defined as an AE that occurred during or after study drug administration and up to the follow-up visit. Safety was also assessed through evaluation of clinical laboratory data. AEs and abnormal laboratory values were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 23.0 or higher).

Data analyses

All endpoints were analyzed in the mitt2 population.

Efficacy endpoints were evaluated using a two-sided 95% confidence interval (CI) calculated using the unadjusted methodology of Miettinen and Nurminen. *P*-values presented are nominal and have not been adjusted for multiplicity.

Safety endpoints were summarized using descriptive statistics.

Study oversight

ReSTORE was conducted in accordance with current regulations, the International Conference on Harmonisation Good Clinical Practice, and Declaration of Helsinki. Independent ethics committees or institutional review boards at participating sites approved the protocol and all amendments. All patients, or their legally authorized representative, provided written informed consent.

RESULTS

Demographics and Baseline Characteristics

Of the 187 patients in the ReSTORE mITT population with mycologically confirmed candidemia and/or IC, 84 were eligible for inclusion in the mITT2 population. This population comprised 38 patients randomly assigned to rezafungin and 46 assigned to caspofungin (**Figure 2**). Baseline demographics and characteristics were generally well balanced between groups (**Table 1**). Mean age of patients was approximately 60 years, most patients were male and White, and the majority of patients in both groups were enrolled due to candidemia alone (rezafungin: 76.3%; caspofungin: 71.7%). In patients with IC, the most common site of infection was intra-abdominal, including the peritoneal space. At enrollment, 16/38 (42.1%) and 21/46 (45.7%) patients in the rezafungin and caspofungin groups, respectively, were in an intensive care unit. Most patients (86.5% [32/37] in the rezafungin group and 76.1% [35/46] in the caspofungin group) had a modified Acute Physiology and Chronic Health Evaluation (APACHE) II score (APACHE II + [15 minus Glasgow Coma Score]) of <20; median was 13 in both groups. At baseline, 23.7% (9/38) and 32.6% (15/46) of patients in the rezafungin and caspofungin groups, respectively, were mechanically ventilated.

Most patients had a central venous catheter (CVC) at baseline (71.1% [27/38] in the rezafungin and 60.9% [28/46] in the caspofungin groups, respectively); approximately one-fifth of patients had a peripherally inserted central catheter. Among patients with a CVC at baseline, fewer patients in the rezafungin group (7.4% [2/27]) had this removed within 48 hours of first positive *Candida* culture compared with the caspofungin group (32.1% [9/28]). *Candida* species were similarly distributed across the two groups; the most frequently isolated species were *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis* complex.

Efficacy of Rezafungin Versus Caspofungin

At Day 30, 26.3% (10/38) and 21.7% (10/46) of patients in the rezafungin and caspofungin groups, respectively, were either known to have died or had unknown survival status (three patients had unknown status [rezafungin: one, caspofungin: two]). The treatment difference (95% CI) for Day 30 ACM mortality was 4.6% (−13.7, 23.5).

At Day 5, the global cure rate was 55.3% (21/38) and 43.5% (20/46) in the rezafungin and caspofungin groups, respectively (treatment difference [95% CI]: 11.8% [−9.7, 32.2]); by Day 14, this was 55.3% (21/38) and 50.0% (23/46), with a treatment difference of 5.3% (−16.1, 26.0; **Figure 3**). At Day 5, the proportion of patients with mycological eradication was 71.1% (27/38) and 50.0% (23/46) in the rezafungin and caspofungin groups, respectively, with a treatment difference (95% CI) of 21.1% (−0.2, 40.2); by Day 14, it was 63.2% (24/38) and 54.3% (25/46), with a treatment difference of 8.8% (−12.4, 29.0; **Figure 3**). Only one patient was classified as a relapse between Day 5 and Day 14: a patient in the caspofungin group had documented eradication at Day 5 but then had breakthrough candidemia on Days 9 and 11.

Median TTNBC was shorter in the rezafungin versus caspofungin group (23.9 hours vs 60.5 hours, respectively; $P = .094$ [nominal]; **Table 2, Figure 4**). At 24 hours following treatment initiation, NBCs were observed in 55.2% (16/29) and 27.3% (9/33) of patients in the rezafungin and caspofungin groups ($P = .0162$ [nominal]), respectively; at 48 hours, NBCs were observed in 58.6% (17/29) and 43.8% (14/32) of patients ($P = .2460$ [nominal]).

Safety

Most patients had ≥ 1 TEAE (92.1% [35/38] and 84.8% [39/46] in the rezafungin and caspofungin groups, respectively; **Supplemental Table S1**). Drug-related TEAEs were reported for five (13.2%) and three (6.5%) patients in the rezafungin and caspofungin groups, respectively. More than half of patients had at least one serious TEAE (55.3% [21/38] in the rezafungin group and 54.3% [25/46] in the caspofungin group). One patient in the rezafungin group had a serious drug-related TEAE (infusion-related reaction) while two serious drug-related TEAEs were reported in the caspofungin group (elevated transaminase levels and anaphylactic shock). The SAE reported in the rezafungin group occurred during the Day 3 placebo infusion and was therefore unlikely to be related to rezafungin. A small number of patients experienced abnormal clinical laboratory evaluations (6 [15.8%] in the rezafungin group and 6 [13.0%] in the caspofungin group).

DISCUSSION

In this pre-planned analysis of the Phase 3 ReSTORE study, we compared once-weekly rezafungin with once-daily caspofungin (followed by optional fluconazole) for the treatment of candidemia and/or IC in patients with a positive culture close to randomization. Our findings show comparable Day 30 ACM and Day 14 global response between rezafungin and caspofungin groups in this population. Because patients with a positive culture from a sample drawn >12 hours before randomization (blood) or >48 hours before randomization (other sites), who theoretically may have cleared their infection by the time of treatment initiation (either spontaneously or as a result of empiric therapy), were omitted from this analysis, this sub-population may represent a more challenging patient population than the primary ReSTORE population. *The safety and tolerability of rezafungin was comparable with caspofungin in this analysis and was consistent with previously published findings from ReSTORE [17] and for first-generation echinocandins [18, 20].*

The efficacy of rezafungin versus caspofungin for the treatment of candidemia and/or IC has been previously reported in the STRIVE and ReSTORE trials [16, 17, 21]. Numerically lower Day 30 ACM rates and numerically higher Day 14 overall cure rates were observed in patients in STRIVE who were treated with rezafungin versus caspofungin (4% vs 13% and 76% vs 67%, respectively) [16]. Primary data for ReSTORE demonstrated non-inferiority of rezafungin versus caspofungin for Day 30 ACM (24% vs 21%; treatment difference 2.4% [95% CI -9.7, 14.4]) and Day 14 global cure (59% vs 61%; weighted treatment difference -1.1% [95% CI -14.9, 12.7]) [17]. This subgroup analysis adds to these prior results reporting the efficacy of rezafungin in the treatment of candidemia and/or IC.

The differentiated stability and pharmacokinetic profile of rezafungin compared to other echinocandins supports a front-loaded, once-weekly dosing regimen [13, 22]. Front-loaded dosing may maximize the drug effect of rezafungin, as a result of its low clearance and long half-life, and the concentration-dependent activity of echinocandins [13, 22, 23]. Additionally, the high plasma concentrations afforded by the front-loaded administration of rezafungin may explain the higher concentrations of rezafungin versus micafungin seen in a murine intra-abdominal abscess model using humanized therapeutic doses of both echinocandins [24]. High rezafungin concentrations within the abscess were observed earlier and remained higher than micafungin concentrations even after 48 hours. The estimated concentration of rezafungin within the abscess also exceeded the mutant prevention concentration [14], thereby potentially reducing the risk of resistant mutant selection. The once-weekly dosing regimen has potential advantages versus daily dosing with first-generation echinocandins, such as fewer infusions, reduced need for peripherally inserted central catheter placement, fewer catheter-associated infections, lower costs, and increased compliance; lower costs and increased compliance may have particular relevance for patients needing long treatment courses [15, 17, 25, 26].

Early efficacy findings from this analysis, and those from the primary and pooled analyses of STRIVE and ReSTORE [16, 17, 21], are consistent with a potential clinical benefit of the front-loaded rezafungin dosing and resultant plasma exposure. *Clearance of candidemia was more rapid in patients treated with rezafungin when compared with caspofungin: TTNBC was numerically shorter and greater proportions of patients had NBC at both 24 and 48 hours in the rezafungin versus caspofungin group. Additionally, a higher proportion of patients had mycological eradication at Day 5 in the rezafungin versus caspofungin group. This may have important implications because early eradication of candidemia may avoid dissemination to distant sites and/or reduce the likelihood of emergence of resistance.*

Differences between rezafungin and caspofungin in early eradication were more pronounced in the present subgroup analysis of patients with a positive culture close to randomization compared with the primary analysis of ReSTORE [17]; median TTNBC was 23.9 hours versus 60.5 hours ($P = .094$; subgroup analysis) and 23.9 hours versus 27.0 hours ($P = .18$; primary analysis) for rezafungin versus caspofungin groups, respectively. Likewise, NBC at 24 hours was observed in 55.2% versus 27.3% (subgroup analysis) and 53.7% versus 46.2% (primary analysis) of patients receiving rezafungin versus caspofungin, respectively [17].

Echinocandins are the recommended first-line treatment for candidemia and IC [6, 7], based on trials that demonstrated their efficacy and improved clinical outcomes versus other antifungal drugs [18, 19, 27]. However, several studies have suggested that first-generation echinocandins may be underdosed [28], especially in critically ill patients [29]. The improved pharmacokinetic profile of rezafungin [11] may explain why the early treatment benefits versus caspofungin were more pronounced in these patients who had a positive *Candida* culture closer to the time of randomization, and hence potentially had more serious infections, when compared with the overall ReSTORE population [17].

The optimal timing of antifungal treatment remains a challenge in the management of patients with candidemia/IC; early and appropriate initiation of antifungal therapy has been demonstrated to impact final outcomes in patients with candidemia and IC, yet treatment is frequently initiated too late [30–34]. Furthermore, diagnostic challenges pose an obstacle to early and appropriate treatment initiation [6]. The results of this analysis focusing on patients with a positive *Candida* culture closer to randomization therefore provide further useful insight to guide and support prompt initiation of candidemia/IC treatment.

Limitations of the analysis include the small sample size of the subgroup population, which means that these findings should be interpreted with caution and that further investigation is needed. Nonetheless, the results presented here are from a pre-planned analysis of a randomized trial.

CONCLUSIONS

This pre-planned subgroup analysis supports previously described findings from ReSTORE and demonstrates the efficacy and safety of weekly rezafungin for the treatment of candidemia and/or IC in patients with a positive culture close to randomization, who may represent patients with more serious infections. ACM at Day 30, global cure at Day 14, and mycological eradication at Day 14 remained comparable between rezafungin and caspofungin groups, with potential early clinical effects, such as the more rapid clearance of *Candida* infection, associated with front-loaded rezafungin exposure.

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Data Sharing Statement: The study protocol is provided in the Appendix. Access to anonymized data can be requested by contacting Enquiries@napp.co.uk. Each request will be reviewed by the sponsor for scientific merit.

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Table 1. Baseline demographics and characteristics (mITT2 population^a)

	Rezafungin (400/200 (N=38)	Caspofungin (70/50 (N=46)
Age, mean $\pm$ SD (range), years	58.9 $\pm$ 14.11 (27, 87)	62.9 $\pm$ 14.55 (20, 87)
<65 years, <i>n</i> (%)	24 (63.2)	25 (54.3)
$\geq$ 65 years, <i>n</i> (%)	14 (36.8)	21 (45.7)
Gender, <i>n</i> (%)		
Male	26 (68.4)	27 (58.7)
Female	12 (31.6)	19 (41.3)
Race, <i>n</i> (%)		
White	26 (70.3)	27 (60.0)
Asian	9 (24.3)	16 (35.6)
African American or Black	2 (5.4)	1 (2.2)
Not reported	1	1
Final diagnosis, <i>n</i> (%)		
Candidemia	29 (76.3)	33 (71.7)
Invasive candidiasis ^b	9 (23.7)	13 (28.3)
Site of infection for invasive candidiasis, <i>n</i> (%)	<i>n</i> =9	<i>n</i> =13
Intra-abdominal (including peritoneal space) ^c	5 (62.5)	8 (61.5)
Catheter tip	0	1 (7.7)
Pancreas (swab)	0	1 (7.7)

Gallbladder – bile	1 (12.5)	0
Pancreatic liquid	0	1 (7.7)
Soft tissue	2 (22.2)	2 (15.4)
Body mass index, <i>n</i> (%) ^d		
<18.5 kg/m ²	4 (11.1)	7 (17.1)
≥18.5 to <25 kg/m ²	16 (44.4)	20 (48.8)
≥25 to <30 kg/m ²	3 (8.3)	9 (22)
≥30 to <40 kg/m ²	11 (30.6)	4 (9.8)
>40 kg/m ²	2 (5.6)	1 (2.4)
Modified APACHE II score ^{e,f}		
≥20, <i>n</i> (%)	5 (13.5)	11 (23.9)
<20, <i>n</i> (%)	32 (86.5)	35 (76.1)
Median (range)	13.0 (3–40)	13.0 (2–37)
ANC <500/μL, <i>n</i> (%)	4 (10.8)	4 (8.7)
Mechanically ventilated at baseline, <i>n</i> (%)	9 (23.7)	15 (32.6)
Peripherally inserted central catheter, <i>n</i> (%)	7 (18.4)	9 (19.6)
Central venous catheter, <i>n</i> (%)	27 (71.1)	28 (60.9)
Central venous catheter removed within 48 hours of first positive <i>Candida</i> culture, <i>n</i> (%)		
Yes	2 (7.4)	9 (32.1)
No	25 (92.6)	19 (67.9)
Parenteral nutrition, <i>n</i> (%)	0	1 (2.2)
Hemodialysis, <i>n</i> (%)	6 (15.8)	4 (8.7)
Received prior immunosuppressants, <i>n</i> (%)	6 (15.8)	3 (6.5)

Received prior norepinephrine, <i>n</i> (%)	6 (15.8)	4 (8.7)
<i>Candida</i> species ^g		
<i>Candida albicans</i>	17 (44.7)	21 (45.7)
<i>Candida glabrata</i>	8 (21.1)	13 (28.3)
<i>Candida tropicalis</i>	7 (18.4)	10 (21.7)
<i>Candida parapsilosis</i> complex	5 (13.2)	7 (15.2)
<i>Candida krusei</i>	2 (5.3)	2 (4.3)
<i>Candida dubliniensis</i>	2 (5.3)	0

^aPatients who had either: (1) a positive culture from blood drawn between 12 hours before and 72 hours after randomization; or (2) a positive culture from another normally sterile site between 48 hours before and 72 hours after randomization. All patients must have received at least one dose of study drug; ^bPatients who progressed from candidemia to invasive candidiasis based on radiological and/or tissue/fluid culture assessment through Day 14; ^cPatients with intra-abdominal candidiasis who had concomitant intra-abdominal bacterial infection were not excluded from the study; ^dTwo patients in the rezafungin group and five patients in the caspofungin group had missing body mass index data; ^eModified APACHE II score is a combination of APACHE II and Glasgow Coma Score and is calculated as APACHE II + (15 minus Glasgow Coma Score); ^fOne patient in the rezafungin group had missing APACHE II score data; ^gSome patients had multiple pathogens at baseline.

ANC, absolute neutrophil count; APACHE, Acute Physiology and Chronic Health Evaluation; mITT2, modified intention-to-treat 2; SD, standard deviation.

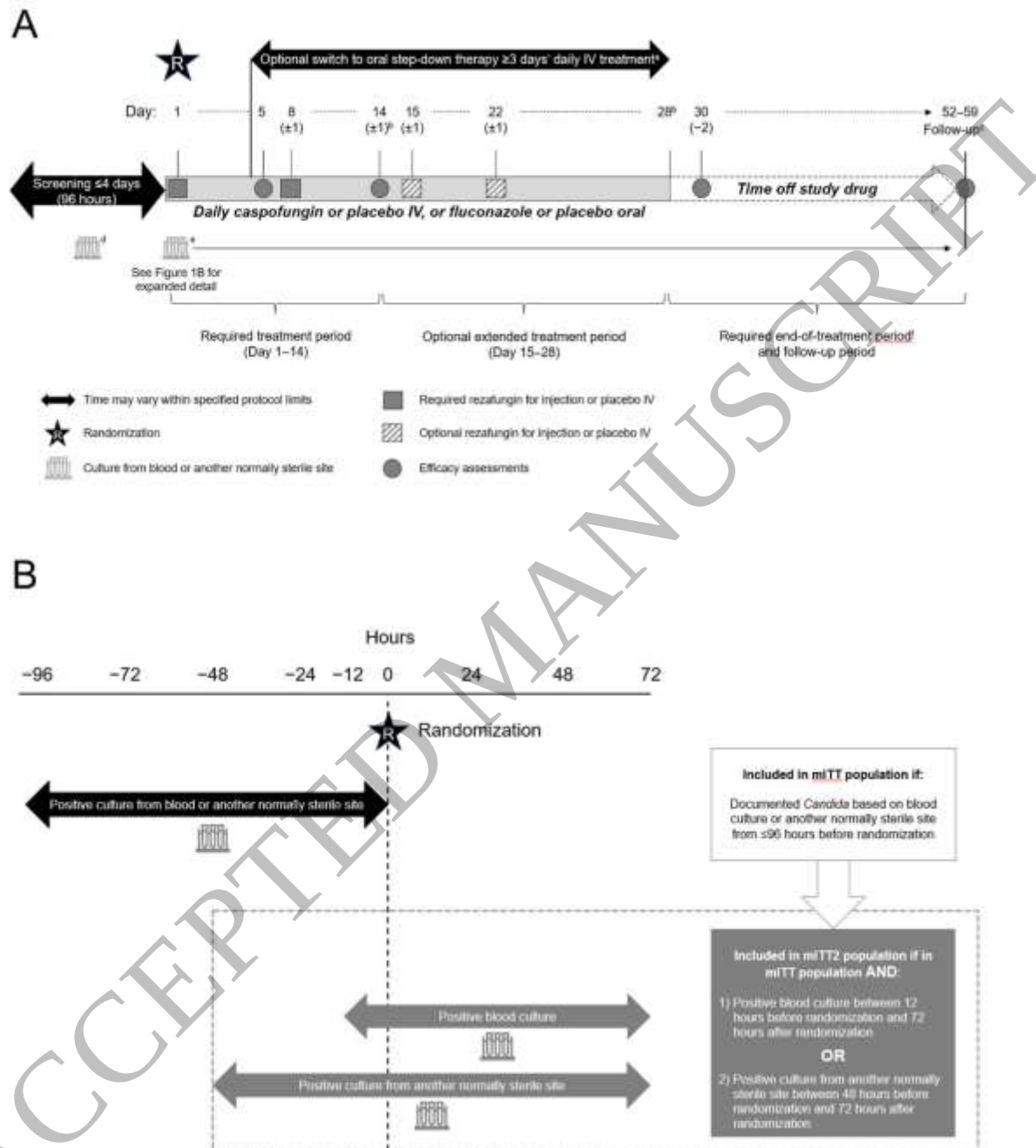
Table 2. Proportion of patients with negative blood culture after the first dose of study drug and time from the first dose of study drug to negative blood culture^a

		Rezafungin (400/200 (N=30) ^a	Caspofungin mg) (70/50 (N=35) ^a mg)
Patients with NBC ^b , <i>n</i> (%)		26/30 (86.7)	24/35 (68.6)
Patients censored ^c , <i>n</i> (%)		4/30 (13.3)	11/35 (31.4)
TTNBC, hours ^d	Median (95% CI)	23.9 (12.3, 90.3)	60.5 (27.0, 112.6)
	<i>P</i> -value ^d	0.094	
Patients with NBC ^b , <i>n</i> (%)			
	At 24 hours	16/29 (55.2)	9/33 (27.3)
	Patients censored ^c	1 (3.3)	2 (6.0)

	Rezafungin (400/200 (N=30) ^a	Caspofungin mg) (70/50 (N=35) ^a mg)
<i>P</i> -value ^e	0.0162	
At 48 hours	17/29 (58.6)	14/32 (43.8)
Patients censored ^c	1 (3.4)	3 (5.7)
<i>P</i> -value ^e	0.2460	

^aOnly patients with a positive blood culture close to randomization and who received ≥ 1 dose of study drug were included in this analysis; ^bWithout subsequent positive culture; ^cPatients were censored if they received an alternative antifungal (ie, other than study drug) for the treatment of the candidemia, died, or were lost to follow-up prior to having the negative blood culture; ^dNominal, from log rank test; ^eNominal, from chi-squared test.

CI, confidence interval; NBC, negative blood culture; TTNBC, time to first negative blood culture.

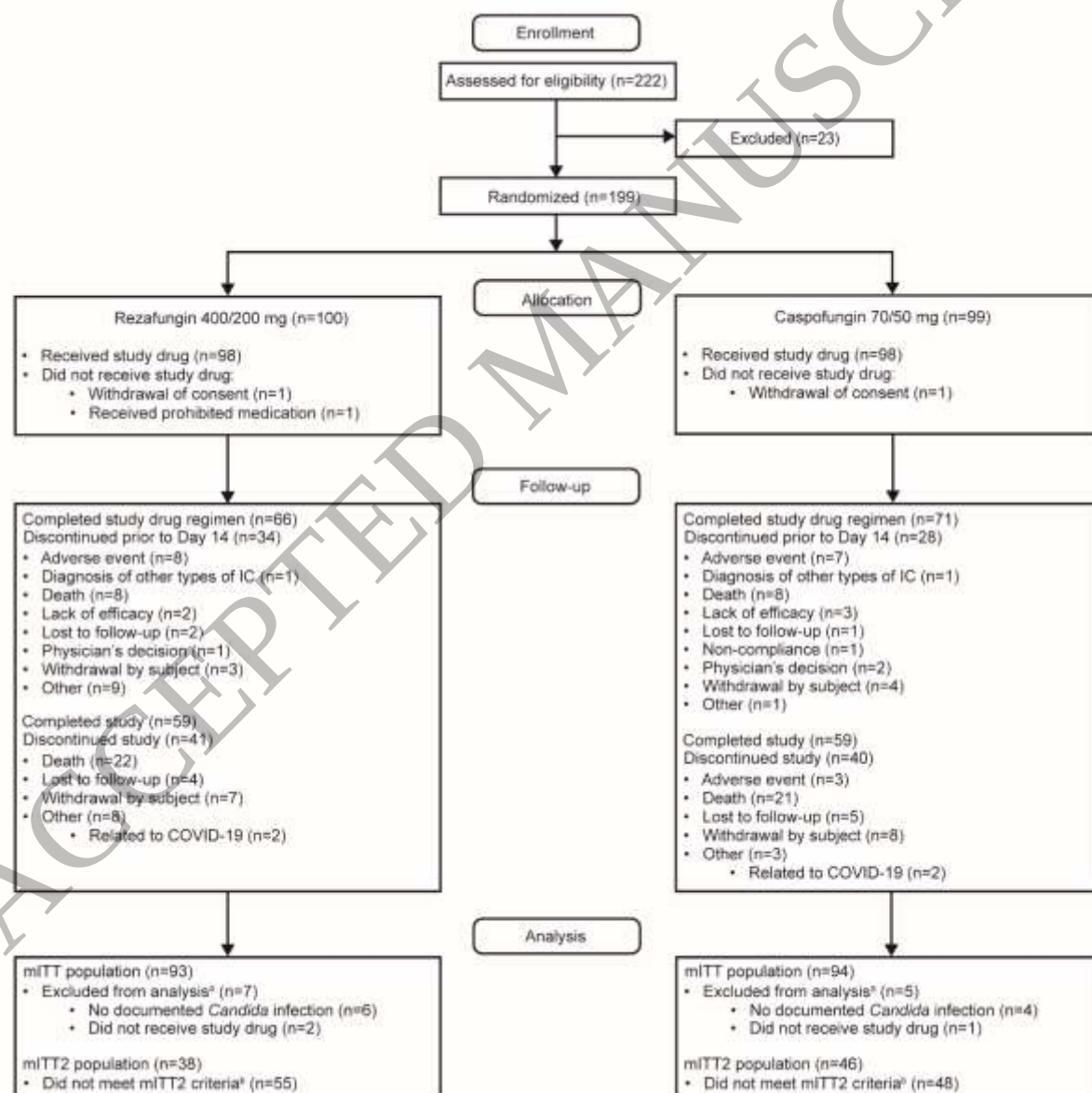
Figure 1. (A) ReSTORE study design. (B) mITT and mITT2 population definitions

^aAfter ≥ 3 days of IV study drug (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever was greater), patients were permitted to switch to oral step-down therapy so long as all criteria specified in the protocol were met. Patients who were switched to oral step-down therapy could switch back to IV study drug therapy in the event of the development of a condition that prevented the subject from taking oral medication (eg, pancreatitis, urgent surgery), but were not permitted to switch back to IV study drug therapy for relapse of candidemia/IC or for intolerance or toxicity due to study drug; ^bThe last required dose of study drug was on Day 14 and the last possible dose of study drug was on Day 28; ^cFollow-up occurred between Days 52 and 59. Patients who stopped study drug early (ie, clinical failures) and required a change in antifungal therapy to treat candidemia

and/or IC were permitted to have an earlier follow-up visit occurring ≥ 30 days from the last weekly dose of IV rezafungin or IV placebo; ^dIf the positive blood culture used to qualify the patient for the study (i.e., screening culture) was drawn >12 hours prior to randomization, an additional set of blood cultures was to be obtained ≤ 12 hours before randomization to determine whether patients were still candidemic at the time of enrolment; ^eBlood cultures were to be repeated daily (preferred) or every other day until the first negative blood culture result for *Candida* spp. with no subsequent positive culture (in cases when one or more samples were drawn and cultured after the first negative culture was available); ^fPatients completed an end-of-treatment visit ≤ 2 days after the last dose of study drug. All safety assessments were completed at the end-of-treatment visit. Efficacy assessments were also to be completed at the end-of-treatment visit.

IC, invasive candidiasis; IV, intravenous; mITT, modified intention-to-treat; mITT2, modified intention-to-treat 2.

Figure 2. Patient disposition in ReSTORE indicating mITT and mITT2 analysis populations

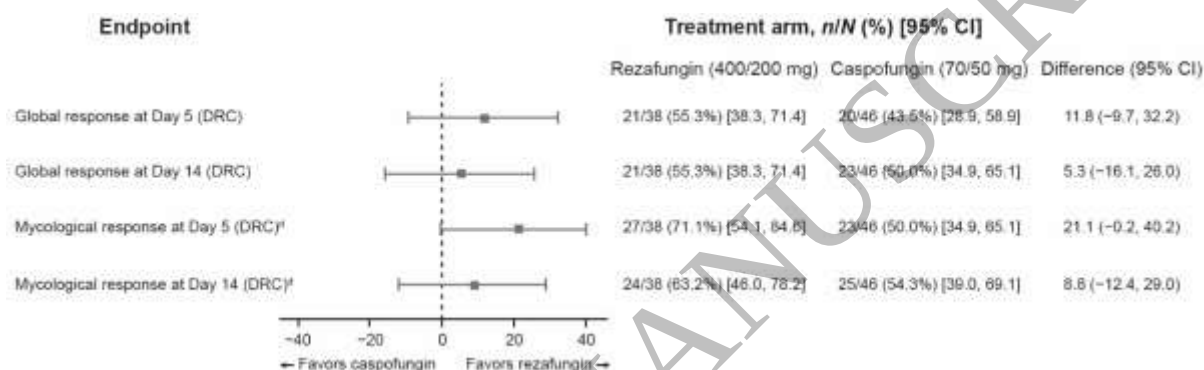


^aSome patients met multiple reasons for exclusion and are included with each exclusion reason met; ^bPatients with either: (1) a positive blood culture drawn between 12 hours before and 72 hours after randomization; or (2) a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization and who received ≥ 1 dose of study drug were included in the mITT2 analysis.

Figure modified from Thompson GR III 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;401:49–59 with permission from Elsevier. © 2022 Elsevier Ltd.

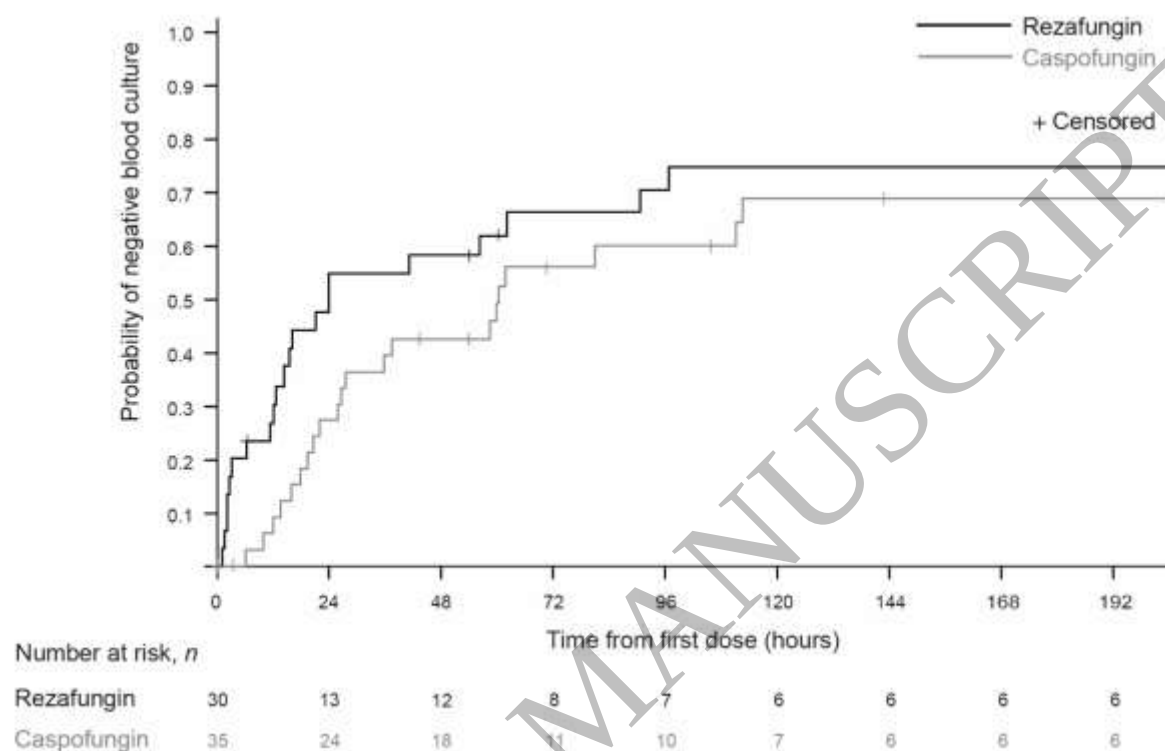
mITT, modified intention-to-treat; mITT2, modified intention-to-treat 2.

Figure 3. Global response^a and mycological eradication^b at Days 5 and 14 in patients treated with rezafungin (400 mg/200 mg) or caspofungin (70 mg/50 mg) (mITT2 population^c)



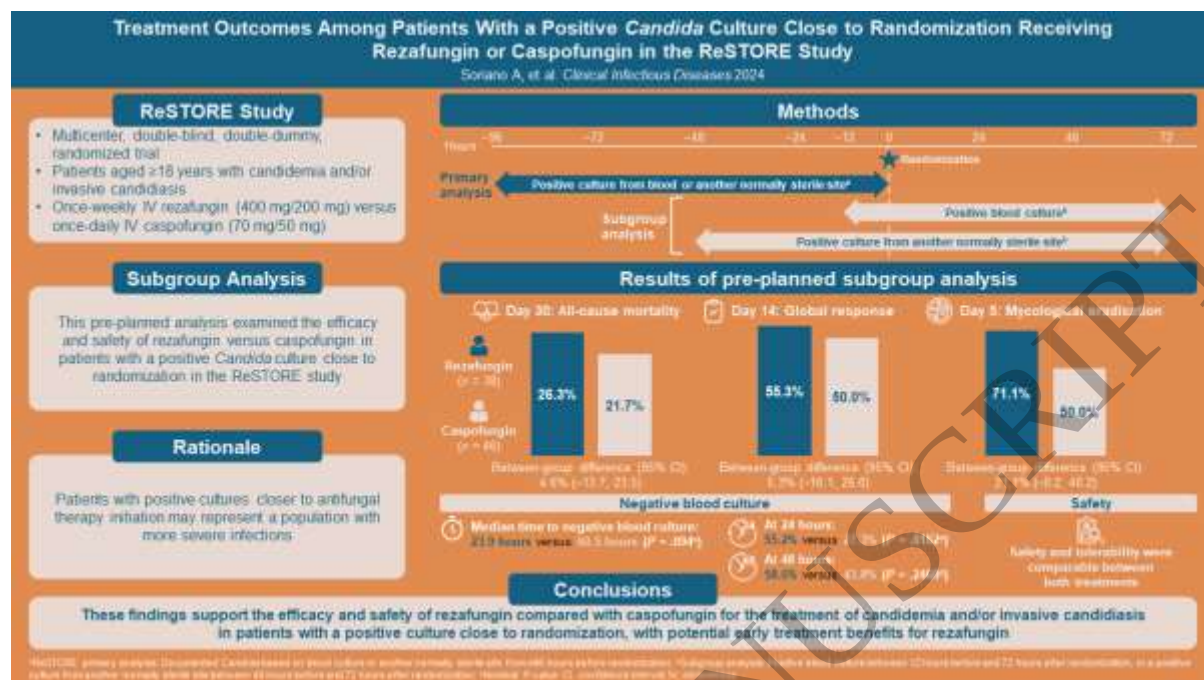
^aBased on clinical cure (as assessed by the investigator, radiological cure [for patients with invasive candidiasis], and mycological eradication) confirmed by an independent, blinded DRC; ^bFor patients with a positive blood culture at baseline, mycological eradication was defined as a negative blood culture on or prior to the day of assessment (ie, Day 5 or 14) with no subsequent positive culture. For patients with a positive culture at baseline from a normally sterile site other than blood, it was either documented (a negative culture from the same normally sterile site on or prior to the day of assessment [ie, Day 5 or Day 14]) or presumed (assessment of clinical and radiological cure [for those with evidence of disease on imaging at baseline] if a specimen from the infected site was not available); ^cPatients with either: (1) a positive blood culture drawn between 12 hours before and 72 hours after randomization; or (2) a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization and who received ≥ 1 dose of study drug; ^dThese were not mutually exclusive outcomes; eradication at Day 5 did not guarantee eradication at Day 14. Only one patient was classified as a relapse between Day 5 and Day 14: a patient in the caspofungin group had documented eradication at Day 5 but then had breakthrough candidemia on Days 9 and 11. CI, confidence interval; DRC, data review committee; mITT2, modified intention-to-treat 2.

Figure 4. Time to negative blood culture in patients treated with rezafungin (400 mg/200 mg) or caspofungin (70 mg/50 mg) (mITT2 population^a)



^aPatients with either: (1) a positive blood culture drawn between 12 hours before and 72 hours after randomization; or (2) a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization and who received ≥ 1 dose of study drug.

mITT2, modified intention-to-treat 2.



Graphical Abstract

CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS⁴⁻⁹

Treatment-naïve resistance rates, with up to **3 years** of evidence⁵⁻⁷

0%
(n=0/1,885)^{*4}
REAL-WORLD EVIDENCE

0.1%
(n=1/953)^{**1,11,11,12}
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years** of evidence¹⁻³

0.03%
(n=10/35,888)^{*4}
REAL-WORLD EVIDENCE

0%
(n=0/615)^{†1,11,11,12}
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY¹⁰

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:



NO PRIOR TREATMENT EXPERIENCE¹³



NO BASELINE RESISTANCE TESTING¹³

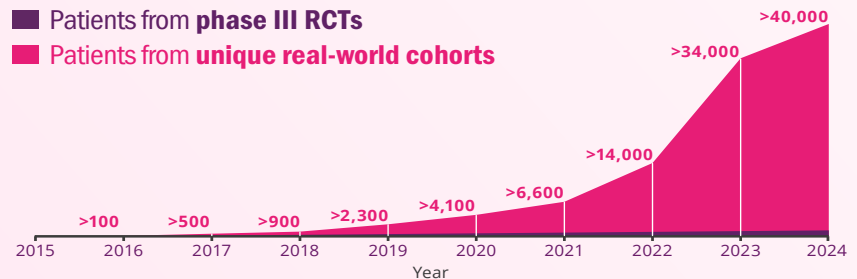


HIGH BASELINE VIRAL LOAD
(>100,000 copies/mL and even >1M copies/mL)^{6,13}



LOW CD4 + COUNT
(≤200 cells/mm³)¹³

■ Patients from **phase III RCTs**
■ Patients from **unique real-world cohorts**



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

LEARN MORE ➔

DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.¹³

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

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ABBREVIATIONS

3TC, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).⁵⁻⁷

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).¹³

‡STAT is a phase IIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.⁶

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.⁷ Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).^{8,9}

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).^{8,13}

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).⁹