Venetoclax and Ibrutinib Pharmacokinetics Unaltered when Coadministered with Rezafungin

Taylor Sandison, MD, MPH
Chief Medical Officer

Abstract #02227

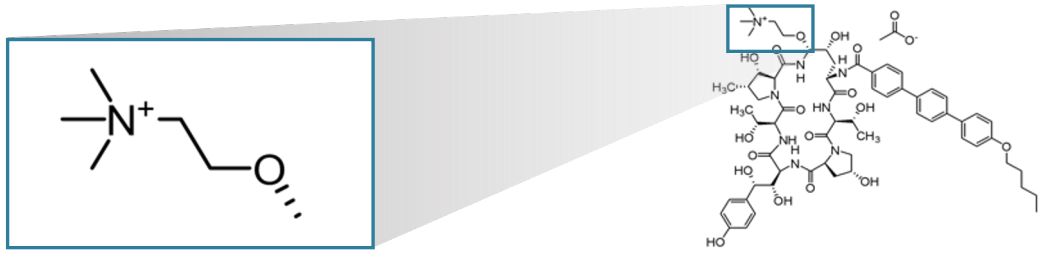
Lisbon, Portugal
23–26 April 2022
32nd ECCMID
EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Disclosures

- This presentation reports data from a Phase 1 study that was funded by Cidara Therapeutics
- All authors are employees and shareholders of Cidara Therapeutics

Rezafungin: A Novel Once-Weekly Echinocandin With Distinctive Properties in Phase 3

Structural Modification Increases Stability and Yields Unique Chemical & Biological Properties



Properties	Evidence
Long-acting PK	Once-weekly dosing as in rezafungin Phase 3 clinical trials[a]
Front-loaded plasma drug exposure	Efficacy: Shorter time to negative blood culture
Broad spectrum activity	*In vivo* efficacy vs *Candida*, *Aspergillus*, and *Pneumocystis* spp.
Observed absence of toxic degradation products	Safety: No observed hepatotoxicity
No DDIs and favorable hepatic and renal safety	Compatibility with commonly used medications

[a]ReSTORE: 1st-line treatment of candidemia and/or invasive candidiasis (completed; study sites in China still recruiting for submission of rezafungin to the Center for Drug Evaluation in China). ReSPECT: 1st-line prophylaxis against invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp., in allogeneic blood and marrow transplant patients (ongoing).

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Rezafungin Phase 3 Program: Two Global, Double-Blind, Randomized Trials vs SOC

	PHASE 3 TREATMENT TRIAL	PHASE 3 PROPHYLAXIS TRIAL
	ReSTORE	ReSPECT
TARGET INDICATION	Treatment of Candidemia and Invasive Candidiasis	Prophylaxis Against IFD caused by *Aspergillus*, *Candida* & *Pneumocystis* in Allogeneic Blood and Marrow Transplant Patients
TRIAL SIZE	187 Patients[a,1] (20% noninferiority margin)	462 Patients[2] (12.5% noninferiority margin)
PRIMARY ENDPOINT	Day 30 All-Cause Mortality (FDA) Day 14 Global Response (EMA)	Day 90 Fungal-Free Survival
COMPARATOR	Caspofungin with Optional Step Down to Fluco	Fluconazole, Posaconazole (if GVHD) and Bactrim

GVHD=graft versus host disease; IFD=invasive fungal disease; SOC=standard of care.

[a]Study sites in China are still recruiting patients for submission of rezafungin to the Center for Drug Evaluation in China.

1. Thompson GR III, et al. 2022 ECCMID LB0244. **2.** Clinicaltrials.gov NCT04368559 accessed 11 Apr 2022.

Increasing Patient Population with Higher Risk of IFD Underscores Need for Safe, Effective Antifungals

- The overall patient population vulnerable to IFD is growing[1-5]
  - Elderly, critically ill (now including severe Covid)
  - Post-surgical, post-transplantation, patients on immunosuppressive therapy
- Antifungal prophylaxis is often used for such patients[6,7] but most commonly used antifungal agents (eg, azoles) can alter the pharmacokinetics of other drugs, including commonly used cancer agents[8,9]
  - CYP3A4 interactions with anastrazole, exemestane, paclitaxel, irinotecan, letrozole, docetaxel, tamoxifen

DDI=drug-drug interaction; IFD=invasive fungal disease.

1. Wisplinghoff et al. *Clin Infect Dis.* 2004;29:309-17. **2.** Andes et al. *Clin Infect Dis.* 2012;54:1110-22. **3.** Magill et al. *N Engl J Med.* 2014;370:1198-208. **4.** Tsay et al. *Clin Infect Dis.* 2020;71:e449-e453. **5.** Seagle et al. *Clin Infect Dis.* 2022;74:802-11. **6.** Chau et al. *Intern Med J.* 2014;44:1364-88. **7.** Mellinghoff et al. *Ann Hematol.* 2018;97:197-207. **8**. Agarwal et al. *Clin Ther*. 2017;39:359-367. **9.** Alzghari et al. *J Oncol Pharm Pract.* 2017;23:476-80.

Potential Complications Between Current Antifungal Agents and Newer Therapies Further Underscore Unmet Needs

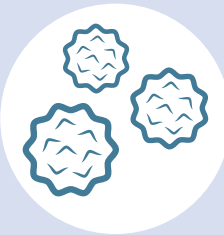
DDIs are common and may preclude optimal treatment

- DDIs with newer agents may lead to[1-6]:
  - Need to reduce dose of primary treatment, such as venetoclax and ibrutinib
  - Need for TDM
  - Delay or discontinuation of antifungal prophylaxis
- Azole-based prophylaxis was discontinued due to toxicity in 14% of patients with newly diagnosed AML treated with venetoclax-containing regimens[2]
  - Mostly hepatotoxicity
  - Also, QTc prolongation, hallucinations, rash, neuropathy, arthralgias, and GI upset

Kinase inhibitors

BTK (eg, Imbruvica)
mTOR (eg, Afinitor)
JAK (eg, Jakafi, Xeljanz)
BCR (eg, Venclexta)
Src (eg, Bosulif, Sprycel)
PI3Kδ (eg, Zydelig)

Immunotherapies



PD-1 (eg, Opdivo, Keytruda)
PD-L1 (eg, Tecentriq)
CTLA-4 (eg, Yervoy)
Interleukins (eg, Aldesleukin)
CAR-T cell (eg, Kymriah, Yescarta)
B cell (eg, Rituxan, Gazyva)

with more to come…

BCR=B-cell antigen receptor; BTK=Bruton's tyrosine kinase; CAR=Chimeric antigen receptor; CTLA-4=Cytotoxic T-lymphocyte antigen-4;JAK=Janus kinase; mTOR=Mammalian target of rapamycin; PI3Kδ=Phosphoinositide 3-kinase delta isoform; PD-1=Programmed cell death protein 1; PD-L1=Programmed death-ligand 1; TDM=therapeutic drug monitoring; TKI=tyrosine kinase inhibitor.

1. Chamilos et al. *Clin Infect Dis.* 2018;66:140-8 **2.** Rausch et al. *Clin Infect Dis.* 2022:ciac230 **3.** Kyi et al. *J Immunother Cancer*. 2014;2:19. **4.** Lindsay et al. *Curr Opin Infect Dis*. 2019;32:538-45. **5.** Mellinghoff et al. *Ann Hematol*. 2018;97:197-207. **6.** Reinwald et al. *Biomark Insights*. 2016;10(Suppl 3):55-68.

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Phase 1 Data

Rezafungin Demonstrated No Notable Drug-Drug Interactions (DDIs)

Drug Interaction Study in Healthy Adults

Drug	Possible Mechanism	Observations	Suggested Action
Tacrolimus	CYP3A4, P-gp	↔ C_{max} ↓ AUC ~15%	No change in dose
Repaglinide	CYP2C8, OATP	↔ C_{max} ↑ AUC ~15%	No change in dose
Metformin	OCT, MATEs	↔ C_{max} ↔ AUC	No change in dose
Rosuvastatin	BCRP, OATP	↑ C_{max} ~12% ↑ AUC ~15%	No change in dose
Pitavastatin	OATP	↔ C_{max} ↔ AUC	No change in dose
Caffeine	CYP1A2	↔ C_{max} ↔ AUC	No change in dose
Efavirenz	CYP2B6	↔ C_{max} ↔ AUC	No change in dose
Midazolam	CYP3A	↔ C_{max} ↔ AUC	No change in dose
Digoxin	P-gp	↔ C_{max} ↔ AUC	No change in dose

Single-center, open-label trial (N=26). Substrate drugs dosed alone for 3 weeks, then with rezafungin for 3 weeks.[1]

No dose adjustments required for these commonly used drugs when rezafungin is co-administered

AUC=area under the curve; BCRP=breast cancer resistance protein; C_{max}=maximum plasma concentration; CYP=cytochrome P450; MATEs=multidrug and toxin extrusion protein; OATP=organic anion transporting polypeptides; OCT=organic cation transporter; P-gp=P-glycoprotein.

1. Ong, et al. EBMT19 2019; poster B196.

Lisbon, Portugal 23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Study Background and Objective

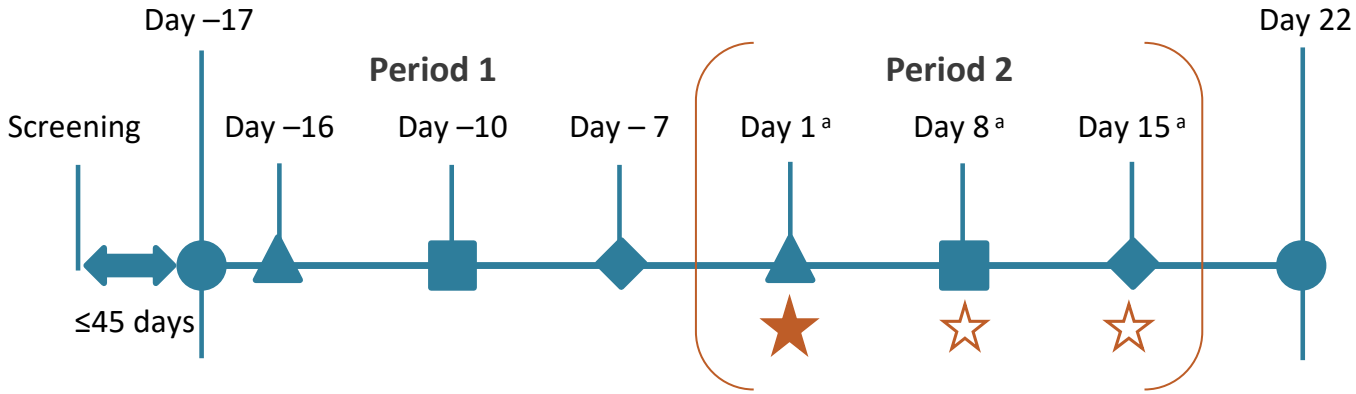
- Following a previous Phase 1 study of rezafungin against common/sensitive drug substrates for a variety of drug metabolizing enzymes and transporter proteins, this study was conducted to evaluate the effect of rezafungin on increasingly used anticancer agents, including venetoclax and ibrutinib

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

DDI Study Design

Open-Label Study in Healthy Adults

- 32 healthy inpatients (16 male [Group 1] and 16 female [Group 2])
- Ibrutinib and venetoclax each administered alone and with rezafungin IV (400 mg then 200 mg once weekly)
- Suitable washout periods between dosing
- Plasma concentrations of ibrutinib and venetoclax determined using validated LC-MS/MS methodologies



Note: There is no Day 0 (Day 1 follows Day –1).

[a] Coadministered drugs given orally ≤2 minutes after the start of rezafungin IV.

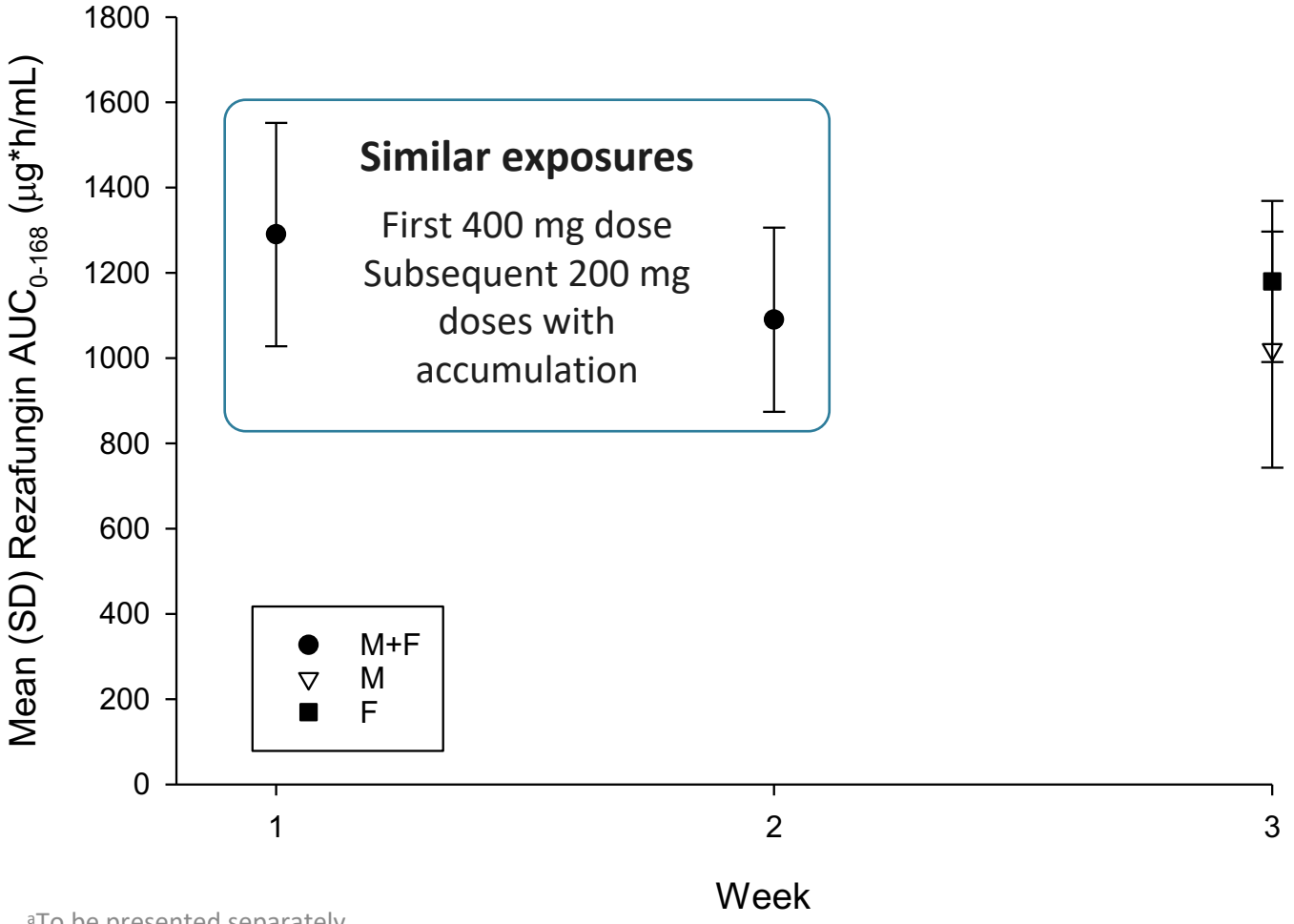
- CRU inpatient stay (check-in Day -17, check-out Day 22)
- Cyclosporine 200 mg (Groups 1 and 2)
- **Ibrutinib 280 mg** (Groups 1 and 2)
- Mycophenolate mofetil 500 mg (Group 1) or **Venetoclax 50 mg** (Group 2)
- Rezafungin IV 400 mg
- Rezafungin IV 200 mg

Ibrutinib and venetoclax doses were markedly reduced to decrease physiological effect but allow for PK assessment

CRU=clinical research unit; LC-MS/MS=liquid chromatography with tandem mass spectrometry.

Result: Rezafungin PK as Expected – No Differences in Rezafungin Exposure with ConMeds

Weekly Rezafungin AUC for 400 mg Followed by 200 mg/Week



As seen in Population PK modeling[a]

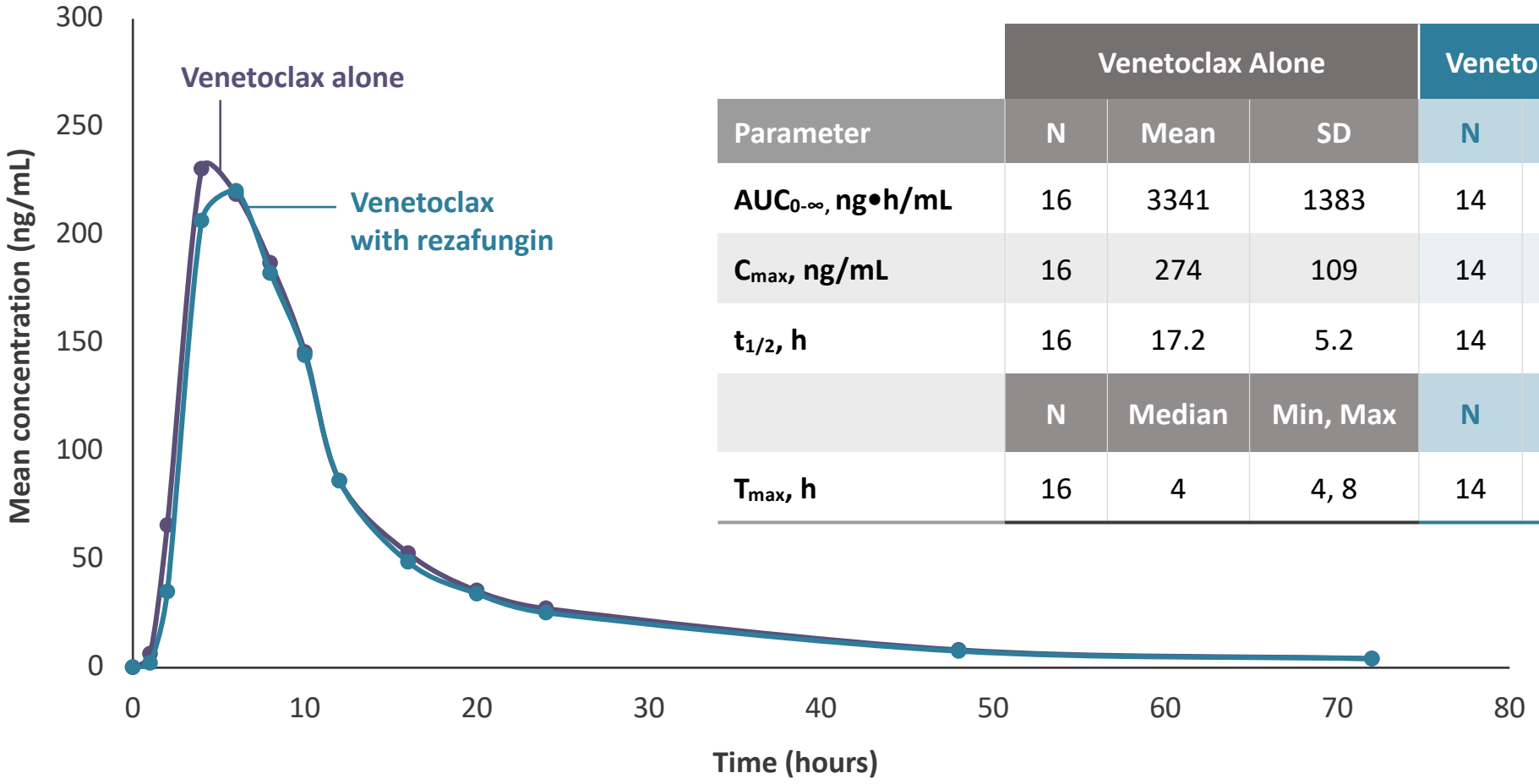
- Sex is not significant covariate
- Albumin and BSA are significant covariates in the model
- Slightly higher exposure in females may be due to underlying BSA differences

[a]To be presented separately.
AUC=area under the curve; BSA=body surface area; F=females; M=males; PK=pharmacokinetics.

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Result: No Clinically Meaningful DDIs between Venetoclax and Rezafungin

Venetoclax concentration over time

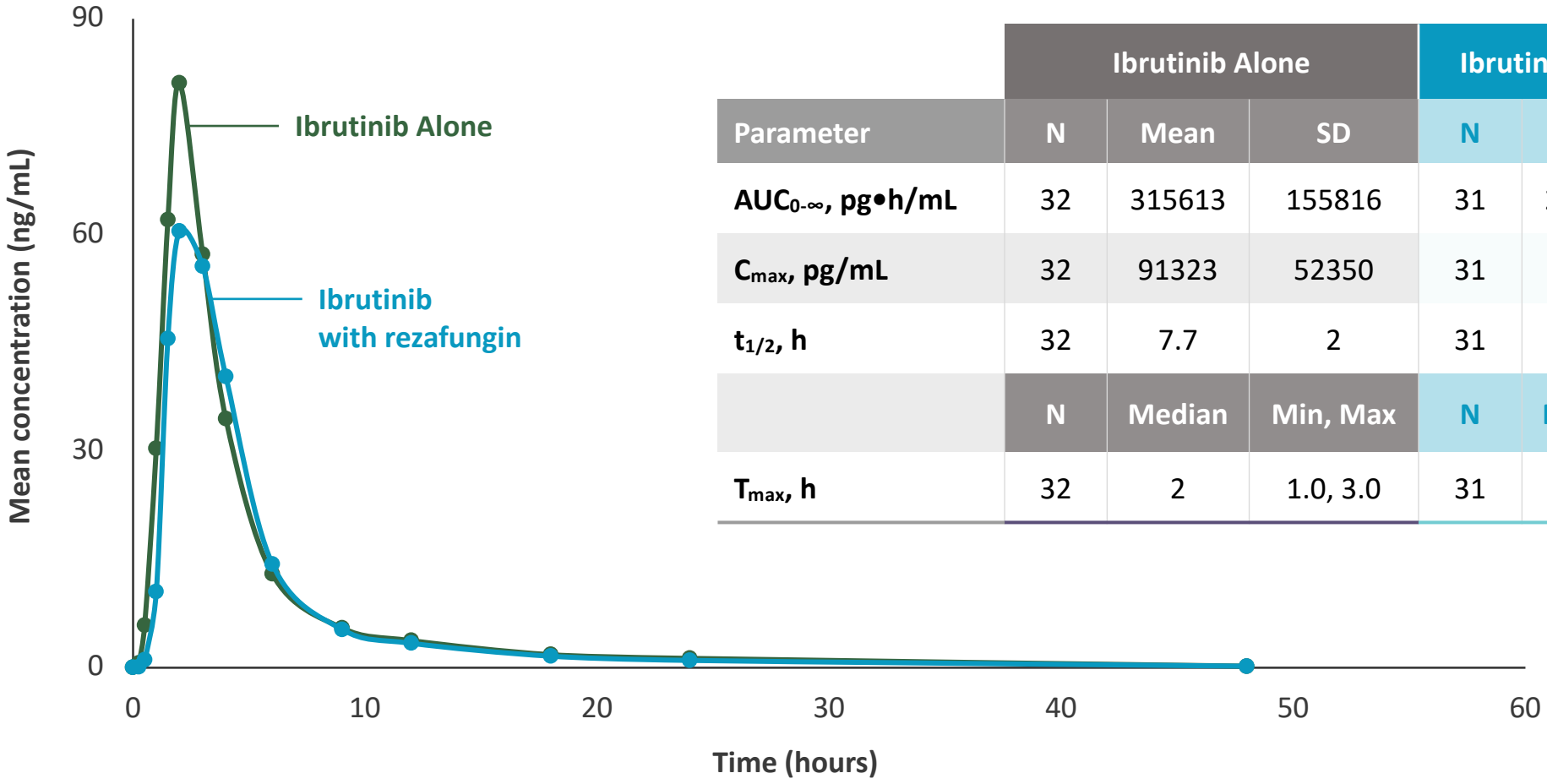


Pharmacokinetics of Venetoclax ± Rezafungin

	Venetoclax Alone			Venetoclax with Rezafungin		
Parameter	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
$AUC_{0-\infty}$, ng•h/mL	16	3341	1383	14	2819	1116
C_{max}, ng/mL	16	274	109	14	246	90
$t_{1/2}$, h	16	17.2	5.2	14	16	4.8
	N	**Median**	**Min, Max**	**N**	**Median**	**Min, Max**
T_{max}, h	16	4	4, 8	14	6	4, 10

Result: No Clinically Meaningful DDIs between Ibrutinib and Rezafungin

Ibrutinib concentration over time



Pharmacokinetics of Ibrutinib ± Rezafungin

	Ibrutinib Alone			Ibrutinib with Rezafungin		
Parameter	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
$AUC_{0-\infty}$, pg•h/mL	32	315613	155816	31	286435	151867
C_{max}, pg/mL	32	91323	52350	31	80013	47021
$t_{1/2}$, h	32	7.7	2	31	7.8	2.1
	N	**Median**	**Min, Max**	**N**	**Median**	**Min, Max**
T_{max}, h	32	2	1.0, 3.0	31	2	1.5, 4.0

Result: No Safety Findings of Concern

TEAE by drug

Number of Subjects with a TEAE, n (%)

Drug	Period 1 (Alone)	Period 2 (w/Rezafungin)
Ibrutinib	2 (5.9)	1 (3.1)
Venetoclax	2 (5.9)	6 (18.8)

- No SAEs or discontinuations due to AE
- Majority of AEs were mild to moderate; one severe AE*

*Severe AE: abdominal pain considered related to administration of rezafungin and venetoclax

- Started on Day 16, ~1 day after coadministration of both drugs
- Subject was transported but not admitted to hospital that day; underwent ultrasounds and CT scan; received ketorolac tromethamine and morphine sulfate IV
- Subject returned to CRU that evening with diagnosis of “gas in the intestines”
- Event considered resolved ~2 days from onset

CT=computed tomography.

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Conclusions

- DDIs due to CYP3A4 interactions between azoles and treatments for hematologic malignancies and/or GVHD may lead to down-dosing, such as venetoclax and ibrutinib, or avoiding antifungal prophylaxis altogether
- Previous DDI study of rezafungin showed no meaningful interactions with commonly used drugs
- The present DDI study showed that no dose adjustments of either venetoclax or ibrutinib are necessary when given in combination with rezafungin
- Rezafungin is a novel once-weekly echinocandin in Phase 3 development for treatment of candidemia/invasive candidiasis and for prevention of IFD caused by *Candida*, *Aspergillus*, *and Pneumocystis* spp.

Rezafungin Presentations at ECCMID - 25 April 2022

8:30 WEST
Session "*Emerging Clinical Data and Interventional Studies*"

Latebreaker: Results from Integrated Analysis of Rezafungin Ph2/Ph3 Trials

12:00 WEST
Poster Hall and Online

Latebreaker: Results from ReSTORE, the Ph3 Trial of Rezafungin in the Treatment of Candidemia and Invasive Candidiasis

Lisbon, Portugal
23–26 April 2022
32nd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES