Poster 96
Abstract 2726

A Phase I Assessment of the Safety and Tolerability Profile of Novel Treatments for Acute Allergic Reactions Administered by Intravenous and Intramuscular Injection Formulations

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ABSTRACT

Rationale. JDP-205 and JDP-207 are developed as novel, first-in-class therapy for acute allergic reactions. JDP-205, a non-sedating antihistamine intravenous injection, is aimed for a faster or immediate onset treatment profile for hospital use, while JDP-207, a non-sedating antihistamine intramuscular formulation, is designed for patient self auto-injection, for the treatment of acute urticaria associated with acute allergic reactions. This Phase-I clinical study was designed to assess their safety and tolerability when administered to human volunteers.

Methods. Twenty-four healthy volunteers were randomized in a 4-period design. The drug products were provided as sterile small volume parenteral injectable products. Single doses of JDP-205 were administered by intravenous injection over 1.5-minute, while JDP-207 was administered by intramuscular injection in the anterolateral thigh muscle slowly within 0.5-minute. Blood samples were collected up to 36-hours. Safety was evaluated through laboratory tests, vital signs, electrocardiogram and adverse events. Some key adverse events were recorded prior to and 3 times after drug administration.

Results. During the study, 22 (91.7%) subjects experienced a total of 66 adverse events; severity ranged from mild to moderate, except for intramuscular injection site pain. No subject took concomitant medications and no subject was withdrawn for safety reasons. The JDP-205 intravenous doses were deemed proportional on drug exposure over 36-hours. JDP-207 intramuscular dose was deemed equivalent to the IV dose on drug exposure (AUC). Over a scale of 0-10, the key adverse events were reported at a mean score of 0 (none, SD 0) by all subjects.

Conclusion. JDP-205 and JDP-207 were judged safe, well-tolerated by the human volunteers. Both products represent promising novel and superior treatment to the current IV diphenhydramine therapy by eliminating many side effects of the current therapy.

INTRODUCTION

JDP-205 and JDP-207 are proprietary injectable products being developed by JDP Therapeutics Inc. as non-sedating antihistamine injection for the treatment of acute allergic reaction, a serious, potentially-fatal condition.

JDP-205 is an intravenous injection product aimed for the Hospital market. JDP-207 is an intramuscular auto-injector for emergency self administration, as no antihistamine autoinjectors currently exist.

METHODS

OVERVIEW

Single center, randomized, single dose, laboratory-blinded, 4-period, 4-sequence, crossover study.

INVESTIGATIONAL PRODUCTS

Treatment-A: **Zyrtec® 10 mg tablet (Reference)**
Dose: A single 10 mg dose
Dosage form: One tablet
Administration: By the oral route with about 240 mL of water

Treatment-B: **JDP-207 10 mg/mL injection (Test)**
Dose: A single 10 mg dose
Injection volume: 1.0 mL
Administration: Intramuscular injection in the anterolateral thigh muscle slowly within a period of 0.5 min

Treatment-C: **JDP-205 10 mg/mL injection (Test)**
Dose: A single 5 mg dose
Injection volume: 0.5 mL
Administration: Intravenous injection over a period of 1 to 1.5 min *via* an indwelling catheter

Treatment-D: **JDP-205 10 mg/mL injection (Test)**
Dose: A single 10 mg dose
Injection volume: 1.0 mL
Administration: Intravenous injection over a period of 1 to 1.5 min *via* an indwelling catheter

KEY INCLUSION / EXCLUSION CRITERIA

Healthy adult volunteers (male and non-pregnant female subjects between of at least 18 years of age, BMI 18.50-30.00 kg/m^2) were selected. Subjects were in good health as determined by a medical history, physical examination (including vital signs and an examination of the anterolateral thigh muscles), electrocardiogram (12-lead ECG) and the usual clinical laboratory tests (hematology, biochemistry, urinalysis) including negative HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethanol and drugs of abuse in urine and negative pregnancy test (for female subjects).

SAMPLE SIZE

Twenty-four subjects were randomized. Assuming an intra-subject CV of about 12% for C_{max}, 9% for AUC_T and 8% for AUC_{inf}.

STUDY PLAN

Subjects were admitted to the study center the evening before the first dose for baseline assessments to confirm eligibility.

After an overnight fast, subjects received the assigned treatment.

A questionnaire was completed prior to and 3 times after each drug administration to evaluate mental sedation, physical sedation and dry mouth.

Safety assessments were performed throughout the study. Vital signs, 12-lead ECG and adverse events were recorded. Safety monitoring included adverse event assessments.

Subjects returned to the study center for subsequent treatment periods and same assessments were performed.

DURATION OF TREATMENT

Subjects spent approximately 34 hours during each housing period; starting the evening before each dose administration until approximately 24 hours afterwards in the clinical facility. Subjects returned to the clinical site for the 36-h sample.

The inter-dose interval was at a minimum of 7 days.

In each study period, plasma samples were collected as follows:

•The first blood sample was collected prior to drug administration
•During the first hour post drug administration, blood samples were collected 2, 4, 6, 8, 10, 15, 20, 30, 45 and 60 minutes post drug administration. In the study periods where the drug is administered by intravenous injection, these blood samples will be obtained from the arm opposite to that used for the injection.
•Subsequently, blood samples will be collected 1.33, 1.67, 2, 2.5, 3, 4, 6, 10, 18, 24 and 36 hours post drug administration.

RESULTS

PHARMACOKINETIC RESULTS

All 24 subjects dosed were considered in the PK analysis; 24 subjects for Treatment A, 23 subjects for Treatment B, 22 subjects for Treatment C and 24 subjects for Treatment D.

PARAMETER	ARITHMETIC MEAN			
	TREATMENT-A (REFERENCE)	TREATMENT-B (TEST)	TREATMENT-C (TEST)	TREATMENT-D (TEST)
C_{max} (ng/mL)	318.04	173.55	988.98	1343.53
ln (C_{max})	5.7450	5.1420	6.8624	7.0580
T_{max} (Hours) *	0.75	4.00	0.06	0.03
AUC_T (ng·H/mL)	2547.23	2620.38	2525.56	2639.78
ln (AUC_T)	7.8304	7.8619	7.8157	7.8596
AUC_{inf} (ng·H/mL)	2650.78	2772.56	2635.61	2745.79
ln (AUC_{inf})	7.8698	7.9162	7.8589	7.8986
$AUC_{T/inf}$ (%)	96.17	94.77	95.80	96.21
K_{el} (Hours^{-1})	0.0948	0.0916	0.0924	0.0934
$T_{½el}$ (Hours)	7.61	7.89	7.74	7.74
F (%)	98.52	103.97	100.00	100.00
Cl_{TOT} (L/Hour)	3.79	3.82	3.94	3.79
VD (L)	41.27	42.66	43.53	41.60

*For T_{max}, the median is presented.
**For Treatment-C, C_{max}, AUC_T and AUC_{inf} are dose normalized.

STATISTICAL RESULTS

COMPARISON	PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
			TREATMENT	TREATMENT		LOWER	UPPER
			Measured Data				
A *vs* D	C_{max}	29.2	312.63	1162.16	26.90	23.44	30.88
	AUC_{inf}	10.9	2617.06	2693.51	97.16	92.21	102.37
A *vs* B	C_{max}	29.2	312.63	170.69	183.16	159.27	210.63
	AUC_{inf}	10.9	2617.06	2761.21	94.78	89.88	99.95
C *vs* D	C_{max}	29.2	952.00	1162.16	81.92	71.10	94.38
	AUC_{inf}	10.9	2565.29	2693.51	95.24	90.24	100.52
B *vs* D	C_{max}	29.2	170.69	1162.16	14.69	12.77	16.89
	AUC_{inf}	10.9	2761.21	2693.51	102.51	97.21	108.10

*For Treatment-C, C_{max} and AUC_{inf} are dose normalized.

PHARMACOKINETIC CONCLUSIONS

For each of the comparisons, each 2 treatments were deemed bioequivalent on drug exposure, where the ratio of geometric LSmeans and corresponding 90% confidence interval for the AUC_{inf} were all within the 80 to 125% range.

Treatments C *versus* D were deemed dose proportional on drug exposure, since the ratio of dose normalized geometric LSmeans and corresponding 90% confidence interval for the AUC_{inf} were within the range of 80 to 125%.

SAFETY RESULTS

Twenty-two (22) (91.7%) of the 24 subjects included in this study experienced a total of 66 adverse events (AE) during the study.

The severity of AEs ranged from mild to moderate, except for intramuscular injection site pain.

None of the AEs judged to be possibly related to the Investigational Products was unexpected.

Negligible levels of mental sedation (assessment of drowsiness, confusion, awareness, attentiveness), physical sedation (assessment of strength, coordination, energy, competence) and dry mouth were reported by the study subjects following administration of JDP-205 and JDP-207.

No serious AEs or deaths were reported during this study.

No subject took concomitant medications during the study.

No subject was withdrawn from the study for safety reasons.

CONCLUSION

Overall, the JDP-205 and JDP-207 drug products tested achieved excellent pharmacokinetic profile, and were generally safe and well tolerated by the healthy subjects included in this study.

JDP's non-sedating antihistamine injection products, for the treatment of acute allergic reactions, represent promising novel and superior treatment to the current IV diphenhydramine therapy by eliminating many side effects of the current therapy.