M1230-05-033

Automated Average Bioequivalence Analysis with Additional Metrics and Statistics to Meet the FDA guidance on Methylphenidate Hydrochloride Using Phoenix® WinNonlin®

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PURPOSE

Methylphenidate Hydrochloride (Concerta®) is approved as a multiphasic modified-release formulation, designed to achieve both rapid onset of activity and sustained activity with a duration of 12 hours. The FDA guidance for Methylphenidate Hydrochloride recommends that partial area under the curve (pAUC) metrics are calculated in addition to the traditional metrics (C_{max} and $AUC_{0-\infty}$) to ensure that a generic formulation (test) is therapeutically equivalent to Concerta® (reference). These additional pAUC metrics are intended to better characterize systemic exposure responsible for the early onset of response, for sustaining the response in the middle of the once-daily dosing interval, and for maintenance of the response in late stage of the once-daily dosing interval. The guidance requires establishing average bioequivalence by calculating 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the pAUCs, C_{max} and $AUC_{0-\infty}$, and showing that they fall within the limits of 80-125%. In addition, to ensure the switchability between Concerta® and generic products, a subject-by-formulation test for each PK metric based on individual bioequivalence methods is recommended. Phoenix® WinNonlin® templates can be used to guarantee standardization and accuracy of the calculations and statistical analysis needed to show bioequivalence for generic products and Concerta®.

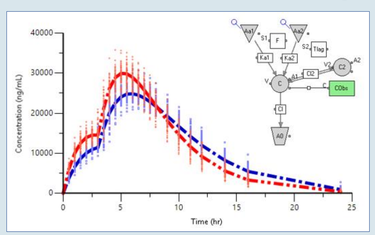
OBJECTIVE(S)

- to demonstrate that the average bioequivalence and individual bioequivalence tests required for Methylphenidate Hydrochloride can be performed in Phoenix WinNonlin,
- to provide users with a WinNonlin project that can be re-executed with their own datasets from Methylphenidate Hydrochloride studies.

METHOD(S)

Phoenix templates in general provide a means of creating a collection of data-processing and computational tools that can be reused with different datasets. A Phoenix template project was developed to meet the specific recommended tests from the FDA guidances on Methylphenidate Hydrochloride[1-5]. The project requires some initial input from the user but automates the calculation of the additional partial AUC parameters and performs the appropriate statistical analysis to test average and individual bioequivalence as specified by the FDA guidance. The guidance also recommends different pAUC time intervals for Fasted versus Fed studies, and the Phoenix project supports both types of studies.

To test the Phoenix project, a proprietary dataset was fit with a population 2-compartment model with two absorption rates (immediate release and extended release with a Tlag). The parameter estimates from the model fit were used to simulate four datasets with increasing levels of noise in the Tlag parameter. Dataset 1 was to provide a baseline test that passed all criteria, so Tlag for Test was simulated as 1% larger than for Reference. In Datasets 2, 3, and 4, this was increased to 10%, 65%, and 171%. These four datasets showed that as Treatment effect on Tlag increased, there were increasing failures in the BE criteria. In addition, Average BE was tested against SAS and Phoenix Individual BE was previously tested against S-PLUS code.



RESULT(S)

A Phoenix template project was created to perform an analysis for Methylphenidate Hydrochloride per the FDA Guidances, and includes these workflows:

Data Entry and Workflow to Prepare Dataset for Further Analysis: The data used should be from a single-dose, two-treatment, four-period, two-sequence, fully replicated crossover design, per the recommendation in the FDA guidances. The user can simply import their own data, map their data columns to contexts (Subject, Sequence, Period, Formulation, Time, and Concentration data), and enter basic information about their data: reference name and test name, Fasted or Fed status, and dosing data. A data processing workflow will automatically prepare the dataset for further analysis by NCA, Average BE, and Individual BE.

Workflow for NCA Analysis: A workflow is provided that computes Cmax, AUCINF_pred, and the required partial areas:

- for Fasted studies: AUC_{0-3}, AUC_{3-7}, AUC_{7-12}
- for Fed studies: AUC_{0-4}, AUC_{4-8}, AUC_{8-12}

All partial areas are computed and then filtered for the final tables. The user can specify additional partial areas if required for alternate formulations.

Workflow for Average Bioequivalence and Individual Bioequivalence: A workflow is provided for Average BE analysis using the FDA's recommended model for replicated data, to test that the drug must meet the usual 80.00% and 125.00% limits for Average BE for the 90% confidence interval of the test-to-reference ratio for AUCINF_pred, Cmax, and the required partial areas. To ensure switchability, this workflow also includes a subject-by-formulation test for each of these parameters, using the Individual Bioequivalence methods in the FDA guidance[6].

Workflows for Final Tables: A workflow is provided to retain only the appropriate Fasted or Fed parameters, and to generate report-ready tables for the Average BE results, for Individual BE results, to list any subjects not used in analyses due to missing observations, and to list subjects completing all four periods.

Results for Average Bioequivalence

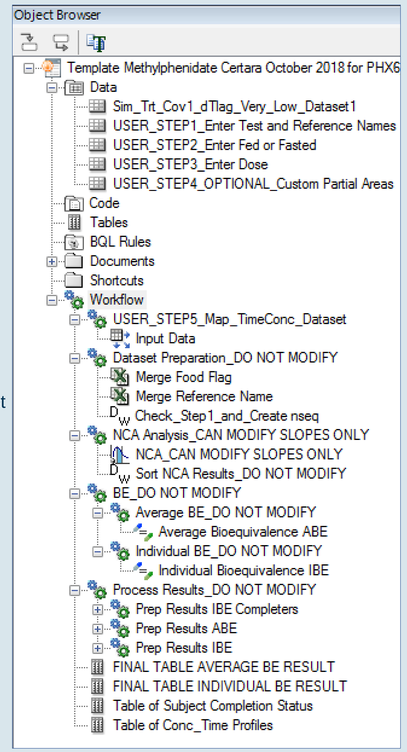
FOOD	Parameter	BE Ratio (%)	90% CI Lower	90% CI Upper
Fasted	AUC_{∞}	95.99	87.05	105.85
Fasted	Cmax	95.94	87.69	104.96
Fasted	AUC(0-3)	104.43	92.62	117.75
Fasted	AUC(3-7)	97.08	87.48	107.74
Fasted	AUC(7-12)	93.97	83.19	106.15
Conclusion: Passed Average BE				

Note: 90% CI must be within [80-125%] to pass ABE

Results to Ensure Switchability (Individual BE)

FOOD	Parameter	SigmaWR	Upper CI	IBE Conclusion
Conclusion: Passed Switchability				
Fasted	AUC_{∞}	0.347	-0.188	Indiv. BE shown for mixed-scaling CI test
Fasted	Cmax	0.256	-0.0481	Indiv. BE shown for mixed-scaling CI test
Fasted	AUC(0-3)	0.377	-0.168	Indiv. BE shown for mixed-scaling CI test
Fasted	AUC(3-7)	0.323	-0.116	Indiv. BE shown for mixed-scaling CI test
Fasted	AUC(7-12)	0.428	-0.274	Indiv. BE shown for mixed-scaling CI test

Note: Upper CI must be <= 0 to pass IBE



CONCLUSION(S)

Phoenix WinNonlin has the capability to perform bioequivalence calculations according to the FDA guidances for Methylphenidate Hydrochloride using a Phoenix template project that requires very minimal input by the user. This Phoenix project can be easily reused with different datasets, and partial area time intervals can also be added if needed for alternate formulations.

The Phoenix project presented in this poster is available for free download at Certara University:

http://www.certarauniversity.com/

REFERENCES

US FDA Draft Guidances on Methylphenidate Hydrochloride:

1. UCM320007, Recommended Sept 2012, Revised Nov 2014, Jul 2018. Extended release tablet, oral.
2. UCM581432, Recommended October 2017. Extended release tablet; oral.
3. UCM520241, Recommended October 2016. Chewable tablet; oral.
4. UCM427808, Recommended December 2014. Extended release suspension; oral.
5. UCM281454, Recommended November 2011, Revised Mar 2015. Extended-release capsule; oral.

US FDA Guidance for Individual Bioequivalence:

6. Statistical Approaches to Establishing Bioequivalence – Appendix G, UCM070244, January 2001.

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