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Clinical Study Report

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Clinical Study Report

An open-label, single-arm, multicenter, phase IV study to evaluate the response to and safety of flexible dose treatment with extended-release paliperidone in patients with schizophrenia

INVEGA R076477SCH4027

Protocol version 2.0 16 FEB 2009; Phase 4

Paliperidone

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EudraCT Number: N/A

DATE STUDY INITIATED: 16 May 2009 (First Patient, First Visit Date)

DATE STUDY COMPLETED: 07 October 2011 (Last Patient, Last Visit Date)

Issue Date: 04 OCTOBER 2012
Prepared by: Janssen Turkey
Report No:

GCP Compliance: This study was conducted in compliance with the Good Clinical Practice, including the archival of essential documents.

Confidentiality Statement

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Status	☐ Draft	☒ Final	☐ Amended
Prepared by:			
Assoc. Prof. Dr. Oktay Özdemir		Signature	Date

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.		
Reviewed by: **Global Trial Manager**		
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Approved by: **Janssen Turkey Medical Director**		
Dr. Çiğdem Dönmez	Signature	Date
Approved by: **Study Statistician**		
Assoc. Prof. Dr. Oktay Özdemir	Signature	Date

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Approved by:
EMEA Therapeutic Area Leader

NOT APPLICABLE Signature Date

Coordinating Investigator

Prof. Dr. Alp Üçok, İstanbul University Faculty of Medicine Psychiatry Department

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signature Date

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SYNOPSIS

Sponsor	Johnson and Johnson Sihhi Malzeme San. ve Tic. Ltd. Sti
Name of Finished Product	Invega
Name of Active Ingredient(s)	Paliperidone ER

Protocol Number: R076477SCH4027

Title of Study: An open-label, single-arm, multicenter, phase IV study to evaluate the response to and safety of flexible dose treatment with extended-release paliperidone in patients with schizophrenia

EudraCT Number: N/A

Coordinating Investigator: Alp Üçok, Prof. Dr. Istanbul University Faculty of Medicine Psychiatry Department, Istanbul

Reference: 16th TPD Annual Meeting - Clinical Training Symposium - Oral Presentation

Study Period: May 2009-October 2011

Clinical Phase: 4

Objectives:

Primary objectives:

The primary objective of this study was to explore the response to treatment of flexible dose of paliperidone in schizophrenic patients who have recent onset (<3 years after the first episode/hospitalization), but either not on antipsychotic medication for at least 3 months or in need of antipsychotic medication switch because of safety and/or lack of efficacy reasons. Response to treatment was measured via change in Personal and Social Performance (PSP) scale.

Secondary objectives:

The secondary objectives are:

- To confirm the response to treatment of flexible dose of paliperidone via the following:
    - Global Assessment of Functioning (GAF) test
    - Positive and Negative Syndrome Scale (PANSS)
    - Relapse rate
- To evaluate the safety of flexible dose of paliperidone via the following tests:
    - Extrapyramidal Symptom Rating Scale (ESRS)
    - Drug Attitude Inventory-10 (DAI-10)
    - Measurement of metabolic status by body weight measurement, vital signs, physical examination findings, and laboratory tests
    - Adverse events (AE) reporting
- To evaluate quality of life via the following test:
    - SF-36 scale

Other objectives:

To evaluate health resource utilization parameters, i.e. hospitalization rate, duration of hospitalization, personnel time use, frequency of use of antipsychotic and other medications, frequency of use of laboratory tests, number of days spent off-work or off-school etc.

Hypothesis:

At the end of 12 months, flexible dose paliperidone treatment was expected to improve functionality and satisfaction of schizophrenia patients as measured by PSP. The expected increase in PSP score was approximately 10-20%.

Study Design:

This is a nonrandomized, single-arm, multicenter clinical trial to explore response to and safety of flexible dose of paliperidone treatment in recently diagnosed schizophrenic patients (<3 years after the first episode/hospitalization), and either not on any antipsychotic treatment at least for 3 months or planned to switch to another antipsychotic agent due to safety or lack of efficacy issues. Both hospitalized patients and outpatients could be included in the study. Patients could switch to any effective dose of paliperidone ER from any oral antipsychotic medication without the need for titration. However, if required, cross-dose adjustment could be done. Maximum 4 weeks of switching period was allowed. Use of anticholinergic drugs was not be restricted. During the study period, flexible dose of paliperidone ER remained within the range of 3-12 mg/day. Flexible dose administration allowed the investigator to adjust the dose individually according to the patient's condition assessed by PANSS scale. The recommended paliperidone ER dose was 6 mg/day. However, some patients could benefit from lower or higher doses within the recommended range of 3-12 mg/day. Baseline data for all analysis were data obtained at Visit 1 prior to the first paliperidone ER treatment. Number of patients per study center was 10-12.

Number of cases (planned and analyzed):

A total of 122 patients were planned to be included in the study. However, 85 patients were enrolled to the study and five of these patients were excluded from the analysis since they failed to meet study criteria.

No Interim analysis had been planned for the study.

Final analysis populations were as follows:

- *Intent-to-treat*: 62
- Safety: 84

Number of patients who completed the study in compliance with the protocol, also by coming to the visit at month 12, was 25. Three patients, who withdrew or was withdrawn from the study within 6 weeks before the last visit, were included in per-protocol analysis.

Main criteria for Diagnosis and Inclusion:

Study population:

The study population included patients diagnosed with schizophrenia according to DSM-IV criteria. Patients to be included in the study had to fulfill all the following inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

Patients had to fulfill ALL the following criteria to be included in this study:

- DSM-IV schizophrenia criteria
- Recently diagnosed with schizophrenia (<3 years after the first episode/hospitalization), but either not on antipsychotic medication for at least 3 months or in need of antipsychotic medication switch because of safety and/or lack of efficacy reasons (Lack of efficacy was defined as subjects with a baseline total PANSS score ≥70 or ≥2 items scoring ≥4 in the Positive or Negative Symptom Subscale or ≥3 items scoring ≥4 in the General Psychopathology Subscale. Lack of tolerability was defined as the presence of clinically significant side effects with the previous antipsychotic medication.)
- 18-65 year old male or female patients
- To be healthy at screening according to physical examination findings and vital signs
- Women at postmenopausal state for at least 1 year, or undergone surgical sterilization; or for women of child-bearing potential, willing to use an effective contraceptive method throughout the study (Effective contraceptive methods include prescribed hormonal contraceptive pills and injections, intrauterine device, barriers, contraceptive patches, and sterilization of the male partner. In addition, urine pregnancy test should be negative at screening for women of child-bearing potential.)
- To be willing and capable to complete the questionnaires
- Having signed the informed consent form
- Men had to agree to use a double barrier method of birth control and not to donate sperm during the study and for 3 months after receiving the last dose of study drug

Exclusion criteria:

Patients with any of the following were excluded from the study:

- Use of clozapine, depot neuroleptics or Risperdal® CONSTA within the last 3 months
- Any instable serious clinical condition including clinically important laboratory abnormalities
- Previous and current tardive dyskinesia symptoms
- History of malignant neuroleptic syndrome
- To be considered carrying high risk regarding adverse effects; homicide and/or suicide
- Pregnancy or nursing
- Participation to any other drug trial within the last 30 days of screening
- Documented known hypersensitivity to the study drug (See Section 3.4, Study Drug)
- Inability to swallow the study medication in one piece with water (the study medication should not be chewed, broken into pieces, dissolved in liquid or crashed, since it may impair the extended release profile)
- To be an investigator or personnel at the study center who are directly involved in this study and other clinical trials, and the family members of this investigator or personnel
- Documented previous or current drug dependence according to DSM-IV criteria
- Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subjects from meeting study requirements

Prohibitions and restrictions:

Patients included in the study were willing to comply with prohibitions and restrictions throughout the study.

- Women continued to use an effective contraceptive method.
- Women who used oral contraceptives also used an additional contraceptive method.

Study Product, Dose and Administration, Lot Number:

There were 4 dosage levels of paliperidone ER (3, 6, 9 and 12 mg/day). In general, the recommended paliperidone ER dose was 6 mg once daily. Some subjects could benefit from higher or lower doses in the recommended range of 3 to 12 mg once daily. Throughout the study, flexible dosing in a range of 3 to 12 mg/day could be used.

Adjustment of the dosage was done at the investigator's discretion, based on each patient's clinical response to study drug, according to the change in PANSS score, and tolerability of the study drug. Subjects were not allowed to change study drug dosages at their own discretion; patients could change the dosage only after consulting with their investigator. Investigators were encouraged to wait 4-5 days before changing dosages to allow the greatest possible efficacy at each dosage level.

Paliperidone 3 mg, 6-mg and 9-mg tablets were used:

- Patients who required a daily dose of 3 mg paliperidone ER took a 3-mg tablet.
- Patients who required a daily dose of 6 mg paliperidone ER took a 6-mg tablet.
- Patients who required a daily dose of 9 mg paliperidone ER took a 9-mg tablet.
- Patients who required a daily dose of 12 mg paliperidone ER took 2 x 6-mg tablet.

Patients could switch from any oral antipsychotic medication to an effective dose of paliperidone ER without the need for titration.

Patients could be cross-tapered in different ways from their previous antipsychotic medication, e.g. the dose of previous antipsychotic drug could be decreased at the time of or after initiation of paliperidone ER. The period of cross-tapering could vary between subjects, since both dosing and timing of transition depended on individual patient characteristics such as kind and severity of current symptoms or adverse events, course of previous relapses and rehospitalizations, or type and dose of previous antipsychotic medication (e.g. with or without anticholinergic and/or sedating properties). For example, for a patient who had been treated with a high dose of a previous antipsychotic or who was at risk of relapse, a higher dose of paliperidone ER could be required while for a patient who was switched because he was sensitive to side effects a lower than the recommended paliperidone ER dose could be considered. As the variability of these clinical factors was high, specific transition instructions were made for this study. However, the transition period, i.e. to initiate the use of paliperidone ER as antipsychotic monotherapy, preferably did not exceed 4 weeks.

Anticholinergic medication use was not limited in this study. All oral antipsychotic medications indicated for the treatment of schizophrenia were stopped at the end of the cross-tapering transition period, which preferably did not exceed 4 weeks (2 Visits).

Reference Treatment, Dose and Administration, Lot Number: None.

Study Drug	Lot No	Administration
Invega 3 mg – 9 mg	8FZT500 9EZSP00 ABZSN00 8EZS400 7LZSC00 9CZTD00 9FZSAOO 9GZSI00 AJZTS00 8GZSNOO 9EZSHOO 9FZS700 9GZSE00 AIZTM00	Oral

Treatment period: Explained in the Study Design section.

Evaluation Criteria:

Efficacy evaluations / criteria:

All patients who received at least one dose of paliperidone ER with at least one post-treatment assessment were included in the analysis (i.e. intent-to-treat [ITT] population for efficacy evaluation).

Analyses included the following:

- Personal and social functioning measured as the change in PSP (Personnel and Social Performance) score
- Change in GAF (Global Assessment of Functioning) score
- Efficacy measured as the change from baseline in PANSS (Positive and negative Syndrome Scale) total score

Safety evaluations:

Physical examination was performed at the screening, at control visits and at the final or discontinuation visit.

ESRS (Extrapyramidal Symptom Rating Scale) assessment was planned and was performed at every visit and at the discontinuation visit.

Body weight was measured and blood samples were collected for the assessment of metabolic side effects (fasting blood glucose and serum lipid profile) at screening and at the final or discontinuation visit.

Patients were asked to complete DAI-10 survey at every visit including screening.

Patients were asked to report AEs at any time; AEs were assessed at all visits after informed consent was obtained.

Percentage of discontinuation due to AEs was recorded.

Other evaluations:

At control visits and at the final or discontinuation visit, quality of life assessment was done and questions were asked about some parameters related with health resource utilization. The items evaluated include the following:

- Change in SF-36 scores (total, physical and mental subscales and domains) for evaluating quality of life
- Frequency of hospitalization and length of hospital stay
- Use of healthcare personnel time
- Frequency of treatment requirement
    - Antipsychotic medications
    - Medications administered to control or treat concomitant conditions
    - Non-pharmacologic treatment
- Frequency of use of laboratory tests
- Number of days spent off-work or off-school due to disease and/or its treatment

Statistical Methods:

Sample size calculation:

Primary evaluation parameter was the change in PSP score at the end of 12 months or discontinuation compared to baseline. Expected increase in PSP score was anticipated to be approximately 10-20%. In order to detect a 10% change in PSP score, with the assumption that the standard deviation of this change would not be wider than 30%, 73 patients with at least one efficacy evaluation after treatment onset were needed (type I error: 5% (two-sided) and power 80%). A sample size of 73 would produce a 95% confidence interval equal to the sample mean (10%) ±7% when the estimated standard deviation was 30%. With the assumption that 40% of the patients would drop out during the study, the number of enrolled patients was decided to be 122.

However, a total of 85 patients were enrolled; 5 patients were excluded because they failed to fulfill inclusion criteria.

Study populations:

Patients who received at least one dose of paliperidone were included in the descriptive analysis of baseline demographic and clinical data (i.e. intent-to-treat –ITT- population for baseline evaluation).

All patients who received at least one dose of paliperidone and who had at least one efficacy evaluation after baseline visit were included in the efficacy analysis (i.e. intent-to-treat with last-observation- carried-forward –ITT-LOCF- population for efficacy evaluation).

Patients who received at least one dose of paliperidone and who had at least one safety evaluation after baseline visit were included in the safety analysis (i.e. intent-to-treat –ITT- population for safety evaluation).

Descriptive statistics was done for all study parameters and the results were expressed as mean, median, standard deviation, interquartile range, min-max values for numeric variables and the counts and percentages for categorical variables.

Primary analysis:

Primary analysis was made to test the significance of change in PSP score at final or discontinuation visit. This analysis was performed by means of Student's paired t test.

Secondary analysis:

The significance of other efficacy parameters (changes in GAF and PANSS scores) was also tested with Student's paired t test or Wilcoxon test for data matched according to distribution characteristics.

Relapse rate was planned to be calculated with two methods: (a) crude relapse rate (the proportion of patients who had relapsed within the follow-up period), (b) relapse rate over time (Kaplan-Meier survival analysis).

The significance of changes in ESRS, DAI-10 and SF-36 scores (total, physical and mental subscales and domains) at final or discontinuation visit was analyzed with Student's paired t test or Wilcoxon test for the data matched according to distribution characteristics.

RESULTS:

The majority of the patients included in the study (n=80) were male, and age average (SS) was 27.5 (7.7). According to DSM criteria 55% of 80 patients were determined to be paranoid and 45% to be other types.

Completion status of 80 patients was as follows:

	n (%)
Completed	25 (31.3)
Discontinued	55 (68.8)
Withdrew his/her consent	18 (22.5)
Lost to follow up	8 (10.0)
Adverse event	14 (17.5)
Lack of efficacy	5 (6.3)
Adverse event AND lack of efficacy	4 (5.0)
Treatment incompliance	3 (3.8)
Other	3 (3.8)

In the ITT population (n=62), most of the patients were male (75.8%) and the age average was (SS) 27.9 (8.0). According to DSM criteria, 56.5% of 62 patients were paranoid and 43.5% were determined to be other types. Inter-episode residual symptoms and episodic course were the most frequent (37.1%) among the patients.

Mean value of total duration of paliperidone use was calculated as (SS) 189 (130) days, with mean baseline dose of 5.4 mg and mean dose of 6.4 mg.

EFFICACY RESULTS:

Primary efficacy parameter was determined as "change from baseline in PSP scale scores". Significant improvement was observed both in total PSP score and in A, B, C and D subscale scores.

		n	Mean (SS)	Median (IQR)	P value
Domain A	**Visit 1**	62	3.71 (0.93)	4 (1)	0.002
	Visit 5	28	2.79 (0.96)	3 (1)	
Domain B	**Visit 1**	62	3.66 (0.85)	4 (1)	0.001
	Visit 5	28	2.71 (0.90)	3 (1)	
Domain C	**Visit 1**	62	2.26 (1.04)	2 (2)	0.004
	Visit 5	28	1.43 (0.69)	1 (1)	
Domain D	**Visit 1**	62	1.87 (0.95)	2 (2)	0.049
	Visit 5	28	1.39 (0.63)	1 (1)	
Total	**Visit 1**	62	50 (12)	50 (15)	<0.001
	Visit 5	28	65 (12)	63 (14)	

There was a significant improvement in the GAF and PANSS scores as secondary efficacy parameters.

	n	Mean (SS)	Median (IQR)	P value
GAF score				
Visit 1	62	45.1 (12.4)	45 (17)	0.001
Visit 5	28	62.4 (12.5)	60 (18)	
PANSS positive symptom subscale score				
Visit 1	62	20.3 (6.6)	20 (10)	0.001
Visit 5	28	11.9 (3.8)	12 (7)	
PANSS negative symptom subscale score				
Visit 1	62	21.9 (6.7)	21 (9)	0.001
Visit 5	28	13.7 (5.6)	13 (10)	
PANSS general psychopathology subscale score				
Visit 1	62	40.6 (11.6)	39 (19)	0.001
Visit 5	28	27.8 (7.1)	27 (9)	
PANSS total score				
Visit 1	62	82.7 (20.8)	81 (32)	0.001
Visit 5	28	53.4 (12.6)	52 (13)	

Relapse was observed in nine patients during the study. Since the number of patients who remained in regular follow up gradually decreased, rough calculation of relapse rate was not made. Relapse-free survival rate calculated with Kaplan-Meier method was 80% in 12 months (annual relapse rate was 20%).

There was a significant increase in SF-36 Health Status survey total scores from mean (SS) 54 (16) to 71 (16) ($p<0.002$); a similar significant improvement was observed in domains and all subscales ($p<0.05$).

SAFETY RESULTS:

84 patients were included in the safety analysis.

The rate of adverse events was 57.1% (n=48), and a total of 115 adverse events were reported. Adverse event was observed at baseline in 23% of the patients (n=20), and new adverse event was reported by 51.2% of the patients (n=43).

When AEs were evaluated generally in two main groups as EPS and AE; EPS was observed in 11 of 84 patients (13.1%) at baseline and in 17 of the patients (20.2%) during the study. In 26 of the patients, EPS was observed at baseline and/or during the study.

The most frequent adverse event at baseline was acathisia, with 5 episodes (16.7% prevalence rate in 30 adverse events). The most frequent adverse event among new adverse events was insomnia, with 15 episodes (17.6% prevalence rate in 85 adverse events).

When AEs were evaluated according to the MEDDRA preferred term, the most frequent AE at baseline was acathisia with 5 episodes (16.7% among 30 AE), followed by insomnia, EPS, sedation and weight gain, with 3 episode in each (10%). Insomnia with 15 episodes (17.8% among 85 AE) and psychotic disorder with 11 episodes (12.9%) were the most frequent new adverse events.

58.3% of adverse events resolved, while 34.8% were still present.

Of a total of 115 adverse events, 29 (25.2%) were mild, 66 (57.4%) were moderate and 20 (17.4%) were severe.

No adjustment was made in treatment dose in 66.1% of the adverse events, and treatment was discontinued due to adverse event in 25.5% of the cases.

In 65.2% of the adverse events, a concomitant medication was initiated due to adverse event.

When the causal relationship between the adverse events and the study drug was evaluated, it was found that 48.7% of the adverse events had no causal relationship with the study drug, and the causal relationship with the study drug was suspicious in 18.3%, possible in 11.3%, probable in 11.3% and highly probable in 10.4%.

	n
Number of patients with one or more AE	48
Number of patients with one or more SAE	12
Number of deaths	0
Number of SAE that led to discontinuation of treatment	10

No significant change was observed in ESRS scale throughout the treatment period (mean (SS) score was 8.39 at Visit 1 (12.07) and 6.68 at Visit 5 (7.79); p=0.513).

DAI-10 scores of the patients showed significant improvement (mean (SS) score was 3.8 at Visit 1(4.4) and 6.7 at Visit5 (3.4); p=0.028).

There was no significant difference at baseline and final visits in terms of the proportion of patients with fating blood glucose, triglyceride, total cholesterol and HDL-cholesterol levels above normal limits. Rate of patients with LDL-cholesterol ≥130 mg/dl was 14.5% at Visit 1 and increased to 33.3% at Visit 5 (p=0.031).

There was a significant increase also in body weight (mean (SS) 73 (16) at Visit 1, and 80 (20) kg at Visit 5; p=0.009) and body mass index (mean (SS) 25.1 (4.4) at Visit 1, and 27.0 (5.7) kg/m^2 at Visit 5; p=0.009). However, there was no difference from baseline in the distribution of patients to BMI categories of 27, 27-29.9 and ≥30 kg/m^2.

RESTRICTIONS OF THE STUDY: It was an open-labeled and single-arm study.

- CONCLUSION:

In this study, significant improvements were observed in the symptoms and functionality, in the physical and mental domain scores and all subscale score of SF-36 scale and in the attitude and thoughts toward their medications of recently diagnosed schizophrenia patients treated with paliperidone ER.
These improvements began as of month 3 and increasingly continued throughout the 12-month treatment.

Quality of life was higher in schizophrenic patients with low BMI and lipid profile

No unexpected safety results were reported in this study.

LIST OF ABBREVIATIONS LİSTESİ

AE	Adverse event
CRF	Case report form
DAI	Drug Attitude Inventory
DCF	Data Correction Form
EMEA	Europe, Middle East and Africa
EPS	Extrapyramidal symptoms
ER	Extended release
ESRS	Extrapyramidal symptom rating scale
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
HRU	Health Resource Utilization
PANSS	Positive and Negative Syndrome Scale
PRO	Patient-reported outcome(s)
PSP	Personal and Social Performance
SF-36	Short Form 36 for Health Status
SPI	Short Product Information
USP	United States Pharmacopeia

ETHICS

Independent Ethics Committee or Institutional Review Board
This study protocol was reviewed by the Independent Ethics Committee.

Ethical Aspects
This study was based on the Declaration of Helsinki and conducted in accordance with the principles of the Good Clinical Practices and the ethical requirements determined by the applicable Legislation on drug trials in Turkey.

Known instances of nonconformance were documented and are not considered to have impacted the overall conclusions of the study.

Subject Information and Consent
Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the purpose of the study, participation/termination conditions, and risks and benefits of treatment.

Consent form was received before any activity was performed about the study. Known instances of nonconformance were documented and are not considered to have impacted the overall conclusions of this study.

Personal data from subjects enrolled in this study was limited to those data necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study, and were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Additional information on the ethical conduct of this study is contained in the Ethical Aspects section of the protocol, which is appended to this report.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator:	Prof Alp Üçok,. MD.
Sponsor's Responsible:	
Medical Director:	Çiğdem Dönmez, M.D
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Statistician:	Assoc. Prof, Oktay Özdemir, MD*
Medical Writer:	Assoc. Prof. Oktay Özdemir, MD
Central Clinical Laboratory:	Central laboratory was not used in this study
[Contract Research Organization]	Assoc. Prof. Oktay Ozdemir, MD Yorum Consulting Ltd Valikonagi Cad. Akkavak Sok. Polat-32/6 Nisantasi ISTANBUL Phone: 90 - 212 - 248 85 85 Fax: 90 - 212 - 248 31 87 (Involved in data management, statistical analysis plan and the writing of the clinical study report in this study)

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