# UTILITY OF THE DOUBLE-BLIND CROSSOVER DESIGN PROTOCOL FOR PROOF-OF-PRINCIPLE PHOTOSENSITIVTY MODEL ASSESSMENT OF PF-06372865

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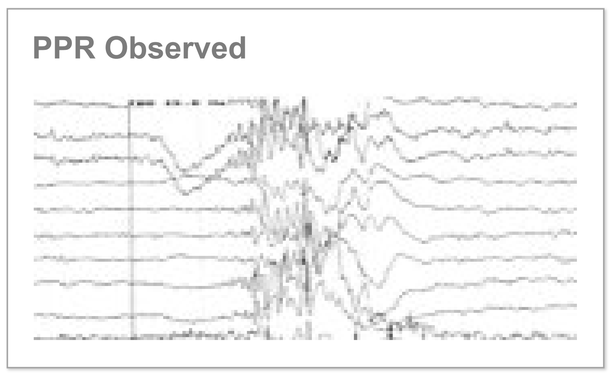
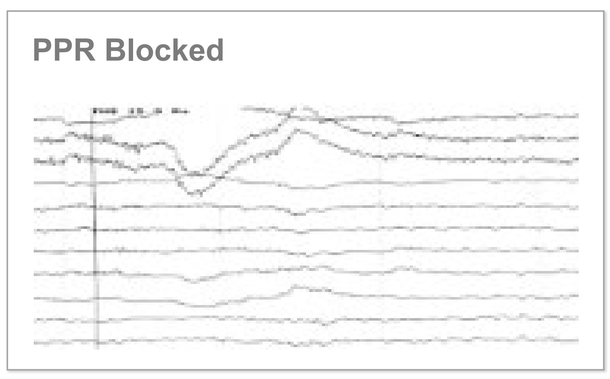
## Rationale

- Whilst the photosensitivity model has been widely used as proof-of-principle of anticonvulsant potential in early clinical development of potential antiepileptic drugs, most prior studies have been single blind, inpatient studies, where the treatment day would immediately follow the placebo day. This trial used the double-blind, cross-over design approach demonstrated by French et al., 2014 to assess novel drug candidate PF-06372865.
- PF-06372865 is a partial PAM of α2/3/5 subunit-containing $GABA_A$ receptors, with minimal activity at α1-containing receptors, which are believed to mediate many of the adverse events associated with benzodiazepines.
- The objective of this Phase 2a study was to assess the activity of PF-06372865 in the photosensitivity model as proof of principle of efficacy in patients with photosensitive epilepsy (NCT02564029). Effects in this model have been demonstrated to substantially increase the likelihood that efficacy will be seen in clinical epilepsy populations [1,2].

## Methods

- A total of 7 subjects (5 female, 2 male) with documented photosensitive epilepsy were randomized and all completed the double-blind, 4 period cross-over study examining single doses of placebo, 17.5 and 52.5 mg PF-06372865 and 2 mg lorazepam (active control).
- Subjects were exposed to intermittent burst of light with different flash frequencies that evoked a generalized photoparoxysmal EEG response (PPR) [1].
- Standardized photosensitivity ranges (SPRs) were recorded at screening and at each subsequent active treatment visit pre-administration of study drug and then at 1, 2, 4 and 6 hours post-administration.
- The primary endpoint was the average least square mean change in the SPR in the subject's most sensitive eye condition (either closed, open, closing), over the first 6 hours post-treatment.




| Flash frqcy (Hz) | 2 | 5 | 8 | 10 | 13 | 15 | 18 | 20 | 23 | 25 | 30 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject xxx | – | – | – | + | | | SPR = 8 | | | | + | – | – | – |

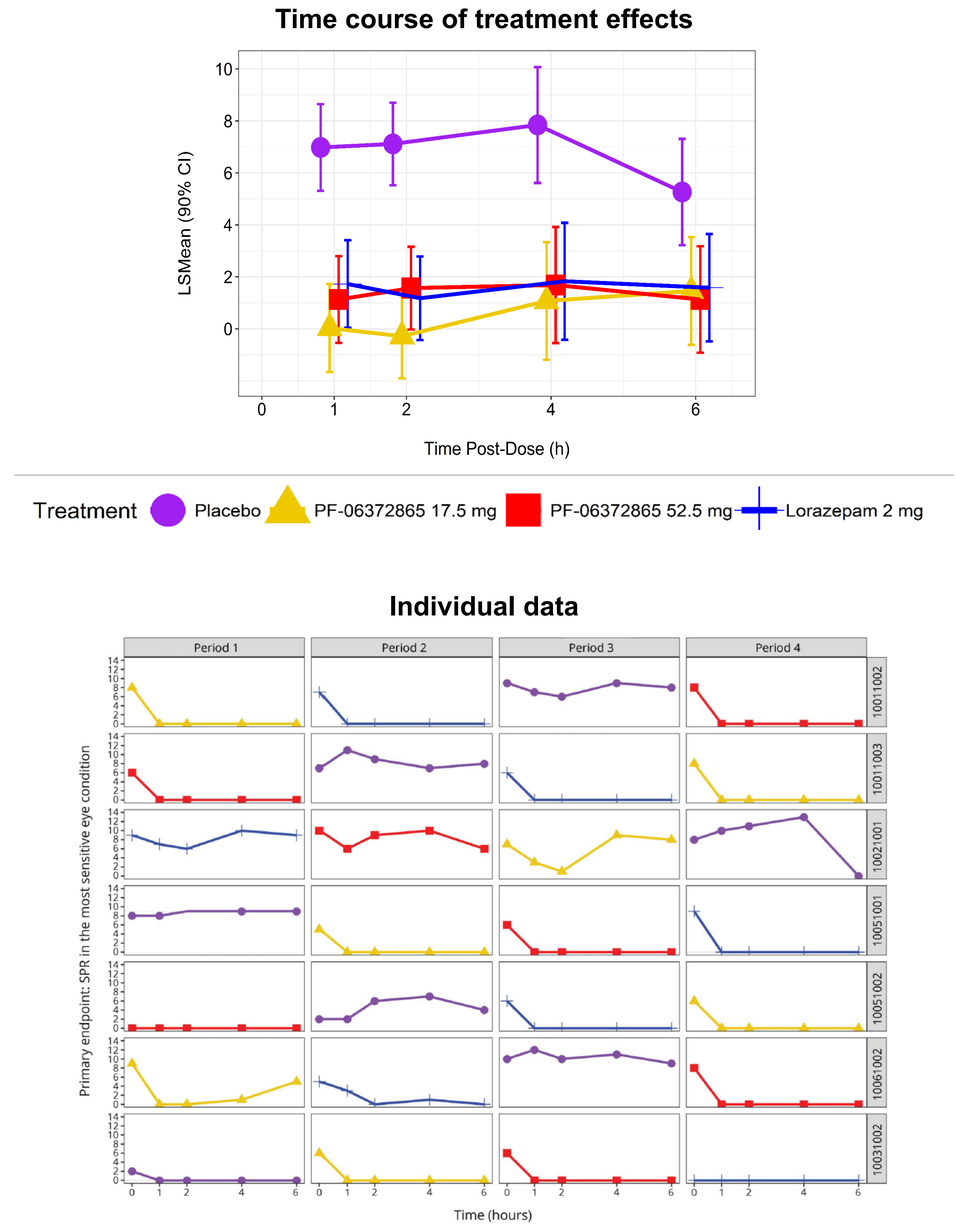
| Sequence | Treatment Period 1 | Treatment Period 2 | Treatment Period 3 | Treatment Period 4 |
|---|---|---|---|---|
| 1 (n = 2) | A | B | C | D |
| 2 (n = 2) | B | D | A | C |
| 3 (n = 2) | C | A | D | B |
| 4 (n = 2) | D | C | B | A |

A: Placebo
B: PF 06372865 17.5 mg
C: PF 06372865 52.5 mg
D: Lorazepam 2 mg
Abbreviation: n = number of subjects

1. French J, et al. Neurotherapeutics (2014) 11:412-418.
2. Yuen E.S.M., Sims J.R. Seizure (2014) 23:490-493.
3. Gurrell R, et al. Neurology (2019) 92(15):e1786-e1795.

## Results

- Both doses of PF-06372865 demonstrated efficacy and superiority over placebo, with 6 out of 7 subjects having complete suppression (SPR = 0 in all 3 eye conditions at the same time point).
- The average response relative to placebo in SPR in the most sensitive eye condition was: 17.5 mg PF-06372865 -6.2 (90% CI: -8.6 to -3.9); 52.5 mg PF-06372865 -5.4 (90% CI: -7.8 to -3.1); 2 mg Lorazepam -5.2 (90% CI: -7.6 to -2.8).
- The Figures below show the mean response vs time for each treatment group and the individual data.




- PF-06372865 was safe and well tolerated and drug concentrations were as expected[3].

## Conclusions

- The crossover trial design allowed for an efficient proof-of-principal trial demonstrating the anticonvulsant efficacy of a novel α2/3/5-subtype selective $GABA_A$ partial PAM in only 7 subjects.
- The double-blind design allowed for the inclusion of a relevant positive control, Lorazepam, without an increase to sample size, to further increase confidence in results. Future proof-of-principle photosensitive epilepsy trials should consider utilizing a double-blind crossover design and the inclusion of an active control[3].

## Additional Information and Disclosures

- PF-06372865 is now part of the portfolio of Cerevel Therapeutics LLC and has been renamed CVL-865. CVL-865 is being positioned for a Ph2 clinical trial in patients with drug-resistant focal onset seizures, estimated to start late 2019.
- One or more authors report potential conflicts which are described in the program.

### About Cerevel

Cerevel is a new biopharmaceutical company formed through a partnership between Bain Capital and Pfizer focused on developing drug candidates to treat disorders of the central nervous system.