SB-773812: Correlation between in-silico and in-vivo metabolism

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Background

SB-773812 is a molecule in development for schizophrenia and has been specifically designed to target antagonism at those receptors believed to be associated with antipsychotic efficacy (D2, D3, 5-HT2A, 5-HT2C, 5-HT6) while designing out affinity at receptors suggested to be linked to the side effects (H1, muscarinic M1-4, D1, adrenergic 1B, adrenergic 1-3) of current antipsychotics. Ideally an antipsychotic drug, used for chronic treatment, should have minimal drug-drug interaction (DDI) liability. The in-vitro data indicated that SB-773812 is metabolised predominantly by CYP3A4 enzyme. To determine the extent to which the inhibition of the 3A4 metabolic pathway could affect the metabolism of SB-773812, ketoconazole (KET) a potent CYP3A4 inhibitor, was co-administered with SB-773812.

SB-773812 PK Profile

SB-773812 PK profile is approximately linear in the range of 2-120 mg (single dose) and 16-120 mg (repeat dose). PK variability (between subjects) is moderate, in the range of 40-50%. Apparent oral clearance is ~ one third of the liver blood flow and the apparent volume of distribution is quite large (25 L/kg). SB-773812 mean terminal half life is ~55 h (range: 29-69 h). Cmax occurs between 4 and 6 hours post dose. Steady state occurs between 14 and 28 days of dosing with a mean accumulation factor of ~ 3.

Objective

The aim of this work was to predict the extent of DDI by developing in-silico model in SimCYP™ and then using the model predictions to guide the study design.

Methods

The physicochemical and PK characteristics for SB-773812, together with the in-vitro kinetic parameters generated, were entered into SimCYP™ (V 9.03). Input parameters for SB-773812 were calculated in-house from in-vitro and in-vivo experimental data, while the CYP3A4 inhibitor (KET), inputs were supplied by the program. An in-silico model for co-administration of SB-773812 and KET was developed and the results were compared with the clinical data.

This model was used to further guide and amend the clinical study part-way through in order to more accurately assess the maximum effect of KET.

Clinical trial design

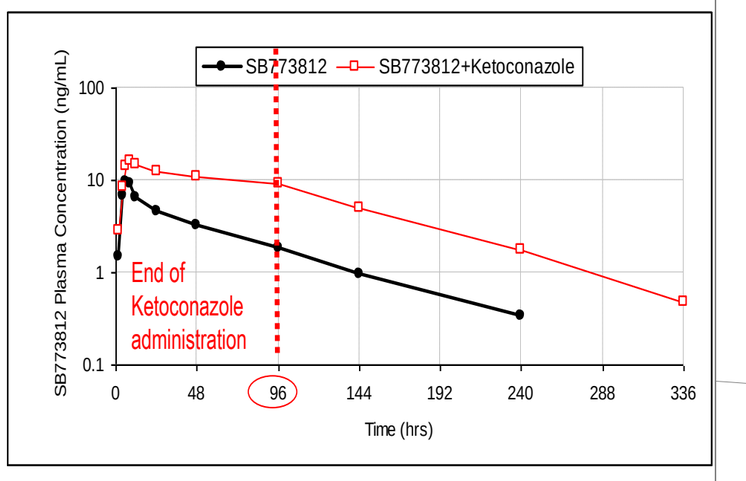
Two groups of KET dosing durations were examined, a total of 20 subjects in group 1 (original study) and 16 subjects in group 2 (amended study) were included in the study.
Single oral dose of KET 400mg (2x200 mg) was given, for 8 days. On day 5 single oral dose of SB-773812 (20 mg) given concomitantly with KET (2x200 mg).

SimCYP™ trial design

Ten trials of healthy volunteers (virtual population) comprising 10 subjects (20-50 years, 50% male/female were used in both group studies.

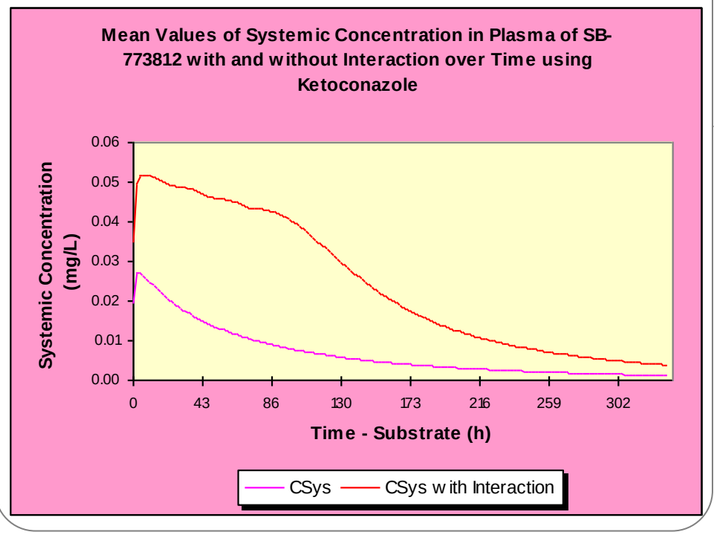
Results

Clinical Results: Original Study (Group 1)

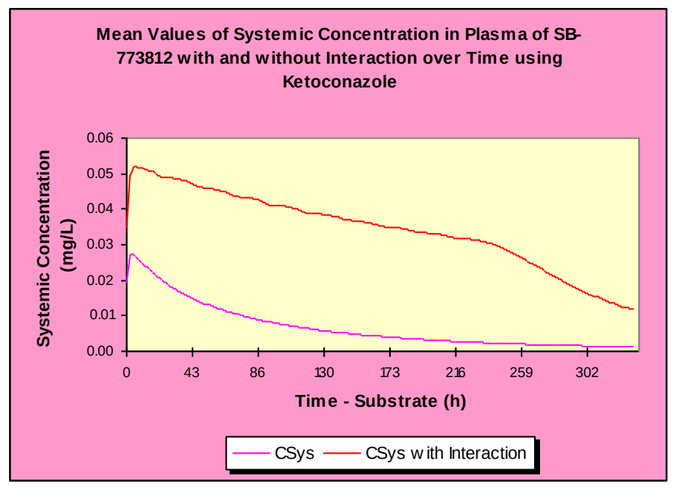


- SB-773812 AUC(0-∞) and Cmax increased approximately 3.3 and 1.6 fold, respectively, indicating that CYP3A4 is deeply involved in SB-773812 metabolism.
- The 3.3 fold increase was considered an underestimation of the true effect (elimination of SB-773812 is not complete after 96 h: $t_{1/2}$= ~55 h).
- It was recommended to extend KET co-administration to 240 h (10 days) post-dose to have a better estimate of the magnitude of interaction. The clinical protocol was then amended.

SimCYP™ Results: Original Study (Group 1)



SimCYP™ Results: Amended Study (Group 2)



DDI with ketoconazole: Data comparison

SB-773812 AUC (0-t) fold change	Group 1 4 days post-dose	Group 2 10 days post-dose
SimCYP™	3.5 (2.8-7.2)	4.8 (1.9-9.2)
Clinical	3.5 (3.2-3.8)	4.8 (4.2-5.6)

Ratios from SimCYP™ and clinical data are expressed as geometric mean ratio with 90% CI given in parentheses

SimCYP™ model predictions matched well with the in-vivo data from the original study (group 1). An interim PK check was conducted with SimCYP™ to understand the extent of interactions of SB-773812 and KET. The interim analysis indicated that extending the co-administration of KET was necessary for assessing the extent of interaction. The in-vivo results from the amended study (group 2) were also in good agreement with in-silico predictions from SimCYP™.

Conclusions

This study was carried out to analyze the interaction of KET co-administration on the PK of SB-773812. In-silico modelling tools such as SimCYP™ are widely and increasingly being used to explore and characterize DDIs. This work illustrates the importance of using in-silico modelling for reliably predicting in-vivo metabolism and DDIs.

References

1. Rostami-Hodjegan A and Tucker GT., *Nat Rev Drug Disov.* **6** (2007) 140-148.
2. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, and Rostami-Hodjegan A (2009) *Expert Opinion on Drug Metabolism & Toxicology*. **5** (2009) 211-223.