ASSESSMENT OF PHOTOTOXICITY POTENTIAL OF DELAFLOXACIN IN HEALTHY MALE AND FEMALE SUBJECTS: A PHASE 1 STUDY

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Abstract

BACKGROUND: Delafloxacin (DLX) is an investigational anionic aminodifluorophenyl fluoroquinolone (FQ) antibiotic in development for treatment of skin infections. DLX was designed to have reduced phototoxicity versus marketed fluoroquinolones.

METHODS: This was a single-blind, placebo- (PBO), active-controlled, randomized, parallel-group study with 52 males and females that received 200 or 400 mg/day of oral DLX or 400 mg oral Lomefloxacin (LMX) or Placebo (PBO) for 6 days. Subject baseline (predose) phototoxicity testing to UVB, UVA, and visible radiation (290-500 nm) by standard monochromator and solar simulator over 3 days and minimal erythema dose (MED) were determined. Two hours after last dose, each subject received radiation (295 +/- 5 - 430 +/- 30 nm) and MED was determined periodically over 48 hours. Phototoxic index (PI; predose MED/postdose MED) was also calculated for each group. Safety was assessed monitoring of adverse events (AEs) throughout dosing and at Day 21.

RESULTS: 47 subjects completed 6 days of dosing. DLX at 200 and 400 mg/day did not demonstrate differences in percent change from baseline in MED at each wavelength (295 - 430 nm) tested by monochromator or solar simulator, but LMX had statistically significant differences* (p<0.05) at two wavelengths at 24 hours after radiation exposure (maximum response). Mean PI results are also reported:

Treatment Group	Wavelength	Mean % Change (SD)	P-value MED within group to Baseline	P-value vs. PBO	P-value vs. LMX	Mean PI (SD)
DLX 200 mg (n=12)	335 ± 30 nm	-1.4 (18.89)	0.723	0.351	<0.001*	1.0 (0.21)
DLX 400 mg (n=11)		0.0 (31.52)	>0.999	0.419	<0.001*	1.1 (0.42)
LMX 400 mg (n=12)		-64.0 (17.11)	<0.001*	<0.001*	NA	3.4 (1.51)
PBO (n=12)		-11.4 (20.08)	0.184	NA	NA	1.2 (0.29)
DLX 200 mg	365 ± 30 nm	-6.2 (16.66)	0.516	0.703	<0.001*	1.1 (0.18)
DLX 400 mg		-7.1 (14.81)	0.281	0.875	<0.001*	1.1 (0.19)
LMX 400 mg		-76.0 (12.94)	<0.001*	<0.001*	NA	5.4 (2.69)
PBO		-7.2 (20.71)	0.422	NA	NA	1.1 (0.27)

* = statistically significant (p≤0.05)

The most common AEs were headache, abdominal pain, diarrhea, and increased ALT. Four subjects were prematurely discontinued due to an AE, 1 in the 200 mg DLX, 2 in 400 mg DLX, and 1 in the PBO groups.

CONCLUSIONS: Both 200 and 400 mg DLX administered for 6 days was well tolerated in healthy adult volunteers. DLX at both doses failed to demonstrate a phototoxic effect, but LMX had moderate phototoxicity at the expected wavelengths of 335 and 365 ± 30 nm.

Introduction

Some members of the fluoroquinolone group, such as ciprofloxacin[1] and lomefloxacin[2] may result in dose-dependent phototoxic reactions if sufficient drug is present in the skin following exposure to adequate radiation of appropriate wavelength. Other drugs and naturally occurring compounds are reported to cause mild phototoxic reactions with a low incidence (<2.4%)[3-4]. Lomefloxacin has been shown to have a greater photosensitivity incidence (4-10%) and severity[5-6] and is used as a positive control in phototoxicity experimentation.

Since the early 1990s, a standardized technique has been used to investigate drug phototoxicity potential using monochromator and solar simulator phototesting.[7] Phototesting performed before and during drug administration can define the nature, severity, wavelength dependency, and duration of the phototoxic effect after cessation. Through comparison of minimal erythema dose (MED) values before and on drug, the minimum radiation dose required to produce perceptible erythema at each solar waveband tested is calculated. The phototoxic index (PI) of an investigational drug can then be defined and compared with a positive control, lomefloxacin, and with placebo.

Methods

This study was a Phase 1, single-blind, placebo- and positive-controlled, randomized, parallel-group study in 52 healthy male and female volunteers. The study was designed to demonstrate the photosensitizing potential and wavelength dependency of delafloxacin, by comparing the response of the skin to ultraviolet A (UVA), ultraviolet B (UVB) and visible radiation prior to and during administration of delafloxacin, lomefloxacin, or placebo. Subjects were screened to verify inclusion/exclusion criteria and underwent baseline photosensitivity testing to UV and visible radiation (by means of a standard monochromator technique) over a period of 3 days; the endpoint used at each wavelength tested was the baseline minimal erythema dose (MED). Eligible subjects were admitted to an ultraviolet- and blue light-screened clinical unit (DDS Medicines Research Limited) and randomly assigned to study drug in a 1: 1: 1: 1 ratio, to receive delafloxacin (200 mg/day or 400 mg/day), placebo, or lomefloxacin 400 mg/day for 6 days. On Study Days 5-6, phototesting was repeated during which each subject had his or her back exposed to selected wavelengths of UVA, UVB and visible light. On Study Day 7, exposed areas were read and the MED was determined. If an abnormal response (reduction in MED of >40% from baseline) was revealed on Study Day 7, phototesting was to be repeated on Study Days 7-9; subjects remained in the DDS until any drug induced photosensitivity had resolved. Safety was assessed by 12-lead electrocardiograms (ECGs), physical examination, laboratory parameters, vital signs, and monitoring of adverse events.

The primary endpoint was the change in MED within subject/group comparing their baseline with on drug/placebo value. A secondary analysis calculated the Phototoxic Index (PI), obtained by dividing the baseline MED value for each individual, and the median MED value for each group, by the post-dose MED value. Data for each waveband tested were analyzed separately; the maximum PI indicated the phototoxic potential of the study drug.

Results

Table 1
DEMOGRAPHIC INFORMATION (ALL RANDOMIZED SUBJECTS)

Baseline Characteristic	DLX 200 mg (n=13)	DLX 400 mg (n=13)	LMX 400 mg (n=13)	PBO (n=13)
Gender				
Female	3 (23%)	3 (23%)	6 (46%)	6 (46%)
Male	10 (77%)	10 (77%)	7 (54%)	7 (54%)
Race				
White	13 (100%)	13 (100%)	13 (100%)	13 (100%)
Age (years)				
Mean (SD)	33.8 (10.83)	35.9 (9.80)	31.6 (10.23)	33.6 (9.75)
Range	19 – 54	19 – 51	19 – 49	18 – 47
Height (cm)				
Mean (SD)	172.8 (8.58)	175.6 (10.05)	173.0 (6.76)	170.7 (10.34)
Range	158.0 – 186.0	161.0 – 194.0	150.0 – 183.0	152.0 – 187.0
Weight (kg)				
Mean (SD)	77.5 (14.94)	76.3 (7.64)	71.6 (11.42)	73.7 (11.06)
Range	51.0 – 97.0	64.0 – 87.0	59.0 – 93.0	52.0 – 88.2
Nicotine Use				
User	5 (38%)	6 (46%)	3 (23%)	5 (38%)
Ex-user	3 (23%)	2 (15%)	3 (23%)	1 (8%)
Non-user	5 (38%)	5 (38%)	7 (54%)	7 (54%)
Alcohol Use				
User	12 (92%)	12 (92%)	12 (92%)	10 (77%)
Ex-user	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-user	1 (8%)	1 (8%)	1 (8%)	3 (23%)

SD = standard deviation

Table 4
SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES GROUPED BY BODY SYSTEM (ALL ADVERSE EVENTS)

	Number (%) of Subjects[a]			
Body System	**DLX 200 mg n=13**	**DLX 400 mg n=13**	**LMX 400 mg n=13**	**PBO n=13**
OVERALL[b]	**7 (54%)**	**9 (69%)**	**4 (31%)**	**10 (77%)**
Body as a whole	3 (23%)	4 (31%)	2 (15%)	3 (23%)
Cardiovascular	0 (0%)	1 (8%)	1 (8%)	1 (8%)
Digestive	4 (31%)	5 (38%)	1 (8%)	1 (8%)
Gastrointestinal	2 (15%)	5 (35%)	1 (8%)	1 (8%)
Other	2 (15%)	1 (8%)	1 (8%)	0 (0%)
Metabolic and Nutritional Disorders	2 (15%)	2 (15%)	1 (8%)	2 (15%)
Musculoskeletal	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Nervous	2 (15%)	0 (0%)	2 (15%)	2 (15%)
Respiratory	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Skin and Appendages	0 (0%)	1 (8%)	2 (15%)	1 (8%)
Special Senses	0 (0%)	0 (0%)	2 (15%)	2 (15%)
Urogenital	0 (0%)	1 (8%)	1 (8%)	1 (8%)

[a]Subjects with more than one event within a body system are counted once in the total for that body system
[b]Numbers of subjects with one or more adverse events

Table 2
MEAN PERCENT CHANGE FROM BASELINE TO DAY 7 IN MED BY MONOCHROMATOR WAVELENGTH AND SOLAR SIMULATOR

Treatment Group	Wavelength	Mean % Change (SD)	P-value MED within group to Baseline[§]	P-value vs. PBO[§§]	P-value vs. LMX[§§]
DLX 200 mg (n=12)	295 ± 5 nm	-0.4 (17.43)	0.492	>0.999	0.612
DLX 400 mg (n=11)		11.9 (18.37)	0.094	0.245	0.328
LMX 400 mg (n=12)		5.8 (18.35)	0.313	0.665	NA
PBO (n=12)		0.7 (14.46)	0.438	NA	NA
DLX 200 mg	300 ± 5 nm	-6.0 (8.86)	0.125	0.973	0.561
DLX 400 mg		-7.9 (11.74)	0.125	0.885	0.475
LMX 400 mg		-3.9 (15.22)	0.75	0.561	NA
PBO		-7.1 (11.11)	0.125	NA	NA
DLX 200 mg	305 ± 5 nm	-4.8 (14.43)	0.375	0.715	0.903
DLX 400 mg		-5.8 (20.65)	0.406	0.614	0.614
LMX 400 mg		-3.2 (21.06)	0.984	0.954	NA
PBO		-1.2 (18.47)	0.711	NA	NA
DLX 200 mg	335 ± 30 nm	-1.4 (18.89)	0.723	0.351	<0.001*
DLX 400 mg		0.0 (31.52)	>0.999	0.419	<0.001*
LMX 400 mg		-64.0 (17.11)	<0.001*	<0.001*	NA
PBO		-11.4 (20.08)	0.184	NA	NA
DLX 200 mg	365 ± 30 nm	-6.2 (16.66)	0.516	0.703	<0.001*
DLX 400 mg		-7.1 (14.81)	0.281	0.875	<0.001*
LMX 400 mg		-76.0 (12.94)	<0.001*	<0.001*	NA
PBO		-7.2 (20.71)	0.422	NA	NA
DLX 200 mg	400 ± 30 nm	-2.8 (6.57)	0.500	0.166	1.000
DLX 400 mg		-9.1 (17.43)	0.250	0.066	0.523
LMX 400 mg		-4.0 (9.88)	0.500	0.166	NA
PBO		0.0 (0.00)	NA	NA	NA
DLX 200 mg	430 ± 30 nm	0.00 (0.0)	NA	NA	NA
DLX 400 mg		0.00 (0.0)	NA	NA	NA
LMX 400 mg		0.00 (0.0)	NA	NA	NA
PBO		0.00 (0.0)	NA	NA	NA
DLX 200 mg	Solar Simulator	5.3 (12.89)	0.250	0.664	0.014*
DLX 400 mg		-0.2 (20.48)	>0.999	0.177	0.119
LMX 400 mg		-15.3 (19.69)	0.039*	0.012*	NA
PBO		6.5 (15.34)	0.078	NA	NA

NA = not applicable
* = statistically significant (p≤0.05)
[§] P-value comparing MED to baseline within treatment groups using Wilcoxon signed rank test.
[§§] P-value comparing MED between treatment groups using Wilcoxon rank sum test.

Table 3
PHOTOTOXIC INDEX RESULTS ON STUDY DAY 7 BASED ON WAVELENGTH AND SOLAR SIMULATOR

Treatment Group	Wavelength	Mean (SD)	Min, Max	P-value vs. PBO[§]	P-value vs. LMX[§]
DLX 200 mg (n=12)	295 ± 5 nm	1.0 (0.19)	0.8, 1.3	0.738	0.469
DLX 400 mg (n=11)		0.9 (0.17)	0.7, 1 .3	0.148	0.393
LMX 400 mg (n=12)		1.0 (0.17)	0.7, 1.3	0.596	NA
PBO (n=12)		1.0 (0.15)	0.8, 1.2	NA	NA
DLX 200 mg	300 ± 5 nm	1.1 (0.10)	1.0, 1.2	0.916	0.719
DLX 400 mg		1.1 (0.16)	1.0, 1.5	0.912	0.559
LMX 400 mg		1.1 (0.19)	0.8, 1.5	0.625	NA
PBO		1.1 (0.16)	1.0, 1.5	NA	NA
DLX 200 mg	305 ± 5 nm	1.1 (0.18)	0.8, 1.4	0.736	0.854
DLX 400 mg		1.1 (0.20)	0.7, 1.4	0.481	0.633
LMX 400 mg		1.1 (0.28)	0.8, 1.7	0.881	NA
PBO		1.0 (0.21)	0.8, 1.4	NA	NA
DLX 200 mg	335 ± 30 nm	1.0 (0.21)	0.8, 1.4	0.244	<0.001*
DLX 400 mg		1.1 (0.42)	0.7, 2.1	0.381	<0.001*
LMX 400 mg		3.4 (1.51)	1.4, 6.8	<0.001*	NA
PBO		1.2 (0.29)	0.8, 1.8	NA	NA
DLX 200 mg	365 ± 30 nm	1.1 (0.18)	0.8, 1.4	0.811	<0.001*
DLX 400 mg		1.1 (0.19)	0.8, 1.5	<0.999	<0.001*
LMX 400 mg		5.4 (2.69)	2.2, 10.0	<0.001*	NA
PBO		1.1 (0.27)	0.8, 1.5	NA	NA
DLX 200 mg	400 ± 30 nm	1.0 (0.08)	1.0, 1.2	0.166	0.964
DLX 400 mg		1.2 (0.34)	1.0, 2.1	0.066	0.551
LMX 400 mg		1.1 (0.15)	1.0, 1.5	0.166	NA
PBO		1.0 (0.00)	1.0, 1.0	NA	NA
DLX 200 mg	430 ± 30 nm	1.0 (0.00)	1.0, 1.0	NA	NA
DLX 400 mg		1.0 (0.00)	1.0, 1.0	NA	NA
LMX 400 mg		1.0 (0.00)	1.0, 1.0	NA	NA
PBO		1.0 (0.00)	1.0, 1.0	NA	NA
DLX 200 mg	Solar Simulator	1.0 (0.14)	0.8, 1.3	0.899	0.011*
DLX 400 mg		1.0 (0.18)	0.7, 1.3	0.228	0.110
LMX 400 mg		1.3 (0.3)	0.8, 1.8	0.012*	NA
PBO		1.0 (0.15)	0.8, 1.2	NA	NA

NA = not applicable
* = statistically significant (p≤0.05)
Min = minimum
Max = maximum
[§] P-value comparing MED between treatment groups using Wilcoxon rank sum test.

Table 5
SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS REPORTED BY 2 OR MORE SUBJECTS IN ANY DOSING GROUP BY COSTART TERM

	DLX 200 mg n=13				DLX 400 mg n=13				LMX 400 mg n=13				PBO n=13			
	MILD	MOD	SEV	TOTAL (%)	MILD	MOD	SEV	TOTAL (%)	MILD	MOD	SEV	TOTAL (%)	MILD	MOD	SEV	TOTAL (%)
Subjects with ≥1 AEs	4	2	1[a]	7(54)	1	8	0	9(69)	1	3	0	4(31)	3	6	1[b]	10(77)
Headache	0	2	0	2(15)	0	2	0	2(15)	1	0	0	1(8)	0	2	0	2(15)
Abdominal Pain	0	0	0	0 (0)	2	1	0	3(23)	0	0	0	0(0)	0	0	0	0(0)
Diarrhea	0	0	0	0(0)	1	4	0	5(38)	0	0	0	0(0)	0	1	0	1(8)
SPGT Increased	2	0	0	2(15)	2	0	0	2(15)	0	0	0	0(0)	2	0	0	2(15)

[a]One subject had 2 severe adverse events (dysphagia and anxiety); [b]One subject had 1 severe adverse event (migraine); MOD = moderate; SEV = severe; AE = adverse event; SPGT = serum glutamic-pyruvic transaminase

Conclusions

- Delafloxacin at 200 and 400 mg/day did not demonstrate clinically significant phototoxic potential at any wavelength tested (295 - 430 nm), while the active comparator, lomefloxacin, demonstrated a moderate degree of phototoxicity at UVA wavelengths 335 nm and 365 nm.
- Statistically significant differences from zero (p<0.05) in percent change from baseline in MED were observed at UVA wavelengths 335 nm and 365 nm in the lomefloxacin group. At these same wavelengths, statistically significant differences in percent change from baseline in MED were also seen when lomefloxacin was compared to both delafloxacin dosing groups and the placebo group.
- Substantially higher mean and median phototoxic index for lomefloxacin group compared to the other 3 dosing groups at wavelengths of 335 nm and 365 nm were found; the maximum PI in the lomefloxacin group at these wavelengths (6.8 and 10.0, respectively) greatly exceeded those in the other 3 dosing groups (1.4 and 1.4, respectively in the delafloxacin 200 mg dosing group, 2.1 and 1.5, respectively, in the delafloxacin 400 mg dosing group, and 1.8 and 1.5, respectively, in the placebo group).
- No statistically significant differences in percent change from baseline in MED were observed at each wavelength tested within the delafloxacin dosing groups or between the delafloxacin dosing groups and the placebo group.
- No evidence of phototoxicity using the monochromator or solar simulator was revealed at either dose of delafloxacin. Delafloxacin at dosages of 200 and 400 mg/day failed to demonstrate a significant phototoxic effect.
- Lomefloxacin, however, revealed phototoxicity as expected within the moderate phototoxic index group at 335 and 365 ± 30 nm test groups, maximal at 24 hours, with susceptibility clearing within 48 hours after drug cessation. Phototoxicity was not demonstrated in the placebo group.
- No deaths or serious adverse events were reported during the conduct of this study.
- Four (4) subjects (1 delafloxacin 200 mg, 2 delafloxacin 400 mg, 1 placebo) were prematurely discontinued from study drug due to the occurrence of at least one adverse event; 3 of these subjects withdrew due to adverse events that were considered possibly or probably related to study drug: headache in an delafloxacin 400 mg subject; diarrhea and abdominal pain in an delafloxacin 400 mg subject; migraine, myasthenia and dizziness in a placebo subject.
- Six subjects (5 delafloxacin 400 mg and 1 placebo) reported diarrhea during the study, all of which were considered to be probably or possibly related to study drug. All cases of diarrhea were sporadic, mild or moderate in intensity, and resolved. This study used unformulated drug in capsule. The planned tablet for oral use is formulated to decrease gastro-intestinal events.
- Delafloxacin administered for 6 days at 200 mg/day and 400 mg/day was well tolerated in healthy adult volunteers.

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