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INSTRUCTIONS FOR EXAMINATION PROJECT

FRAME STORY

You are working as a modelling scientist in the M&S (Modelling and Simulations) group at Big Pharma Inc. You have just received the results of the phase 1 study of BPI889. BPI889 is a follow-up compound to indinavir which is under development as a treatment against HIV/AIDS.

The phase 1 study focused on the pharmacokinetics (PK) of BPI889. A double-blind, randomized, cross-over study design was used with two arms: placebo and 200 mg of study drug (BPI889) as add-on to current standard of care treatment. Blood samples were collected at 30 min, 1, 2, 3, 6, 12 and 24 h post dose for study drug concentration determination. Concentrations of standard of care regiment was not determined.

In vitro experiments have revealed that cytochrome P450 enzymes are involved in the elimination of BPI889. The clinical team is concerned that variants of these enzymes will have a clinical impact on the PK of the compound. To investigate this risk, genetic testing was performed on all subjects of the phase 1 study.

A pharmacokineticist of the DMPK group who is also working on the project has given you some tips on how to assess elimination of a compound and how clinical impact is defined, see emails at the end of this document.

EXAMINATION PROJECT

In this project, you will be working with two data files: BP1889_genetics_XX.dat, containing the result of the genetic testing of the subjects and BPI889_PK_XX.csv, containing the results of the PK sampling of the arm where the subjects received BPI889.

You will receive a template for the report, listing the absolute minimum requirements in terms of operations to perform.

TASK

Your main task is to assess, statistically and graphically, whether genetic variations affect the elimination of BPI889, investigate the potential clinical impact of genetic correlation and create a supporting report for the clinical team.

In detail this entails:

1. Identifying which individuals that have functional SNP's in the codon for CYP3A4, 2C9, 2C19, 2D6 and 2E1 and classify the individuals as wildtype, heterozygote variant or homozygote variant.
2. Arrange the genetic information in a format that is suitable for covariate analysis with PK data.
3. Perform a graphical exploration of the PK of BPI889 and demographics of interest.
4. Assess the relationship between genetic variations and elimination, classify potential correlations it in terms of additive, dominant or recessive and investigate the clinical impact.
5. Create a report with supporting calculations and graphics including your conclusion.

Start by downloading the required files from the course at the student portal. Under the Documents tab, click on "Examination Project". From the file browser, get the file "final_project_key.pdf". Open this file on your local computer to find the number you have been assigned. Using this number in place of "XX", find and

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download the raw result of the full genetic testing from "SNP_data" (**BP1889_genetics_XX.dat**) and the PK profiles from "PK_data" (**BPI889_PK_XX.csv**). The genetics files are modified BLAST output in plain text and the PK files are comma-separated format (plain text or spreadsheet).

The assignment has been organized under the assumption that you will use Python for the initial data processing (up to the covariate input, step 1 and 2) and R for the statistical analysis and graphical exploration (step 3,4 and 5).

The project is an individual task.

REPORT AND GRADE

The report should consist of the supporting evidence for your conclusion related to each of the bullets listed in the task description.

The script(s) you used to complete the task should be uploaded to the student portal before the deadline (see schedule and introduction). Make sure the file(s) runs on a new system/in a new session.

Feedback will be emailed within 1 week from the deadline and resubmission with corrected report is due 1 week after receiving the feedback.

The grade of the course is based on the script. Readability, solutions avoiding redundant code or promoting re-usage and use of existing libraries/packages is promoted. Code that does not run on the examiners' systems after being downloaded from the student portal are considered failed.

TIPS FROM YOUR FRIEND THE PHARMACOKINETICIST

Below are screen shots of email conversations between you and your friend, Amy in the DMPK group:

To: #######@bigpharmainc.com
Cc:
Bcc:
Subject: Re: How to assess elimination?
Signature: None

Hi,
Sure!
I think you need to calculate clearance. That's the best estimate of elimination

CL = Dose/AUC

There are several ways of calculating AUC but I would suggest the trapezoidal rule. Use that to get the AUC from 0->24h and then use the last measured concentration divided by the slope of the last three observations to account for the remaining AUC: 24h -> infinity.

Good luck :)

Amy

From: ############
Sent: 31. October 2016 11:23
To: Amy Metabolomics
Subject: How to assess elimination?

Hi Amy,
I need to get an estimate of the elimination of BPI889 to assess whether the elimination is related to any of the CYP variants we've tested in the phase 1 study. Could you help me?

Many thanks!

To: #######@bigpharmainc.com
Cc:
Bcc:
Subject: Re: Clinical impact of BPI889
Signature: Signature #2

Ohh interesting!
I guess the most clinically important aspect is the average concentration for a repeated dosing, since there is a risk of side effects if the average concentration to too high. Use the following equation to calculate average concentration:

C = Dose*F/(CL*tau)

Assess the average concentration for 200, 400 and 800 mg (since 400 and 800 mg are also tested in the phase 2). Assume once daily dosing (tau = 24 h) and a bioavailability (F) = 0.9. I think that would be responsible assumptions. Remember to state the assumptions for your calculations.

See you Tuesday at the briefing!

Amy

From: ############
Sent: 11. November 2016 09:47
To: Amy Metabolomics
Subject: Clinical impact of BPI889

I need your help again!
I did find a correlation between the elimination an[redacted]but clearance isn't really the best way of presenting the results to the clinicians in the team. What would you use to show clinical impact of this finding to the clinical team?

Thanks! I own you!