Clinical validation of a quantitative systems pharmacology (QSP) model for nerve-growth-factor (NGF) therapies

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Introduction

Despite a marked increase in the application of quantitative systems pharmacology (QSP), its role in drug development and regulatory decision making has not yet been well established. Case studies presented to date have often been retrospective in nature and may not be considered compelling enough by decision makers and regulators to significantly increase their confidence in the approach. On the other hand, due to fact that QSP is often applied in early stages of research [1], prospective predictions may never reach the point of clinical validation due to high attrition rates. Therefore, there is an urgent need for sharing case studies of clinical validation of prospective QSP model predictions [2].

Methods

Previously, we developed a QSP model of the nerve growth factor (NGF) pathway to guide selection and validation of novel targets for the treatment of pain [3]. A key, non-intuitive prediction from the model was that the concentrations to achieve clinically-meaningful analgesic efficacy for a small-molecule inhibitor of the tropomyosin receptor kinase A (TrkA) are very high (i.e. ~100-fold the *in vitro* potency). Clinical results in a battery of human evoked pain models for the first "peripherally-restricted pan-Trk inhibitor", PF-06273340, were very recently published [4] and we analysed the pharmacokinetic-pharmacodynamic (PKPD) results and compared this with our previous QSP predictions. PKPD data were extracted from the publication [4] with WebPlotDigitizer and analysed using the semi-compartmental modelling approach proposed by Kowalski and Karim [5], implemented in Phoenix version 7.

Results

PF-06273340 only met the decision rule on one of the five primary endpoints (UVB skin thermal pain detection threshold) at the highest dose tested (400 mg). Graphical exploration of the PKPD relationship showed marked hysteresis(Figures 1 and 2). An apparently linear effect-site concentration-effect relationship (Figure 3) was obtained using a semi-compartmental model [5]. Through extrapolation of the model, we estimated the efficacious concentration required to mirror the effect observed with reference treatment (600 mg ibuprofen) to be 795ng/ml, which is ~275-fold and ~20-fold the primary pharmacology IC_{50} based on total and unbound plasma concentration, respectively (Figure 3). Assuming that these are estimates of the lower end of the concentration-effect relationship and that higher multiples are required to match the clinical efficacy of NGF monoclonal antibodies, we conclude that the data are consistent with the prospective QSP model predictions for a selective TrkA inhibitor [3], also because some of efficacy observed with PF-06273340 may be related to its TrkB activity [4]. This potential gain in efficacy would however be offset by a smaller therapeutic window over TrkB-mediated side effects in the central nervous system [6]

FIGURE 1: PK and PD of PF-06273340 (4)

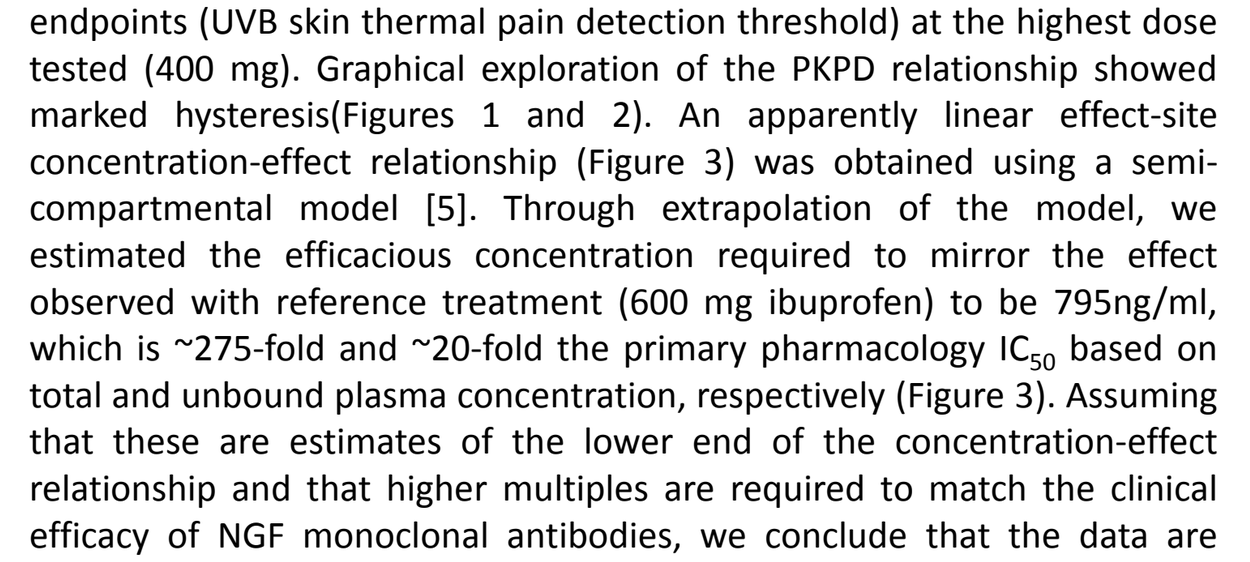


FIGURE 2: Plasma PKPD relationship for PF-06273340

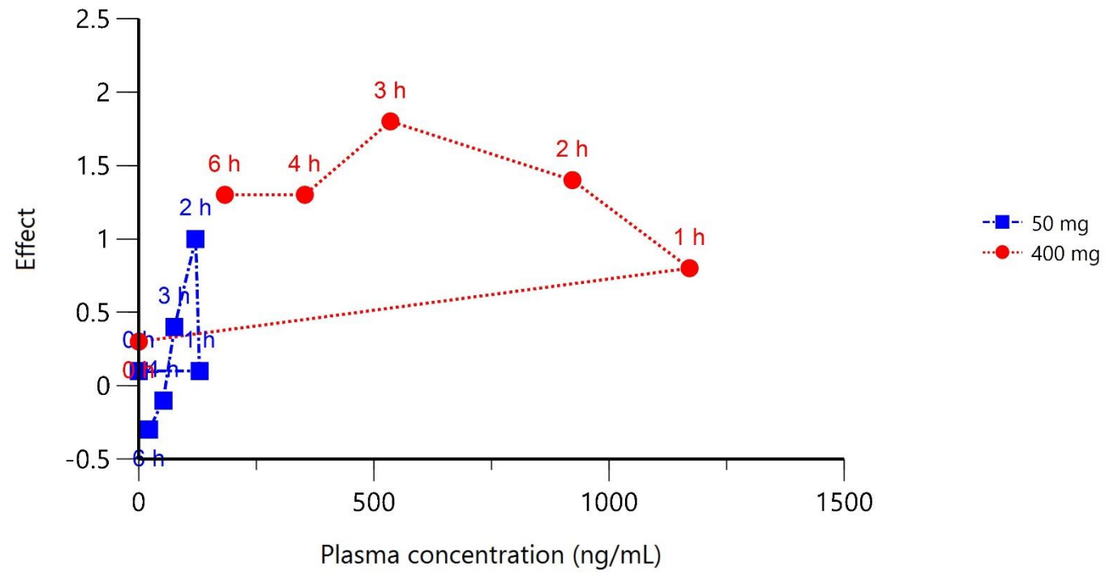
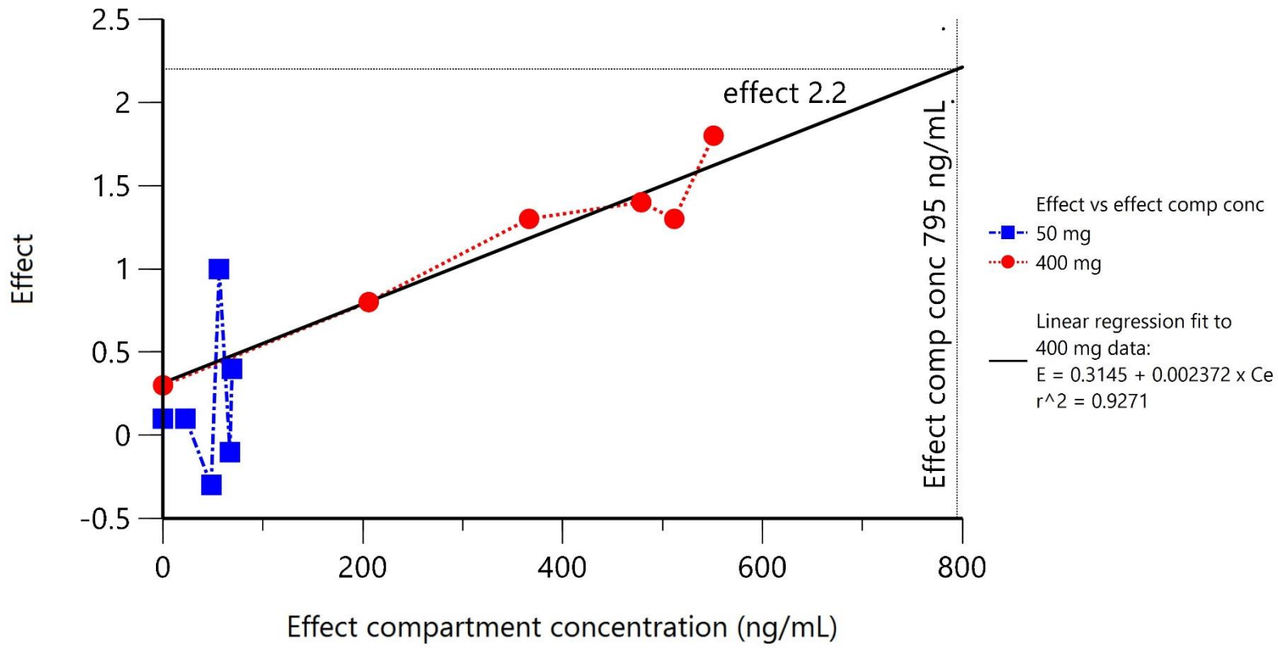


FIGURE 3: Effect compartment PKPD relationship for PF-06273340 (dotted line indicates efficacy obtained with 600 mg ibuprofen)



Conclusions

This analysis provides clinical validation of our QSP model for NGF therapies in pain. Given the very high predicted multiples of IC_{50} required to produce efficacy better than standard of care, we propose that it may not be possible to develop a peripherally-restricted small-molecule TrkA inhibitor with an acceptable therapeutic index for the treatment of pain. The quantitative guidance provided by the QSP model for the first-in-human study design is in line with new regulatory expectations with regards to calculation of starting dose and subsequent dose escalations [7]. Due to the modular nature of the model, it can be updated and extended when new biological insights become available [8] and to date we have applied it to 5 programs of different compounds/mechanisms. A mathematically reduced version of the full model has also been developed, which is more amenable for pharmacometric applications in clinical development [9].

References

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