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Published in:
Photochemical & Photobiological Sciences

DOI:
[10.1039/c8pp00019k](https://doi.org/10.1039/c8pp00019k)

Publication date:
2018

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Dawe, R. S., Ferguson, J., Ibbotson, S., Lawrence, L., Paulson, S., Duffy, E., & Cammarata, S. (2018). Lack of phototoxicity potential with delafloxacin in healthy male and female subjects: comparison to lomefloxacin. *Photochemical & Photobiological Sciences*, 17(6), 773-780. <https://doi.org/10.1039/c8pp00019k>

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LACK OF PHOTOTOXICITY POTENTIAL WITH DELAFLOXACIN IN HEALTHY MALE AND FEMALE SUBJECTS: COMPARISON TO LOMEFLOXACIN

Short Title: Delafloxacin lack of phototoxicity

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1 **ABSTRACT**

2 **Aims:** Delafloxacin is a fluoroquinolone antibiotic recently approved by the FDA for treatment of acute
3 bacterial skin and skin structure infections (ABSSSI). Delafloxacin was assessed for phototoxicity
4 potential compared with a known phototoxic fluoroquinolone.

5 **Methods:** A Phase 1, investigator-blind, placebo/active-controlled, randomized, parallel-group study
6 was conducted in 52 healthy male and female volunteers who received 200 or 400 mg of oral
7 delafloxacin, 400 mg oral lomefloxacin or placebo once daily for 6 days. This study evaluated the
8 photosensitizing potential and possible wavelength dependency of delafloxacin by comparing the
9 response of the skin to ultraviolet A (UVA), ultraviolet B (UVB) and visible radiation prior to and during
10 administration of delafloxacin, lomefloxacin as a positive control, or placebo. Adverse events were
11 monitored throughout the study.

12 **Results:** Forty-seven subjects completed six days of dosing, and no evidence of phototoxicity was seen
13 with delafloxacin. Delafloxacin at 200 and 400 mg/day and placebo did not demonstrate differences in
14 percent change from baseline in minimal erythema dose at all tested wavelengths (295 - 430 nm) by
15 monochromator and solar simulator. Lomefloxacin, the positive control, had statistically significant
16 differences ($p < 0.05$) at UVA wavelengths of 335 and 365 ± 30 nm 24 hours after radiation exposure
17 (maximum response). The phototoxic index results were significantly higher for lomefloxacin at 335nm
18 and 365nm compared to placebo and delafloxacin.

19 **Conclusions:** 200 and 400 mg of delafloxacin administered for 6 days were well tolerated in healthy
20 adult volunteers. Delafloxacin and placebo failed to demonstrate a phototoxic effect but lomefloxacin,
21 the positive control, demonstrated moderate phototoxicity.

22

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23 Clinical trial registration numbers are not required for phase 1 studies.

24

25 Key Words: Phototoxicity, delafloxacin, fluoroquinolone, Structure-activity-relationship

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26 **INTRODUCTION**

27 Antibiotics of the quinolone class have been associated with photosensitivity through the
28 mechanism of phototoxicity. This was noted with the earliest related compound, nalidixic acid.
29 However with development of subsequent new generations of quinolone antibiotics, it is clear that the
30 phototoxicity risk varies by compound and its associated structure activity relationships (SAR).¹ While
31 the mechanism involved in the phototoxic properties of fluoroquinolones (FQ) are not completely
32 understood, these reactions are more commonly associated with specific FQs, particularly lomefloxacin,
33 clinafloxacin, sitafloxacin, and sparfloxacin.²⁻⁴ As an example, lomefloxacin has been shown to be
34 associated with a high incidence of significant photosensitivity (4-10%) and has been used as a positive
35 control in phototoxicity studies.^{5,6}

36 In descending order, the rank of fluoroquinolone antibiotics (FQ) related to their phototoxic
37 potential is as follows; lomefloxacin, fleroxacin, clinafloxacin, sparfloxacin, sitafloxacin, enoxacin
38 pefloxacin, ciprofloxacin grepafloxacin, gemifloxacin, levofloxacin, norfloxacin, ofloxacin,
39 trovafloxacin.^{3,7-13} Gatifloxacin and moxifloxacin have not been linked to phototoxic events.^{14,15} It had
40 been easy to correlate the presence of a halogen at position 8 of the quinolone nucleus with phototoxic
41 events. To be certain, clinafloxacin, lomefloxacin, sitafloxacin and sparfloxacin feature either a fluorine
42 or a chlorine at that position (**Figure 1**). However, Hayashi et al provided a more nuanced structure-
43 activity relationship to phototoxicity, employing the severity of erythema around rat eyes as the key
44 biological data. What they demonstrated was that – when substitution at N1 was small, such as an ethyl
45 or cyclopropyl group, or when the N1 substitution was large and nonpolar, such as a 2,4-difluorophenyl
46 – the presence of a halogen at C8 indeed resulted in severe erythema. By contrast, they showed no
47 erythema, in the presence or absence of a halogen at C8, when there was a large N1 substitution with
48 more polarity, such as an 5-amino-2,4-difluorophenyl group.¹

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49 Delafloxacin has three molecular features that collaborate to deliver a unique profile: at N1, it
50 has a large, more polar 6-amino-3,5-difluoropyridine group; at C7, it is the only fluoroquinolone lacking
51 completely a basic group and at C8 it features a halogen (chlorine) (**Figure 1**). Structure-activity
52 highlight the collaboration among all three in delivering its unique antimicrobial spectrum, including the
53 unique activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Delafloxacin is approved in
54 the United States for the treatment of ABSSSI, where the causative agents include MRSA, and currently
55 being studied for the treatment of community-acquired bacterial pneumonia. Our working hypothesis is
56 that combinations of these unique molecular features will lead to differentiated profiles, including in the
57 safety arena. The Hayashi SAR suggests that the combination of the large, polar substitution at N1 with
58 the halogen at C8 will lead to a positive profile in the arena of photosafety. To that end and to further
59 evaluate the phototoxicity potential of delafloxacin, phototesting was conducted in healthy human
60 volunteers using a validated and standardized procedure with comparison to the positive control
61 lomefloxacin as well as to placebo. The study was designed to demonstrate the photosensitizing
62 potential and possible wavelength dependency of delafloxacin, by comparing the response of the skin in
63 the UVB range narrow wavebands at 290 nm, 300 nm, and 305 nm, UVA range wavebands at 335
64 nm, and 365 nm, and in the visible range 430 nm, generated using a monochromator and solar
65 simulator, prior to and during administration of delafloxacin, lomefloxacin, or placebo.

66 **Methods**

67 **Dose Selection**

68 The doses of delafloxacin were selected based on the pharmacokinetic and safety profiles
69 demonstrated in early clinical studies.¹⁶ The 400 mg/day oral dose of delafloxacin (unformulated drug-in
70 capsule) used in this study generated maximum plasma concentrations (C_{max}) of delafloxacin, which
71 overlap with those seen with the formulated 450mg oral tablet planned for market use. The C_{max} levels

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72 were used for risk assessment as this plasma parameter is considered most predictive for
73 phototoxicity.¹⁷ The dose of lomefloxacin was selected based on clinical data that indicate a phototoxic
74 potential exists at ≥ 400 mg/day.¹⁴

75 **Study design**

76 This Phase 1, investigator -blind, placebo- and positive-controlled, randomized, parallel-group
77 study enrolled 52 healthy male and female volunteers. **(Figure 2)** An independent ethics committee
78 approved the study protocol, and the trial was conducted in accordance with the Declaration of Helsinki
79 and International Conference on Harmonisation Good Clinical Practice. All subjects provided written
80 informed consent.

81 Subjects included in the study were men and non-pregnant women between 18 to 55 years of
82 age, in general good health that had skin types I-III according to the Dermatology Scale of sun-reactive
83 skin types.¹⁸ Subjects were restricted from using alcohol, caffeine, nicotine, and grapefruit juice until the
84 final study evaluation was complete. Volunteers were not enrolled in the study if they took any strong
85 inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin) of CYP3A within one month prior to starting
86 the trial, were on any chronic medications, had a history of clinical photosensitivity, or if they ever
87 experienced hypersensitivity, allergic, or adverse reactions to FQs. Potential subjects with clinically
88 significant skin diseases (e.g., acne) or multiple tattoos also had to be excluded as these conditions could
89 have affected/obscured skin reactions or restricted skin surface area available for phototesting.

90 Eligible subjects were admitted to a single center (DDS Medicines Research Limited, Dundee)
91 and randomly assigned to receive blinded study drug in one of four treatment groups: delafloxacin (200
92 mg or 400 mg, unformulated drug in capsule), placebo, or lomefloxacin 400 mg, each given orally daily
93 for 6 days. The details of phototesting technique are outlined below. The endpoint used at each
94 waveband tested was the baseline minimal erythema dose (MED) i.e. the minimum amount of

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95 irradiation capable of producing a faint but definite erythema within the area of irradiation observed at
96 24 and 48 hours. In addition, a secondary analysis calculated the Phototoxic Index (PI), obtained by
97 dividing the baseline MED value for each individual, and the median MED value for each group, by the
98 post-dose MED value. Safety was assessed by 12-lead electrocardiograms (ECGs), physical examination,
99 laboratory parameters, vital signs, and monitoring of adverse events.

100 Phototesting Procedures

101 Clinical phototesting was performed using the monochromator and solar simulator (a simulator
102 of midday equatorial sunlight, so proportionately producing a lot of the shorter, erythemogenic, UVB
103 wavelengths) as previously reported in standard phototoxicity studies.¹⁹ The solar simulator can miss
104 important UVA phototoxicity (as erythema from the shorter UVB wavelengths limits the dose of longer
105 wavelengths that can be delivered) but testing with this helps to ensure we do not miss a complex
106 phenomenon causing phototoxicity through a broad mixture of wavelengths).²⁰ The skin of the mid-
107 upper back was identified as the test area in all subjects. During the 3 weeks prior to study drug
108 administration, as a screening procedure, the subject's MEDs at each waveband were determined over 3
109 consecutive days. On the first day, a geometric range of radiation dose was used. This resulted in an
110 approximate MED for each waveband. On the subsequent days, the precise MED was determined by
111 narrowing the gap between the MED and the no-response value, using smaller increments of 20%.
112 Subjects were suitable for enrollment only if the MED was found to be within normal limits.

113 The MED was determined for ultraviolet and visible light wavebands 290±5 [half-maximum
114 bandwidth] nm, 300±5 nm, 305±5nm, 335±30nm and 365 through to 430±30 nm, which cover the
115 biologically important regions: 290-315 nm (UVB), which is mainly responsible for sunburn reactions;
116 315-400 nm (UVA), which is commonly involved in drug-induced cutaneous phototoxicity; and 400-700
117 nm (visible spectra). Each subject was examined for evidence of erythema at 0 (prior to dosing) and at

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118 5, 10, 15 and 30 minutes post-irradiation for immediate reactions. Subjects were re-examined at 24 and
119 48 hours post-irradiation for delayed reactions. Previous work on the fluoroquinolones has recorded
120 maximal photosensitivity at 24 hours post-dose.¹⁴

121 During Study Days 1 through 6, subjects received the assigned dose of study drug. On Study Day
122 5, 2 hours post-dosing (near C_{max} plasma levels), a range of radiation doses were administered at each
123 waveband and an approximate MED was calculated for each waveband. If it became apparent that the
124 subject had become very photosensitive, the phototesting dosage schedule was adjusted. On Study Day
125 6, the exact MED was determined by narrowing the gap between the MED and the no-response values
126 using small increments of 20% of the irradiation dose. Assessments were performed of the Study Day 6
127 phototesting sites on Days 7 and 8 (approximately 24 and 48 hours post-irradiation). The results of tests
128 performed on Study Day 6 and assessments made on Days 7 and 8 were to be clinically acceptable prior
129 to discharge on Study Day 8. Subjects with a PI >5 at Study Day 7 were to undergo careful
130 photoprotection and repeat testing on Study Day 21.

131 Any subjects whose MED at any waveband was significantly reduced (>40%) during the study
132 drug administration were re-tested at the sensitive wavebands on a daily basis until their MED returned
133 to within 40% of baseline. Phototesting was conducted, as routine with all wavebands through to
134 430±30nm. There were plans to test to longer wavebands if photosensitivity was detected to the
135 430±30nm waveband and if there had been significant 400±30nm waveband photosensitivity, short and
136 long-pass filters were to be used to determine whether or not there was visible wavelength
137 phototoxicity with its possible implications for the retina.

138 If a subject had a PI >5 on Study Day 7, this subject was required to be re-examined for delayed
139 erythema/pigmentation on Study Day 21.

140 **Statistical analyses**

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141 For the sample size requirement calculations, it was assumed, based on earlier studies, that the
142 standard deviation about mean PI was 1.68 and 1.43 for lomefloxacin and placebo, respectively. The
143 sample size was determined to give 90% power to detect as significant at $P \leq 0.05$ with two-tailed testing
144 a difference between mean phototoxic indices of ≥ 2 .

145 The primary outcome measure of the study was the change in MED at each waveband within
146 subject/group comparing their baseline with on drug/placebo value. Data for each waveband tested
147 were analyzed separately where the maximum PI indicated the phototoxic potential of the study drug.
148 The significance of within-subject changes in MED at each wavelength within each dosing group was
149 assessed by means of the Wilcoxon's signed rank test.

150 Based on a previously-defined, PI values scoring system, phototoxicity was graded as absent
151 (PI < 1.4), mild (PI 1.4-3), moderate (PI ranging from >3-6), or severe (PI > 6) at each testing timepoint.²¹

152 The phototoxic index PI was compared between treatment groups using the Kruskal-Wallis equality of
153 populations test to first test for any differences between groups and then, for pairwise comparisons
154 between groups, the Mann-Whitney *U* test (Wilcoxon rank sum test) and related methods for
155 confidence intervals for differences in medians as implemented in Stata 14 (Stata 14, StataCorp, Texas,
156 2016).

157 RESULTS

158 Subject demographics

159 Fifty-two (52) subjects were randomized in the study and took study drug, with 13 subjects each
160 receiving delafloxacin 200 mg, delafloxacin 400 mg, lomefloxacin 400 mg, or placebo, respectively.
161 Forty-five subjects completed the study; 2 additional subjects in the lomefloxacin dosing group
162 completed the 6-day dosing period but one subject withdrew consent before completing all study
163 procedures and another subject did not return for Study Day 21 phototesting. Both of these subjects

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164 were included in the phototoxicity analyses. **(Figure 2)** One, 2 and 1 subjects on delafloxacin 200mg,
165 delafloxacin 400mg and placebo, respectively, dropped from the study due to adverse events, discussed
166 further in safety section. No blind breaks were reported. Among all randomized subjects, no
167 statistically significant differences were observed among the dosing groups in gender, age, height, or
168 weight. The majority of the subjects were male (65%) and white (100%). The mean age of all
169 randomized subjects was 33.7 years (range from 18 to 54 years). The mean weight was 74.8 kg (range
170 from 51 to 97 kg). The mean height was 173 cm (range from 152 to 194 cm).

171 **Outcomes**

172 Subjects who completed at least 6 days of dosing (N=47) were included in the analyses of
173 phototoxicity. At doses of 200 and 400 mg/day, delafloxacin did not demonstrate clinically significant,
174 phototoxic potential at any wavelengths tested (295 to 430 nm and solar simulator), while the active
175 comparator, lomefloxacin, demonstrated a moderate degree of phototoxicity at UVA wavelengths 335
176 nm and 365 nm **(Tables 1 and 2)**.

177 There was no evidence of phototoxicity revealed in the placebo group. There were no
178 statistically significant differences from zero in percent change from baseline in MED observed within
179 the delafloxacin 200 mg/day and 400 mg/day dosing groups or the placebo group at each wavelength
180 tested (295±5 nm to 430±30 nm and solar simulator). There were no significant differences between
181 placebo and either delafloxacin regimen in percent change in MED from baseline.

182 Statistically significant differences from zero in percent change from baseline in MED were
183 observed at UVA wavelengths 335 nm and 365 nm in the lomefloxacin group (p<0.05). At these same
184 wavelengths, statistically significant differences in percent change from baseline in MED were also seen
185 when lomefloxacin was compared to both delafloxacin dosing groups and the placebo group. A

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186 summary of mean percent change from baseline to Day 7 in MED by monochromator waveband and
187 solar simulator is presented in Table 1.

188 Substantially higher PI values were also demonstrated by the lomefloxacin group compared to
189 the other 3 dosing groups at wavelengths of 335 nm and 365 nm. The maximum PI in the lomefloxacin
190 group at these wavelengths (6.8 and 10.0, respectively) greatly exceeded those in the other 3 dosing
191 groups (1.4 and 1.4, respectively, in the delafloxacin 200 mg dosing group, 2.1 and 1.5, respectively, in
192 the delafloxacin 400 mg dosing group, and 1.8 and 1.5, respectively, in the placebo group) (**Table 2**).
193 Dot plots of the outcomes at 335 ± 30 nm and 365 ± 30 nm are displayed in **figures 3 and 4**. The difference
194 in PIs across the 4 groups for 365 ± 30 nm waveband is unlikely to be a chance finding ($P=0.0001$). The
195 difference in medians (or strictly, the median of the differences) for lomefloxacin vs. placebo is 3.9 (95%
196 CI 2.0 to 6.9, $P<0.0001$). The difference in medians for delafloxacin 200mg/day vs. placebo was 0 (95% CI
197 -0.3 to 0.2 , $P=0.78$). The difference in medians for delafloxacin 400mg/day vs. placebo was 0 (95% CI –
198 0.3 to 0.2 , $P=0.95$). No visible wavelength phototoxicity was detected.

199 None of the subjects in the delafloxacin 200 mg/day group had abnormal MED responses
200 (reduction of $>40\%$ from baseline) on Study Day 7. Two subjects in the delafloxacin 400 mg group and 1
201 placebo subject had abnormal MED responses on Study Day 7 and returned for day 8 assessments,
202 which were normal.

203 All 12 subjects in the lomefloxacin group had abnormal MED responses at day 7; 6 of these
204 subjects returned to less than 40% baseline by day 9 and so did not require further testing. Six of the
205 lomefloxacin subjects required further phototesting on Study Day 21 because of persistent
206 photosensitivity at day 9; one subject did not return for this follow-up. Repeat phototesting in these
207 subjects showed that the photosensitivity had resolved by day 21. There was no evidence of abnormal
208 pigmentation at Study Day 21 in any of the subjects.

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209 **Safety**

210 The most common study drug-related adverse event in the delafloxacin 200 mg and 400 mg
211 groups were associated with the digestive system (31% and 38% respectively). Five subjects in the
212 delafloxacin 400 mg/day and 1 subject in the placebo group reported diarrhea during the study, all of
213 which were considered to be probably or possibly related to study drug. Additionally, all cases of
214 diarrhea were sporadic, mild, or moderate in intensity, and resolved spontaneously. Four subjects (1
215 delafloxacin 200 mg, 2 delafloxacin 400 mg, and 1 placebo) were prematurely discontinued from study
216 drug due to the occurrence of at least one adverse event. Three of these subjects withdrew due to
217 adverse events considered possibly or probably related to study drug (headache in one delafloxacin 400
218 mg subject; diarrhea and abdominal pain in one delafloxacin 400 mg subject; migraine, myasthenia and
219 dizziness in a placebo subject). No clinically meaningful patterns of changes in vital signs values, ECG,
220 and laboratory values were observed during the study.

221 **DISCUSSION**

222 While a halogen atom at position 8 of a FQ can expand the spectrum of antibacterial activity and
223 improve oral bioavailability, they have been rarely used in FQs due to the severe phototoxicity caused by
224 this substitution.⁴ Attempts to reduce or avoid phototoxicity have led to the development of FQs with a
225 methoxy group at position 8. While these FQs did not cause phototoxicity in clinical studies, this
226 substitution produced agents with decreased antibacterial activity.¹ However SAR work has shown that
227 the phototoxic potential of FQs may be influenced by other substitutions on the quinolone core
228 molecule. The presence of a large bulky substitution at position 1 mitigated phototoxicity associated
229 with the halogen at position 8 in an animal model. This work demonstrated that with specific
230 substituents, new types of 8-halogeno quinolones with high levels of antibacterial activity but without
231 severe phototoxicity could be developed.¹

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232 The results in this clinical study are consistent with the findings in the previously reported
233 animal study, where a compound with an aminodifluoropyridine at position 1, as seen with delafloxacin,
234 appears to have less risk for phototoxicity even when there is a halogen at position 8 in the quinolone
235 molecule. At dosages of 200 and 400 mg/day, delafloxacin failed to demonstrate a significant
236 phototoxic effect. It is important to note that C_{max} levels were used for risk assessment as this plasma
237 parameter is considered most predictive for phototoxicity.¹⁷ The 400 mg/day oral dose of delafloxacin
238 in this study was unformulated drug-in capsule and generated a C_{max} of delafloxacin, which overlaps with
239 that seen with the formulated 450mg oral tablet currently approved for use in the U.S. No differences in
240 phototoxic effect were seen between the 200 and 400 mg/day doses. The classical pattern of
241 fluoroquinolone phototoxicity as detected in previous phototoxicity studies with other fluoroquinolones
242 (i.e., a UVA phenomenon maximal at 24 hours) was not seen with delafloxacin. However, lomefloxacin
243 revealed phototoxicity within the moderate phototoxic index group at the 335 and 365±30 nm
244 wavebands, maximal at 24 hours, with susceptibility clearing within 48 hours after drug cessation.
245 Phototoxicity was not demonstrated in the placebo group. Using the solar simulator, the mean and
246 median phototoxic index of the lomefloxacin group was higher than in the other 3 dosing groups, with
247 statistically significant differences between lomefloxacin and both the placebo and 200 mg delafloxacin
248 group. Whether measured *via* change in MED or by PI, delafloxacin 200 and 400 mg doses had no
249 phototoxic effect and were comparable to placebo. **(Tables 1 and 2)**

250 There were plans to test to longer wavebands if photosensitivity was detected to the 430±30nm
251 waveband and if there had been significant 400±30nm waveband photosensitivity, short and long-pass
252 filters were to be used to determine whether or not there was visible wavelength phototoxicity with its
253 possible implications for the retina. If a drug was found to be significantly photosensitizing and for the
254 photosensitivity to extend into the visible part of the spectrum then this would have potential
255 implications for adverse effects on the retina. However, in this study, as there was no significant

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256 photosensitivity detected at the UVB and UVA wavebands tested, there was therefore no indication or
257 requirement to extend phototesting into the visible part of the spectrum.

258

259 While informative, phase 1 studies, with a focus on a small number of healthy volunteers, may
260 miss toxicities encountered in clinical practice. In a pooled analysis of 741 subjects from two Phase 3
261 trials of delafloxacin in the treatment of ABSSSI, there were no cases of phototoxicity reported.²²
262 Additionally, monitoring in clinical use will be prudent.

263

264 Conclusion

265 Oral delafloxacin was well tolerated in this study, with the most common event being mild to
266 moderate gastrointestinal events. Of note, this study used unformulated drug in capsule which
267 generated a C_{max} of delafloxacin which overlaps with that seen with the formulated 450mg tablet
268 currently approved for use in the US. Previous studies have shown differences in phototoxic potential
269 between the fluoroquinolones. The results of this trial showed that both doses of delafloxacin were
270 safe, well tolerated, and did not demonstrate clinically significant phototoxic potential at any
271 wavelength tested in healthy adult volunteers.

272

273 Acknowledgements.

274 These data were presented in part during ICAAC 2015 in San Diego CA (poster #F-1198a).

275 This phase 1 trial was not registered at ClinicalTrials.gov

276

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277 *Funding and Transparency Declarations*

278 Three authors (LL, ED, SC) are employed by Melinta Therapeutics, Inc.; all research was funded by

279 Melinta Therapeutics, Inc. The other authors were compensated for their work on this study and have

280 no further conflicts of interest to declare.

281

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336 **Tables and Figures**

337 **Table 1.** Mean Percent Change from Baseline to Day 7 in MED by Monochromator Wavelength and
 338 Solar Simulator

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

340 NA= not applicable

341 * = statistically significant (p≤0.05)

342 [§] P-value comparing MED to baseline within treatment groups using Wilcoxon signed rank test.343 ^{§§} P-value comparing MED between treatment groups using Wilcoxon rank sum test.

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346 **Table 2.** Phototoxic Index (PI) Results on Study Day 7 Based on Wavelength and Solar Simulator

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Treatment Group	Wavelength	Mean (SD)	Min, Max	P-value vs. PBO [§]	P-value vs. LMX [§]
DLX 200 mg (n= 12) DLX 400 mg (n= 11) LMX 400 mg (n= 12) PBO (n=12)	295 ± 5 nm	1.0 (0.19) 0.9 (0.17) 1.0 (0.17) 1.0 (0.15)	0.8, 1.3 0.7, 1.3 0.7, 1.3 0.8, 1.2	0.738 0.148 0.596 NA	0.469 0.393 NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	300 ± 5 nm	1.1 (0.10) 1.1 (0.16) 1.1 (0.19) 1.1 (0.16)	1.0, 1.2 1.0, 1.5 0.8, 1.5 1.0, 1.5	0.916 0.912 0.625 NA	0.719 0.559 NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	305 ± 5 nm	1.1 (0.18) 1.1 (0.20) 1.1 (0.28) 1.0 (0.21)	0.8, 1.4 0.7, 1.4 0.8, 1.7 0.8, 1.4	0.736 0.481 0.881 NA	0.854 0.633 NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	335 ± 5 nm	1.0 (0.21) 1.1 (0.42) 3.4 (1.51) 1.2 (0.29)	0.8, 1.4 0.7, 2.1 1.4, 6.8 0.8, 1.8	0.244 0.381 <0.001* NA	<0.001* <0.001* NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	365 ± 5 nm	1.1 (0.18) 1.1 (0.19) 5.4 (2.69) 1.1 (0.27)	0.8, 1.4 0.8, 1.5 2.2, 10.0 0.8, 1.5	0.811 <0.999 <0.001* NA	<0.001* <0.001* NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	400 ± 5 nm	1.0 (0.08) 1.2 (0.34) 1.1 (0.15) 1.0 (0.00)	1.0, 1.2 1.0, 2.1 1.0, 1.5 1.0, 1.0	0.166 0.066 0.166 NA	0.964 0.551 NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	430 ± 5 nm	1.0 (0.00) 1.0 (0.00) 1.0 (0.00) 1.0 (0.00)	1.0, 1.0 1.0, 1.0 1.0, 1.0 1.0, 1.0	NA NA NA NA	NA NA NA NA
DLX 200mg DLX 400mg LMX 400mg PBO	Solar Simulator	1.0 (0.14) 1.0 (0.18) 1.3 (0.30) 1.0 (0.15)	0.8, 1.3 0.7, 1.3 0.8, 1.8 0.8, 1.2	0.899 0.228 0.012* NA	0.011* 0.110 NA NA

348 NA= not applicable

349 * = statistically significant (p≤0.05)

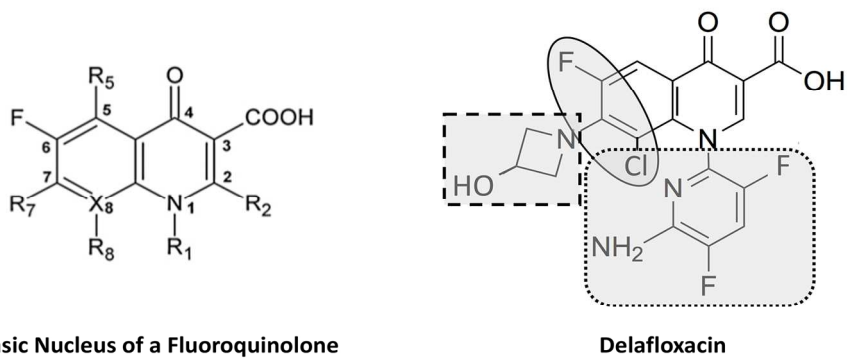
350 Min = minimum

351 Max = maximum

352 [§] P-value comparing MED between treatment groups using Wilcoxon rank sum test.

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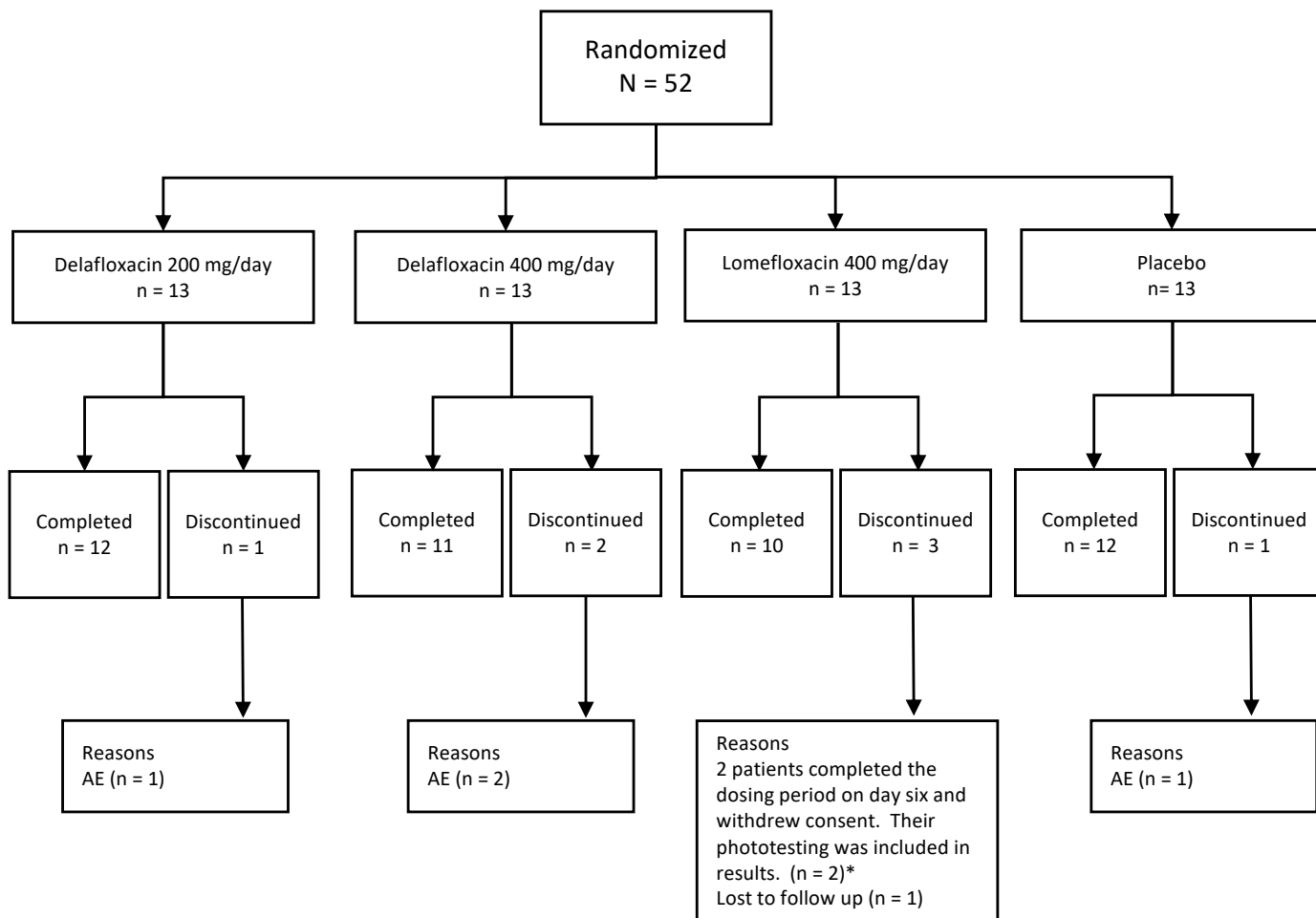
Large and heavily substituted N1 (dotted square) and unique polarity (oval) offer photo-safety regardless of presence of a halogen.

Anionic nature (dashed square) and bulky molecule at N1 (dotted square) lower CNS toxicity.

Figure 1

154x83mm (300 x 300 DPI)

Figure 2. CONSORT diagram of patient disposition



* Subjects who completed at least 6 days of dosing (N=47) were included in the analysis of phototoxicity.

Figure 3. Dotplots of Phototoxic Index Results at 335nm

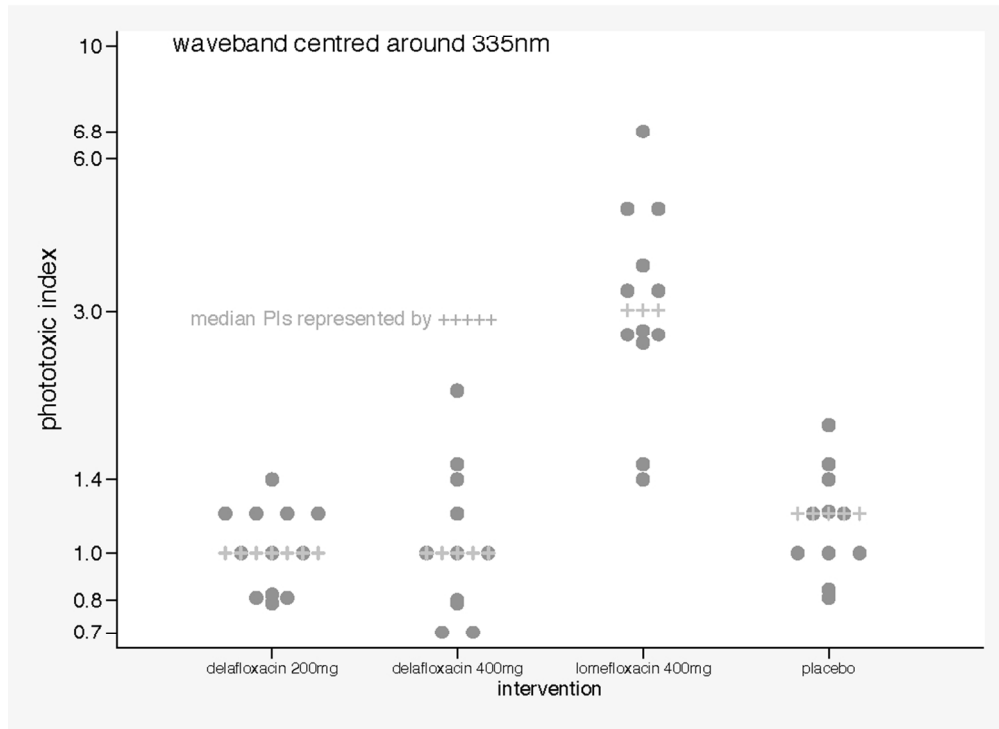


Figure 3

139x111mm (200 x 200 DPI)

