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| Duke Clinical Research Institute Clinical Trials Statistics | |
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| Version: 4.0 | Effective Date: 31 Jan 2017 |
| Form Title: Agreement to Planned Analyses | |


Agreement to Planned Analyses

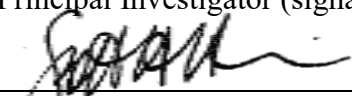
Trial: KP415.E01

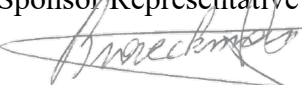
Analysis Plan Date: 8/8/2018

- Purpose of analysis plan(s):
- DMC/Interim analysis or safety report
 - Substudy analysis
 - Final (main trial) analysis
 - Confirmatory analysis
 - Operational reporting
 - Central Statistical Surveillance
 - Outcomes registry analysis
 - Addendum to analysis plan version 2.0
 - Other: [Click here to enter text.](#)

In signing this document, I am confirming that I have reviewed and approve the analysis plan(s) referenced above.

| | |
|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Faculty/Reviewing Biostatistician (signature):  | Faculty/Reviewing Biostatistician's Title: Associate Professor of Biostatistics |
| Printed name: Sheng Luo | Date: 8/9/2018 |

| | |
|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Principal Investigator (signature):  | Principal Investigator's Title and Affiliation: Professor of Psychiatry & Behavioral Sciences |
| Printed name: Scott H. Kollins | Date: 09AUG2018 |

| | |
|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Sponsor Representative (signature):  | Sponsor Representative's Title and Institution: Vice President, Clinical Development Kempharm, Inc |
| Printed name: Rene A Braeckman | Date: 9 August 2018 |

Sponsor approval required whenever sponsor requests to review the analysis plan.

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Clinical Trials Statistics

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A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled,
Parallel Efficacy Laboratory Classroom Study with KP415 in Children with
Attention-Deficit/Hyperactivity Disorder

Protocol: KP415.E01

08 AUG 2018

Addendum to the Statistical Analysis Plan

KemPharm, Inc.
1180 Celebration Blvd, Suite 103
Celebration, FL 34747
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In addition to the analyses described in Version 2.0 of the Statistical Analysis Plan (SAP), the following post-hoc analyses will be performed as outlined below. The rationale for the post-hoc analyses is to assess the primary and secondary endpoints (SKAMP and PERMP) using an alternate baseline definition (at Visit 6) to correct for differences in SKAMP-C scores between KP415 and placebo observed at pre-dose Visit 6.

Two new sets of analyses will be performed:

1. Change from baseline SKAMP and PERMP scores (SKAMP-C, SKAMP-A, SKAMP-D, PERMP-A, and PERMP-C) using the Visit 6 pre-dose assessment as baseline.

To estimate the difference between test (KP415) and control (placebo), a repeated measures analysis using MMRM will be performed similar to the primary efficacy analysis. The exact same model and covariates will be used as described in Version 2.0 of the SAP; the only difference will be the definition of baseline. Baseline will be defined as the pre-dose measurement at Visit 6 rather than the pre-dose measurement at Visit 5.

Below is a sample table of how the results for the primary efficacy endpoint using SKAMP-C score changes from pre-dose Visit 6 will be presented:

| | KP415 (N=) | Placebo (N=) | Treatment Difference: KP415-Placebo |
|-------------------------------------------|--------------|---------------|----------------------------------------|
| Pre-Dose (Baseline Visit 6) Mean (SD) | xx.x (xx.x) | xx.x(xx.x) | |
| Average Post-Dose Change from Baseline | | | |
| LS Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| 95% Confidence Interval | (xx.x, xx.x) | (xx.x, xx.x) | (xx.x, xx.x) |
| p-value | | | x.xxx |

Similar to the analysis described above, MMRM will be used to estimate the least square means, SEs and their corresponding 95% confidence intervals (CIs) between treatment groups for each post-dose time point at Visit 6 for the SKAMP and PERMP endpoints (SKAMP-C, SKAMP-A, SKAMP-D, PERMP-A, and PERMP-C).

Below is a sample table of how those results will be presented:

| Visit 6 | Change from Baseline (Visit 6 pre-dose) in SKAMP-C Score | | | | |
|--------------------------------------------------------------------------|----------------------------------------------------------|---------------|----------------------------|--------------------------|---------|
| Time point | LS Mean (SE) | | Difference in LS Mean (SE) | 95 % Confidence Interval | p-value |
| | KP415 (N=) | Placebo (N=) | KP415-Placebo | KP415-Placebo | |
| 0.5 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 1 hour post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 2 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 4 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 8 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 10 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 12 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 13 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| Mean difference in change from baseline across all post-dose time-points | | | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |

Onset and duration of the clinical effect of KP415. Using the change from baseline (pre-dose Visit 6 – alternate definition) SKAMP-C score at each post-dose Visit 6 time point and the alternate definition of baseline (pre-dose Visit 6) as covariate, the onset and duration of clinical effect will be analyzed. The onset of effect is defined as the first post-dose assessment time showing statistical significance ($p < 0.05$) between KP415 and placebo as measured by the SKAMP-C Score. The duration of treatment effect is defined as the length of the time interval, such that statistical significance was reached at each time point of this interval. Onset and duration results will be presented in a table.

2. Absolute SKAMP and PERMP values with Visit 6 baseline as a covariate.

Similar to the primary efficacy analysis, a repeated measures analysis using MMRM will be performed to estimate the difference in absolute SKAMP-C scores between treatment groups. The MMRM model will include post-dose time (session), treatment, the interaction of time and treatment, and site as fixed effects, and subject as random effect; and, the pre-dose SKAMP-C scores (at Visit 6) will be pre-specified in the model as a covariate. The model-adjusted means of all post-dose SKAMP-C scores for each treatment group and treatment group differences (KP415-placebo) with standard errors (SEs) and 95% confidence intervals (CIs) will be presented. SAS procedure PROC MIXED will be utilized to conduct the analysis. If the model specified is not estimable, the compound symmetry type of the covariance matrix will be used. The SAS code for the MMRM model for the SKAMP-C primary efficacy endpoint is as follows:

```
proc mixed data=adef method=reml;
Class trt02p usubjid atptn siteid;
Model aval= trt02p atptn trt02p*atptn base siteid/ ddfm=residual solution chisq;
repeated atptn /type= toep group=trt02p local subject=usubjid rcorr;
parms / ols;
Lsmeans trt02p/diff cl pdiff alpha=0.05;
run;
```

trt02p=treatment group; usubjid=subject ID number; atptn= assessment time point; siteid=site; aval= absolute SKAMP-C score, base = SKAMP-C baseline (pre-dose at Visit 6) score

Below is a sample table of how the results for the primary efficacy endpoint using absolute SKAMP-C scores and pre-dose Visit 6 as covariate will be presented:

| | KP415 (N=) | Placebo (N=) | Treatment Difference: KP415-Placebo |
|------------------------------------------|---------------|---------------|----------------------------------------|
| Pre-Dose (Baseline Visit 6) Mean (SD) | xx.x (xx.x) | xx.x(xx.x) | |
| Absolute Scores | | | |
| LS Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| 95% Confidence Interval | (xx.x , xx.x) | (xx.x , xx.x) | (xx.x , xx.x) |
| p-value | | | x.xxx |

MMRM will be used to estimate the least square means, SEs and their corresponding 95% confidence intervals (CIs) between treatment groups for each post-dose time point at Visit 6 for the SKAMP and PERMP endpoints (SKAMP-C, SKAMP-A, SKAMP-D, PERMP-A, and PERMP-C).

Below is a sample table of how those results will be presented:

| Visit 6 Time point | Absolute SKAMP-C Score | | | | |
|------------------------------------------------|------------------------|---------------|----------------------------|--------------------------|---------|
| | LS Mean (SE) | | Difference in LS Mean (SE) | 95 % Confidence Interval | p-value |
| | KP415 (N=) | Placebo (N=) | KP415-Placebo | KP415-Placebo | |
| 0.5 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 1 hour post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 2 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 4 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 8 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 10 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 12 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| 13 hours post-dose | xx.x(xx.x) | xx.x(xx.x) | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |
| Mean score across all post-dose time-points | | | xx.x(xx.x) | (xx.x , xx.x) | x.xxx |

Onset and duration of the clinical effect of KP415. Using the absolute SKAMP-C score at each post-dose Visit 6 time point and the alternate definition of baseline (pre-dose Visit 6) as covariate, the onset and duration of clinical effect will be analyzed. The onset of effect is defined as the first post-dose assessment time showing statistical significance ($p < 0.05$) between KP415 and placebo as measured by the absolute SKAMP-C Score. The duration of treatment effect is defined as the length of the time interval, such that statistical significance was reached at each time point of this interval. Onset and duration results will be presented in a table.

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