Safety and Pharmacokinetics of Solithromycin in Subjects with Hepatic Impairment

P-1686

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Abstract

Objectives: To evaluate the safety, pharmacokinetics (PK), and protein binding of solithromycin in subjects with mild, moderate and severe hepatic impairment compared to healthy subjects with normal hepatic function (matched for age, weight, and gender).

Methods: This was a Phase 1, open-label, multiple-dose study in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment and healthy matched control subjects with normal hepatic function. All subjects received a once-daily dose of 800 mg on Day 1 followed by 400 mg on Days 2 through 5.

Results: 33 subjects were enrolled: 8 with mild impairment (mean Child-Pugh score 5.625), 8 with moderate impairment (mean Child-Pugh score 7.375), 8 with severe impairment (mean Child-Pugh score 10.625), and 9 healthy controls with normal hepatic function. One subject, a healthy control, discontinued study drug after 2 doses due to a rash; all other subjects (n=32) completed the study. Overall, the number of subjects reporting treatment-emergent AEs in the hepatic impaired cohorts (mild n=1, moderate n=4, severe n=4) was no greater than in the control group (n=4). The most commonly reported AEs were mild diarrhea and mild headache.
After 5 days of solithromycin administration, mean changes from baseline in liver function tests on Day 8 were not clinically significant in any cohort and did not differ significantly between cohorts. For ALT (IU/L), mean (±SD) changes by cohort: control = 2.6±4.47, mild = 4.0±8.00, moderate = 7.8±6.92, severe = 6.3±14.61. For AST (IU/L), mean (±SD) changes by cohort: control = -0.6±2.92, mild = 0.4±5.93, moderate = 0.1±10.56, severe = 5.8±22.44. For direct bilirubin (mg/dL), mean (±SD) changes by cohort: control = 0.00±0.053, mild = 0.00±0.076, moderate = 0.03±0.046, severe = 0.04±0.207. No individual change from baseline in any liver function test was considered clinically significant.
PK parameters on Day 5 were compared between the hepatic impaired cohorts and the control group, and geometric mean ratios were calculated (see Table).

Comparison	Parameter	Test Group	Reference Group	Geometric Mean Ratio (%) (test/reference)	90% Confidence Intervals
Mild versus Control	Cmax(ng/mL)	785.957	649.126	121.08	64.38 - 227.71
	AUC0-t(ng*hr/mL)	8872.658	7554.940	117.44	56.64 - 243.50
	AUC0-tau(ng*hr/mL)	7900.103	10491.88	75.30	47.89 - 118.39
Moderate versus Control	Cmax(ng/mL)	683.897	649.126	105.36	56.02 - 198.14
	AUC0-t(ng*hr/mL)	8902.279	7554.940	117.83	56.83 - 244.31
	AUC0-tau(ng*hr/mL)	7509.789	10491.88	71.58	45.52 - 112.55
Severe versus Control	Cmax(ng/mL)	504.311	649.126	77.69	41.31 - 146.11
	AUC0-t(ng*hr/mL)	8306.315	7554.940	109.95	53.03 - 227.95
	AUC0-tau(ng*hr/mL)	6175.788	10491.88	58.86	37.44 - 92.55

No accumulation was noted in any of the hepatic impaired cohorts on Day 5, though an increased half-life (h) was observed in the severe group (control = 8.9, mild = 10.2, moderate = 10.4, severe = 15.7).
The mean plasma protein binding percentage, at Day 5 C_{max}, was not significantly affected by mild or moderate hepatic impairment, but was slightly lower in the severe cohort.

Conclusions: Macrolide antibiotics, like solithromycin, are primarily metabolized and excreted through liver-dependent mechanisms; this study evaluated the safety and PK of solithromycin in patients with chronic liver disease. No dosage adjustment is needed when administering solithromycin to patients with mild, moderate, or severe hepatic impairment. Solithromycin was well tolerated in this patient population and no significant differences in safety, compared to healthy controls, were noted.

Introduction

Solithromycin (CEM-101) is a 4th generation macrolide antibiotic, a fluoroketolide, and it is being developed in both oral and intravenous formulations for the treatment of serious bacterial infections. In a Phase 2 study in patients with community-acquired bacterial pneumonia (CABP), treatment with a once-daily 5-day regimen of solithromycin showed comparable efficacy to, and was better tolerated than, levofloxacin [Oldach 2013]. A Phase 2, single-dose study in patients with uncomplicated urogenital gonorrhea showed microbiological success rates of 100% at the 2 doses evaluated [Hook 2013]. Solithromycin is currently being evaluated in 2 Phase 3 CABP studies [NCT01756339 and NCT01968733].
Solithromycin may be used to treat infections in patients with hepatic impairment. CYP3A4 metabolism and hepatic elimination are likely its major metabolic and clearance pathways. Solithromycin is metabolized by CYP3A4 and, as a mechanism-based inhibitor of CYP3A isozymes (IC50 value for CYP3A4 of <0.41 µg/mL), it inhibits its own metabolism. It does not induce CYP3A isozymes. Biliary excretion in animal models is extensive and in humans the majority of radioactivity was excreted in the feces after administration of radiolabeled [^{14}C]-solithromycin (Schneider 2014).

Materials and Methods

This was an open-label, non-randomized, parallel-group study conducted at 2 centers in the United States during 2013. The study was conducted in accordance with Good Clinical Practice guidelines and conformed to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to enrollment. Male and female subjects with mild, moderate, and severe hepatic impairment (Child-Pugh Scores ranged from 5 to 12), ages 18 to 75 years with a total body mass index (BMI) ≥18 and ≤40 kg/m2 were enrolled. A cohort of healthy matched control subjects with normal hepatic function, matched for age (±10%), weight (±20%) and gender (approximately the same ratio of males to females), was also enrolled. All subjects had to provide written informed consent, to adhere to the lifestyle guideline restrictions, and be confined to the clinical research unit as required by the protocol. Subjects were required to have a QTcF ≤470 milliseconds and to have aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ the upper limit of normal (ULN) for healthy control subjects and <6 × ULN for hepatic impaired subjects. Subjects with hepatorenal syndrome or a surgical porto-caval shunt were excluded, however subjects who had undergone a TIPS procedure could be enrolled. Concomitant use of medications that are moderate to strong substrates, inhibitors, or inducers of CYP3A4 was prohibited.
Subjects with mild impairment and matched controls received one dose of 800 mg (4 × 200 mg) on Day 1 followed by once daily 400 mg doses (2 × 200 mg) on Days 2 through 5. In all cases, the study medication was administered under the direct supervision of study staff. The first and last dose (Days 1 and 5) were administered in the fasted state and subjects consumed approximately 240 mL of water with each dose. Subjects were confined in the study center during the 5-day dosing period and for at least 72 hours after the last dose for PK sampling. All subjects returned for a follow up visit 14 (±2) days after the last dose. Preliminary PK and safety data were reviewed from the previous groups prior to dosing the next group (moderate and severe hepatic impairment groups) to determine if dosage modifications were required.
Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and adverse events (AEs). Blood samples for measurement of plasma concentrations of solithromycin and its active side-chain metabolites, N-Acetyl-CEM-101 and CEM-214, were collected. Plasma samples were stored frozen at -70 ºC and analyzed in batches using a validated liquid chromatography/mass spectrometry (LC/MS) method at a central laboratory.
Additional blood samples were obtained 4 hours (at predicted Cmax) postdose on Days 1 and 5 to measure unbound solithromycin concentrations in plasma for evaluation of protein binding. These samples were stored frozen at -70 ºC after collection, incubated in batches in an equilibrium dialysis chamber, and samples from each side of the membrane were analyzed a using a validated LC/MS method at a central laboratory.
Pharmacokinetic parameters were calculated from the plasma solithromycin, N-Acetyl-CEM-101, and CEM-214 concentration-time data following dosing on Days 1 and 5. An analysis of variance (ANOVA) was performed on the ln-transformed PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tau}$, and C_{max} for solithromycin, as applicable, between each impaired group and the control group, using PROC MIXED of SAS® (Version 9.3) for Day 1 and Day 5 separately. The ANOVA model included group as a fixed effect. Each ANOVA included calculation of least-square means (LSM), the difference between LSM of the impairment Group (Groups A [mild], B [moderate], or C [severe]) over the healthy matched control group (Group D), and the standard error and 90% confidence interval (CI) associated with this difference. These were transformed back to the original concentration or ratio scale and the geometric mean values were reported. Ratios of means and their 90% CIs were expressed as a percentage of the impaired group over the matched control group. The comparisons of interest were Group A versus Group D, Group B versus Group D, and Group C versus Group D.

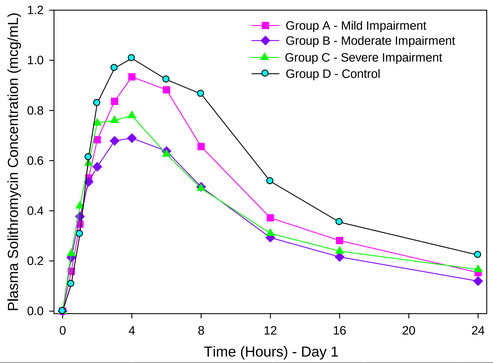
Results

Thirty-three subjects were enrolled in the study and assigned to treatment. Eight subjects with mild hepatic impairment (mean Child-Pugh Score 5.625), 8 with moderate hepatic impairment (mean Child-Pugh Score 7.375) and 8 subjects with severe hepatic impairment (mean Child-Pugh Score 10.625) were enrolled as well as 9 healthy matched controls. The demographic characteristics of the subjects are shown below and the groups were well matched for age, weight, and gender.

Trait	N	Child-Pugh Class A	B	C	Healthy Control	Hepatically Impaired (combined)
		8	8	8	9	24
Gender	Female	3 (38%)	0 (0%)	3 (38%)	3 (33%)	6 (25%)
	Male	5 (63%)	8 (100%)	5 (63%)	6 (67%)	18 (75%)
Race	Asian	2 (25%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)
	White	6 (75%)	8 (100%)	8 (100%)	9 (100%)	22 (92%)
Ethnicity	Hispanic or Latino	2 (25%)	5 (63%)	5 (63%)	5 (56%)	12 (50%)
	Not Hispanic or Latino	6 (75%)	3 (38%)	3 (38%)	4 (44%)	12 (50%)
Age (yrs)	Mean	56.9	57.1	55.6	57.9	56.5
	Minimum	49	49	42	51	42
	Maximum	67	68	65	66	68
Weight (kg)	Mean	77.13	89.24	85.04	77.40	83.80
	Minimum	68.0	71.0	65.2	66.0	65.2
	Maximum	106.9	115.3	110.5	89.6	115.3
Body Mass Index (kg/m²)	Mean	27.138	29.475	31.225	27.289	29.279

Results

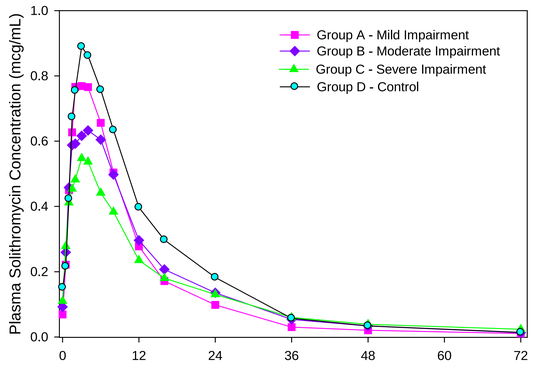
Day 1 Pharmacokinetic and Statistical Results



Comparison	Parameter	Geometric LS Means: Test Group	Geometric LS Means: Reference Group	Geometric Mean Ratio (%) (test/reference)	90% Confidence Intervals	Intra-subject %CV
Mild versus Control	C_{max} (ng/mL)	782.360	709.038	110.34	46.56 - 261.51	134.12
	$AUC_{0\text{-}t}$ (ng*hr/mL)	7076.697	6447.173	109.76	39.03 - 308.72	183.98
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	8039.657	12375.53	64.96	30.02 - 140.59	100.49
Moderate versus Control	C_{max} (ng/mL)	558.338	709.038	78.75	33.23 - 186.63	134.12
	$AUC_{0\text{-}t}$ (ng*hr/mL)	6328.977	6447.173	98.17	34.90 - 276.10	183.98
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	9491.375	12375.53	76.69	34.62 - 169.88	100.49
Severe versus Control	C_{max} (ng/mL)	711.649	709.038	100.37	42.35 - 237.88	134.12
	$AUC_{0\text{-}t}$ (ng*hr/mL)	7847.223	6447.173	121.72	43.28 - 342.34	183.98
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	9112.076	12375.53	73.63	33.24 - 163.09	100.49

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

Day 5 Pharmacokinetic and Statistical Results



Comparison	Parameter	Geometric LS Means: Test Group	Geometric LS Means: Reference Group	Geometric Mean Ratio (%) (test/reference)	90% Confidence Interval	Intra-subject %CV
Mild versus Control	C_{max} (ng/mL)	785.957	649.126	121.08	64.38 - 227.71	85.78
	$AUC_{0\text{-}t}$ (ng*hr/mL)	8872.658	7554.940	117.44	56.64 - 243.50	104.18
	$AUC_{0\text{-}tau}$ (ng*hr/mL)	7900.103	10491.88	75.30	47.89 - 118.39	54.92
Moderate versus Control	C_{max} (ng/mL)	683.897	649.126	105.36	56.02 - 198.14	85.78
	$AUC_{0\text{-}t}$ (ng*hr/mL)	8902.279	7554.940	117.83	56.83 - 244.31	104.18
	$AUC_{0\text{-}tau}$ (ng*hr/mL)	7509.789	10491.88	71.58	45.52 - 112.55	54.92
Severe versus Control	C_{max} (ng/mL)	504.311	649.126	77.69	41.31 - 146.11	85.78
	$AUC_{0\text{-}t}$ (ng*hr/mL)	8306.315	7554.940	109.95	53.03 - 227.95	104.18
	$AUC_{0\text{-}tau}$ (ng*hr/mL)	6175.788	10491.88	58.86	37.44 - 92.55	54.92

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LSMEANS from the ANOVA.
% Geometric Mean Ratio = 100*(test/reference)

- Based on ratios of LSM, there were no apparent trends in C_{max} and AUC with regard to the degree of hepatic impairment and compared to the control group. After 5 days of dosing, an increased half-life (h) was observed in the severe group (control = 8.9, mild = 10.2, moderate = 10.4, severe = 15.7).
- The protein binding of solithromycin was evaluated 4 hours postdose on Days 1 and 5 and was slightly lower for subjects with moderate and severe hepatic impairment compared to control subjects. Hepatic impairment had a minimal effect on the protein binding of solithromycin following multiple QD dosing for 5 days, with a decrease in mean %protein bound of approximately 9%, from 71% to 62%, between subjects with severe hepatic impairment relative to the control group with normal hepatic function.

Results

Solithromycin was well tolerated by both healthy subjects and hepatically impaired subjects. No deaths or serious AEs were reported in this study. Overall, 16 treatment-emergent AEs were reported by 13 subjects, with 9 of 24 (38%) hepatic impaired subjects and 4 of 9 (44%) healthy matched controls reporting AEs. Thirty-two subjects completed the study in accordance with the protocol; 1 subject (a healthy control) was discontinued by the Investigator after dosing on Day 2 due to the AE of rash. This subject was replaced with another healthy control.

	Child-Pugh Class A	B	C	Healthy Control	Hepatically Impaired
Number of Subjects Dosed	8	8	8	9	24
Number of Subjects With Adverse Events	1 (13%)	4 (50%)	4 (50%)	4 (44%)	9 (38%)
Gastrointestinal disorders	1 (13%)	4 (50%)	2 (25%)	1 (11%)	7 (29%)
Diarrhea	1 (13%)	4 (50%)	2 (25%)	0 (0%)	7 (29%)
Gastritis	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)
General disorders and administration site conditions	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (4%)
Non-cardiac chest pain	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (4%)
Investigations	0 (0%)	0 (0%)	1 (13%)	1 (11%)	1 (4%)
Blood creatine phosphokinase increased	0 (0%)	0 (0%)	1 (13%)	0 (0%)	1 (4%)
Hepatic enzyme increased	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)
Nervous system disorders	0 (0%)	0 (0%)	1 (13%)	2 (22%)	1 (4%)
Headache	0 (0%)	0 (0%)	1 (13%)	2 (22%)	1 (4%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)
Rash	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)

^ Adverse events are classified according to MedDRA® Version 15.1.

The most common AE was mild diarrhea, reported a total of 7 times by 7 (21%) subjects, including 1 mildly hepatic-impaired subject, 4 moderately hepatic-impaired subjects, and 2 severely hepatic-impaired subjects. No clinically important ECG shifts from normal at baseline to abnormal postdose were observed. There were no clinically significant shifts in chemistry, hematology, or coagulation parameters in this study. Many hepatic impaired subjects had liver function tests above ULN at baseline and throughout the study. For this reason, mean changes from baseline results on Day 6 (after 5 days of study drug administration) and Day 8 (upon discharge) for ALT, AST, and direct and total bilirubin are presented below:

Laboratory Test	Day	Child-Pugh Class A	B	C	Healthy Controls
ALT (IU/L)	6	6.4 ± 10.16	6.9 ± 8.85	2.5 ± 9.83	4.6 ± 6.16
	8	4.0 ± 8.00	7.8 ± 6.92	6.3 ± 14.61	2.6 ± 4.47
AST (IU/L)	6	3.4 ± 7.98	-1.5 ± 7.73	0.0 ± 26.47	-0.4 ± 2.45
	8	0.4 ± 5.93	0.1 ± 10.56	5.8 ± 22.44	-0.6 ± 2.92
Direct bilirubin (mg/dL)	6	0.06 ± 0.151	0.03 ± 0.046	0.11 ± 0.247	0.04 ± 0.092
	8	0.00 ± 0.076	0.03 ± 0.046	0.04 ± 0.207	0.00 ± 0.053
Total bilirubin (mg/dL)	6	0.00 ± 0.237	0.04 ± 0.288	0.14 ± 0.573	0.03 ± 0.198
	8	-0.13 ± 0.128	-0.01 ± 0.247	0.00 ± 0.548	-0.03 ± 0.167

Conclusions

- Solithromycin, given orally as an 800 mg loading dose on Day 1 followed by 400 mg on Days 2 to 5, was safe and well tolerated by the hepatic-impaired and healthy matched subjects in this study.
- The AE profiles of hepatic-impaired subjects did not differ significantly from the age-, weight-, and gender-matched control subjects.
- Mean changes from baseline in liver function tests were also similar between hepatic impaired and healthy subjects.
- The PK of plasma solithromycin in subjects with mild and moderate hepatic impairment were similar to that in subjects with normal liver function.
- There was no evidence of accumulation in hepatic impaired subjects.
- These data suggest that no dosage adjustment is needed for solithromycin administration in patients with chronic liver disease, regardless of the degree of hepatic impairment.

References

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