Pharmacokinetic modeling of PYM50028 (Cogane™) predicts once daily dosing can achieve plasma levels in PD patients associated with preclinical efficacy

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Introduction

- PYM50028, a novel orally active neurotrophic factor modulator, is efficacious in preclinical models of Parkinson´s disease (PD) (Zhang *et al.,* 2008; Visanji *et al*., 2008; Johnston *et al*., 2009).
- Preclinical efficacy is associated with a plasma C_{max} of approximately 400 ng/ml.
- A safety, tolerability and pharmacokinetic (PK) study of PYM50028 was conducted in healthy volunteers (HV) and patients with PD using an oral solution formulation (Priestley *et al*., 2009)
- In patients with PD, a single dose of 150 mg/day produced a plasma C_{max} of approximately 480 ng/ml after 28 days of dosing.
- Systemic exposure to PYM50028 and its major metabolite PYM50038, was dose proportional and the profiles in HV were similar to those in patients with PD.

Objectives

- To develop an appropriate compartmental mathematical model that represents clinical PK data generated for PYM50028 and PYM50038.
- To apply the model to simulate plasma levels of PYM50028 and PYM50038 associated with different daily dose levels of PYM50028 in oral solution.
- To predict a dose level that can achieve a plasma C_{max} of approximately 400 ng/ml for PYM50028, supporting dose selection for a Phase 2 study.

Results

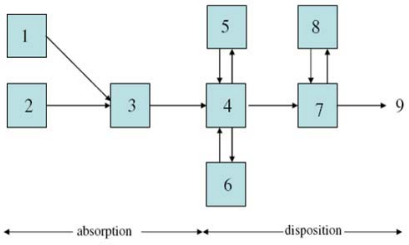

Figure 1. A two-segment, first-order absorption, multi-compartment disposition model was considered to best represent the data. Compartments 1–3 are associated with absorption of PYM50028. Compartments 4-8 are associated with the disposition of PYM50028 and PYM50038.

Daily Dose (mg/day)	PYM50028*		PYM50038*	
	C_{max} (ng/ml)	$AUC_{0\text{-}24\ h}$ (ng.h/ml)	C_{max} (ng/ml)	$AUC_{0\text{-}24\ h}$ (ng.h/ml)
5	16.2	206	6.63	113
25	81.2	1030	33.2	567
50	162	2060	66.3	1133
75	244	3090	99.5	1700
100	325	4120	133	2267
120	390	4944	159	2720
150	487	6180	199	3400
175	568	7210	232	3967
200	649	8240	265	4533

*Data presented are for Day 28.

Table 1. The model predicted the C_{max} and $AUC_{0\text{-}24\ h}$ of PYM50028 and PYM50038 at steady state (Day 28) for a variety of daily doses. A daily oral dose of 120 mg is predicted to give a plasma C_{max} of 390 ng/ml and an $AUC_{0\text{-}24\ h}$ of 4944 ng.h/ml at steady state. These data have been used in the selection of the dose levels for a Phase 2 study in patients with early stage PD (CONFIDENT-PD; NCT01060878).

Methods

- Ten single or multi-segment input (mathematical) models were fitted simultaneously to the mean PYM50028 and PYM50038 plasma concentration profiles using TOPFIT Version 2.0 (Heinzel *et al* .,1993).
- Each input segment (i) was defined by the relative dose fraction (fa,i); the input rate constant (ka,i); and the lag time (tlag,i).
- Weighting of 1/[plasma concentration] was applied.
- The fit was evaluated using Akaike's information criterion (AIC), visual inspection and correlation coefficient.
- The selected PK model was fitted to pooled plasma concentrations of PYM50028 and PYM50038 generated following daily oral doses of 150 mg of PYM50028 to healthy subjects and patients with PD.
- Plasma C_{max} and $AUC_{0\text{-}24\ h}$ for PYM50028 and PYM50038 were derived from the model for a range of dose levels between 5 - 200 mg/day (**Table 1**).

Summary

- A compartmental mathematical model was developed to represent clinical PK data generated for PYM50028 and PYM50038.
- This was used to predict a dose that can achieve a plasma C_{max} of approximately 400 ng/ml for PYM50028.

Conclusions

- A two-segment, first-order absorption, multi-compartment disposition model best represented the clinical PK of PYM50028 and PYM50038.
- This model predicts that doses of ≥120 mg/day will produce a peak plasma concentrations of PYM50028 in PD patients at steady state of at least 400 ng/ml, a level that has been shown to be efficacious in animal models of PD.

References

Heinzel G, Woloszczak R, Thomann P. (1993). Gustav Fischer, Stuttgart.
Priestley *et al*. (2009) Parkinson Rel Disord. **15** Suppl 2: iii-iv, P1.218.
Visanji *et al*., FASEB J. **22**(7), 2488-97.
Zhang *et al*., (2008). FEBS Letters. **582**, 956-960.
Johnston *et al.,* (2009) Parkinson Rel Disord. **15***:* Suppl. 3, iii-iv, S1-S244.

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