Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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Title of Trial:	A randomised, double-blind study designed to assess the bioequivalence and adhesion properties of transdermal clonidine-Vistanex™ compared to transdermal clonidine-Oppanol® following transdermal administration in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial Site:	[redacted] USA
Publications:	Data from this trial have not been published
Clinical Phase:	I
Objectives:	The primary objective of the trial was to establish the bioequivalence of transdermal clonidine prepared with Oppanol® brands of polyiobutylene (PIB) compared with transdermal clonidine prepared with Vistanex™ brands of PIB. A further objective was to evaluate the adhesion performance of the Oppanol® PIB transdermally-delivered clonidine system over 7 days of wear.
Methodology:	Randomised, double-blind, 2-way crossover design, followed by a period for assessment of adhesive properties of the clonidine patch (adhesion phase). In the crossover part of the trial, subjects were treated with Catapres®-TTS delivering 0.3 mg clonidine/24 h (TTS-3) in the Oppanol® formulation (test treatment T1), then after a washout period, were crossed over to the Vistanex™ formulation (reference treatment R1) or vice versa. After another washout period, in the adhesion phase, subjects were treated simultaneously with Oppanol® (test treatment T2) and Vistanex™ (reference treatment R2) patches, each delivering 0.1 mg clonidine/24 h (TTS-1).

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No. of Subjects:	
Planned:	Entered: 60
Actual:	Entered: 58 Sequence T1R1 followed by simultaneous T2R2: Entered: 29 Treated: 29 Analysed (for primary endpoint): 29 Sequence R1T1 followed by simultaneous T2R2: Entered: 29 Treated: 29 Analysed (for primary endpoint): 28
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male or non-pregnant female volunteers, age ≥18 and ≤65 years, body mass index (BMI range), ≥18.5 and ≤32 kg/m^2
BI Investigational Products:	Catapres®-TTS-3 (0.3 mg/24 h) with Oppanol® (T1) Catapres®-TTS-1 (0.1 mg/24 h) with Oppanol® (T2)
Doses:	Crossover phase: 0.3 mg/24 h (T1) for 7 days Adhesion phase: 0.1 mg/24 h (T2; simultaneous application with R2) for 7 days (168 h)
Mode of Admin.:	Transdermal
Batch Nos.:	Catapres®-TTS-3: B143000031 Catapres®-TTS-1: B143000032
Comparator Products:	Catapres®-TTS-3 (0.3 mg/24 h) with Vistanex™ (R1) Catapres®-TTS-1 (0.1 mg/24 h) with Vistanex™ (R2)
Doses:	Crossover phase: 0.3 mg/24 h (R1) for 7 days Adhesion phase: 0.1 mg/24 h (R2; simultaneous application with T2) for 7 days
Mode of Admin.:	Transdermal
Batch Nos.:	Catapres®-TTS-3: B143000016 Catapres®-TTS-1: B143000017
Duration of Treatment:	Subjects were treated for 7 days with either T1 or R1, followed by a washout period of 7 days, and then were crossed over to the other treatment (R1 or T1) for 7 days. After a 3 day washout period, subjects were treated simultaneously with T2 and R2 for 7 days.

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Criteria for Evaluation:

Clinical Pharmacology / Other:	Primary endpoints: AUC_{0-168} and C_{avg} (average of clonidine plasma concentrations on Days 5, 6, and 7) Secondary endpoints: $AUC_{0-\infty}$ and C_{max} Further endpoints: t_{max}, adhesiveness (% daily adherence and mean adherence), and amount of clonidine remaining in the transdermal patch after 7 days (168 h) of wear
Safety:	Physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), laboratory tests, adverse events, local tolerability

Statistical Methods:

To assess bioequivalence, the statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'group', 'sequence', 'subjects within sequences', 'period' and 'treatment'. For the primary endpoints, the geometric mean (gMean) ratios for test/reference treatment and 2-sided 90% confidence intervals (CIs) were calculated using an acceptance range of 80.00 to 125.00%. This method is equivalent to 2 one-sided t-tests, each at the 5% significance level. CIs were calculated based on the residual error from the ANOVA. Secondary endpoints were analysed in the same way as primary endpoints. Descriptive statistics were calculated for all primary and secondary endpoints and for further endpoints (in particular for adhesion data). No interim analysis was planned or performed.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 58 subjects was entered in the trial and treated. Thirty subjects were female (51.7%) and 28 were male (48.3%). Of the 58 subjects, 37 were of White race (63.8%), 20 were Black/African American (34.5%), and 1 was American Indian/Alaska Native (1.7%). Mean age was 41.3 years (SD 13.0) and mean BMI was 26.95 kg/m^2 (SD 3.63). Of the 58 subjects, 55 (94.8%) completed the planned observation time. Of the 3 subjects who did not complete the observation time, 1 subject was removed from the trial due to noncompliance with trial site rules; 1 subject discontinued participation due to accidental early patch removal; and 1 subject withdrew informed consent for private reasons. At least 1 primary endpoint was evaluable for 57 of 58 subjects (98.3%). The subjects were admitted to the trial site and remained there for the duration of the treatment periods, thereby ensuring compliance with trial medication administration and with the trial protocol.

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Clinical Pharmacology / Other Results:

Pharmacokinetics and inferential statistical assessment of bioequivalence: When 0.3 mg clonidine/24 h was applied either as the Oppanol® formulation (T1) or as the Vistanex™ formulation (R1), the unadjusted gMean values for the primary endpoints AUC_{0-168} and C_{avg} of clonidine were comparable: AUC_{0-168} values were 87400 and 91500 pg·h/mL and C_{avg} values were 733 and 748 pg/mL for T1 and R1, respectively. Secondary endpoints C_{max} and $AUC_{0-\infty}$ of clonidine were also similar between the treatments. Median t_{max} values were the same for both patches, at 144 h.

Comparison of T1 to R1 gave an adjusted gMean ratio of 102.33% (90% CI 95.74%, 109.37%) for AUC_{0-168} and 104.25% (90% CI 98.37%, 110.49%) for C_{avg}. For the secondary endpoints, gMean ratios were 102.78% (90% CI 97.25%, 108.63%) for $AUC_{0-\infty}$ and 104.04% (90% CI 98.15%, 110.29%) for C_{max}. Therefore, the gMean ratios for the primary and secondary endpoints were contained in the predefined bioequivalence acceptance range of 80.00 to 125.00% (see table below).

Parameter	Oppanol® (T1)[1] Adj. gMean	Vistanex™ (R1)[2] Adj. gMean	Adj. gMean ratio (%)	2-sided 90% CI (%)	Intra-indiv. gCV (%)
AUC_{0-168} (pg·h/mL)	82518	80641	102.33	95.74, 109.37	19.0
C_{avg} (pg/mL)	697.33	668.89	104.25	98.37, 110.49	16.6
$AUC_{0-\infty,pred}$ (pg·h/mL)	119130	115900	102.78	97.25, 108.63	15.8
C_{max} (pg/mL)	813.52	781.90	104.04	98.15, 110.29	16.7

[1]N=52
[2]N=50

Assessment of adhesion: Percent adhesion was evaluated for each patch for each subject over 7 days (168 h) of wear at 8 assessment times. Mean adhesion was greater than 90% for all 4 patch types when data from all assessment times were included (see table below).

Patch	N	Mean adhesion (%)	Standard deviation (%)
TTS-3 Oppanol®	57	95.22	2.32
TTS-3 Vistanex™	57	93.53	5.81
TTS-1 Oppanol®	56	96.27	3.55
TTS-1 Vistanex™	56	96.35	1.74

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Clinical Pharmacology / Other Results (continued):

Assessment of adhesion (continued): Hodges-Lehmann point estimates were calculated for each time at which adhesion was assessed. At the 90% CI, Oppanol® was equal to or superior to Vistanex™ for both TTS-3 and TTS-1. A single Hodges-Lehmann point estimate including data from all assessment times indicated that TTS-3 Oppanol® performed slightly better than TTS-3 Vistanex™ and that TTS-1 Oppanol® had comparable performance to TTS-3 Vistanex™. There were 2 subjects with adhesion failures, 1 with TTS-3 Vistanex™ and 1 with TTS-1 Oppanol®.

Assessment of residual clonidine: The percent of clonidine remaining in the patch after 7 days of wear was similar between TTS-3 Oppanol® and TTS-3 Vistanex™, at 65.94±10.07% and 65.06±9.37% (mean±SD), respectively.

Safety Results:

Of the 58 subjects treated in all periods, 53 (91.4%) reported AEs, and for all 53 subjects, at least 1 AE was considered by the investigator to be related to trial treatment. Of the 57 subjects treated with TTS-3 Vistanex™, 45 (78.9%) reported AEs. Of these 57 subjects, 42 (73.7%) reported AEs that were considered by the investigator to be related to trial treatment. Of the 57 subjects treated with TTS-3 Oppanol®, 46 (80.7%) reported AEs; for all 46 subjects (80.7%), at least 1 AE was considered by the investigator to be related to trial treatment. For the treatment period in which TTS-1 Vistanex™ and TTS-1 Oppanol® were applied simultaneously, 56 subjects were treated and AEs were reported for 23 (41.1%). Of these 56 subjects, 19 (33.9%) reported AEs that were considered by the investigator to be related to trial treatment (see table). There were no AEs leading to discontinuation of trial treatment or other significant AEs according to ICH E3. There were no significant AEs, AEs of severe intensity, or deaths or other SAEs.

	TTS-3 Vistanex™		TTS-3 Oppanol®		TTS-1 Vist™+Opp®		Total on-treatment	
Subjects (N)	57	(100.0)	57	(100.0)	56	(100.0)	56	(100.0)
With any AE	45	(78.9)	46	(80.7)	23	(41.1)	53	(91.4)
With drug-related AE[1]	42	(73.7)	46	(80.7)	19	(33.9)	53	(91.4)

[1]Investigator-defined

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Safety Results (continued):

TTS-3 Vistanex™: The most frequently reported AEs by system organ class (SOC) were general disorders and administration site conditions, reported by 31 of 57 subjects (54.4%). The most frequent preferred terms (PTs) in this class were application site erythema in 19 of 57 subjects (33.3%) and application site papules in 8 of 57 subjects (14.0%). The second most frequent SOC was gastrointestinal (GI) disorders, in 13 of 57 subjects (22.8%); the most frequent PT in this class was infrequent bowel movements, reported for 8 of 57 subjects (14.0%). The PT orthostatic hypotension was reported for 3 of 57 subjects (5.3%).

TTS-3 Oppanol®: As for TTS-3 Vistanex™, the most frequently reported AEs by SOC were general disorders and administration site conditions, in 37 of 57 subjects (64.9%). The most frequent PTs were application site erythema in 23 of 57 subjects (40.4%) and application site papules in 12 of 57 subjects (21.1%). The second most frequent SOC was GI disorders, in 15 of 57 subjects (26.3%); the most frequent PT was infrequent bowel movements, reported for 6 of 57 subjects (10.5%). The PT orthostatic hypotension was reported for 11 of 57 subjects (19.3%).

TTS-1 Vistanex™ + TTS-1 Oppanol®: AEs were reported for 23 of 56 subjects (41.1%). As for the treatment periods in which TTS-3 patches were applied, the most frequently reported AEs by SOC were general disorders and administration site conditions, in 15 of 56 subjects (26.8%). The most frequent PTs in this class were application site erythema in 10 of 56 subjects (17.9%) and application site papules in 6 of 56 subjects (10.7%). The second most frequent SOC was nervous system disorders, in 6 of 56 subjects (10.7%). No orthostatic hypotension was reported.

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Safety Results (continued):	Safety laboratory/vital signs assessments: No laboratory assessment was considered to be clinically relevant or was considered by the investigator to be an AE. There were no relevant mean changes in any laboratory parameter. Systolic and diastolic blood pressure demonstrated changes consistent with administration of an antihypertensive medication. All mean values for vital signs had returned to levels similar to baseline by the end of trial visit. As indicated above, for 3 subjects treated with TTS-3 Vistanex™ and for 11 subjects treated with TTS-3 Oppanol®, decreases in systolic and/or diastolic blood pressure met prespecified criteria in the Clinical Trial Protocol for orthostatic hypotension and were therefore classified as AEs. In most subjects, orthostatic hypotension was not accompanied by any other signs or symptoms. However, for 2 subjects treated with TTS-3 Oppanol®, dizziness was reported as a coincident AE. Local tolerability: Over 168 h, some evidence of dermal irritation was observed in 27 of 56 subjects (48.2%) for TTS-3 Vistanex™, in 31 of 57 subjects (54.4%) for TTS-3 Oppanol®, for 14 of 55 subjects (25.5%) for TTS-1 Vistanex™, and for 16 of 55 subjects (29.1%) for TTS-1 Oppanol®. In all cases, the changes were minimal or mild.
Conclusions:	The gMean ratios for all primary and secondary pharmacokinetic endpoints were contained in the predefined bioequivalence acceptance range of 80.00 to 125.00%. The Oppanol® and Vistanex™ patches can therefore be considered bioequivalent. Including data from all assessment times, mean adhesion was ≥90% for all patch types. Assessment of residual clonidine indicated similar performance for the Oppanol® and Vistanex™ patches. Safety assessments demonstrated that both the Oppanol® and Vistanex™ patches were safe and well tolerated in the healthy subjects who participated in the trial.