Methodology to Evaluate the Photosensitivity Potential of an Investigational Product in Healthy Volunteer Subjects

Allyson C. Marshall[1], Michael Tuley[1], Jonathan S. Dosik[1], Maureen Damstra[1], Derek Grimes[1], and Jon C. Anderson[1]

[1] TKL Research, Inc., One Promenade Boulevard, Fair Lawn, NJ 07410

Abstract

TKL Research Inc. (TKL) designed and implemented a Phase 1 clinical trial to assess the photosafety of an investigational product (IP) using a partially-blind, randomized, parallel group, placebo-controlled study design. Healthy volunteers were enrolled and randomized in a 3:1 manner to receive the IP or placebo (Part A) or the known photosensitizing agent ciprofloxacin (Part B). Subjects in Parts A and B received the drug (IP, placebo, or ciprofloxacin) for a predetermined period of time followed by photosensitivity assessments for 72 hours after the administration of the last dose. Photosensitivity was determined by calculating the minimal erythema dose (MED testing) for skin exposed to a series of ultraviolet light A (UVA)/UVB exposures. Skin test sites were analyzed for erythema and superficial skin reactions.

Introduction

An IP may display the potential for photosensitization due to its photochemical characteristics, data from preclinical and nonclinical studies, or general human safety information. The International Conference on Harmonization (ICH) S10 Photosafety Evaluation of Pharmaceuticals Guidance recommends the following characteristics which, if met, may present a concern for photosensitization: IP absorbs photons in the 290-700 nm range, generates a reactive species following absorption of UV-visible light, and distributes sufficiently to light-exposed tissues such as the skin or eyes. In order to assess the safety of an IP meeting one or more of these criteria, a clinical trial should be conducted in order to determine the phototoxicity (acute light-induced tissue response to a photoreactive chemical) and photoallergy (immune mediated reaction to a chemical induced by the formation of photoproducts after a photochemical reaction) potential of the IP.

Objectives

Primary Objective:

To evaluate the photosensitivity potential of the IP as assessed by the Photosensitivity Index (PI), changes in MED, erythema, and local skin reactions following exposure to UVA and UVB radiation.

Secondary Objectives:

To assess the relationship between the photosensitivity response and pharmacokinetics of the IP and to evaluate the photosensitivity potential of ciprofloxacin as assessed by the PI, changes in MED, erythema, and local skin reactions following exposure to UVA and UVB radiation.

Subject Population

Healthy males and females, 18-55 years old, were recruited to this clinical trial. Key inclusion and exclusion criteria for qualification are presented below.

Inclusion Criteria

- In good health, as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening;
- Fitzpatrick skin type I, II, or III (see Table 1);
- Vital signs within an acceptable range;
- Body mass index (BMI) within the range of 18 - 35 kg/m^2.

Table 1: Fitzpatrick Skin Types

Fitzpatrick Skin Type	Description
I	Always burns easily, never tans
II	Always burns easily, tans minimally
III	Burns moderately, tans gradually

Exclusion Criteria

- Use of another investigational drug at the time of enrollment, or within 5 half-lives or 30 days (whichever is longer) of enrollment;
- History of hypersensitivity to the IP or to drugs of other similar chemical classes, or fluoroquinolone antibiotic such as ciprofloxacin;
- Past medical history of clinically significant ECG abnormalities or clinically significant ECG abnormalities at baseline;
- History of cancer of any organ system including the skin within the past 5 years;
- Pregnant or nursing women;
- Women of child-bearing potential, defined as all women capable of becoming pregnant, unless they were using effect methods of contraception;
- Use of a known photosensitizing material within 30 days prior to dosing, any prescription drugs or herbal supplements within 30 days prior to dosing, over-the-counter (OTC) mediation and dietary supplements within 2 weeks prior to dosing;
- History of severe reactions from exposure to sunlight.

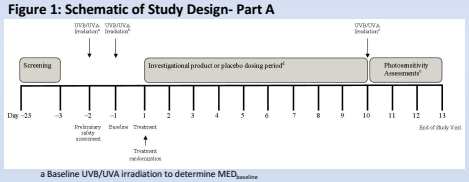
Methodology

This clinical trial, designed to evaluate the photosensitivity potential of the IP, was a partially blind, randomized, parallel group, placebo-controlled study. Healthy male and female adult volunteers were recruited and those who passed screening assessments, complied with inclusion and exclusion criteria, and provided written consent, were enrolled in the study. Approximately 48 subjects (36 subjects in Part A; 12 subjects in Part B) were enrolled to allow for at least 42 completed subjects. Subjects were randomized in a 3:1 ratio.

PART A

Part A was conducted according to a randomized, double-blinded, placebo-controlled design to assess the photosensitivity potential, safety and tolerability, and pharmacokinetics of multiple doses of the IP. Subjects were randomized in a 3:1 manner to receive the IP or placebo. Subjects were given a dosing regimen of the IP over an appropriate period of time in order to reach pharmacokinetic steady state; subjects receiving placebo followed the same dosing schedule (see Figure 1, 10-day dosing period to achieve steady state shown). Light exposure occurred following the last dose of either IP or placebo, and on-treatment photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) were performed at 10 minutes, and 1, 24, 48, and 72 hours after irradiation.

Figure 1: Schematic of Study Design- Part A



a Baseline UVB/UVA irradiation to determine $MED_{baseline}$
b Baseline UVB/UVA irradiation to confirm and fine tune $MED_{baseline}$ calculated on Day -2
c UVB/UVA irradiation to determine $MED_{on\ drug}$
d Dosing period of IP, placebo, or positive control (ciprofloxacin) in accordance with current clinical standards

Skin Reaction Grading Scales

Table 2 presents the skin grading scales used for scoring erythema, local skin reactions, and superficial effects following irradiation

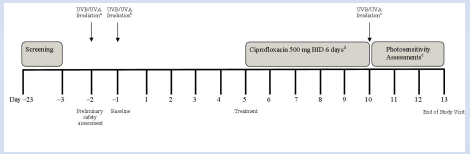
Table 2: Skin Reaction Grading Scales

Erythema Grading Scale	Local Skin Reaction	Superficial Effects Grading
0 No evidence of erythema	E Edema-swelling, spongy feeling when palpated	g Glazing
1 Very slight erythema (barely perceptible)	P Papule-red, solid, elevation	y Peeling
2 Well defined erythema	V Vesicle-small elevation containing fluid	c Scab, dried film of serous exudate of vesicular or bullous reaction
3 Moderate to severe erythema	B Bullous reaction-fluid filled lesion (blister)	d Hyperpigmentation (reddish-brown discoloration of test-site)
4 Severe erythema (beet redness)	S Spreading-evidence of the reaction beyond the irradiated area	h Hypopigmentation (loss of visible pigmentation at test site)
	W Weeping-result of a vesicular or bullous reaction-serious exudate	f Fissuring-grooves in the superficial layers of the skin
	I Induration-solid, elevated, hardened, thickened skin	
	- Response occurs ≤25% of test site	

PART B

Part B was conducted according to an open-label, observer-blinded design to assess the photosensitivity potential of ciprofloxacin (a mild photosensitizer) as a positive control. Subjects received their first dose of 500 mg ciprofloxacin on the morning of Day 5. Twelve (12) hours later, subjects received their second dose of 500 mg ciprofloxacin. Subjects continued a twice-daily dosing regimen through to the morning of Day 10 to ensure they reached pharmacokinetic steady state (see Figure 2). Light exposure occurred on Day 10 at 1 hour post-dose, and on-treatment photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) were performed at 10 minutes, and 1, 24, 48, and 72 hours after irradiation.

Figure 2: Schematic of Study Design- Part B



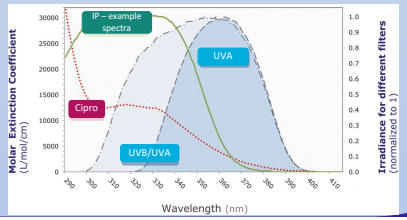
Photosensitivity Testing

Skin test sites were irradiated with the following 3 conditions:

1. Full range solar UVB/UVA (290 to 400 nm, UBV content ~10%), simulating midday summer outdoor sun exposure
2. UVA only (320 to 400 nm, UVB content <0.03%), simulating indoor exposure behind window glass
3. Full solar range UVB/UVA (1/2 MED) + UVA (16 J cm-1) to account for different skin types and individual sensitivities

Subjects were exposed to a series of full range solar UVB/UVA exposures (condition 1) and UVA only exposures (condition 2), each 25% greater than the previous dose. Skin sites were evaluated for erythema or skin darkening. The MED was defined as the lowest dose that produced uniform redness (condition 1) or darkening (condition 2). Inflammatory skin reactions were scored according to Table 2.

Figure 3: Spectral Properties



Statistical Analysis

$$\text{Photosensitivity Index} = \frac{MED_{baseline}}{MED_{on\ drug}}$$

*Photosensitivity indices at 10 min, 1 h, and 24 h were performed using $MED_{baseline}$ values at the corresponding timepoint. Photosensitivity indices at 48 h and 72 h were performed using the $MED_{baseline}$ 24 h value.

The absence of photosensitivity was demonstrated when the 90% confidence interval (CI) of the mean difference in PI between the treatment and placebo groups at 1 h and 24 h post irradiation was within the range of [-0.4, 0.4], based on literature for ciprofloxacin. A mixed model for repeated measures on PI values at each time point was carried out with treatment, time, and their interaction as fixed effects and subject as a random effect. P-values, PI estimates, and 90% CIs for the IP and placebo were calculated from the model.

$$\%\ \text{change} = \frac{MED_{on\ Drug} - MED_{baseline}}{MED_{baseline}} x\ 100$$

*A positive photosensitivity response was defined as a decrease in mean MED on >40%.

Results

A photosensitivity study conducted with this design will yield the following results:

- Subject characteristics (i.e., demographics, disposition)
- $MED_{baseline}$ and $MED_{on\ drug}$ at predetermined timepoints following irradiation for IP, positive control, and placebo
- Calculation of PI following irradiation with UVB/UVA and UVA-only radiation at predetermined timepoints for IP, positive control, and placebo
- Skin grading for local skin reactions at predetermined timepoints for IP, positive control, and placebo
- Pharmacokinetics of IP (blood samples may be obtained to monitor pharmacokinetic parameters in order to ensure IP has achieved steady state levels
- Safety and tolerability via monitoring of adverse events.

References

D. Bauer, R.L. Soon, K. Kulmatycki, Y. Chen, A. Noe, J. Chen, J.S. Dosik, and D. Meyers, The DGAT1 Inhibitor Pradigastat does not Induce Photosensitivity in Healthy Human Subjects: A Randomized Controlled Trial Using Three Defined Sunlight Exposure Conditions, *Photochemical and Photobiological Studies*, 2016, **15**, 1155-1162

T.B. Fitzpatrick, The Validity and Practicality of Sun-Reactive Skin Types I through VI, *Arch. Dermatol.*, 1988, **124**, 869-871.

L.E. Boccumini, C.L. Fowler, T.A. Campbell, L.F. Puertolas, and K.H Kaidbey, Photoreaction potential of Orally Administered Levofloxacin in Healthy Subjects, *Ann. Pharmacother.*, 2000, **34**, 453-458.

K.H. Kaidbey and A.M. Kligman, The Acute Effects of Longwave Ultraviolet Radiation on Human Skin, *J. Invest. Dermatol.*, 1979, **72**, 253-256.

A.M. Kligman and K.H. Kaidbey, Human Models for Identification of Photosensitizing Chemicals, *J. Natl. Cancer Inst.*, 1982, **69**, 269-272.

Contact Information

For more information on TKL Research, Inc. including clinical trial design, services, and photosensitivity studies, please contact:

Derek Grimes dgrimes@tklresearch.com