Office of Clinical Pharmacology
Pharmacometrics

NDA	20-717
Submission	(b) (4) 021
Drug Name	Modafinil
Indication	Excessive Sleepiness Due to Narcolepsy
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Executive Summary

PROVIGIL® (modafinil) Tablets are approved for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypoapnea syndrome (OSAHS), and shift work sleep disorder (SWSD). In the current submission, pediatric patients (6-16 years old) with excessive sleepiness associated with narcolepsy were administered 100, 200 or 400 mg once daily. For (b) (4) the current submission, the primary measures for demonstrating effectiveness were Multiple Sleep Latency Test (MSLT) and the Clinical Global Impression of Change (CGI-C). All three doses were superior to placebo for the objective effectiveness variable (MSLT). However, in terms of primary subjective effectiveness variable (CGI-C), only 100 mg demonstrated statistical superiority over placebo, whereas doses of 200 and 400 mg were not significantly different from placebo. It is not clear why higher doses were not as effective as 100 mg dose. There is no clear dose-response or exposure-response relationship for either variable and it would appear that doses lower than 100 mg could be effective. There is insufficient evidence to conclude that decreased appetite, psychiatric and skin related safety events are not related to modafinil concentrations. Sponsor should consider exploring dose ranges lower than 100 mg.

Recommendations

The Office of Clinical Pharmacology has reviewed the application and is recommending that the sponsor should

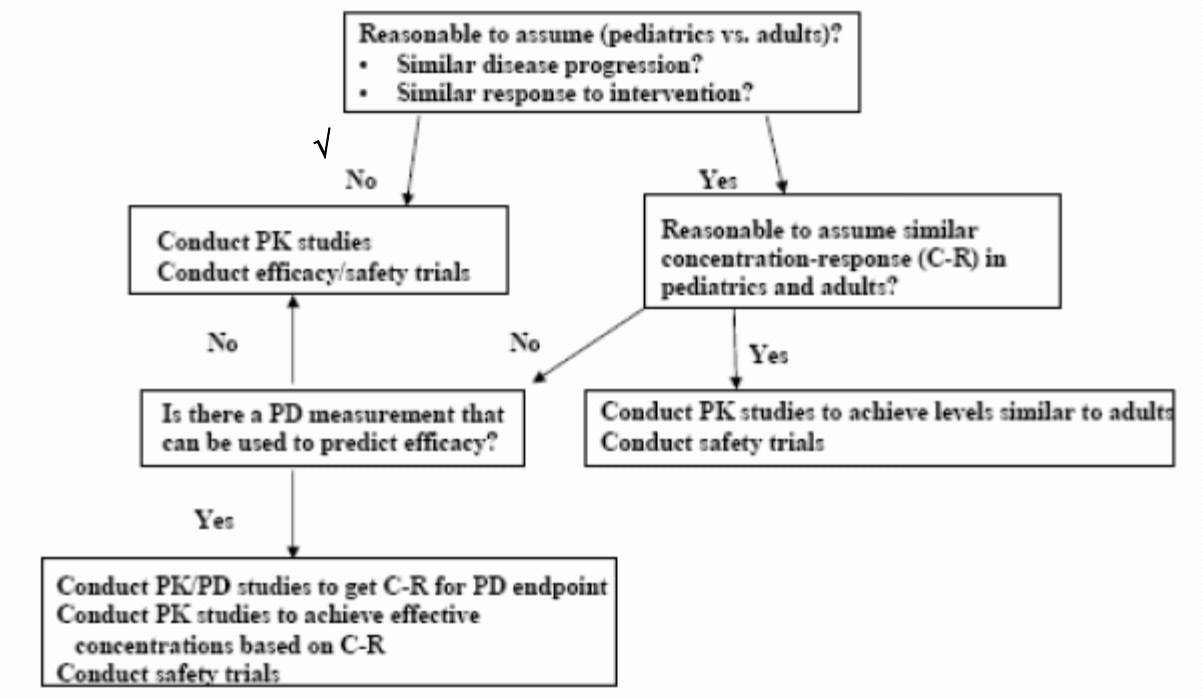
- Explore doses lower than 100 mg.
- Use similar body weight based cutoff's for determining the dose (similar dosing pattern which was used for Nuvigil® (ADHD)).
- (b) (4) the sponsor should either manufacture a lower strength (50 mg tablet) or score the 100 mg tablet.
- (b) (4)

Background

PROVIGIL® (modafinil) Tablets is approved for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). A supplemental New Drug Application is under review by the United States (US) Food and Drug Administration (FDA) for the use of modafinil for the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD). A Pediatric Written Request (later amended) (PWR) to evaluate the use of PROVIGIL therapy in pediatric patients (children and adolescents ages 6 through 16 years) with excessive sleepiness associated with narcolepsy was sent by the FDA on 17 June 2004. Modafinil has been evaluated in more than 4000 subjects/patients (adults and children) in clinical studies. Of these, a total of 934 adults with narcolepsy (n=369), OSAHS (n=292), and SWSD (n=273) received modafinil in double-blind, placebo-controlled studies, and 933 children and adolescents with ADHD have received modafinil in clinical studies. The effectiveness and safety of modafinil to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, OSAHS, and SWSD was demonstrated in 6 placebo-controlled clinical studies in the US. Modafinil was effective in reducing excessive sleepiness associated with narcolepsy or OSAHS (at dosages of 200 and 400 mg/day), and SWSD (at dosages of 200 mg).

The Phase 3 clinical program included 1 adequate and well-controlled study (study 3027) of 6 weeks duration to evaluate the efficacy and safety of PROVIGIL (100, 200, and 400 mg/day) in pediatric patients with excessive sleepiness associated with narcolepsy. In this study, efficacy was assessed, in comparison to placebo treatment, using a physiological measure of excessive sleepiness (ie, Multiple Sleep Latency Test [MSLT]), clinician ratings of global improvement (ie, Clinical Global Impression of Change [CGI-C]), and a subjective rating of excessive sleepiness (ie, Pediatric Daytime Sleepiness Scale [PDSS]. In addition, the dose-response relationship of PROVIGIL and an assessment of population pharmacokinetics was performed. (b) (4) No separate pharmacokinetic studies were conducted as there was prior information on pharmacokinetics in similar age groups (ADHD patients)

The following pediatric decision tree explains the rationale for the clinical studies:



An overview of the studies included in this submission is provided in Table 1.

Table 1: Studies Conducted for the Pediatric Written Request

Study number (number of PROVIGIL-/placebo-treated patients)	
Controlled Phase 3 double-blind	**Uncontrolled Phase 3 open-label**
Narcolepsy C1538/**3027**/NA/MN (123/42)	Narcolepsy or OSAHS C1538/**3029**/AD/US[b] (148/0)
OSAHS C1538/**3028**/AP/MN[a] (19/7)	Narcolepsy or OSAHS C1538/3034/AD/US (46/45)

NOTE: Studies were conducted in pediatric patients.
[a] Enrollment terminated early, only safety data for PROVIGIL-treated patients from this study is provided in this submission.
[b] For study 3029, an interim safety report is being submitted with this Pediatric Written Request. No efficacy findings are discussed.
OSAHS=obstructive sleep apnea/hypopnea syndrome.

Regulatory Questions

I will focus on three key regulatory questions:

1. Did the sponsor make a good faith effort to characterize the dose-response relationship and identify a no-effect dose for modafinil?
2. Did the sponsor adequately characterize pharmacokinetics of modafinil?
3. Is there any exposure-safety relationship that could improve benefit/risk profile of modafinil?

Other questions of interest:

1. (b) (4)
2. Are there any differences in effectiveness in younger (less than 12 years of age) vs older (greater than 12 years of age) patients?
3. Did patients who showed psychiatric, skin related adverse events have higher exposures relative to others who did not?

Question 1: Did the sponsor make a good faith effort to characterize the dose-response relationship and identify a no-effect dose for modafinil?

The Pediatric Written Request for modafinil required that **The studies "must" also define an interpretable dose-response relationship, including the identification of a no-effect dose."**

The choice of dose was based on matching exposure in pediatrics with that in adults. The pharmacokinetic information obtained in ADHD development plan was used to derive dose that would match exposure in pediatrics observed after a dose of 200 mg in adults. The information on modafinil exposure in pediatrics and adults after 200 mg oral dose is shown in table below:

Table 1: Mean Pharmacokinetic Parameters of 200 mg of Modafinil Following Multiple-Dose Administration in Children and Adults

Pharmacokinetic parameter (units)	Children (6-12 years of age)	Adults
C_{max} (µg/mL)	9.5	6.4
t_{max} (h)[a]	3.0	2.5
$t_{1/2}$ (h)[b]	8.2	15.9
$AUC_{0-\tau}$ (µg·h/mL)	100	79
CL/F (mL/min/kg)	1.1	0.5
V/F (L/kg)	0.8	0.8
CL/F (mL/min)	35	44
V/F (L)	27	65
R_{obs}	1.0	1.5

SOURCE: Study report supplement C1538d/113/BA/US and study CEP-2101.
[a] Median.
[b] Harmonic mean.
$AUC_{0-\tau}$=area under the plasma concentration by time curve from time zero to the time of the last measurable drug concentration; C_{max}=maximum observed plasma drug concentration; $t_{½}$=elimination half-life; t_{max}=time to maximum observed drug concentration; CL/F=total oral clearance; V/F=oral volume of distribution; R_{obs}=observed accumulation.

As can be seen in Table1 above, exposures after 200 mg oral dose in pediatrics are higher than that in adults. Since PK are linear, (doses from 200 to 800 mg in adults have been shown to show dose-proportional increases in Cmax and AUC), one would expect that a dose of 100 mg would result in an AUC of 50 µg•h/mL. Although no formal dose-proportionality study has been conducted in pediatric patients, the dose of modafinil was not shown to be a significant covariate in the population pharmacokinetic modeling. Doses of 200 and 400 mg would result in pediatrics AUCs much higher than studied in adults.

Registration trials in adults clearly showed that there is no difference in the effectiveness between 200 and 400 mg doses as reflected in the PROVIGIL label approved for adults.

Table 1. Average Baseline Sleep Latency and Change from Baseline at Final Visit (MWT and MSLT in minutes)

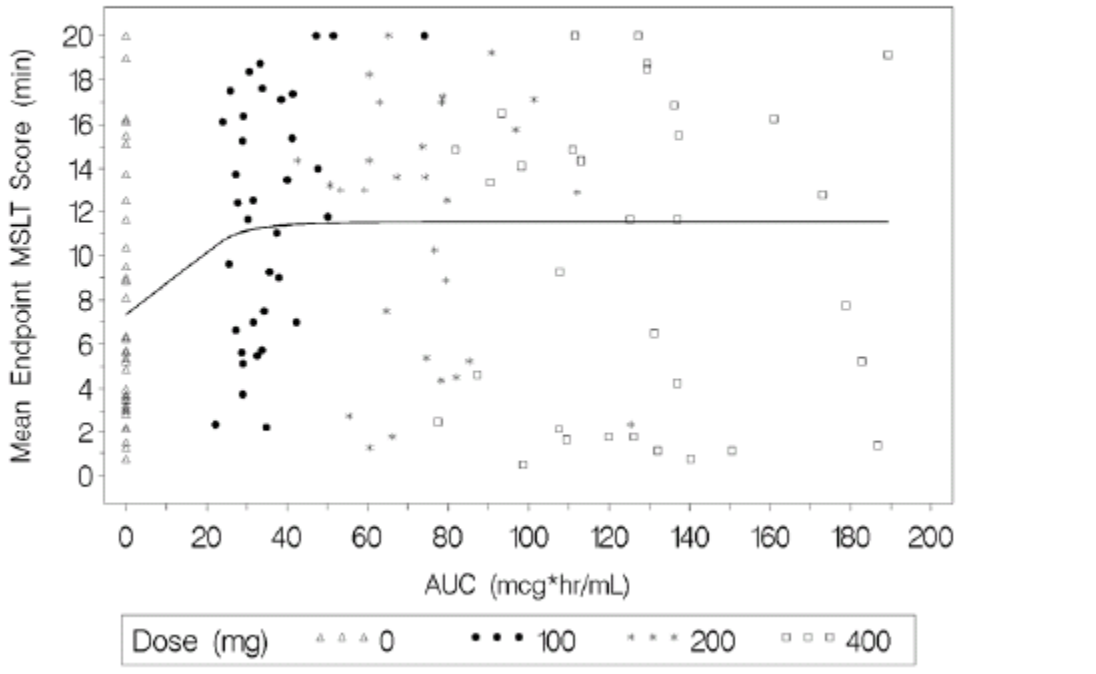
Disorder	Measure	PROVIGIL 200 mg *		PROVIGIL 400 mg *		Placebo	
		Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Narcolepsy I	MWT	5.8	2.3	6.6	2.3	5.8	-0.7
Narcolepsy II	MWT	6.1	2.2	5.9	2.0	6.0	-0.7
OSAHS	MWT	13.1	1.6	13.6	1.5	13.8	-1.1
SWSD	MSLT	2.1	1.7	-	-	2.0	0.3
*Significantly different than placebo for all trials (p<0.01 for all trials but SWSD, which was p<0.05)							

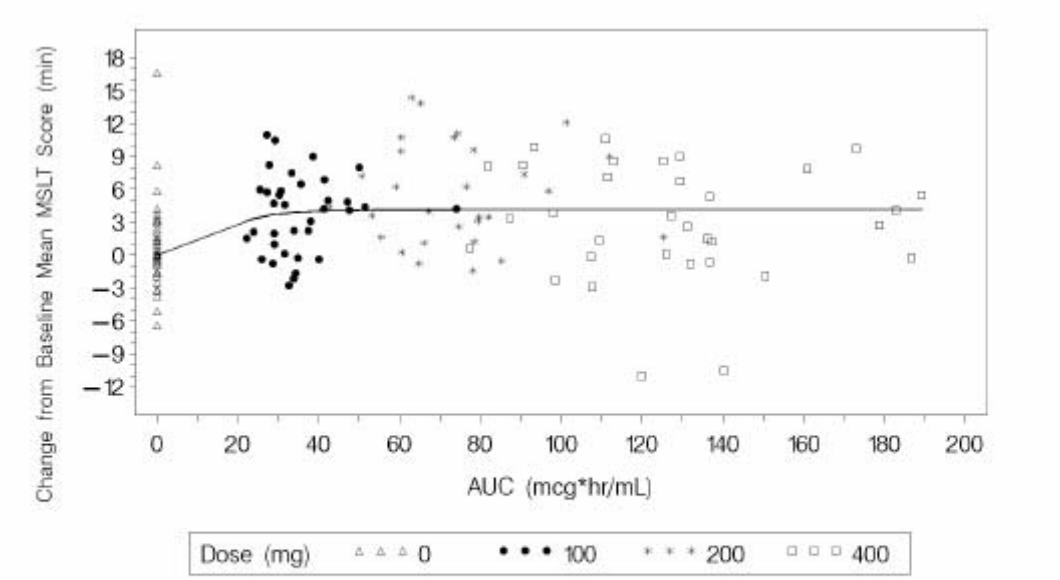
Retrospectively, it appears that the choice of doses in the upper range were unnecessary. The choice of lower dose is still also a matter of concern since the exposures (AUC) are not really hugely that different between adults (79 µg•h/mL) and pediatrics (50 µg•h/mL). Ideally, the sponsor should have studied a dose of 25 mg which would have resulted in exposures of about 12.5 µg•h/mL. It is not clear if the Agency commented on the selection of the doses at the protocol stage.

The next question that would be of interest would be **"Can we use the exposure-response instead of the dose-response relationship, in pediatrics, to extrapolate to lower doses and comment on what would be a 'no-effect' dose?**

Unlikely. The sponsor performed exposure (AUC at steady state)-response (Multiple Sleep Latency Test; MSLT) analysis to comment on the benefit at lower doses than studied. The plot of mean MSLT scores at endpoint vs AUC at steady state is shown below. The observed change from baseline MSLT and the best fit regression line are shown in figure below:

Scatterplot of Mean MSLT Scores at Endpoint Versus AUC_{SS}, Stratified by Dose with the Final Exposure-Response Model Fit Overlaid





Note: Model developed on endpoint mean MSLT data, but plotted as change from baseline. The plot is for a typical patient assuming a baseline value of 7.34 minutes, and assuming the estimated typical placebo response at 6 weeks is the estimated value of 7.34 minutes.

SOURCE: Report CP-05-002.

Sponsor's Comments:

"The above figure illustrates that the exposures achieved with the 100-mg dose are already on the flat portion of the exposure-response curve, with all dose levels showing a significant difference compared to placebo. The model also suggests that modafinil doses less than 100 mg may not be sufficient to achieve adequate efficacy. The model predicts that AUC that produces 50% effect is 16.9 µg•h/mL. However, due to the lack of data in the ascending portion of the Emax curve, there is some uncertainty regarding this parameter. The steady-state exposure required to achieve 95% of the maximal response for a 7.34-minute baseline value on the MSLT, is 36.4 µg·h/mL".

Reviewer's Comments: Clearly as seen in the graph there is no data on change in MSLT between 0 and 20 µg•h/mL. This can lead to wrong conclusions on the estimated dose that would result in at least 50% clinical benefit. Extrapolations beyond and below studied exposures is discouraged from effectiveness point of view. In conclusion, the data as analyzed by the sponsor does not effectively address the issue of no-effect exposure/dose level.

Based on the review of the analysis conducted by the sponsor, the sponsor did not meet the requirements of "**The studies "must" also define an interpretable dose-response relationship, including the identification of a no-effect dose."** Clearly there is lack of information on no-effect dose.

Question 2: Did the sponsor adequately characterize pharmacokinetics of modafinil in pediatrics (6-16 year old children and adolescents)?

Yes, the sponsor did adequately characterize the pharmacokinetics of modafinil in pediatrics (6-16 year old children and adolescents). The pharmacokinetics of modafinil in ADHD patients has already been reviewed by FDA.

The summary of the pharmacokinetic parameters is shown in table below. Body weight was a significant covariate for clearance and volume of distribution. However, no body weight based adjustments are being proposed here.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
	Population Mean	%SEM	Final Estimate	%SEM
k_a (1/hr)	1.14	27.6	94.0	42.8
CL/F (L/hr)	2.10	4.9	17.2	38.1
Exponent of weight on CL/F	0.349	30.7		
Vc/F (L)	19.1	6.9	6.2	313
Slope of weight on V/F (L/kg)	0.492	20.3		
Q/F (L/hr)	0.448	24.3	NA	NA
Vp/F (L)	16.3	65.6	NA	NA
Lag Time (hr)	0.401	9.3	NA	NA
Residual Variability (%CV)	23.0	18.7	NA	NA
Minimum Value of the Objective Function = 624.230				

NA not applicable.

The sponsor utilized the rich data from studies conducted in ADHD pediatric patients to supplement the sparse data collected from current study. Briefly, in ADHD pediatric patients the following are the important details to note:

Dose Ranges Studied

As can be seen from the tables below doses from 85-425 mg/day were studied.

Table 1: Clinical Studies Included in the Population Pharmacokinetic Analysis

Clinical Trial Phase	Title	Treatment Regimen	PK Sample Collection Times
		C1538d/113/BA/US	
Phase 1	A Randomized Open-Label Study to Compare the Relative Bioavailability of 170 mg of Modafinil Film-Coated Tablets to 200 mg of PROVIGIL® and to Assess the Pharmacokinetic and Safety Profile of Multiple Doses of the Modafinil Film-Coated Tablets Administered at Doses of 340 and 425 mg to Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	Day 1: 170 mg/day Day 8: 200 mg/day Or Day 1: 200 mg/day Day 8: 170 mg/day Day 9 to 22: titrate up to 340 mg (<30 kg) or 425 mg (≥30 kg)	Day 1, 8, and 22; pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, and 24 hr after dosing
		C1538d/309/AD/US	
Phase 3	A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Flexible-Dosage (up to 425 mg/day), Parallel-Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	Days 1-2: 85 mg/day Days 3-7: 170 mg/day Days 8-14: 255 mg/day Days 15-21: 340 mg/day Day 22: 425 mg/day	Screening, and Weeks 1, 2, 3, 5, 7 and 9 (or early termination)

Table 1: Clinical Studies Included in the Population Pharmacokinetic Analysis (Continued)

Clinical Trial Phase	Title	Treatment Regimen	PK Sample Collection Times
		C1538d/310/AD/US	
Phase 3	A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dosage (340 or 425 mg/day), Parallel-Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, Including a 2-Week (Blinded) Withdrawal Period	Days 1-2: 85 mg/day Days 3-4: 170 mg/day Days 5-6: 255 mg/day Days 7-8: 340 mg/day If <30 kg Day 9-week 7: 340 mg/day Weeks 8-9: 340 mg/day or placebo Or if ≥30 kg Day 9-week 7: 425 mg/day Weeks 8-9: 425 mg/day or placebo	Screening, and weeks 1, 2, 3, 5, 7, and 9 (or early termination)
		C1538d/311/AD/US	
Phase 3	A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Flexible-Dosage (up to 425 mg/day), Parallel-Group Study to Evaluate the Efficacy and Safety of Modafinil (Film-Coated Tablet) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	Titrate to optimal dose: Days 1-2: 85 mg/day Days 3-7: 170 mg/day Days 8-14: 255 mg/day Days 15-21: 340 mg/day Day 22 and greater: 425 mg/day	Screening, and weeks 1, 2, 3, 5, 7, and 9 (or early termination)
		C1538d/312/AD/US	
Phase 3	A 1-Year, Open-Label, Flexible-Dosage Study to Evaluate the Safety and Continued Efficacy of Modafinil (Film-Coated Tablet Formulation) in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder	Days 1-2: 85 mg/day Days 3-5: 170 mg/day Days 6-9: 255 mg/day Days 10-14: 340 mg/day; after Day 14 may be increased to 425 mg	At each monthly visit, and at the 8-month visit for patients continuing treatment from study C1538d/113/BA/US: pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 9, and 12 and 24 hours after the last dose

Age Ranges Studied:

The following histograms show the distribution of patients across the various studies included in the analysis. As can be seen in this graph below there are sufficient number of patients in each age group. Also one should note that in PK modeling, Age is included as a continuous variable.

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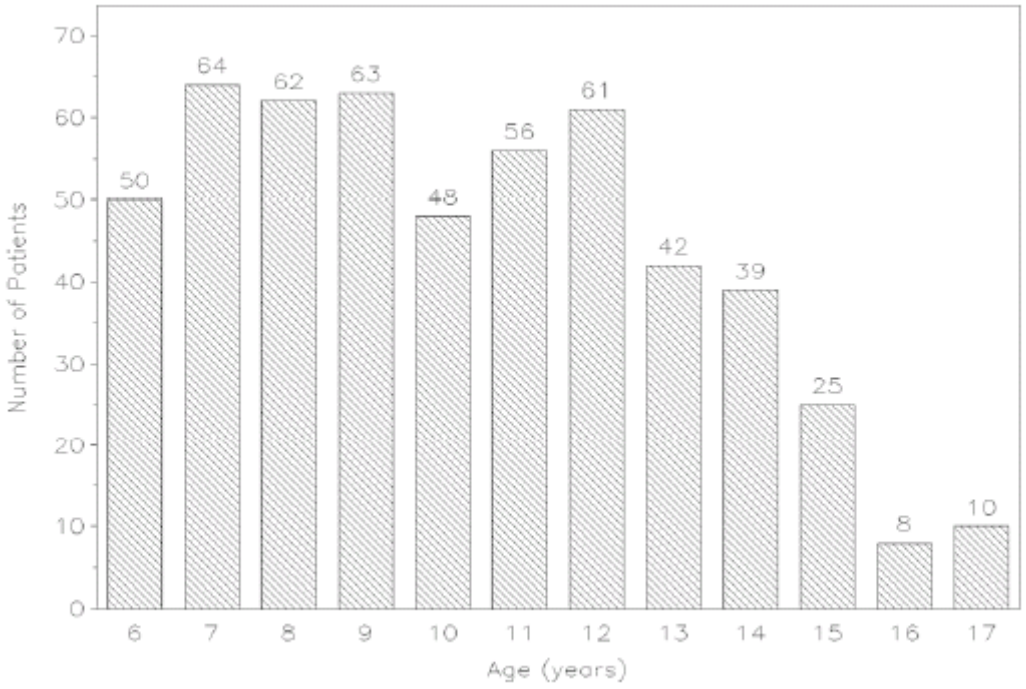
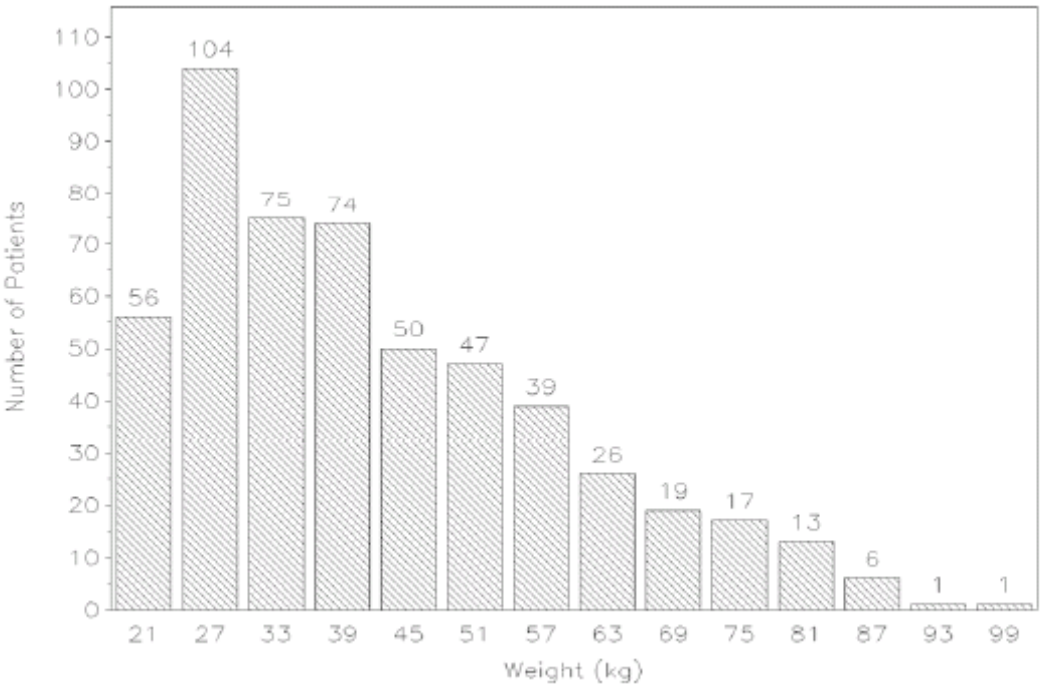




Gender

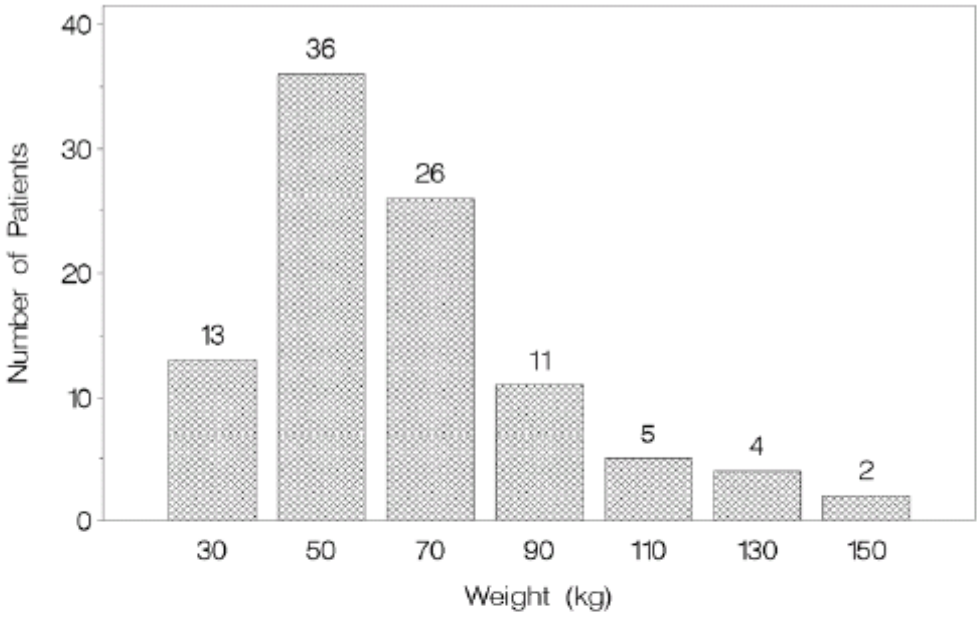
As can be seen from tables below data from 399 males and 153 females was included in the PK analysis in ADHD patients.

Demographic Characteristics	Study C1538d/113/BA/US
Age (years)	
N	24
Mean (SD)	9.0 (2.3)
Median	8.5
Min-Max	6.0-13.0
Weight (kg)	
N	24
Mean (SD)	32.9 (12.0)
Median	28.9
Min-Max	18.6-58.2
BMI (kg/m^2)	
N	24
Mean (SD)	17.7 (2.8)
Median	16.9
Min-Max	13.0-23.5
Gender, N (%)	
Male	17 (70.8)
Female	7 (29.2)
Ethnicity, N (%)	
Caucasian	13 (54.2)
Black	9 (37.5)
American Indian/Alaskan Native	2 (8.3)

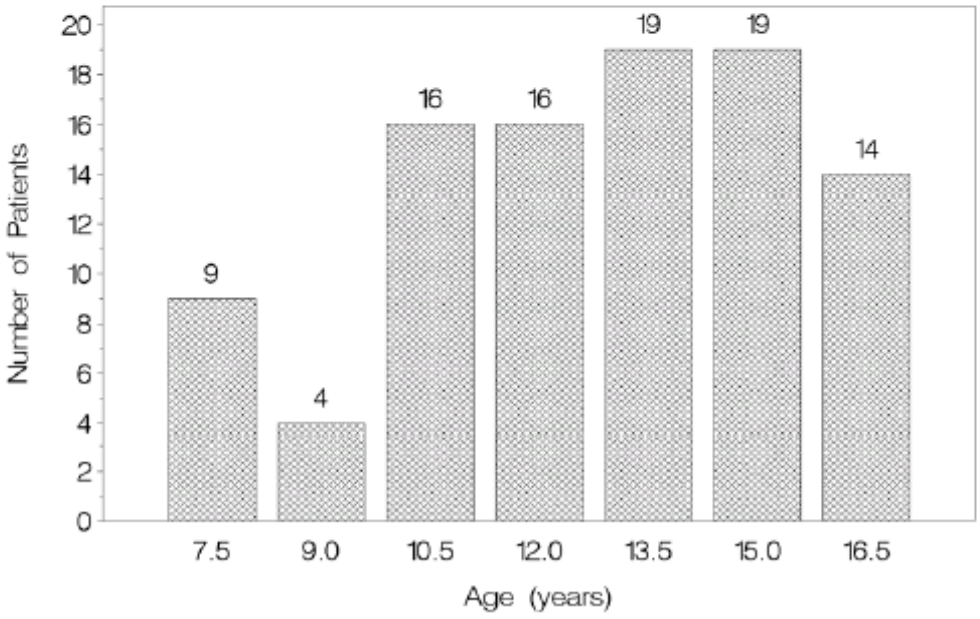
Demographic Characteristic	Study C1538d/309/AD/US	Study C1538d/310/AD/US	Study C1538d/311/AD/US	Study C1538d/312/AD/US	Pooled Phase 3 Studies*
Age (years)					
N	123	120	162	330	528
Mean (SD)	10.0 (2.6)	10.2 (3.0)	10.5 (2.9)	10.2 (2.9)	10.2 (2.9)
Median	10.0	10.0	10.5	10.0	10.0
Min-Max	6.0-16.0	6.0-17.0	6.0-17.0	6.0-17.0	6.0-17.0
Weight (kg)					
N	123	120	162	330	528
Mean (SD)	40.0 (16.0)	40.7 (16.7)	43.5 (16.3)	42.0 (16.8)	41.7 (16.6)
Median	36.3	35.8	41.3	37.5	38.1
Min-Max	20.0-87.1	19.6-98.0	19.5-84.0	18.8-101.6	18.8-98.0
BMI (kg/m^2)					
N	123	120	162	330	528
Mean (SD)	19.3 (3.9)	19.3 (3.8)	19.9 (3.8)	19.6 (4.0)	19.6 (3.9)
Median	18.5	18.3	19.3	18.6	18.6
Min-Max	13.1-34.6	12.8-35.6	14.0-32.4	13.3-35.6	12.8-35.6
Gender, N (%)					
Male	89 (72.4)	89 (74.2)	111 (68.5)	244 (73.9)	382 (72.3)
Female	34 (27.6)	31 (25.8)	51 (31.5)	86 (26.1)	146 (27.7)
Ethnicity, N (%)					
Caucasian	88 (71.5)	95 (79.2)	126 (77.8)	254 (77)	405 (76.7)
Black	23 (18.7)	15 (12.5)	16 (9.9)	41 (12.4)	66 (12.5)
Asian	0 (0)	0 (0)	3 (1.9)	1 (0.3)	3 (0.6)
American Indian/Alaskan Native	2 (1.6)	1 (0.8)	2 (1.2)	4 (1.2)	6 (1.1)
Pacific Islander	1 (0.8)	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Other	9 (7.3)	9 (7.5)	15 (9.3)	29 (8.8)	47 (8.9)

* Note: study C1538d/312/AD/US was an open-label continuation of prior studies. Two-hundred seven of the 330 patients in study C1538d/312/AD/US enrolled following participation with active treatment in studies C1538d/309/AD/US, C1538d/310/AD/US, and C1538d/311/AD/US. The remaining 123 patients were enrolled from the same prior studies but were on placebo treatment.

The distribution of children in Study 3027 (Narcolepsy Pediatric Patients) across age and weight ranges is shown in figure below. Please do note that the distribution is being shown only for 97 patients who were included in the PK evaluation. In the PK evaluation dataset, 53 male and 44 female subjects were included.
There was a good distribution of patients across age ranges.



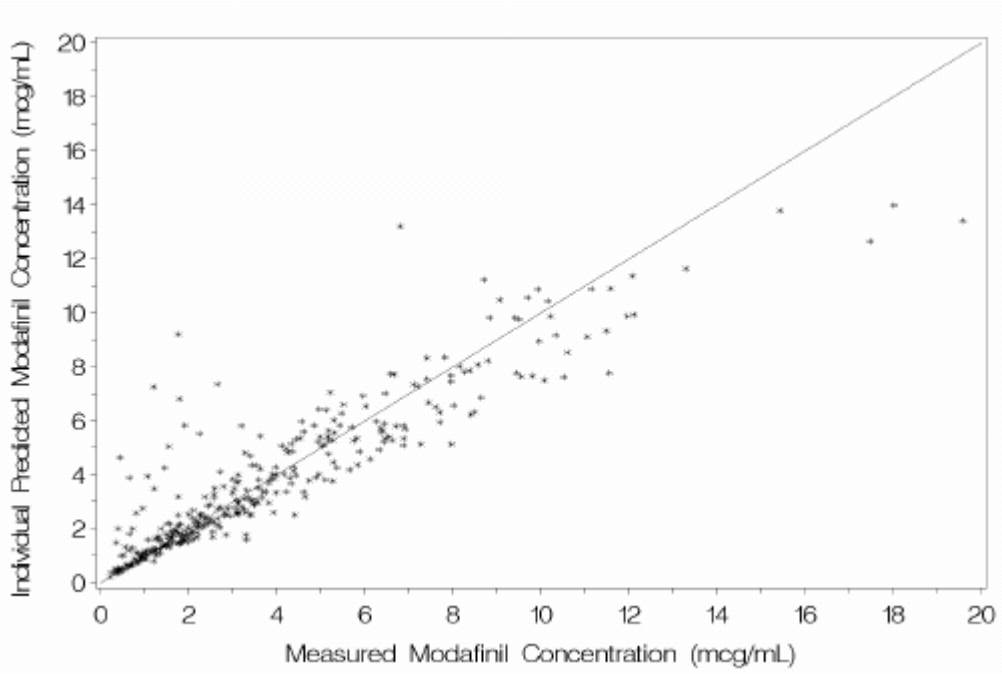
The number under bars represents median of the range of values for that bar.



The number under bars represents median of the range of values for that bar.

(2) Is there any difference in PK between ADHD patients and narcolepsy patients?

No. In pediatric patients with narcolepsy, sparse blood samples (3-4 per subject at various time points during the entire trial in narcolepsy patients) were obtained. Sponsor applied the model developed in patients with ADHD and showed that the concentrations were predictable based on the model developed earlier (i.e., in ADHD Study). The model was previously reviewed by FDA (NDA: 202717; SE1-018: Reviewer: Dr Christine Garnett) and was found to be acceptable. The graph showing the relationship between observed and predicted concentrations of modafinil in patients with narcolepsy is shown here:

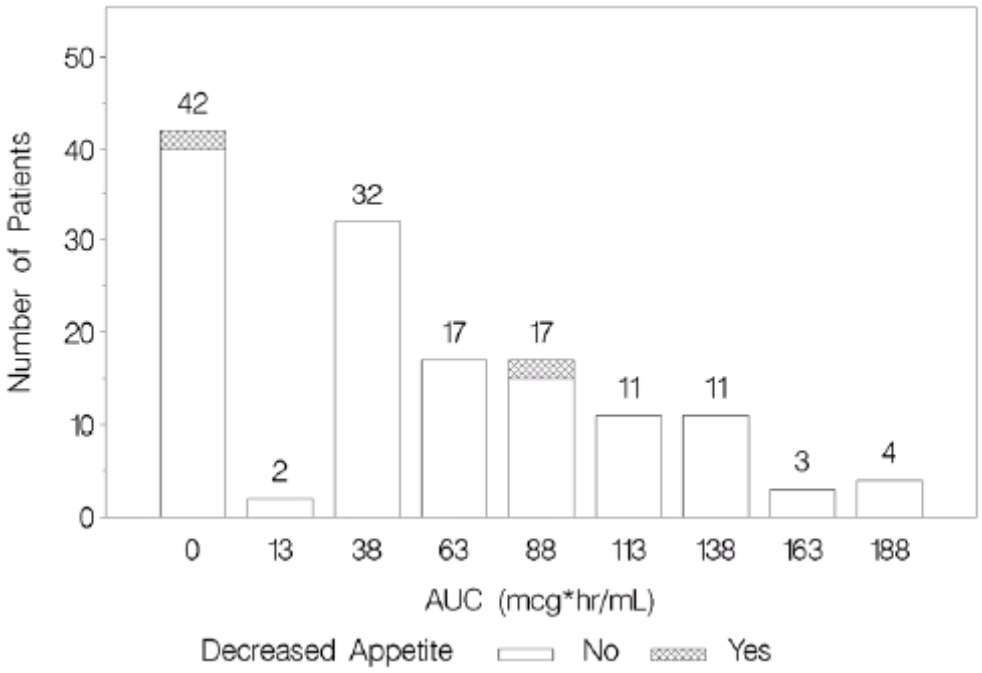


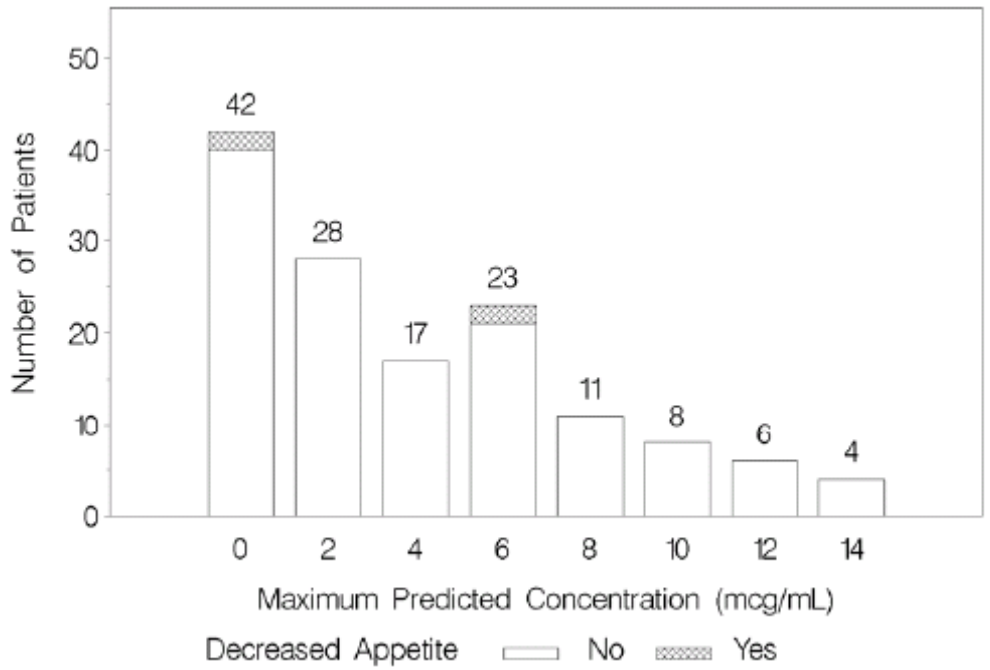
The above graph shows the relationship between measured modafinil concentrations in narcolepsy patients and those predicted using the model developed in ADHD patients. On the basis of these results, the pharmacokinetic profile of modafinil in pediatric patients does not differ as a result of underlying disease condition (i.e., ADHD versus narcolepsy). Therefore, the pharmacokinetic data obtained in pediatric patients with ADHD and reported in this summary are reflective of those in pediatric patients with narcolepsy.

4. Is there any exposure-safety relationship that could improve benefit/risk profile of modafinil?

Sponsor's Comments:

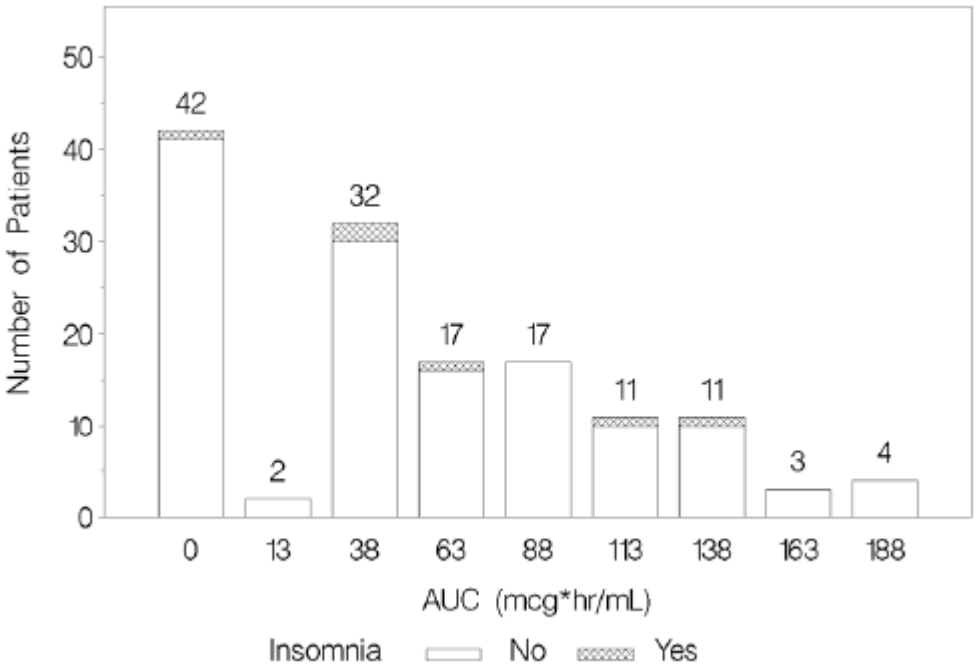
Exploratory analyses of the occurrence of insomnia and decreased appetite adverse events were performed, including summarizations of the various exposure measures, stratified by the occurrence or lack of occurrence of the adverse events. In addition, contingency tables of the occurrence of the adverse events by discrete levels of the exposure measures and covariates were generated. Graphical displays were used to determine if a relationship between occurrence of adverse events and exposure exists.
The frequency of occurrence for both insomnia and decreased appetite was very low. Therefore, due to the low frequency of adverse events, no formal modeling efforts were applied for the exposure-safety analysis and only descriptive summaries are presented.
Three patients receiving modafinil and two patients receiving placebo experienced mild decreased appetite. Overall, the incidence of decreased appetite was low (active drug 2.4% and placebo 4.8%). Only two of these patients (one each at the 200 and 400 mg dose levels) had PK data available. The AUC_{SS} and C_{max} values for patients with decreased appetite were well within the range of values for patients who did not experience decreased appetite in the corresponding dose groups. Overall, in these limited data, there was no evidence of a relationship between AUC_{SS} or C_{max} and occurrence of decreased appetite.

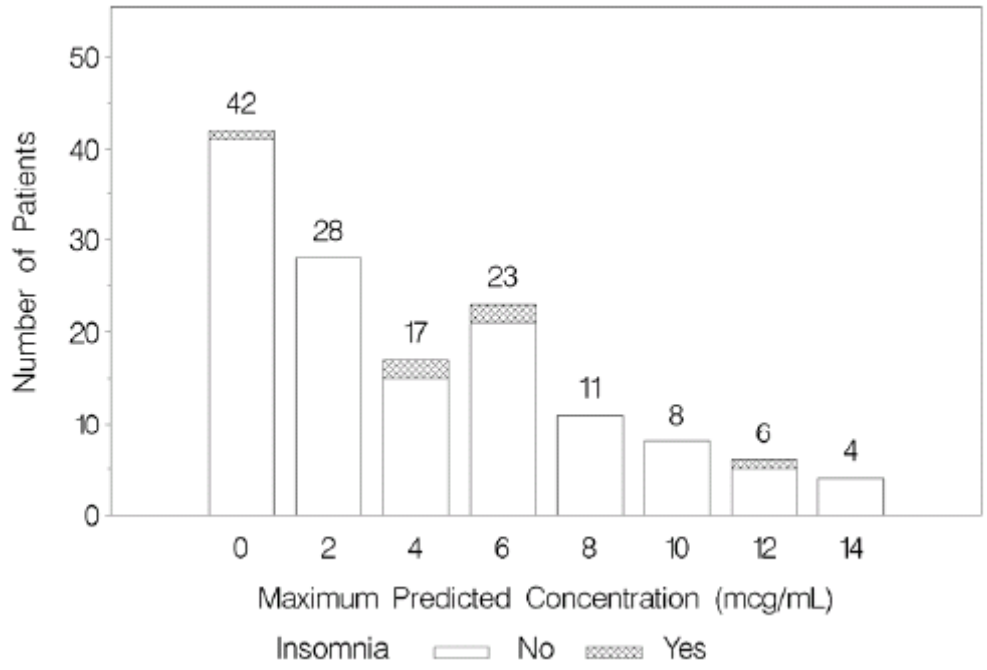




Distribution of AUCSS and Cmax, Stratified by Decreased Appetite for the Safety Analysis

Six patients receiving modafinil and one patient receiving placebo experienced insomnia. Overall, the incidence of insomnia was also low (4.9% on active drug and 2.4% on placebo). Five patients experiencing insomnia had PK data available. Of the seven patients who experienced insomnia, severity was mild in six of the patients. Of the five patients with insomnia and available PK data, the one patient who experienced moderate insomnia exhibited the highest AUCSS and predicted Cmax. At each dose level, the mean AUCSS and Cmax values were higher in the patients with insomnia relative to those patients without insomnia, but were well within the range of values for the corresponding dose groups not experiencing insomnia. Overall, there was no evidence of a relationship between AUCSS or Cmax and the occurrence of insomnia in these limited data.





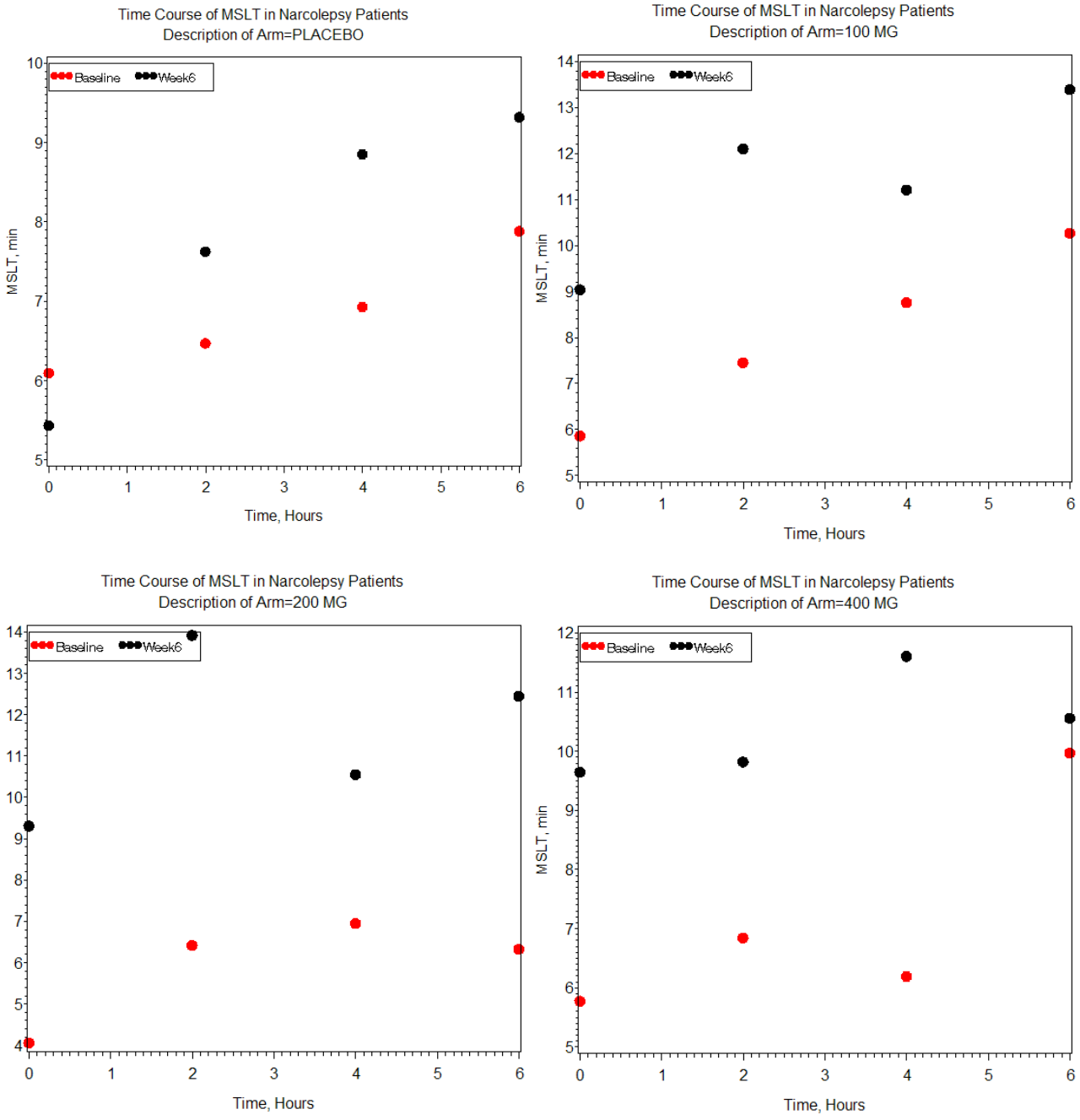
Distribution of AUC_{SS} and C_{max}, Stratified by Insomnia for the Safety Analysis

Reviewer's Comments

There is clearly lack of evidence to rule out that the safety events are related to modafinil exposure.

1. [redacted] (b) (4)

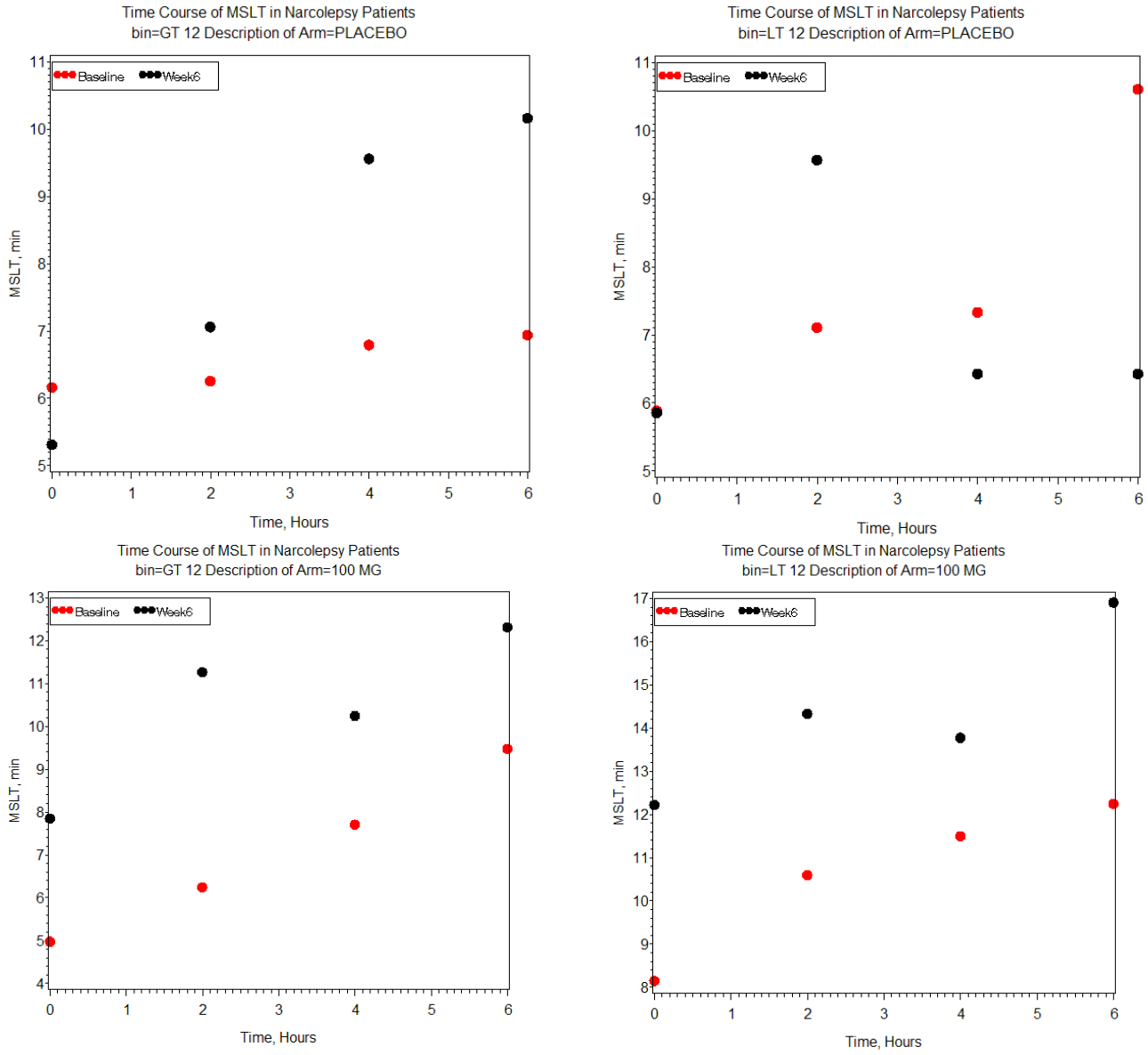
The following figure shows the time course of MSLT after placebo, 100, 200 and 400 mg modafinil till 6 hours. There is no data which would show if the drug effects are back to the pre-dose level after a dose on week 6. [redacted] (b) (4)



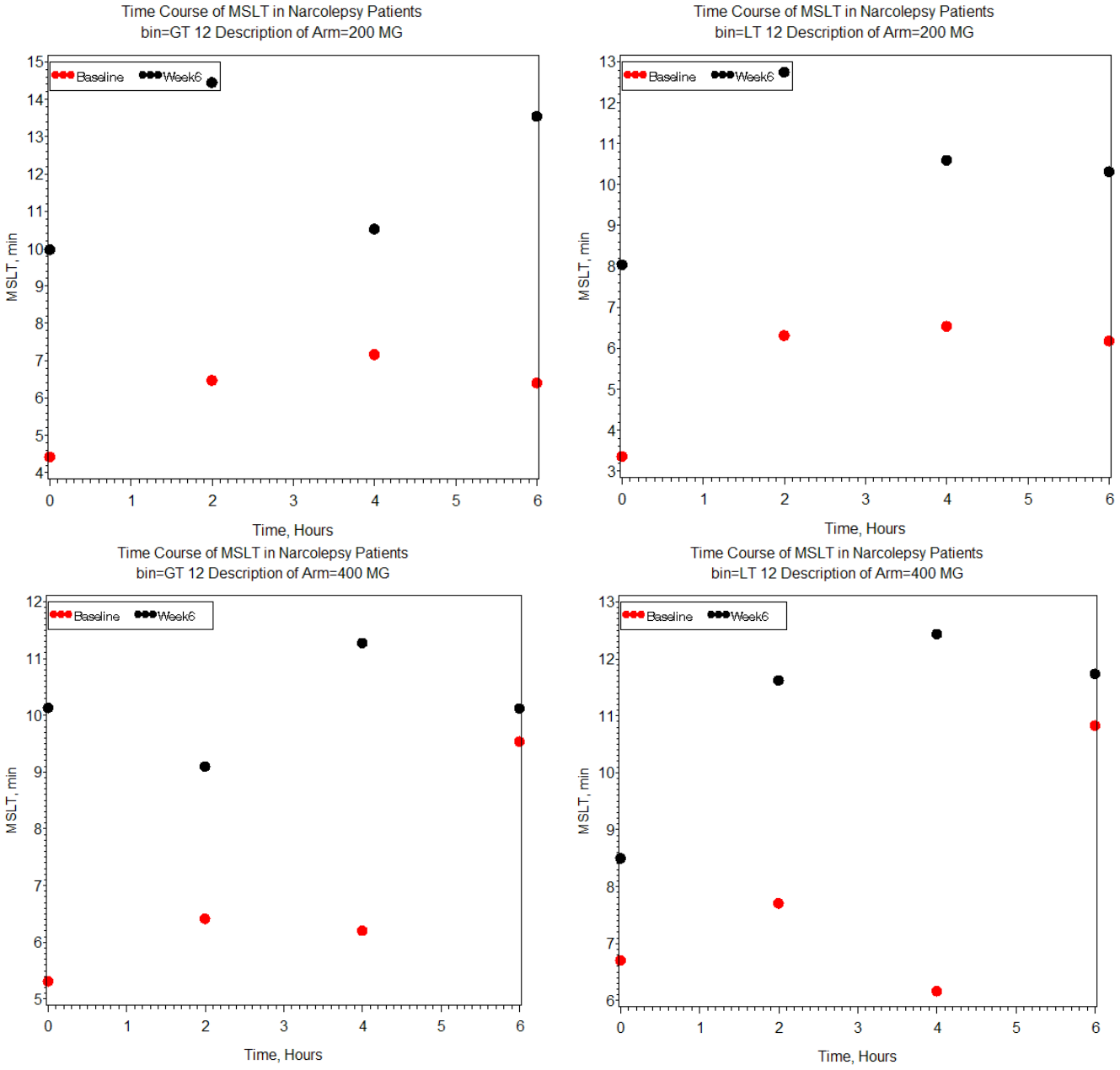
Mean Time course of MSLT at baseline and various treatment arms (Placebo, 100, 200 and 400 mg) in the study.

2. Are there any differences in effectiveness in younger (less than 12 years of age) vs older (greater than 12 years of age) patients?

The following figure shows the time course of MSLT at various doses in patients less than 12 years of age (LT 12) and greater than 12 years of age (GT 12). It does not appear that the effectiveness is different in patients who are less than 12 years in comparison to greater than 12 years group.



Mean time course of MSLT at baseline and various treatment arms (Placebo, 100, 200 and 400 mg) in patients whose age is greater than 12 years.



Mean time course of MSLT at baseline and various treatment arms (Placebo, 100, 200 and 400 mg) in patients whose age is less than 12 years.

3. Did patients who showed psychiatric, skin related adverse events have higher exposures relative to others who did not in all the data combined from various studies?

There is insufficient evidence to conclude that psychiatric and skin related adverse events are not related to modafinil concentrations. Modafinil concentrations were not obtained in the open label phase studies to clearly understand any exposure-safety relationship. However, most adverse events of hostility were considered to be possibly or probably related to study drug treatment. Please refer to the Medical Officer's review for more details.

Conclusions

There is no clear evidence of dose-response relationship in pediatric patients with narcolepsy. There is no evidence that doses less than 100 mg would not be efficacious. It is possible that lower doses could be equally effective and cause less adverse events. Also another interesting aspect to note that sponsor has proposed weight based dose adjustment for Nuvigil® (R-enantiomer of Modafinil) where patients <30 kg and ≥30 kg. It was observed during the study in ADHD pediatric patients, both doses of modafinil administered (340 mg/day to patients <30 kg and 425 mg/day to patients ≥30 kg) resulted in comparable systemic exposure. It is not clear why similar weight cut-off approaches are not used for PROVIGIL®. (b) (4)

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Filing Form

APPEARS THIS WAY ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20717**	**Brand Name**	**PROVIGIl ®**
OCPB Division (I, II, III)	**I**	**Generic Name**	
Medical Division	**Division of Neuropharmacological Drug Products**	**Drug Class**	
OCPB Reviewer	**Venkatesh Atul Bhattaram**	**Indication(s)**	**Excessive Sleepiness Due to Narcolepsy**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**Tablets**
		Dosing Regimen	(b) (4)
Date of Submission	**21st December 2005**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Cephalon**
PDUFA Due Date		**Priority Classification**	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary		1	1	**Sparse Samples**
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:		1	1	**Sampling in Phase III only**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:		1	1	
Population Analyses -				
Data rich:				
Data sparse:		1	1	
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Is there evidence of dose-response in pediatrics** (b) (4) **?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Venkatesh Atul Bhattaram**	
Secondary reviewer Signature and Date	**Joga Gobburu/ Ramana Uppoor**	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Atul Bhattaram
8/16/2006 11:20:18 AM
BIOPHARMACEUTICS

Jogarao Gobburu
8/16/2006 11:56:50 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/16/2006 01:49:00 PM
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