Clinical Study Report

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-26489112

Protocol No.: 26489112NAP2001

Title of Study: A Non-Randomized, Within Subject Placebo-Controlled Exploratory Study of the Effects of JNJ-26489112 on the Photic Induced Paroxysmal EEG Response in Subjects with Photosensitive Epilepsy

EudraCT Number: 2007-004254-93

Coordinating Investigator: Eduoard Hirsch, MD, Hopital Civil, [redacted] France

Publication (Reference): None

Study Period: 17 December 2007 to 21 July 2008. Database lock – 19 June 2009

Phase of Development: 2

OBJECTIVES:

- To determine oral doses of JNJ-26489112 that result in complete suppression or reduction of intermittent photic stimulation (IPS) induced photoparoxysmal-EEG response (PPR), a marker of antiepileptic activity.
- To assess the safety, tolerability, pharmacokinetics and pharmacokinetic/ pharmacodynamic relationship of JNJ-26489112 in subjects with photosensitive epilepsy.

METHODS:

- This was a multicenter, non-randomized, single-blind, within subject, placebo-controlled study.
- Subjects were screened within 50 days prior to Day 1 and then admitted to the Unit on Day –1.
- All subjects received the following treatments in a single-blind fashion: a single dose of placebo on Day 1, a single dose of JNJ-26489112 on Day 2, and a second single dose of placebo on Day 3.
- If reduction or complete suppression of photosensitivity range (i.e. the upper and lower frequencies of the IPS induced PPR) was observed at the last timepoint on Day 3, subjects

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were given the option to remain in the Clinical Research Unit (CRU) for a Day 4 to have the photosensitivity range measured at 48, 52, and 56 hours after the JNJ-26489112 Day 2 dose.

- No study medication was administered on the optional Day 4.
- For each subject, the follow-up visit occurred 7 to 10 days after the subject's last study drug administration.
- The duration of subject participation was approximately 6 weeks.
- A pharmacogenomic blood sample (10 mL) was collected from subjects who had given separate written informed consent for this component of the study.
- For the first 4 subjects, the dose of JNJ-26489112 was 1000 mg on Day 2, with matching doses of placebo given on Day 1 and Day 3. The dose of JNJ-26489112 was escalated in Cohort 2 to 2000 mg, and then escalated again in Cohort 3 to 3000 mg. Dose escalations occurred based upon the following pre-specified criteria:
  - Three of 4 subjects did not have complete suppression of photosensitivity or reduction of the photosensitivity range by at least 3 points in at least 3 out of 4 consecutive time points (hours 1 – 12) of the photosensitivity scale in at least one eye condition (during closure, closed, open) on Day 2 or Day 3 as compared to Day 1 (baseline).
  - The maximum tolerated dose administered to healthy subjects in previous studies was not reached.
  - A dose that provided exposure of the no observed adverse effect level (NOAEL) [C_{max} 117 µg/mL, AUC_{24h} 1,850 µg.h/mL] from dog 4-week oral toxicology studies was not reached.
- The original protocol was issued on 27 June 2007 and there were 3 protocol amendments (Amendment INT-1, dated 15 November 2007; Amendment INT-2, dated 07 December 2007 and Amendment INT-3, dated 04 June 2008).
- Amendment INT-1 changed protocol language for clarity.
- Amendment INT-2 changed exclusion criteria for subjects who had received an experimental drug from 90 days to 60 days before start of study.
- Amendment INT-3 extended screening window, refined the evaluation of the pharmacodynamic data and included women of childbearing potential.

Number of Subjects (planned and analyzed):

A total of 32 male or female subjects were planned, 12 were enrolled, randomized and included in the safety and pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:

- Males or postmenopausal/surgically sterile females between 18 and 60 years of age, inclusive. Women of childbearing potential may be enrolled provided these women agree to utilize an acceptable method of birth control.
- Body Mass Index (BMI) between 18.5 and 35 kg/m^2 (inclusive); BMI= $weight/height^2$
- Firm documented diagnosis of idiopathic, photosensitive epilepsy with a generalized photoparoxysmal EEG response.
- A photosensitive range in response to IPS equal to or greater than 4 points in at least one eye condition at screening.

- Male subjects who are not sterile and are unwilling to use condoms for the duration of the study, ensure that their partner practices contraception or refrain from sexual intercourse (and until 90 days after the last dose of study medication).

Test Product, Dose and Mode of Administration, Batch No.:

JNJ-26489112, given orally as a 100 mg/mL suspension dispersed in a 0.5% weight/weight (w/w) hypromellose solution. Batch Nos. 50038C, 50082C and 50168C.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Placebo, given orally as an aqueous solution of 0.5% (w/w) hypromellose containing 1μg/mL denatonium benzoate in 20mL purified water, as a bittering agent. Batch Nos. 50049C, 50134C, 50185C.

Duration of Treatment:

All subjects received a single oral dose of placebo on Day 1, a single oral dose of JNJ-26489112 on Day 2 (1000 mg, 2000 mg, or 3000 mg), and a second single oral dose of placebo on Day 3.

Criteria for Evaluation:

Pharmacokinetics

- Venous blood samples of 4 mL were collected to determine the concentrations of JNJ-26489112 and its major metabolite, JNJ-38792442, in blood and plasma at on Day 2 at predose, 1, 2, 3, 4, 5, 6, 7, 8 and 12 hours postdose; and on Day 3 at predose, 4, and 8 hours postdose. For subjects also taking other antiepileptic drugs, additional blood samples were taken at predose, 2, 4, 6, and 8 hours postdose on Day 1 and Day 2 to determine concentrations of antiepileptic drugs. The exact dates and times of blood sampling were recorded in the case report form (CRF).
- Blood samples were collected from an intravenous cannula or by direct venipuncture if required (e.g. the cannula was not functioning).
- Plasma and blood samples were analyzed to determine concentrations of JNJ-26489112 and its metabolite, JNJ-38792442, using a validated, selective and sensitive liquid chromatography-mass spectrometry (LC-MS/MS) method at Keystone Analytical, [redacted]., USA.
- Based on the individual concentration-time data, using the actual sampling times, the following pharmacokinetic parameters of JNJ-26489112 and JNJ-38792442 in blood and plasma were estimated in all subjects receiving a dose of JNJ-26489112:
  - t_{max} Time of maximum observed plasma concentration
  - C_{max} Maximum observed plasma concentration
  - AUC_{last} Area under the plasma concentration-time curve from time 0 to t hours post dosing, calculated by linear trapezoidal summation (time t is the time of the last quantifiable concentration (C_{last}))
  - $AUC_{0\text{-}24\ h}$ Area under the plasma concentration-time curve from time 0 to 24 hours post dosing, calculated by linear trapezoidal summation
  - AUC_{∞} AUC extrapolated to infinity, calculated as $AUC_{last}+C_{last}/\lambda_z$
  - CL/F total clearance of drug after extravascular administration, corrected for absolute bioavailability (F), calculated (if the data allows) as Dose/AUC_{∞}
  - $t_{½}$ terminal half-life, defined as $0.693/\lambda_z$

  - λ_z elimination rate constant, determined by linear regression of the terminal points of the ln-linear concentration-time curve

- The plasma concentration of all AEDs taken by the subjects during the study were listed.

Pharmacodynamics

- IPS was performed to determine the photosensitivity range predose and at 1, 2, 3, 4, 5, 6, 7, 8, and 12 hours postdose on Days 1, 2, and 3. (Optional Day 4 assessments, based upon the response at Day 3, include 48, 52, and 56 hours after Day 2 study drug dose).
- The IPS assessment followed a standard procedure using a Grass-type PS 33 photic stimulator (or a Grass-type PS photic stimulator which goes up to 60 Hz) with an unpatterned lamp glass at a distance from the nasion of approximately 300 mm, and with an intensity of 100 cd/m^2/flash.
- Prior to the first IPS- EEG assessment on Days 1 to 3, a 2-minute baseline EEG run occurred, which consisted of 1 minute with eyes closed and then 1 minute with eyes open. Subjects were seated and instructed to fixate on the center of the lamp. Trains of flashes at constant frequency were delivered for 4 to 6 seconds. Intervals between the successive flash trains at a given frequency lasted at least 5 seconds.
- The following frequencies were tested: 2, 4, 8, 10, 13, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz. First, the lower limit was established by starting with 2 Hz stimulation and testing successive increasing standard frequencies (as defined above) until generalized EEG epileptiform activity was elicited. Then the upper sensitivity limit was defined, beginning at 60 Hz and decreasing the flash frequency in a stepwise manner until diffuse/generalized epileptiform activity was again elicited. IPS sensitivity was tested for each of 3 eye conditions: during closure, closed, and open.
- As soon as diffuse/generalized EEG epileptiform activity appeared, the stimulation at the frequency in question was terminated. This procedure was performed in a hospital setting under the supervision of a qualified physician. This procedure did not result in any actual seizure activity in this study and in general very rarely results in actual seizure activity. If a seizure were to occur, trained and experienced medical staff were on hand to intervene as required.
- Electroencephalograph (EEG) tracings, recorded during IPS sessions, were digitally recorded on a CD-ROM, coded and evaluated independently by one blinded clinical expert to determine the effects on the photosensitivity range. A change in photosensitivity range was calculated from the differences in the sensitivity range on the scale of frequencies given above. Each frequency tested represents one point on the scale; for example, a change from 10 and 25 Hz (lower and upper limits) to 18 and 20 Hz would give a difference of 7 - 2 = 5 points.

Efficacy

- A positive response was defined as a reduction of the photosensitivity range (PSR) by at least 3 points of the photosensitivity scale in at least 3 out of 4 consecutive time points as compared to matched timepoints during the baseline (placebo-dosing) Day 1 (1 to 12 hours) in at least 1 eye condition (during closure, closed, open) on Day 2 or Day 3.
- Complete suppression was defined as a PSR value = 0 in 3 out of 4 consecutive timepoints as compared with matched timepoints during the baseline Day 1 with a minimum baseline timepoint PSR of 3, in at least 1 eye condition (during closure, closed, open) on Day 2 or 3.

Pharmacogenomics

- A 10 mL blood sample was collected from subjects who had consented to the pharmacogenomic component of the study.

Safety

- Twelve-lead ECGs, vital signs (including orthostatic), physical examination (with oral temperature), neurological examination, and clinical safety laboratory testing (hematology, chemistry, coagulation, and urinalysis) were completed during the conduct of this study. Based upon the finding of retinal atrophy in the 6-month albino rat toxicology study, an optional ophthalmological evaluation which in most cases was several months since completion of the study was offered to study participants.
- Adverse events and concomitant medications were collected starting after signing of the informed consent until the final study procedure at the follow-up visit. Adverse events were recorded whenever spontaneously submitted. In addition, adverse events were specifically queried daily during the subject's stays in the Unit and at subsequent clinic visits.

Statistical Methods:

Pharmacokinetics

- Pharmacokinetic parameters of JNJ-26489112 and its metabolite, JNJ-38792442, were summarized, and descriptive statistics (including means, median, standard deviations, and coefficients of variation) were generated for each dose group.

Pharmacodynamics

- Statistical summaries of the pharmacodynamic data included all subjects who received at least 1 dose of study medication (JNJ-26489112 or placebo) and had pharmacodynamic measurements. The analysis on IPS was mainly based on the data from the central reader. If the data from the central reader was not available, the data from the local reader was used if available.

Efficacy

- The change in the photosensitivity range on each day from the matched time-point on Day 1 under 3 eye conditions (closure, closed and open) was provided. A positive response was defined as a reduction in photosensitivity range (PSR) by at least 3 points in at least 3 out of 4 consecutive time points (hours 1 –12) in at least 1 eye condition (during closure, closed, open) on Day 2 or Day 3 as compared to Day 1 (baseline). A complete suppression was defined as PSR being zero in at least 3 out of 4 consecutive time points (1 to12 hours) in at least 1 eye condition (during closure, closed, open) on Day 2 or Day 3 and where the PSR was at least 3 points or higher for those same 4 consecutive time points on Day 1 (baseline).

Safety

- The reporting of the safety data included the incidence and type of adverse events and concomitant medications, plus absolute values and changes in: blood pressure, heart rate, clinical laboratory safety data, 12-lead ECG measurements, along with physical and neurological examination data from predose to all postdose timepoints (by day). For those subjects who underwent follow-up ophthalmologic testing, a listing of the clinical data will be provided.

RESULTS:

- Of the 12 subjects enrolled, randomized and treated, 11 subjects completed the study (Table 1).
- 12 subjects were included in the Safety population and 11 in the PK population (1 subject did not receive JNJ-26489112).

Table 1: Study Completion/Withdrawal Information
(Study 26489112NAP2001: All Subjects Analysis Set)

	------- JNJ-26489112 -------			
Subject Completed Treatment/trial Reason for Withdrawal/termination	1,000 mg (N=5) n (%)	2,000 mg (N=4) n (%)	3,000 mg (N=3) n (%)	Total (N=12) n (%)
Total no. subjects WITH DISPOSITION STATUS	5 (100)	4 (100)	3 (100)	12 (100)
Completed	4 (80)	4 (100)	3 (100)	11 (92)
Withdrawn	1 (20)	0	0	1 (8)
Ineligible to continue	1 (20)	0	0	1 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Cross-reference: Attachment 1.1

- Subjects were healthy men and women aged 18 to 40 years, inclusive. Demographics and baseline characteristics were similar between treatment groups and consistent with the inclusion and exclusion criteria described in the protocol (Table 2, Attachment 1.2, Appendix 1.1).

Table 2: Demographic and Baseline Characteristics
(Study 26489112NAP2001: Safety Analysis Set)

	---------- JNJ-26489112 ----------			
	1,000 mg (N=5)	2,000 mg (N=4)	3,000 mg (N=3)	-- Total - (N=12)
Age (years)				
N	5	4	3	12
Mean	22.2	33.5	27.0	27.2
SD	3.19	9.15	8.66	8.12
Median	22.0	37.0	22.0	22.0
Minimum	18	20	22	18
Maximum	27	40	37	40
Sex, n (%)				
N	5	4	3	12
Male	1 (20.0)	0	2 (66.7)	3 (25.0)
Female	4 (80.0)	4 (100)	1 (33.3)	9 (75.0)
Race, n (%)				
N	5	4	3	12
White	5 (100)	4 (100)	3 (100)	12 (100)
Weight (kg)				
N	5	4	3	12
Mean	67.04	68.45	75.13	69.53
SD	19.168	1.692	7.379	12.494
Minimum	54.0	67.0	67.0	54.0
Maximum	101.0	70.6	81.4	101.0
Height (cm)				
N	5	4	3	12
Mean	166.7	165.3	176.2	168.6
SD	7.77	4.27	4.75	7.24
Median	167.3	164.0	176.0	168.7
Minimum	154	162	172	154
Maximum	175	171	181	181
Baseline body mass index (kg/m2)				
N	5	4	3	12
Mean	24.06	25.05	24.27	24.44
SD	6.168	0.686	3.121	3.993
Median	21.70	25.25	23.50	23.80
Minimum	19.6	24.1	21.6	19.6
Maximum	34.9	25.6	27.7	34.9

tsub02.rtf generated by dsub02.sas.
Cross-reference: Attachment 1.2

- Medications other than paracetamol were taken by 14 subjects; the use of these medications are not considered to have effected the results and conclusions of the study (Attachment 1.3).

PHARMACOKINETIC RESULTS:

Pharmacokinetic supporting data are provided in Attachment 2 as follows: actual blood sampling times relative to dosing are provided in Attachments 2.1 and 2.2 ; individual plasma and blood concentrations are listed and summarized in Attachments 2.3, 2.4, 2.5, 2.6 and 2.7; individual pharmacokinetic parameters are listed and summarized in Attachments 2.8, 2.9, 2.10, and 2.11; the number of data points used for the estimation of the elimination rate constant are listed in Attachments 2.12, 2.13, 2.14, and 2.15; Mean concentration-time profiles (linear and semilog) are displayed in Attachments 2.16, 2.17, and 2.18; composite

concentration-time profiles (linear and semilog) are displayed in Attachments 2.19 and 2.20; individual concentration-time profiles (linear and semilog) are displayed in Attachments 2.21 and 2.22; individual and mean pharmacokinetic parameters vs. dose plots are displayed in Attachments 2.23 and 2.24.

Analytical Results

Plasma and blood samples were analyzed to determine concentrations of JNJ-26489112 and JNJ-38792442 by Keystone Analytical Inc., [redacted] USA, using a validated LC-MS/MS method. For JNJ-26489112 in plasma and blood, the range of quantitation was 100 to 50,000 ng/mL and the lower limit of quantitation (LLOQ) was 100 ng/mL. For JNJ-38792442 in plasma and blood, the range of quantitation was 10 to 5,000 ng/mL and the LLOQ was 10 ng/mL. Samples were analyzed between 05 April 2008 and 24 September 2008. All assay criteria were met.

Dataset Analyzed

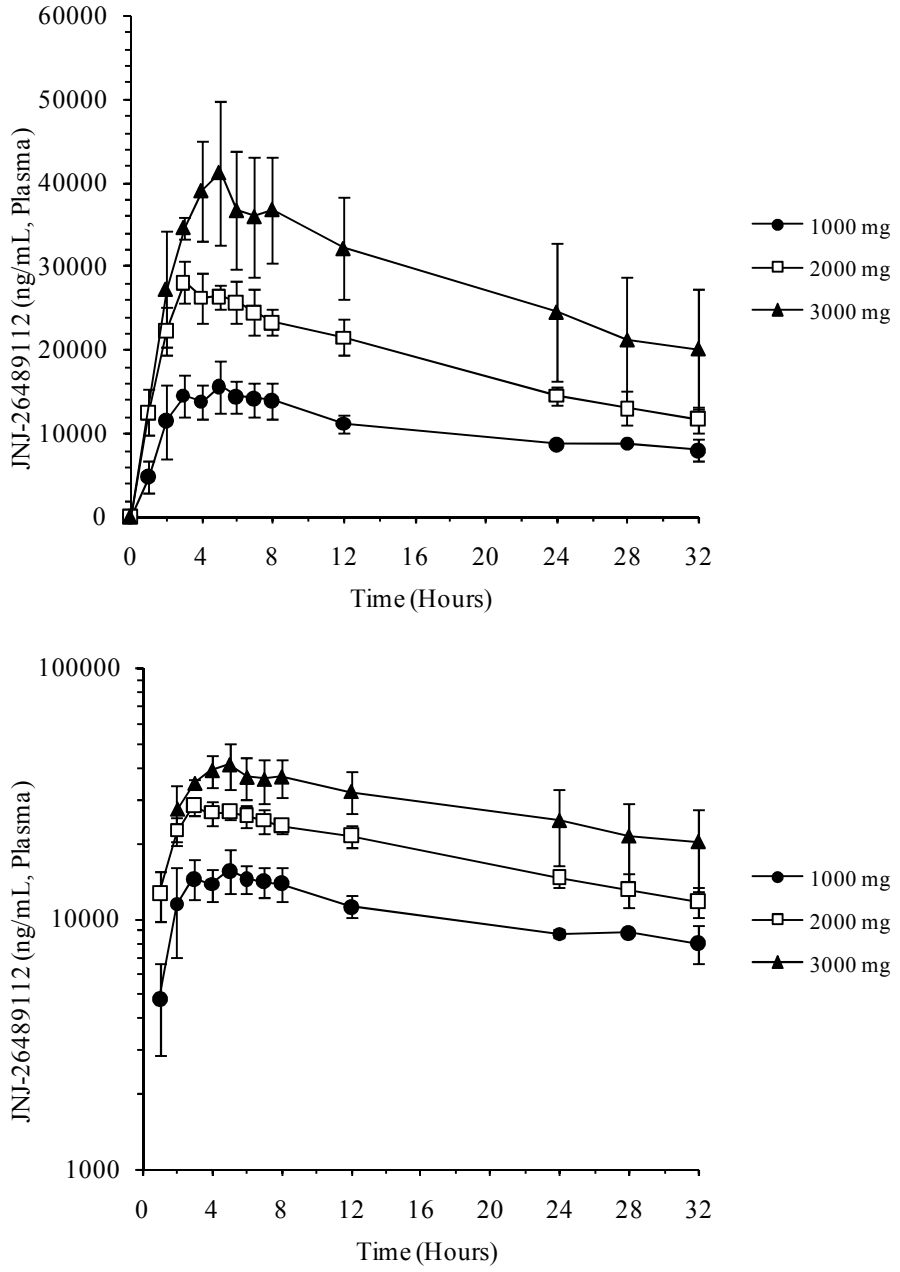
- Twelve male and female subjects were enrolled in the study and randomized to receive a single oral dose of JNJ-26489112 on Day 2 at three dose levels: 1,000 mg (n=5), 2,000 mg (n=4), 3,000 mg (n=3). Blood samples were obtained at scheduled times and assayed for JNJ-26489112 and JNJ-38792442 concentrations in plasma and blood.
- Subject [redacted] withdrew early from the study prior to dosing on Day 1 and was excluded from the pharmacokinetic analysis of JNJ-26489112 and its metabolite, JNJ-38792442 in plasma and blood. Subject [redacted]'s pharmacokinetic samples following the 8 hour sample were not received for analysis and was only included in the evaluation of C_{max} and t_{max} in plasma. The following subjects were excluded from the pharmacokinetic analysis of JNJ-26489112 and JNJ-38792442 in blood as samples were not received for analysis: 1,000 mg: [redacted] 2,000 mg: [redacted] 3,000 mg: [redacted].
- Blood sampling times relative to dose administration were used in the pharmacokinetic analysis of JNJ-26489112 and JNJ-38792442. Concentration values below the quantification limit in plasma and blood were set to 0 in the pharmacokinetic analysis. Due to AUC_{∞} extrapolation values exceeding >25%, terminal phase parameters (AUC_{∞}, $t_{1/2}$, CL/F, λ_z) were excluded from the descriptive statistics.
- Subjects already receiving a concomitant antiepileptic drug continued therapy and serial blood samples were obtained and assayed for antiepileptic drug concentrations in plasma on Days 1 and 2. Pharmacokinetic parameters were not estimated for the antiepileptic drugs.

Pharmacokinetic Results in Plasma

- Mean (SD) concentration-time profiles of JNJ-26489112 and JNJ-38792442 in plasma are displayed in Figure 1 and Figure 2, respectively. Mean (%CV) pharmacokinetic parameters of JNJ-26489112 and JNJ-38792442 in plasma are listed in Table 3 and Table 4, respectively. Individual concentrations of antiepileptic drugs over time are listed in Table 5.
- The median time to reach C_{max} of JNJ-26489112 in plasma was similar at all dose levels, ranging from 3.73 to 5.04 hours postdose following single dose administration (Table 3).
- Exposure to JNJ-26489112 in plasma increased proportionally with dose (Table 3). For doses in a ratio of 1:2:3, mean C_{max}, $AUC_{0\text{-}24\ h}$, and AUC_{last} increased at a ratio of 1:1.8:2.6, 1:1.9:2.8, and 1:1.9:2.8, respectively.

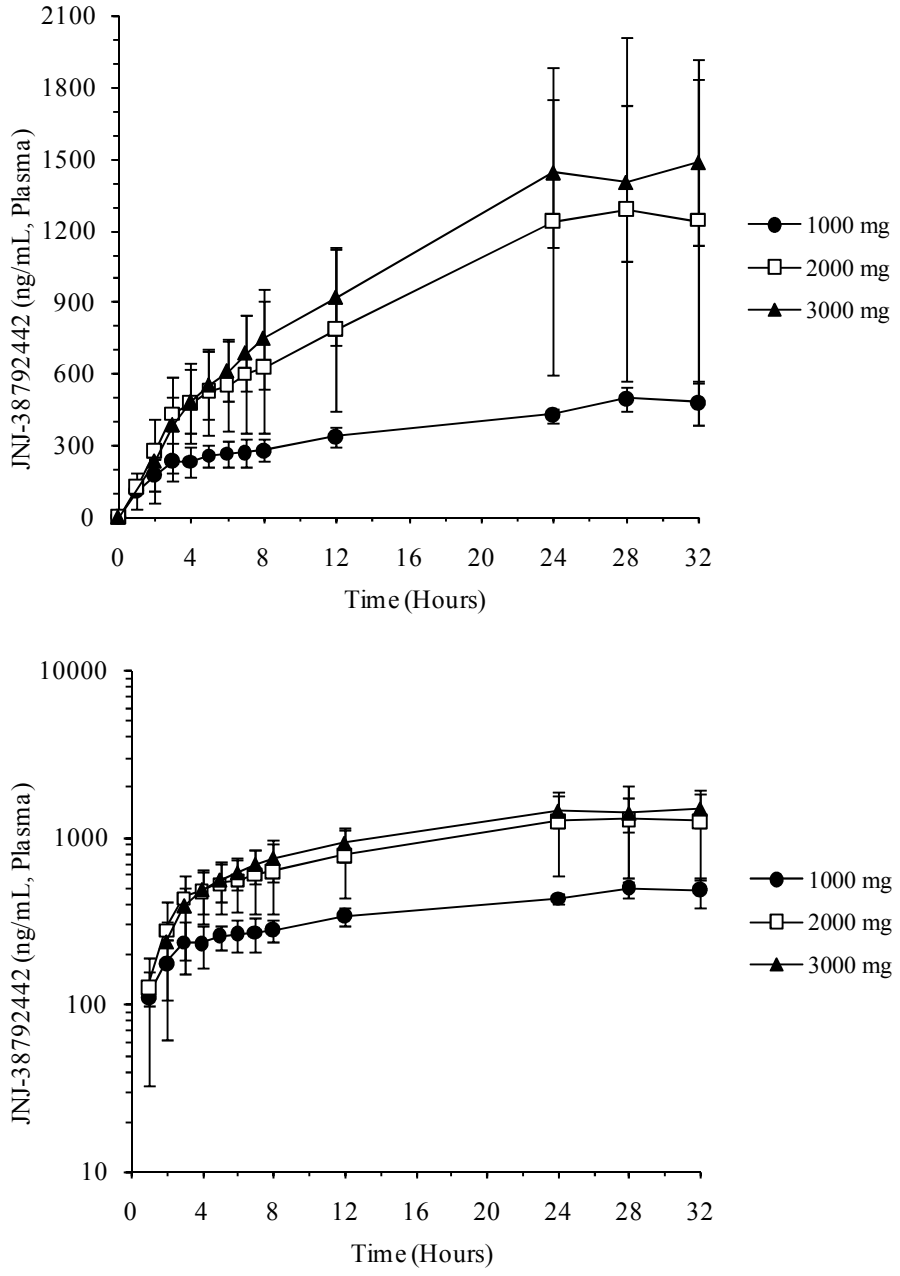
- The time to reach C_{max} of JNJ-38792442 in plasma was delayed significantly compared to JNJ-26489112 with median t_{max} ranging from 28.04 to 31.97 hours postdose following single dose administration (Table 4).
- Exposure to JNJ-38792442 in plasma increased in a nonlinear manner with increasing doses of JNJ-26489112 (Table 4). For JNJ-26489112 doses in a ratio of 1:2:3, mean C_{max}, $AUC_{0\text{-}24\ h}$, and AUC_{last} of JNJ-38792442 increased at a ratio of 1:3.2:3.5, 1:2.3:2.7, and 1:3.4:2.8, respectively.
- Compared to JNJ-26489112, exposure to JNJ-38792442 was very low. Mean metabolite/parent ratios for C_{max}, $AUC_{0\text{-}24\ h}$, and AUC_{last} ranged from 0.0246 to 0.0433, 0.0255 to 0.0322, and 0.0303 to 0.0486, respectively (Table 4)
- In the limited number of subjects available, antiepileptic drug concentrations do not appear to be affected by the coadiministration of JNJ-26489112 when comparing time-matched concentrations on Day 1 and Day 2 (Table 5).

Figure 1: Mean (SD) JNJ-26489112 Concentration-Time Profiles in Plasma Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001



Cross-reference: Attachment 2.16

Figure 2: Mean (SD) JNJ-38792442 Concentration-Time Profiles in Plasma Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001



Cross-reference: Attachment 2.16

Table 3: Mean (%CV) JNJ-26489112 Pharmacokinetic Parameters in Plasma Following a Single Oral Dose of JNJ-26489112

Study 26489112NAP2001

Treatment	C_{max} ng/mL	t_{max}[a] h	$AUC_{0\text{-}24\ h}$ h.ng/mL	AUC_{last} h.ng/mL
1,000 mg, n=4	16150	5.04	258593[b]	327982[b]
	(15.2)	(1.23-6.00)	(5.4)	(3.2)
2,000 mg, n=4	28275	3.73	478463	635498
	(8.5)	(3.00-5.00)	(9.3)	(20.7)
3,000 mg, n=3	41967	4.92	729871	907755
	(17.1)	(3.08-5.70)	(20.2)	(23.1)

[a]Median (Min-Max)
[b]n=3
Cross reference: Attachment 2.8

Table 4: Mean (%CV) JNJ-38792442 Pharmacokinetic Parameters in Plasma Following a Single Oral Dose of JNJ-26489112

Study 26489112NAP2001

Treatment	C_{max} ng/mL	t_{max}[a] h	$AUC_{0\text{-}24\ h}$ h.ng/mL	AUC_{last} h.ng/mL	Metabolite/Parent Ratio		
					C_{max}	$AUC_{0\text{-}24\ h}$	AUC_{last}
1,000 mg, n=4	437	28.04	7,606[b]	11,440[b]	0.0246	0.0255[b]	0.0303[b]
	(33.7)	(7.92-32.20)	(10.0)	(7.8)	(42.8)	(4.8)	(5.3)
2,000 mg, n=4	1,402	30.59	17,859	38,410	0.0433	0.0322	0.0486
	(64.6)	(23.98-48.27)	(45.4)	(85.5)	(63.1)	(40.4)	(62.3)
3,000 mg, n=3	1,517	31.97	20,774	32,497	0.0322	0.0257	0.0324
	(22.9)	(23.98-32.73)	(21.3)	(21.7)	(29.4)	(36.0)	(36.2)

[a]Median (Min-Max)
[b]n=3
Cross reference: Attachment 2.9

Table 5: Individual Concentrations of Antiepileptic Drugs in Plasma on Day 1 (Alone) and Day 2 (With JNJ-26489112)

Study 26489112NAP2001

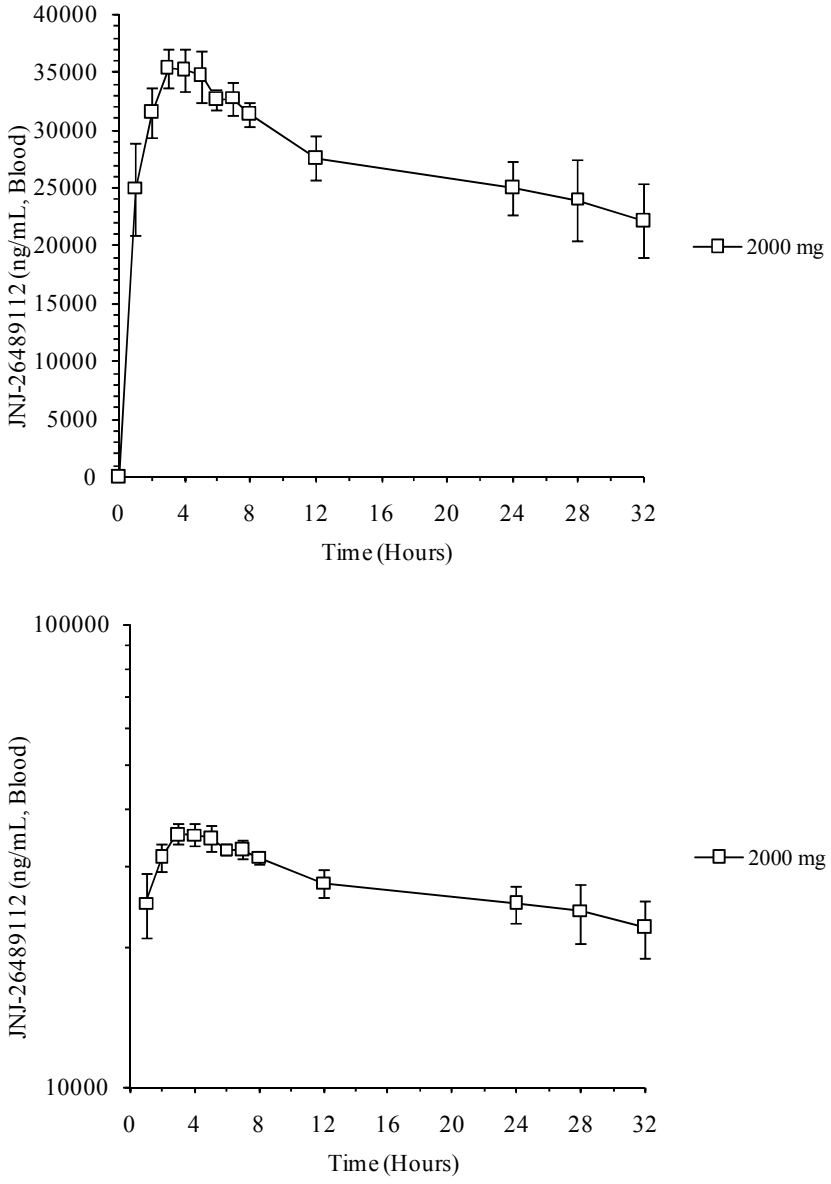
AED Concentration (ug/mL, Plasma)[a]											
		AED Alone (DAY 1)					AED + JNJ-26489112 (DAY 2)				
SUBSTANCE	SubjID	0 h	2 h	4 h	6 h	8 h	0 h	2 h	4 h	6 h	8 h
CARBAMAZEPINE	[redacted]	22	25	23	23	21	21	21	19	19	18
LAMOTRIGINE		0.8	0.8	0.7	0.7	0.6	0.9	0.7	0.65	0.6	0.5
		3.48	3.30	2.87	2.50	2.46	3.30	3.14	2.87	2.52	2.48
		7.70	6.20	3.98	4.50	6.78	6.96	6.36	6.29	8.32	NS
LEVETIRACETAM		26.0	18.7	14.3	10.6	8.8	34.0	24.5	20.0	15.8	9.4
		10.3	7.2	5.8	4.7	2.9	12.1	8.1	6.0	4.8	2.7
		38.3	27.1	21.0	16.3	11.9	34.2	23.4	18.5	14.6	NS
		33.8	31.1	25.6	21.1	16.6	38.5	27.5	22.4	21.4	18.1
TOPIRAMATE		9.1	8.9	7.5	6.6	7.2	8.7	8.0	6.5	6.2	5.2
VALPROIC ACID		52.0	52.0	NS	NS	NS	NS	NS	NS	NS	NS
		49.0	54.6	59.5	51.5	45.4	38.4	50.9	56.5	49.1	48.0

[a]Concentration unit for CARBAMAZEPINE was umol/L
NS: No Sample
Cross reference: Attachment 2.7

Pharmacokinetic Results in Blood

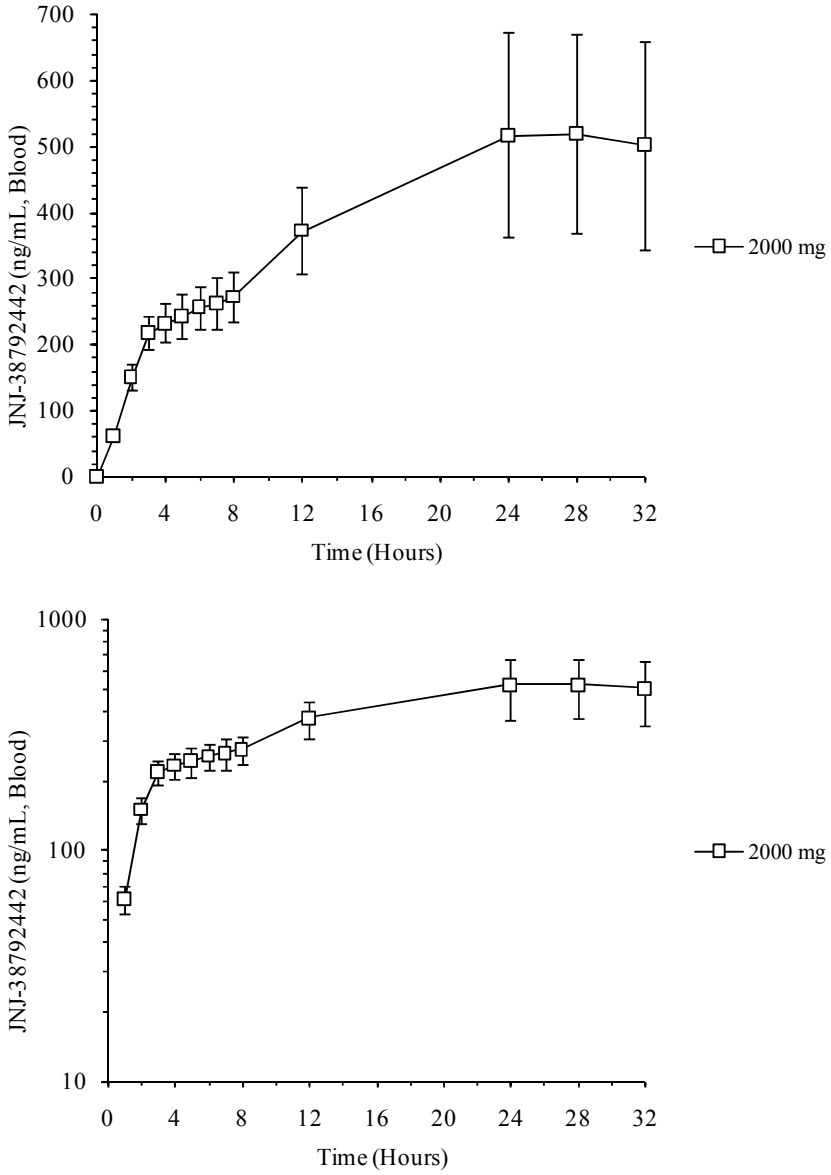
- Mean (SD) concentration-time profiles of JNJ-26489112 and JNJ-38792442 in blood are displayed in Figure 3 and Figure 4, respectively. Mean (%CV) pharmacokinetic parameters of JNJ-26489112 and JNJ-38792442 in blood are listed in Table 6 and Table 7, respectively.
- Due to a reduced number of subjects whose blood samples were analyzed for concentrations of JNJ-26489112 and JNJ-38792442 in blood, only the 2,000 mg group is presented below.
- The median time to reach C_{max} of JNJ-26489112 in blood was 3.30 hours postdose following a 2,000 mg single oral dose, which is similar to that in plasma (Table 3 and Table 6).
- Exposure to JNJ-26489112 in blood was higher compared to plasma (Table 3 and Table 6). JNJ-26489112 blood to plasma ratios of mean C_{max}, $AUC_{0\text{-}24\ h}$ and AUC_{last} were 1.26, 1.39, and 1.37, respectively, in subjects receiving 2,000 mg of JNJ-26489112.
- The median time to reach C_{max} for JNJ-38792442 in blood was delayed significantly compared to JNJ-26489112 (32 vs. 3.3 hours) following a 2,000 mg single oral dose of JNJ-26489112 (Table 6 and Table 7). Median t_{max} of JNJ-38792442 in blood was similar to plasma (32 vs. 30.59 hours) following a 2,000 mg single oral dose of JNJ-26489112 (Table 4 and Table 7).
- Exposure to JNJ-38792442 in blood was lower compared to plasma (Table 4 and Table 7). JNJ-38792442 blood to plasma ratios of mean C_{max}, $AUC_{0\text{-}24\ h}$ and AUC_{last} were 0.37, 0.45, and 0.32, respectively, for the JNJ-26489112 2000 mg dose group.
- Compared to JNJ-26489112, exposure to JNJ-38792442 in blood was very low. Mean metabolite/parent ratios of the 2,000 mg dose group for C_{max}, $AUC_{0\text{-}24\ h}$, and AUC_{last} were 0.0127, 0.0104, and 0.0123, respectively (Table 7).

Figure 3: Mean (SD) JNJ-26489112 Concentration-Time Profiles in Blood Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001



Cross-reference: Attachment 2.17

Figure 4: Mean (SD) JNJ-38792442 Concentration-Time Profiles in Blood Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001



Cross-reference: Attachment 2.17

Table 6: Mean (%CV) JNJ-26489112 Pharmacokinetic Parameters in Blood Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001

Treatment	C_{max} ng/mL	t_{max}[a] h	$AUC_{0\text{-}24\ h}$ h.ng/mL	AUC_{last} h.ng/mL
1,000 mg, n=1	28,400	1.23	528,478	695,589
2,000 mg, n=3	35,767	3.30	665,179	871,780
	(4.9)	(3.00-5.00)	(2.1)	(3.2)
3,000 mg	NAs	NAs	NAs	NAs

[a]Median (Min-Max)
NAs: Not Assessable
Cross reference: Attachment 2.10

Table 7: Mean (%CV) JNJ-38792442 Pharmacokinetic Parameters in Blood Following a Single Oral Dose of JNJ-26489112
Study 26489112NAP2001

Treatment	C_{max} ng/mL	t_{max}[a] h	$AUC_{0\text{-}24\ h}$ h.ng/mL	AUC_{last} h.ng/mL	Metabolite/Parent Ratio		
					C_{max}	$AUC_{0\text{-}24\ h}$	AUC_{last}
1,000 mg, n=1	318	32.20	4,325	6,813	0.00972	0.00711	0.00850
2,000 mg, n=3	525	32.00	7,949	12,427	0.0127	0.0104	0.0123
	(28.7)	(23.98-33.13)	(17.4)	(22.0)	(24.5)	(16.9)	(20.4)
3,000 mg	NAs	NAs	NAs	NAs	NAs	NAs	NAs

[a]Median (Min-Max)
NAs: Not Assessable
Cross reference: Attachment 2.11

PHARMACODYNAMIC/EFFICACY RESULTS:

- In Cohort 1, a total of 3 subjects ([redacted]) receiving 1,000 mg of JNJ-26489112 reported a positive response on Day 2 during 2 eye conditions. On Day 3, Subjects [redacted] and [redacted] also reported a positive response during 2 and 3 eye conditions, respectively.
- In Cohort 2, all 4 subjects reported at least one positive response or complete suppression after receiving 2,000 mg of JNJ-26489112. Subjects [redacted], and [redacted] had a positive response in one or more eye conditions on Day 2. On Day 3, Subject [redacted] had positive response during all three eye conditions. Additionally, Subject [redacted] had a positive response during eyes open and Subject [redacted] had a positive response during eye closure, and complete suppression while eyes were open on Day 3.
- In Cohort 3, all 3 subjects reported at least one positive response or complete suppression after receiving 3,000 mg of JNJ-26489112. Subjects [redacted] and [redacted] had a complete suppression on Day 2 while eyes were in closure and closed. On Day 3, all 3 subjects in Cohort 3 had a positive response in one or more eye conditions.
- Summary of responder by each subject and eye condition was presented in Table 8 below.

Table 8: Summary of Responders by Subject and Eye Condition
Study 26489112NAP2001

Subject	Dose	Day	Eye Condition		
			Closure	Closed	Open
[redacted]	1,000 m g	Day 2 (1-12hr)	–	+	+
		Day 3 (1-12hr)	–	–	–
	1,000 m g	Day 2 (1-12hr)	+	+	–
		Day 3 (1-12hr)	–	+	+
	1,000 m g	Day 2 (1-12hr)	–	–	–
		Day 3 (1-12hr)	–	–	–
	1,000 m g	Day 2 (1-12hr)	+	+	–
		Day 3 (1-12hr)	+	+	+
	2,000 m g	Day 2 (1-12hr)	–	–	+
		Day 3 (1-12hr)	–	–	–
	2,000 m g	Day 2 (1-12hr)	–	+	+
		Day 3 (1-12hr)	+	–	∅
	2,000 m g	Day 2 (1-12hr)	+	+	–
		Day 3 (1-12hr)	+	+	+
	2,000 m g	Day 2 (1-12hr)	–	+	+
		Day 3 (1-12hr)	–	–	+
	3,000 m g	Day 2 (1-12hr)	∅	∅	–
		Day 3 (1-12hr)	+	–	–
	3,000 m g	Day 2 (1-12hr)	∅	∅	–
		Day 3 (1-12hr)	+	+	–
	3,000 m g	Day 2 (1-12hr)	–	–	–
		Day 3 (1-12hr)	–	–	+

+ : A positive response.
– : A negative response.
∅: A complete suppression.
Cross reference: Attachments 2.25 and 2.26

PHARMACOGENOMIC RESULTS:

Pharmacogenomic results will be reported separately.

SAFETY RESULTS:

- 7 (58%) of 12 subjects reported at least 1 treatment-emergent AE (TEAE); 1 (20%) of 5 subjects in the 1,000 mg group, 3 (75%) of 4 subjects in the 2,000 mg group and 3 (100%) of 3 subjects in the 3,000 mg group.
- The most common TEAEs reported by subjects receiving JNJ-26489112 were headache (reported by 3 (25%) of 12 subjects), dizziness (reported by 3 (25%) of 12 subjects), nausea (reported by 3 (25%) of 12 subjects), fatigue (reported by 2 (17%) of 12 subjects) and skin irritation (reported by 2 (17%) of 12 subjects) (Table 9).

- All TEAEs were rated as Grade 1, with the exception of one report each of nausea, fatigue, palpitations, tachycardia, and two reports of dizziness being rated as Grade 2 (Attachment 3.1) and considered to be either not related, possibly related, of doubtful relationship, or probably related to study drug; only the Grade 2 nausea was deemed to be very likely related to study drug (Attachment 3.2).
- All TEAEs were transient with spontaneous resolution with no intervention with the exception of skin irritation due to ECG electrodes that was treated with a topical water-based emulsion (Attachment 3.3).
- There was no apparent dose-related increase in the incidence or duration of TEAEs following administration of JNJ-26489112.

Table 9: Treatment-Emergent Adverse Events by Body System and Preferred Term
(Study 26489112NAP2001: Safety Analysis Set)

	---------- JNJ-26489112 ----------			
Body System or Organ Class Dictionary-derived Term	1,000 mg (N=5) n (%)	2,000 mg (N=4) n (%)	3,000 mg (N=3) n (%)	Total (N=12) n (%)
Total no. subjects WITH ADVERSE EVENTS	1 (20)	3 (75)	3 (100)	7 (58)
Nervous system disorders	1 (20)	2 (50)	3 (100)	6 (50)
Dizziness	0	0	3 (100)	3 (25)
Headache	1 (20)	1 (25)	1 (33)	3 (25)
Lethargy	0	0	1 (33)	1 (8)
Somnolence	0	1 (25)	0	1 (8)
Gastrointestinal disorders	1 (20)	2 (50)	0	3 (25)
Nausea	1 (20)	2 (50)	0	3 (25)
Abdominal pain upper	1 (20)	0	0	1 (8)
Dry mouth	0	1 (25)	0	1 (8)
Dyspepsia	0	1 (25)	0	1 (8)
Cardiac disorders	0	0	2 (67)	2 (17)
Palpitations	0	0	1 (33)	1 (8)
Tachycardia	0	0	1 (33)	1 (8)
General disorders and administration site conditions	1 (20)	1 (25)	0	2 (17)
Fatigue	1 (20)	1 (25)	0	2 (17)
Skin and subcutaneous tissue disorders	1 (20)	0	1 (33)	2 (17)
Skin irritation	1 (20)	0	1 (33)	2 (17)
Psychiatric disorders	0	1 (25)	0	1 (8)
Depression	0	1 (25)	0	1 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
Tae01.rtf generated by dae01.sas.
Cross-reference: Attachment 3.3

- There were no deaths or serious adverse events reported.
- There were no discontinuations due to adverse events.
- Laboratory values outside of the normal range were observed in several subjects, but these were considered not to be clinically significant by the investigator.
- There were no clinically significant findings, treatment-related trends in supine or standing systolic and diastolic blood pressure, pulse rate or clear evidence of postural effects on blood pressure following administration of JNJ-26489112. Orthostatic changes in blood pressure were noted for several subjects, but these changes were observed following placebo and active doses, and showed no correlation with JNJ-26489112 dose level or dosing time and were deemed by the investigator to not be of any clinical significance.
- Electrocardiogram (ECG) values outside of the normal range were observed in several subjects (QT, QT/QTc), but these were considered not to be clinically significant by the investigator.
- There were no clinically significant changes from baseline in the physical examinations performed following administration of JNJ-26489112 in subjects with photosensitive epilepsy.
- There were no clinically significant changes in ophthalmologic examinations following conclusion of the study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION:

- Single oral doses of JNJ-26489112 up to 3,000 mg were generally well tolerated in male and female subjects with a diagnosis of idiopathic, photosensitive epilepsy.
- All adverse events were mild or moderate in severity, limited in duration, and, in general, resolved without intervention.
- There were no serious adverse events and no subjects withdrew due to an adverse event.
- There were no clinically significant physical examinations, laboratory, vital signs, or ECG monitoring abnormalities reported.
- There were no clinically significant findings in follow-up ophthalmologic examinations.
- Median t_{max} of JNJ-26489112 in plasma was similar across dose groups, ranging from 3.73 to 5.04 hours
- Exposure to JNJ-26489112 in plasma increased proportionally with dose.
- Median t_{max} of the major metabolite JNJ-38792442 in plasma was similar across dose groups but delayed compared to JNJ-26489112, ranging from 28.04 to 31.97 hours.
- Exposure to JNJ-38792442 in plasma increased in a nonlinear manner and was overall, much lower compared to JNJ-26489112.
- In the 2,000 mg dose group, pharmacokinetic parameters of JNJ-26489112 in blood were higher compared to plasma, suggesting JNJ-26489112 binds to blood cells. However, JNJ-38792442 pharmacokinetic parameters in blood were lower compared to plasma, suggesting a transfer restriction into the blood cells. The median t_{max} of the 2,000 mg dose group remained similar between blood and plasma for both JNJ-26489112 and JNJ-38792442.

- In the limited number of subjects available, antiepileptic drug concentrations in plasma did not appear to be affected by the coadiministration of JNJ-26489112 when comparing time-matched concentrations on Day 1 and Day 2.
- The majority of subjects had a positive response or complete suppression on Day 2 or 3 during one or more eye condition following a single oral dose of JNJ-26489112.
- A single 3,000 mg dose of JNJ-26489112 resulted in complete suppression of the IPS induced photoparoxysmal-EEG response in 2 of 3 subjects.

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