Clinical Study Program for 505 (b) (2) NDA Application – The Fast Path to Approval

Juan He*, Masood Bhatti, and Lorelei Lutter, BioPharma Services Inc. Toronto, ONT, Canada

Abstract

The 505(b)(2) application is one type of NDA, and it potentially saves pharmaceutical companies time and money. This route can be utilized for a wide range of products with limited change from an approved drug. One change suited for 505 (b)(2) application is the application of modified release technology to achieve improved therapeutic and safety profiles with the existing approved products. There have been several approvals exemplifying this, such as Stavzor ® (soft gel of valproic acid) and Zolpimist® (oral spray of zolpidem).

Clinical pharmacokinetic studies comparing the bioavailability of active pharmaceutical moiety from the modified release products to that of the innovator are the important part of the 505 (b)(2) submissions, serving as the bridge of PK response and therapeutic efficacy. The program usually starts with the initial trial comparing overall bioavailability of the compound of interest from modified-release and innovator formulations under the fasted condition. If the desirable bioavailability is obtained, the food effect of the modified-release formulation should be tested; the consistent food effect which was seen in innovator is preferable. The steady-state comparative pharmacokinetics assessment should be carried out to investigate the accumulation of both modified-release and innovator formulations.

Drug interaction studies will provide useful information especially when the compound is metabolized via CYP 2D6 or 3A4. Chronopharmacokinetics should be assessed if the compound is known to produce different systemic and peak exposures at morning or evening dosing. The dose-strength equivalence and dose-proportionality studies are essential, if the new products will have more than one strength. The special population (renal and hepatic) PK studies are added value to 505 (b)(2) programs.

The gender and age effect should be explored in the aforementioned studies. The active metabolite(s) should be assessed for understanding of the biotransformation, and the chiral assay should be employed when the products involve the active enantiomers.

The clinical studies described above have a similar design to those within an ANDA program. The trials are 2-way crossover with 2-sequences; except for dose-proportionality and special population studies. The trials are easily handled from clinical practice and data analysis perspectives. Such programs can provide efficient FDA approval. There are about 30 505 (b)(2) applications approved during 2008. An example of 505 (b)(2) clinical program will be discussed.

505 B2 Route

Covers product that is similar to an approved drug but is not eligible for filing in an ANDA, usually it is the product with the modified release mechanism from the existing immediate release product.
Requires applicant to file patient certifications with application and serve notice on NDA holder and patent owner.
Requires several clinical trials to cover the comparative Pharmacokinetics (PK) studies of the drug exposure between the original and similar products in healthy subjects. The trials may also include the Pharmacodynamics (PD) end point for a PK/PD correlation for the modified release product.
Such trials may be easier and faster to conduct and analyze the study data compared to phase III trials.

Clinical Studies for Compound MRA01

MRA01 is an intended 505 b2 new product with the extended release feature of the product A01.

Available strengths:
A01: 25, 50, and 100 mg
MRA01: 200, 300, and 400 mg

The product A01 is given as b.i.d. and 100 mg each time in the morning, with the Tmax about 1 hours and half-life was around 10 hours. The compound is metabolized by CYP 450 2D6 and with a active metabolite of Hydroxy A01.

The intended dosing interval for MRA01 is once daily with 200 mg to achieve the similar overall bioavailability. The expected peak plasma concentration is around 8 to 10 hours from the dissolution study of MRA01.

Initial Fasted Study

Initial study for the comparable Bioavailability under the fasted condition with 36 healthy subjects.

The study will be single dose, two-way crossover, two periods, two treatments with A01 and MRA01.

Trt A: 100 mg A01 bid (total daily dose: 200 mg)

Trt B: 200 mg MRA01 od (total daily dose: 200 mg)

Sampling time points:
Trt A (bid): 0 (pre-dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, 22, 24, 36, and 48 hours post dosing
Trt B (od): 0 (pre-dosing), 1, 2, 3, 4, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 18, 20, 24, 36, and 48 hours post dosing

The expected outcome will be:

Comparable overall bioavailability of the compound from both products (AUCs and Cmax, Tmax will be the main PK parameters)

*For the primary author, contact Ms. Juan He at jhe@biopharmaservices.ca.

Initial fasted Study (con't)

The sample size (number of subjects) should be powered enough (using the available or pilot data) to assess the relative bioavailability between the MRA01 and A01 especially the Single dose fasted and multiple-dose as well as the food effect studies.

The exposure of both parents A01 and Hydroxy-A01 should be assessed for fasted and all other studies.

It is advisable to use the chiral assay for the main studies such as single dose fasted/multiple dose studies.

The urine data may be collected for the further characterize the PK of the modified release products.

Safety data for this study and this fasted and all 505 B2 studies should be tabulated and analyzed in the study reports.

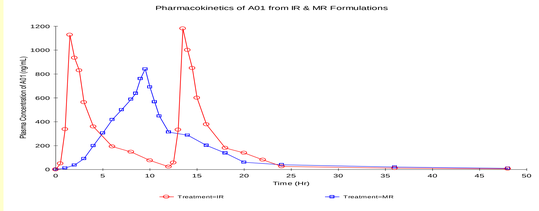
Tables & Graphs

Pharmacokinetics and Statistical Analysis for the Bioavailability between the two products are shown in the tables below.

The PK parameters and drug plasma concentrations were evaluated using Mixed/GLM procedure from SAS® with the factors of treatments, period, sequence, and subjects within sequence.

Product	AUC (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
A01	7339	1181	1.5 (13.5-12)
MRA01	6796	842	9.5

Relative Bioavailability	Ratio (MRA01/A01)	90% CI	P
AUC	93.87%	85% - 114%	0.037
C_{max}	72.03%	59% - 78%	0.129



Food Effect Study

If the fasted study showed comparative bioavailability to the current IR product, then a food effect study will carried out with the MR investigational product.

The study will be single dose, two-way crossover, two periods, two treatments with MRA01 in 28 healthy subjects.

Trt A: 200 mg MRA01 od under fed condition (total daily dose: 200 mg)

Trt B: 200 mg MRA01 od under fasted condition (total daily dose: 200 mg)

Sampling time points are the same for both Trt A and Trt B:
0 (pre-dosing), 1, 2, 3, 4, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 18, 20, 24, 36, and 48 hours post dosing

The expected outcome will be: Similar food effect of the compound MRA01 to the existing A01 (AUCs and Cmax, Tmax are the main PK parameters).

Multiple-Dose Study

Steady State comparative Bioavailability study after the fasted and food effect studies showed favorable results.

The study will be multiple-dose, two-way crossover, two periods, two treatments with A01 and MRA01 for 5 days for each treatment (T1/2: 10 hours) in 36 healthy subjects.
Trt A: 100 mg A01 bid (total daily dose: 200 mg)
Trt B: 200 mg MRA01 od (total daily dose: 200 mg)
Sampling time points:
Trt A (bid): 0 (pre-dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, 22, 24, 36, and 48 hours post dosing
Trt B (od): 0 (pre-dosing), 1, 2, 3, 4, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 18, 20, 24, 36, and 48 hours post dosing
Note: at least 3 pre-dose should be taken for steady state assessment.

The expected outcome will be: Comparable overall bioavailability of the compound from both products at the steady state.

DDI/Dose Proportionality

1. A drug-drug interaction (DDI) study using the CYP 2D6 probe (Quinidine) will also be conducted since the drug A01 is metabolized by CYP 450 2D6. The study will be 2 way crossover with or without Quinidine in 24 healthy subjects.

2. Since there are 3 dose strengths for product MRA01 available, the dose proportionality/dose strength equivalent study should be carried out. The study can be 3 way crossover with 3 periods of 200, 300, and 400 mg study doses in 27 healthy subjects.

3. Statistical Consideration for Data Analysis:
- the 80% to 125% confidence interval can be used for drug interaction and the dose proportionality
- the regression analysis should be carried out for the dose proportionality study.
- the main Pk parameters used for assessment should be both AUC and C_{max}

4. Expected outcome:
Similar drug interaction and proportionality to the existing immediate release product A01

Gender/Age/Chronopharmacokinetical Studies

1. Gender analysis can be done within other studies such as single dose fasted/multiple-dose studies

2. Age factor can be investigated within a single dose, two periods, two treatment, parallel designed study in 16 subjects in each study arms.

3. Since the A01 is given in the morning for better bioavailability, the MRA01 should be tested under both morning and evening dosing regimens.

The chronopharmacokinetic study will be single dose, two-way crossover, two periods, two treatments with MR01 in 36 healthy subjects (the study should be powered enough for relative bioavailability study).
Trt A: 200 mg MRA01 od under fasted condition in the morning (total daily dose: 200 mg)
Trt B: 200 mg MRA01 od under fasted condition in the evening (total daily dose: 200 mg)

4. Statistical Consideration for Data Analysis
- the 80% to 125% confidence interval can be used
- the main PK parameters used for assessment should be both AUC and Cmax

Special Populations (Renal/Hepatic)

1. The renal study with MRA01 will be done in a 3 way parallel studies with 10 subjects in each study arm. The will be 3 groups of subjects with normal renal function (Creatinine Clearance > 80 mL/min), mild renal impairment (Creatinine Clearance 50 - 80 mL/min) or moderate renal impairment (Creatinine Clearance 30 - 50 mL/min) patients.

2. The hepatic study with MRA01 will also be done in a 3 way parallel design with 10 subjects in each study arm. Similarly, the will be 3 groups of subjects with normal hepatic function, mild and moderate hepatic impairment patients according to Child-Pugh category.

3. Statistical Consideration for Data Analysis:

- model the renal or hepatic function with the PK parameters with the regression analysis
- the main PK parameters used for assessment should be both AUC and CL

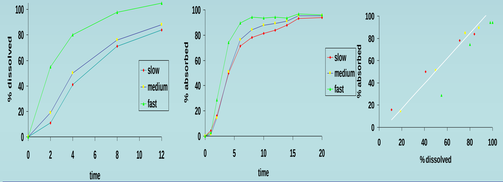
IVIVC

- Correlation or relationship between in vitro performance (usually dissolution) and in vivo performance of a drug formulation (absorption). It's used to set up the modified release product specification.

- Usually there will be slow, target (medium), and fast release formulations for investigation.

- The IVIVC PK study usually is crossover design with 4 periods and 4 treatments as following in 24 healthy subjects:
-Trt A: IV formulation (if IV is not available then use IR product)
-Trt B: Slow release formulation of MRA01
-Trt B: Medium release formulation of MRA01
-Trt D: Fast release formulation of MRA01

- IVIVC Method: Obtain in vitro dissolution profiles
Obtain in vivo plasma conc. profile
Estimate in vivo time course using deconvolution
Correlation - % dissolved vs % absorbed



PK/PD Correlation

The study will be single dose, two-way crossover, two periods, two treatments with A01 and MRA01 in about 24 healthy subjects.

The PK parameters will be Cmax and AUC from a single dose study

PD end point for MRA01 is the blood pressure change from the same single dose study with different time points.

The correlation between the Cmax/AUC and the blood pressure will be carried out for both treatments.

Conclusion

505 B2 provides a fast route for a similar product for FDA marketing approval due to the short duration and smaller sample size of the trials in healthy subjects.

Minimum fasted, food effect, and multiple dose studies if the drug accumulates to start.

Sample size for such PK/PD trials are much smaller than the efficacy phase III trials, usually in the range of 30 to 50 subjects per trial depending on the compounds.

DDI, dose proportionality, gender, age are good to investigate. Special population studies provide additional information for treatment.

An IVIVC (in vitro-in vivo correlation) study will be useful to set up the product specification.

A PK/PD correlation study will be very useful for supporting efficacy.