Clinical assessment of mocravimod as a victim of drug-drug interactions via CYP3A4 metabolism and transporters

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Background

Mocravimod (MOC), a novel sphingosine-1-phosphate receptor (S1PR) modulator in phase 3 development in patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplantation (allo-HCT), is predominantly metabolized via the cytochrome (CYP)3A4 pathway based upon in vitro data. The therapeutic effect is prevention of lymphocyte egress from lymphoid organs. MOC and its active metabolite mocravimod-phosphate (MOC-P) is a victim of BCRP but not of OAPT1B1 or OATP1B3 transporters. Preliminary pharmacokinetic (PK) modeling of phase 1b data suggested that CYP3A4 inhibitors and cyclosporin (CsA) could increase exposure to MOC and MOC-P significantly. Given the co-administration of MOC with CYP3A4 inhibitors (e.g. azoles and CsA) in allo-HCT patients, two phase 1 studies were conducted to evaluate the drug-drug interactions (DDI) of MOC in combination with itraconazole (ITZ) or CsA.

Methods

Both studies consisted of 2 treatment periods and a washout period of at least 4 weeks (Fig 1). In period 1, healthy volunteers (HV) received a 3-mg MOC dose in the morning of Day 1 after a standard breakfast. In period 2, a daily dose of 200 mg ITZ after a standard breakfast was given until Day 13. On day 5, the HV received a standard breakfast, their daily ITZ dose, followed by a 3-mg MOC dose 60 minutes after the ITZ dose. Or, in period 2, twice daily dosing of 100 mg CsA was given until Day 7. On day 2, the HV received CsA dose, followed by a 3-mg MOC dose 60 minutes after the CsA dose.

Figure 1: A) ITZ study design B) CsA study design
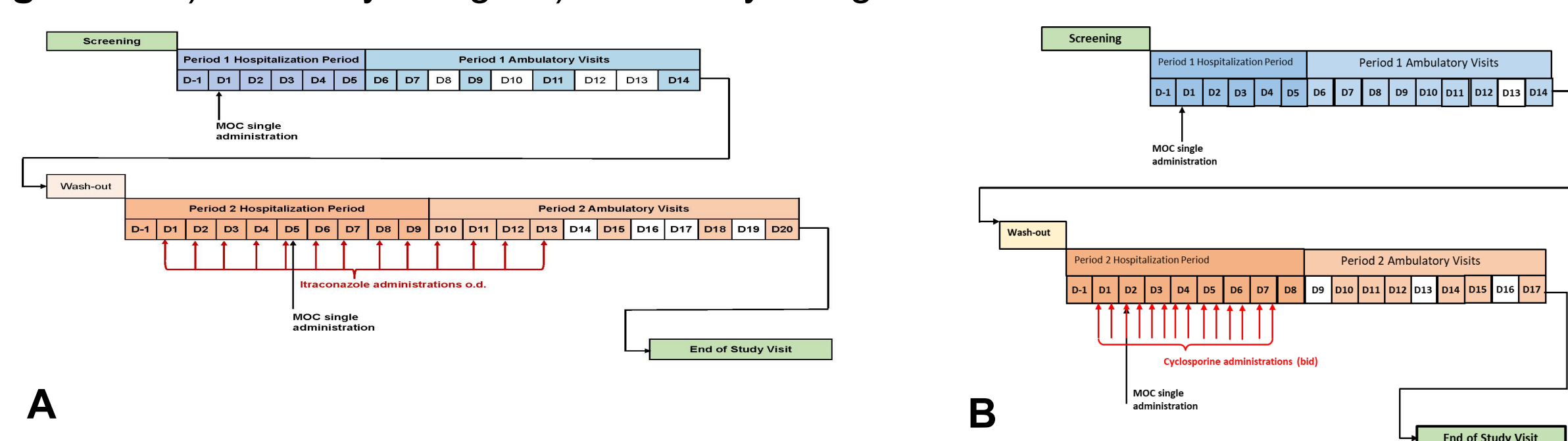
Blood samples were collected over 360 hours for the determination of MOC and its active metabolite MOC-P. Both were determined in whole blood using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Both have long half-lives of ~110 hours and therefore AUC_{0-inf} was determined using population pharmacokinetic (popPK) non-linear mixed effect modeling in NONMEM. Previously developed MOC and MOC-P models were taken as base models. Based on the obtained individual PK estimates, the individual AUC_{0-inf} for MOC and MOC-P, in the absence and presence of ITZ, were derived. Ratios of geometric least square (LS) means and 90% CIs were constructed for AUC_{0-inf} and C_{max}. Safety was assessed by monitoring AEs, clinical laboratory parameters, vital signs, and ECGs.

In the CsA study, pulse rate (PR) for PD analysis was measured as part of vital signs assessments, and at additional timepoints (0,0.5,1,2,3,4,6,8,10,12 and 24 hrs) Nadir of PR ($PR_{nadir(0-24)}$) and area under the effect curve ($AUE_{(0-24)PR}$) based on trapezoidal rule on nominal times per individual were calculated.

Table 2: PK Results

ITZ Study (N=19)				
Analyte	Parameter	MOC 3 mg + ITZ 200 mg (Test)	MOC 3 mg (Ref)	GMR% (90% CI)	Intra-patient variability CV%
MOC	C_{max}	1.16	1.17	**99.42 (91.61, 107.89)**	14.61
MOC	AUC_{0-inf}	152.41	137.55	**110.80 (103.89, 118.17)**	11.48
MOC-P	C_{max}	1.07	1.17	**92.21 (84.50, 100.63)**	15.61
MOC-P	AUC_{0-inf}	167.38	160.57	**104.24 (97.48, 111.48)**	11.97

CsA Study (N=19)				
Analyte	Parameter	MOC 3 mg + CsA 100 mg (Test)	MOC 3 mg (Ref)	GMR% (90% CI)	Intra-patient variability CV%
MOC	C_{max}	0.88	0.77	**114.53 (109.54 – 119.75)**	7.94
MOC	AUC_{0-inf}	144.80	110.37	**131.20 (124.47 – 138.30)**	9.39
MOC-P	C_{max}	1.81	0.97	**187.42 (166.30 – 211.21)**	21.49
MOC-P	AUC_{0-inf}	177.79	121.46	**146.38 (134.66 – 159.13)**	14.92

AUC_{0-inf}: area under the blood concentration time curve from time 0 to time infinity; C_{max}: maximum blood concentration; CI: confidence interval; CsA: cyclosporine; CV%: coefficient of variation; GMR: geometric mean ratio; ITZ: itraconazole; MOC: mocravimod; MOC-P: mocravimod-phosphate

In total, 46 subjects were enrolled (25 in ITZ and 21 in CsA study). Both studies had 19 completers each. Baseline characteristics were typical for a healthy population.

Figure 2: Mean PK blood concentration-time profiles of MOC and MOC-P
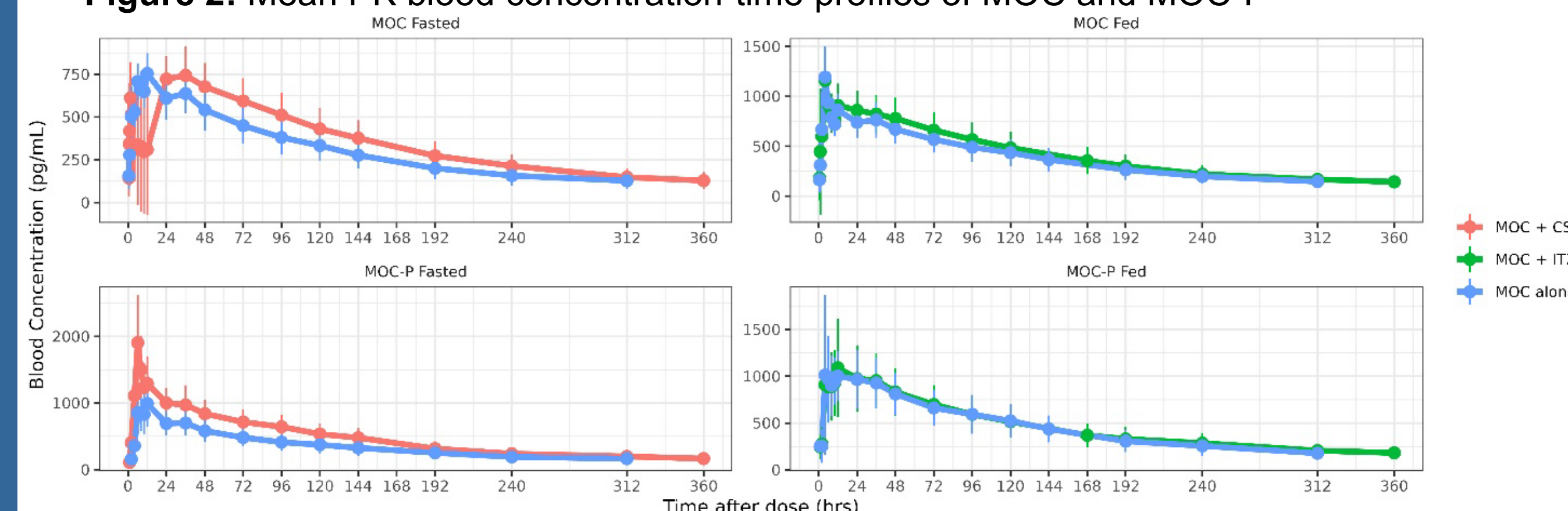
Population PK modeling for CsA as covariate

MOC: Covariate of CsA on clearance and zero-order bioavailability (F_{abs0}) was evaluated. No effect of CsA on clearance. The estimated value of the relative bioavailability under the influence of CsA co-administration was increased by an approximate 18% (95% confidence interval: 8% to 29%) for MOC.
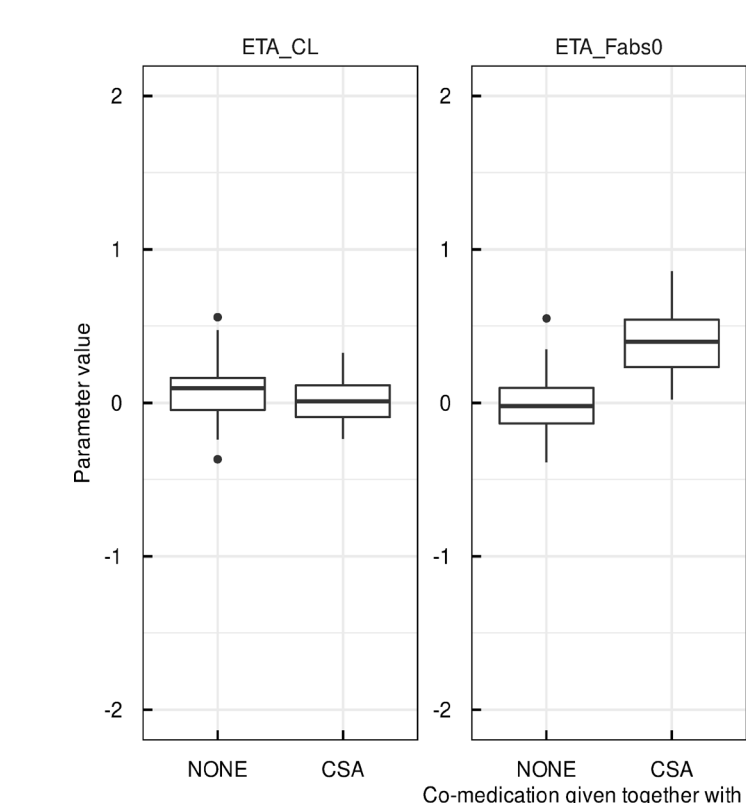
MOC-P: Covariate of CsA on F_{abs0} and the time of the zero-order transfer process were evaluated. The estimated effect of CsA on the bioavailability is ~59%. However, the model showed instability in the trajectories of the objective function value and the estimated effect is higher than suggested by the bioequivalence testing.

Modeling indicated a potential small effect of BCRP inhibition by CsA on the absorption phase of MOC and MOC-P and showed no effect on clearance (CYP3A4). ITZ (PgP and CYP3A4 inhibitor) did not show an effect on the absorption or elimination.

PD results and Safety

The most common TEAEs were bradycardia and decreased absolute lymphocyte counts (ALC)

No serious TEAEs and no fatal TEAEs were reported

Figure 3: Lymphocytes counts (× 10^9/L)

No differences in ALC reduction are observed with or without co-administration
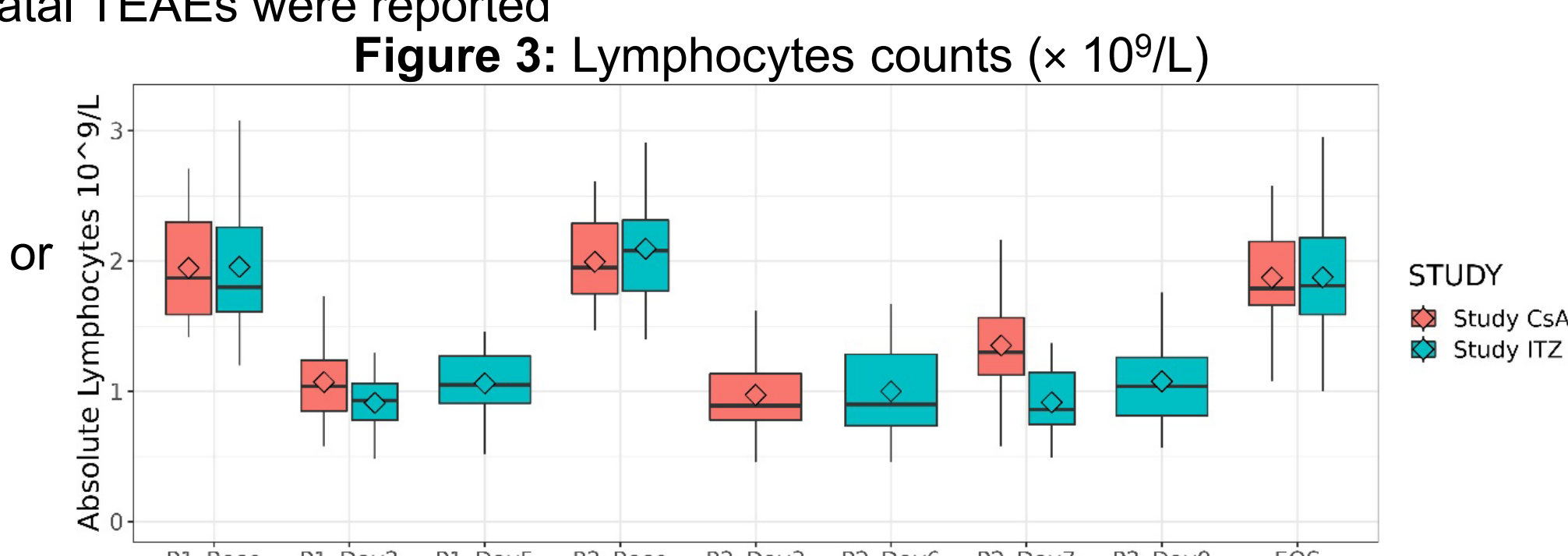
Table 3: Summary of supine PR parameters in CsA study

Treatment		AUE^{PR} (0-24) (h*bpm)	PR_{nadir} (0-24) (bpm)
MOC	N	21	21
	Mean (SD)	1280 (104)	46.5 (6.35)
	[Min;Max]	(1110 - 1470)	(40.0 - 54.0)
MOC + CsA	N	19	19
	Mean (SD)	1310 (114)	47.0 (4.01)
	[Min;Max]	[1110; 1470]	[40.0; 54.0]

AUE: area under the effect curve; bpm: beats per minutes; CsA: cyclosporine; N: Number of subjects; PR: pulse rate; SD: standard deviation

For AUE_{0-24}, a 13.96 (hrs*bpm) (90% CI - 18.89 to 46.82) difference was found for MOC alone. These results are comparable with the first dose reduction in PR observed for several S1P1R modulators.

The effect of MOC with or without co-administration of CsA showed a small difference in PR_{nadir} of -0.58 (90%CI -1.66 to 0.50) bpm, indicating a lower value for MOC in combination with CsA.

Table 4: Incidence of TEAEs by preferred term, n (percent) of participants

System organ class	ITZ DDI Study		CsA DDI Study	
	MOC 3mg N=25 n (%)	MOC 3mg + ITZ N=19 n (%)	MOC 3mg N=21 n (%)	MOC 3mg + CsA N=19 n (%)
Cardiac disorders	23 (92.0)	18 (94.7)	21 (100)	19 (100)
Eye disorders	1 (4.0)	0	0	0
Gastrointestinal disorders	1 (4.0)	2 (10.5)	0	1 (5.3)
General disorders and administration site conditions	1 (4.0)	0	1 (4.8)	1 (5.3)
Infections and infestations	2 (8.0)	0	0	0
Investigations	19 (76.0)	13 (68.4)	10 (47.6)	10 (52.6)
Nervous system disorders	5 (20.0)	3 (15.8)	0	3 (15.8)
Renal and urinary disorders	0	1 (5.3)	0	0
Reproductive system and breast disorders	1 (4.0)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (5.3)	0	0
Skin and subcutaneous tissue disorders	1 (4.0)	0	0	0

- The majority of TEAEs in both treatment periods were mild or moderate toxicity grade. Four cases of ALC decreases were reported as severe.
- TEAEs that occurred after MOC +/- ITZ or CsA were similar and consistent with known adverse reactions of MOC 3 mg.

Conclusion

MOC, ITZ and CsA were generally well tolerated when administered alone or in combination.

PK of MOC and MOC-P are bioequivalent with or without co-administration of multiple doses of the strong CYP3A4 inhibitor ITZ and a minor interaction is observed when co-administered with CsA.

MOC can be co-administered with CYP3A4 inhibitors such as azoles or CsA without dosage adjustments in allo-HCT patients.

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