Population pharmacokinetics and exposure-response analysis of sleep parameters for JNJ-42847922/MIN-202, a novel Orexin 2 receptor antagonist

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BACKGROUND

- The orexin system regulates wake-sleep states. [1] Orexin 2 receptor (OX2R) blockade may normalize hyperarousal and promote sleep [2]
- JNJ-42847922/MIN-202 is a novel, high affinity OX2R antagonist under investigation for insomnia treatment [3, 4]

OBJECTIVES

- To characterize JNJ-42847922 pharmacokinetics (PK) in healthy volunteers and insomnia patients
- To model exposure-response (E-R) of sleep parameters in insomnia patients with/without major depressive disorder (MDD)
- To assess the impact of PK differences on sleep parameters

METHODS: popPK modeling

- The design of the studies included in the popPK analysis is shown in Table 1. One study (NCT02837692 in Table 1) is currently ongoing and results may be re-evaluated after its completion.
- Non-linear mixed effects modeling approach was applied for PK model development. Model selection was driven by change in objective function value (OFV), standard error of parameter estimates, shrinkage, as well as goodness-of-fit plots and visual predictive checks (VPCs)
- Physiologically plausible PK covariates were tested via stepwise covariate modeling ($p<0.05$ and $p<0.01$ for forward and backward steps, respectively)
- Model building and simulations were performed in NONMEM v7.2. [5]

Table 1. Studies design used for popPK model development

Study	Population	Age*	No. subjects	JNJ-42847922 dose levels#
NCT02464046	Insomnia	18-65	26	40 mg
NCT02578472	Healthy	18-55	36	40 mg
NCT02837692	Healthy	Coh 1: ≥65 Coh 2: 18-45 Coh 3: 20-60	54	10 mg 20 mg

*Coh 1: elderly non-Asian; Coh 2: young healthy non-Asian; Coh 3: healthy Japanese
#Once-day administration (tablet) 3-5h after dinner

Table 2. Summary of patients characteristics for studies included in the popPK model

Characteristic	Mean or count	SD	Range
Gender			
Male	53	-	-
Female	63	-	-
Race			
Non-Asian	96	-	-
Japanese	20	-	-
Age (years)	42.3	15.7	22—77
Weight (kg)	71.2	13.2	45.8—106.6
Height (cm)	171.3	10.7	151—204.4
CLcr (mL/min)	108.4	29.0	47.3—199.8

SD: standard deviation; CLcr: creatinine clearance

METHODS: Exposure-response modeling

- Latency after Persistent Sleep (LPS) data collected via 8-hour polysomnography (PSG) from 3 patient studies with similar dosing conditions and dose range (Table 3) were modeled. Wake After Sleep Onset (WASO) data were modeled only in insomnia patients (study NCT02464046)
- The 3 studies were performed in different patient populations with potentially different responses on PSG parameters. In study NCT02067299, lights-off took place 1 hour before the usual bed time of the patients ("phase-shift") in order to improve detectability of drug effect in a relatively small simple size. Due to these heterogeneity in study designs, E-R modeling was carried on independently on each study and, if warranted by the results, two or more studies could be combined in a joint analysis
- Sleep parameters were modeled using the general model below, using an additive residual error model on the natural logarithm of the endpoint:

$$PSG_i = bas_i \times (1 - plac_i) \times eff_i \qquad eff_i = \left(1 - \frac{C_i}{IC_{50} + C_i}\right)$$

where PSG_i represents LPS or WASO data in the i-th subject, bas_i is a baseline parameter, $plac_i$ is the potential placebo effect (parametrized as $\theta/(1+\theta)$, with $\theta>0$), C_i is the exposure metric (ie dose, Cavg, concentration at a given time point) and IC_{50} the value of the exposure metric associated to 50% reduction of the sleep parameter (or ID_{50}, if dose was used). Model building and simulations were performed in NONMEM v7.2 [5]

- In order to describe the distribution of the drug effect at a given JNJ-42847922 dose level, the dose-response curve with 90% prediction interval, which incorporated inter-individual variability in PK and PD, was then projected over a dose range between 0-40 mg
- If a given exposure metric (e.g. Cavg) was more predictive of response than dose alone, the impact of differences in PK (due to covariates) on drug effects was evaluated using PK and E-R model parameters

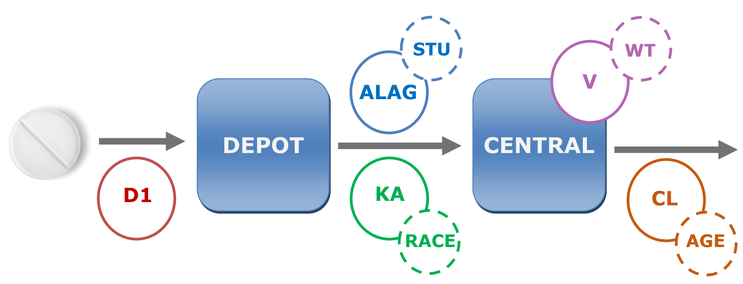
Table 3. Studies included in the exposure-response analysis

Study	Population	Age	No. subjects	Design	JNJ-42847922 dose levels
NCT02464046	Insomnia	18-65	26	2-way cross-over, placebo-controlled, PSG on nights 1 and 5	40 mg[1]
NCT02067299	MDD+insomnia symptoms	18-64	20	4-way cross-over, placebo controlled	10, 20, 40 mg[2]
NCT02476058	MDD[3]	18-64	48	Parallel group, placebo-controlled, PSG on nights 1, 5, and 10[4]	20 mg[5]

[1] Tablet formulation, once-daily administration for 5 days, 3-5 h after dinner
[2] Oral suspension, single dose administration, 4-5h after dinner
[3] Only insomnia-positive subjects (i.e. average screening LPS >= 30 min and no screening LPS < 20 min) were included in the analysis
[4] Only nights 1 and 10 were used for E-R modeling
[5] Tablet formulation, once-daily administration for 28 days, 3-5 h after dinner

RESULTS: popPK modeling

- A one-compartment model with sequential absorption (zero order followed by a first order with lag time) and linear elimination (Figure 1) adequately described JNJ-42847922 PK. All parameters except lag time for study NCT02578472 had CV<30% (Table 4) and VPCs were acceptable (Figure 2)
- The estimated elimination half-life was 2.2 hours. Drug concentrations were low (~10% of Cmax) at 8 hours after dosing and were negligible after 24 hours (Figure 3), which suggests limited or no accumulation with QD dosing
- Age, weight, and race (Japanese vs non-Asian) were statistically significant covariates, although magnitude of effects was relatively small (to be re-evaluated after completion of ongoing study NCT02837692) (Figures 1 and 3)



STUDY-ALAG	RACE—KA	WT–V	AGE-CL
Absorption lag-time is different across the studies (design)	Absorption rate in Japanese is 50% smaller than in non-Asian	Volume of distribution increases 30% (27-35 L) doubling the weight (50 to 100 kg)	Clearance decreases 5% (0.5 L/h) for each increment of 10 years of age

Figure 1. Population PK model structure and covariate effects

Table 4. Population PK parameter estimates

Parameter	Estimate	CV (%)	Shrinkage (%)
Absorption rate (1/h) - Non-Asian	2.352	8.6	.
Absorption rate (1/h) - Japanese	1.148	13.4	.
Clearance (L/h)	9.724	3.6	.
Volume of distribution (L)	30.84	2.8	.
Lag time - Study NCT02464046 (h)	0.055	16.9	.
Lag time - Study NCT02578472 (h)	0.130	183.5	.
Lag time - Study NCT02837692 (h)	0.120	9.5	.
Time duration order zero absorption, D1 (h)	0.149	14.3	.
Slope linear decrease in clearance with increase of age	-0.005	18.8	.
Exponent of power relationship between volume of distribution and weight	0.385	15.5	.
IIV KA (%)	89.8	18.3	14.4
IIV CL (%)	38.7	15.1	2.3
IIV V (%)	26.8	15.4	7.8
IIV ALAG (%)	58.6	27.3	33.4
Residual variability (%)	44.0	9.0	15.3

Random effect parameters (interindividual, IIV, and residual variablility) - Exponential model. Correlation between CL and V = 0.907. Covariate relationships were linear for age on CL and power for weight on V, centered at the median values in the population (ie 39.5 years for age and 70.8 kg for weight)

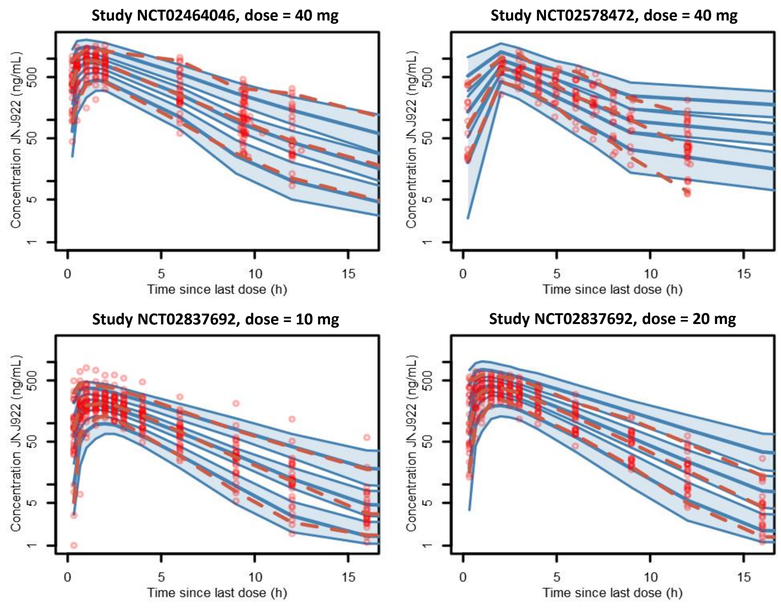
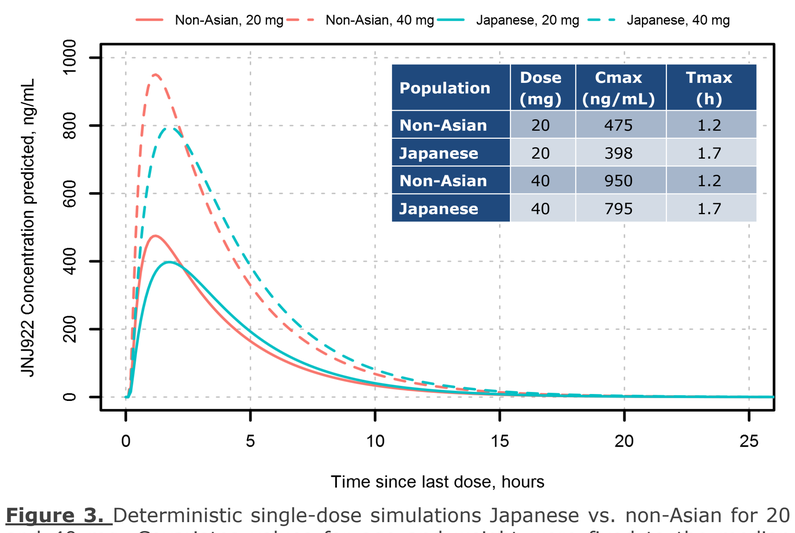


Figure 2. Visual predictive check of the popPK model paneled by study and dose based on 1000 replicates. Median (red solid line), 5th and 95th percentiles (red dashed lines) of the observed data are compared to the 95% confidence intervals (blue shaded areas) for the median, 5th and 95th percentiles of the simulated data.



Population	Dose (mg)	Cmax (ng/mL)	Tmax (h)
Non-Asian	20	475	1.2
Japanese	20	398	1.7
Non-Asian	40	950	1.2
Japanese	40	795	1.7

Figure 3. Deterministic single-dose simulations Japanese vs. non-Asian for 20 and 40 mg. Covariates values for age and weight were fixed to the median population value for study NCT02837692

RESULTS: Exposure-Response modeling

- E-R on LPS was detected in the insomnia study NCT02464046 and in MDD study NCT02067299. The dose associated to 50% LPS reduction from placebo (ID50) was estimated as 24 mg and 6 mg in the two studies, respectively. WASO analysis of the insomnia study showed an E-R signal driven by average plasma concentration (Table 5)
- The placebo effect (1-*plac*) on LPS was 57% in study NCT02464046 and 6% in study NCT02067299. An E-R relationship for LPS in study NCT02476058 could not be identified
- Inter-individual variability (IIV) in drug effect on LPS could not be further explained by IIV in PK: plasma concentrations at 15min, 30min, 1h, 1h30min post-dose in study NCT02464046 did not predict LPS change any better than dose alone. Parameter estimates for LPS are provided in Table 5
- Based on the study in insomnia patients, a 20 mg dose is expected to result in about 55% of placebo LPS (Figure 4). Night 1 vs 5 was not a statistically significant covariate of drug effect
- Changes in apparent drug clearance with age (-5% every 10-year age increment, Table 5) are not expected to result in significant changes in drug effect (75% vs 69% of placebo WASO at 30 vs 80 years old for a dose of 40 mg, due to reduced clearance with age)

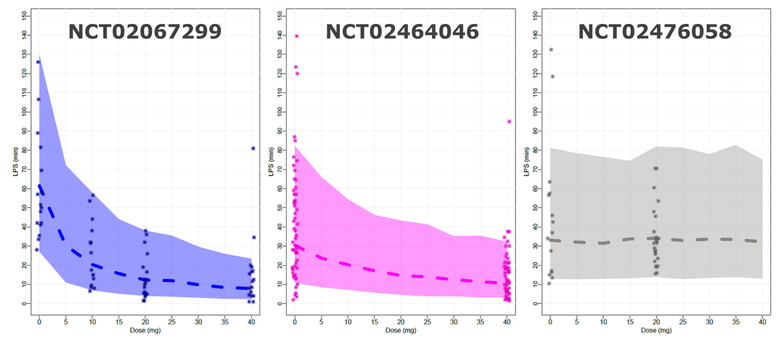


Figure 4. Dose-response relationship for LPS in the 3 PSG studies (median and 90% prediction interval from 1,000 simulated subjects)

Table 5. Exposure-response parameter estimates (CV%)

Parameter	LPS NCT02067299	LPS NCT02464046	LPS NCT02476058	WASO NCT02464046
TV *bas*	66 min (12%)	74 min (8%)	54 min (8%)	108 min (7%)
TV *plac*[1]	6% (180%)[2]	57% (23%)[2]	35% (38%)[2]	49% (22%)[2]
TV ID_{50}	6 mg (26%)	24 mg (22%)	Not identifiable	-
TV IC_{50}	-	-	-	489 ng/mL (27%)
IIV *bas*	28% (69%)[3]			11% (>100%)[3]
IIV *plac*[4]	100% (39%)[3]			90% (39%)[3]
IIV ID_{50}	95% (34%)[3]		Not identifiable	-
IIV IC_{50}	-	-	-	0% (fixed)
RUV	62% (13%)[3]			51% (16%)[3]

TV: typical value. IIV: inter-individual variability (log-normally distributed). RUV: residual unexplained variability (additive in log scale)
[1] Expressed as % reduction from baseline
[2] CV% with respect to parameter θ
[3] CV% with respect to parameter ω^2 (IIV) or σ^2 (RUV)
[4] IIV with respect to parameter θ

CONCLUSIONS

- A one-compartment PK model with linear absorption and elimination adequately captured the PK of JNJ-42847922/MIN-202, dosed as tablet 3-5 hours after dinner in the dose range 10-40 mg
- The short half-life of JNJ-42847922/MIN-202 results in relatively low plasma concentrations at 8 hours post-dose, with negligible accumulation after multiple daily dosing
- In insomnia patients, JNJ-42847922/MIN-202 potently reduced latency to persistent sleep (about 55% of placebo value with a 20 mg dose)
- The different ID50 and placebo effect in study NCT02067299 compared to study NCT02464046 may be possibly explained by the presence of a phase-shift in the former study
- Based on this preliminary evaluation of JNJ-4284792/MIN-202 PK and exposure-response, possible differences in PK identified by the covariate analysis are expected to result in limited impact on drug effects

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Presented at the Population Approach Group in Europe (PAGE) 26th Meeting
June 6-9 2017, Budapest, Hungary