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): S. Luo	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.

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

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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	Absolute 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 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.

Listing of new tables and figures

Table	Post-hoc Analysis of Mean SKAMP-C Endpoint Primary Analysis	Intent-to-Treat Population
Table	Post-hoc Analysis of Mean SKAMP-C Endpoint Primary Analysis	Per-Protocol Population
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Table	Post-hoc Analysis of Onset and Duration of Clinical Effect of KP415 as Measured by Mean Change in SKAMP-C Scores	Per-Protocol Population
Table	Post-hoc Analysis of Mean SKAMP-D Scores by Time Point	Intent-to-Treat Population
Table	Post-hoc Analysis of Mean SKAMP-D Scores by Time Point	Per-Protocol Population
Table	Post-hoc Analysis of Mean Change in SKAMP-D Scores by Time Point	Intent-to-Treat Population
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Table	Post-hoc Analysis of Mean SKAMP-A Scores by Time Point	Intent-to-Treat Population
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Table	Post-hoc Analysis of Mean Change in PERMP-C Scores by Time Point	Intent-to-Treat Population
Table	Post-hoc Analysis of Mean Change in PERMP-C Scores by Time Point	Per-Protocol Population
Figure	Post-hoc Analysis of Treatment Difference in Change in Means Over Time in SKAMP-C Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Means Over Time in SKAMP-C Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Change in Means Over Time in SKAMP-A Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Means Over Time in SKAMP-A Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Change in Means Over Time in SKAMP-D Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Means Over Time in SKAMP-D Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Change in Means Over Time in PERMP-A Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Means Over Time in PERMP-A Scores	Intent-to-Treat Population
Figure	Post-hoc Analysis of Treatment Difference in Change in Means Over Time in PERMP-C Scores	Intent-to-Treat Population

Figure	Post-hoc Analysis of Treatment Difference in Means Over Time in PERMP-C Scores	Intent-to-Treat Population