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Research Article

Single-Dose, Open-Label, One-Way Pharmacokinetic Studies in the Mexican Population to Evaluate the Bioavailability and Food Effect on the Pharmacokinetics of 30-mg Extended-Release Nifedipine Tablets

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ABSTRACT

Purpose: The nifedipine immediate-release formulation has been associated with reflex sympathetic nervous system activation leading to several adverse effects such as flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia. Development of a modified-release formulation represents a challenge, particularly the development of a once-daily formulation. Therefore, these studies evaluated the pharmacokinetic profile of a new 30-mg Extended-Release Nifedipine Tablets in Mexican population. The formulation [ANHITEN-A®] was manufactured by Ultra Laboratorios S.A. de C.V. [Jalisco, Mexico] with number of batch 9JN134A and expiration date September 2021.

Methods: They were a single-center, single-dose, open-label, one-way trial. Study A was evaluated at a fasted state [at least 10 hours] and Study B was evaluated at a fed state [30 minutes before dosing]. The studies population were 14 [per study] healthy male and female adult [aged 18-55 year] Mexican volunteers. These trials comprised one day treatment period and a 7-day wash-out period before final evaluation. Serial blood samples were collected before and after dosing and evaluated by UPLC-MS/MS. The bioavailability of the 30-mg Extended-Release Nifedipine Tablets was assessed Non-Compartmental Pharmacokinetic analysis and in accordance with local law regulation. Tolerability and safety were evaluated throughout the research.

Findings: The non-compartmental model [NCA] pharmacokinetic parameters obtained are mean [SD] C_{max} 43.95 [16.082] ng/mL and 100.71 [42.441] ng/mL, t_{max} 7.2 [3.326] h and 4.7 [2.343] h, $AUC_{0\infty}$ 739.100 [224.436] ng h/mL and 676.605 [355.791] ng h/mL, $t_{1/2}$ 8.1 h [2.081] and 5.6 [2.174] h, V_d/F 526.46 [238.67] L and 434.35 [218.15] L and CL/F 44.49 [15.98] L/h and 56.97 [32.03] L/h for fasted [trial A] and fed [trial B] state, respectively. C_{max} and $t_{½}$ values showed statistically significant differences [$p<0.05$] between studies, with the higher C_{max} values for the fed state [trial B] and higher $t_{½}$ values for the fasted state [trial A], data correlated with dose-dumping effect. Only two Adverse Events [AEs] were reported in trial A, headache, in trial B, two AEs of headache were reported.

Implications: The pharmacokinetic modifications observed in trial B [compared to trial A] may be therapeutically relevant; plasma concentrations at 24 hours in studies A and B show that dosing after food intake decreases the maintained time of the Minimum Effective plasma Concentration with a duration of 24 hours in trial A and 12 hours in trial B. Variations in plasmatic concentrations associated with the dosage condition; higher C_{max} values for the fed state [trial B] and higher t½ values for the fasted state [trial A], did not impact the presence of adverse events, that was similar between studies.

Keywords: Bioavailability; Dose-dumping; Extended-Release; Healthy subject; Mexican; Nifedipine

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INTRODUCTION

Hypertension is a chronic disease produced by several factors, among which stand out genetic factors [not modifiable] and factors associated with daily life [modifiable], which are: Excessive sodium intake, smoking, physical inactivity, obesity, among others [1]. It has been demonstrated that effective treatment of hypertension, reduces the incidence of renal and cerebrovascular complications, and improves patient prognosis. However, blood pressure control still be a challenge [2]. Hypertension first-line therapy includes dihydropyridine Calcium Channel Blockers [CCBs] drug class, which are useful in other conditions such as angor pectoris [alone or combined], atrial fibrillation, ventricular hypertrophy, and pregnancy [3].

Nifedipine, developed in 1972, is a dihydropyridine calcium channel blocker, exerts its effect by acting as an arterial vasodilator, binding to the L-type channel in arterial tissue preventing the influx of calcium ions which allows for vasodilation, increasing myocardial tissue oxygen supply. Additionally, calcium ions regulate smooth muscle contractions that indirectly contributing to an increase in cardiac contraction [inotropic effect] and heart rate [chronotropic effect], these effects can be secondary prevented by nifedipine blockade of L-type calcium channels [4].

After oral dosage nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract. Due to the extensive first-pass metabolism, a bioavailability between 43% and 77% is obtained [5]. On research subjects, the 30-mg Extended-Release formulation reaches the maximum plasma concentration [Cmáx] at 3.00 hours [C_{max} first peak] and 8.00 hours [C_{max} second peak] post-dosing [6]. It is highly protein-bound [92%-98%] and its volume of distribution at a steady state is 0.62–0.67 L/kg [7]. Undergoes the first-pass metabolism in the intestinal wall and liver, 40% of nifedipine is converted to inactive metabolites, mainly by oxidative processes [modulated by CYP3A], which are eliminated primarily in the urine [8]. The plasma elimination half-life of nifedipine extended-release tablets is, mean [SD], 6.78 [2.52] hours [6].

The nifedipine immediate-release formulation has been associated with reflex sympathetic nervous system activation leading to several adverse effects such as flushing, tachycardia, worsening myocardial ischemia, and cerebrovascular ischemia [9]. Therefore, several modified release formulations have been developed and have been shown better safety profile and therapeutic results comparable with other antihypertensive groups such as β-blockers, angiotensin receptor blockers or diuretics [10].

Finally, nifedipine is a low solubility drug [Biopharmaceutical Classification System [BCS] class II] [11], the development of a modified release formulation represents a challenge, particularly the development of a once-daily formulation that provides a smooth, predictable plasma concentration [12], less adverse events and a greater therapeutic adherence [13].

RESEARCH SUBJETCS AND METHODS

Ethics considerations

Full evaluation was performed by two clinical trials [Study A and Study B]. Before study start-up, research protocols and informed consent forms, following local law, were reviewed, and approved by the independent ethics committee Unidad Clínica de Bioequivalencia S. de R.L. de C.V. [Jalisco, Mexico] and by the Mexico Ministry of Health; Federal Commission for Prevention Against Health Risks [COFEPRIS by its acronym is Spanish]. The clinical trials were conducted under the current version of the World Medical Association's Code of Ethics for research involving humans [Declaration of Helsinki], Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and applicable local regulatory requirements. These studies were registered at clinicaltrials.gov [identifier NTC].

Study design

They were a single-center, single-dose, open-label, one-way trial (Figure 1). Study A was evaluated at a fasted state [at least 10 hours] whereas Study B was evaluated at a fed state [30 minutes before dosing]. The trials population were healthy male and female adult [aged 18-55 years] Mexican volunteers. These studies comprised one day treatment period and a 7-day wash-out period before final evaluation.

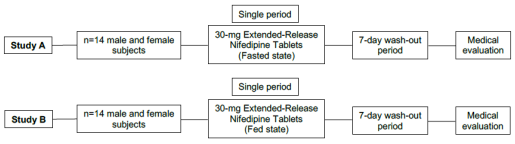

Figure 1: Study design of 30-mg extended-release Nifedipine tablet evaluation.

The trials were conducted at the Unidad Clínica de Bioequivalencia S. de R.L. de C.V. [Jalisco, Mexico]. Volunteers were submitted for a 37-hour confinement period, admitted to the investigational site from around 5:00 PM on day 0 until around 8:00 AM on day 2, for drug dosing, safety and tolerability assessment, and pharmacokinetic blood sampling. Included subjects received a 30 mg-extended-release nifedipine tablet with 250 mL of water on fasted [trial A] or fed [trial B] state. During the confinement period, subjects received a 2300-kcal standardized diet and were restricted from water for at least 4 hours after dosing, breakfast of trial B was an approximately 800-kcal high-fat and high-calorie meal. Blood sampling and determination of vital signs at time intervals were made. After finalizing the scheduled activities subjects were discharged from the unit and return at 36.00 and 48.00-hours post-dosing for pharmacokinetic blood sampling. Adverse Events, information; duration, severity, causality, and outcomes were recorded by the Principal Investigator or site staff members. All subjects were medically monitored closely throughout the whole study.

Study population

All subjects provided writing informed consent form before the conduction of any protocol-related procedures or assessments. 18-55 years old healthy male or female volunteers were enrolled. A Body Mass Index [BMI] in the interval 18-27 kg/m^2 was required. Clinically health status was determined at screening visit with the collection of the clinical record, physical examination, 12-lead ECG [electrocardiogram], complete blood cell count, blood chemistry, blood pregnancy test, urinalysis and urine drug screening. Additionally, at day 0, urine pregnancy test and breath alcohol test, were made. Key exclusion criteria included history or evidence of drug or alcohol abuse, clinically significant abnormalities in medical history or laboratory tests, history of significant gastrointestinal surgery or disease, 14-day prior consumption of prescription or over-the-counter drugs and grapefruit or caffeine/

xanthine consumption within 10 hours before the dosing.

Sample size

No formal sample size estimation was performed. The present pharmacokinetic studies aimed to explore the bioavailability of the extended-release nifedipine tablets at fasted and fed state. The sample size was determined according to scientific literature about the sample size of pilot studies [14-16] and local law regulation. A total sample size of 14 subjects per Study [A or B] were included.

Pharmacokinetic and bioanalytical assessments

Blood samples of 10 mL each were obtained at 0 h [before dosing] and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 24.00, 36.00 y 48.00 h after dosing. Samples were collected into heparinized tubes and centrifuged at 3500 rpm for 5 minutes at 4°C. The resulting plasma was transferred into labeled cryovials, frozen and stored immediately at -70°C until its analysis.

Bioanalytical method was developed and validated by CINASI, S. de R.L. de C.V. [Jalisco, Mexico] according U.S. Food and Drug Administration [FDA] guidelines and Mexican normativity. Pharmacokinetic parameters were determined from analyzed plasma by Ultra Performance Liquid Chromatography coupled Tandem Mass Spectrometry [UPLC-MS/MS]. Nifedipine and the Internal Standard [IS] carbamazepine were extracted by liquid-liquid extraction using hexane: dichloromethane [70:30 v/v] mixture. These components were mixed for 3 minutes and centrifuged at 3500 rpm for 2 minutes at 5°C. The organic phase was removed and evaporated by drying in a stream of nitrogen at room temperature. The extracts were reconstituted with a fixed volume of acetonitrile: Water [50:50 v/v] and 5 µL were injected into the chromatographic system [Acquity equipment, Waters, Inc., Milford, MA, USA] with a column Acquity UPLC™ BEH C18 [Waters, Inc] 2.1 × 50 mm, 1.7 µm. The mobile phase consisted of ammonium formate 10 mM and acetonitrile [40:60 v/v]. The flow rate was 0.2 mL/min. Detection and quantification were measured using a triple quadrupole mass spectrometry system TQD [Waters Corporation]. Detection was through positive electrospray ionization [ESI+], using the ionic transitions of 347.19>315.35 m/z and 237.22>194.19 m/z for Nifedipine and IS, respectively.

The calibration range of the method was 1 to 300 ng/mL. Quality control samples were included in every analytical run [during method validation and analyzed samples] to verify performance. These quality controls were at 3, 24, and 230 ng/mL concentrations. The validation of the chromatographic analytical method was performed to evaluate selectivity, linearity, precision, accuracy, stability [stock solution, freeze-thaw cycles, autosampler, processed sample, short and long-term stability], and robustness.

Tolerability assessments

Tolerability was assessed by adverse-events monitoring [prevalence and severity of adverse events], physical examination [before dosing and before discharge], vital sign measurements [before dosing and at 1.00, 3.00, 6.00, 10.00, 12.00, 24.00, 36.00 y 48.00 h after dosing].

Statistical analysis

To reveal any potentially relevant difference in the subjects demographic data, and to support the use of data from the further analysis, descriptive statistics of demographic data were made. Per-protocol population [subjects with evaluable pharmacokinetic data] were included in the pharmacokinetic analysis.

The parameters to be determined were: C_{max}; time when C_{max} [t_{max}] is reached; the Area Under the Curve [AUC] until the last measurable concentration [AUC_{0-t}] and extrapolated to infinity [$AUC_{0-\infty}$]; elimination constant [Ke]; plasma elimination half-life [$t_{1/2}$]; mean residence time from zero to last sampling time [MRT_{0-t}]; the volume of distribution [V_d/F] and the apparent oral clearance [CL/F]. Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 8.2 software [Certara L.P., NJ. USA], to carry out a pharmacokinetic adjustment to the best compartmental model between the One-compartment Open Model and the Two-compartment Open Model using the Akaike criterion as selection criteria. In addition, it was complemented by also conducting the Non-Compartment Pharmacokinetic Analysis. Statistical analysis of the mean values for the pharmacokinetic parameters was conducted using Statgraphics Centurion version 18.1.12 software [StatPoint, Inc., Herndon, Virginia].

Intention to treat population [subjects who received at least 1 dose of a study drug] were included in the tolerability assessments, evaluation was made descriptively and consider all adverse events observed.

RESULTS

Baseline demographic characteristics

Study A and Study B were conducted at the same time [January 15_{th}, 2021-January 18_{th}, 2021] on independent areas of the research site. A total of 32 subjects were evaluated, 04 were considered as screening failure, with 28 eligible subjects being finally included [14 research subjects per study]. Study A and B were finalized with all 28 volunteers.

Demographic characteristics of subjects: Age, sex, height, body mass index, and weight, are shown in Table 1. The total Study A population consisted of male and female subjects with a mean [SD] age of 28.57 [8.28] years, a height of 165 [8] cm, a weight of 64.17 [7.31] kg, and a body mass index of 23.34 [2.18] kg/m^2. Finally, the total Study B population consisted of male and female subjects with a mean [SD] age of 29.71 [8.24] years, a height of 171 [8] cm, a weight of 70.71 [7.97] kg, and a body mass index of 23.97 [1.42] kg/m^2. Demographic characteristics were similar throughout both studies.

Table 1: Demographic characteristics of the total study research subjects. Data are given as mean (SD).

Characteristic	Study A (n=14)	Study B (n=14)
Age (years), mean (SD)	28.57 (8.28)	29.71 (8.24)
Sex (%)		
Female	6 (42.86)	5 (20.83)
Male	8 (57.14)	9 (79.17)
Height, m, mean (SD)	165 (8)	171 (8)
Weight, kg, mean (SD)	64.17 (7.31)	70.71 (7.97)
BMI, kg/m^2, mean (SD)	23.34 (2.18)	23.97 (1.42)

Pharmacokinetics of nifedipine

After submitting the data to the Phoenix WinNonlin 8.2 version software to carry out the pharmacokinetic fit between the One-Compartment Open Model [OCOM] and the Two-Compartment Open Model [TCOM] of the 14 subjects per study, the sum of

squares were used, the correlation coefficient between the plasma concentration value observed with the plasma concentration value predicted by the compartmental model, the Akaike Information Criterion [AIC], and the Bayesian Schwarz Criterion as descriptive parameters of the pharmacokinetic adjustment; considering the AIC as the most ponderable criteria.

The analysis demonstrated that one subject [03, trial A] and two subjects [01 and 11, trial B] did not fit any of the two pharmacokinetic models, eight volunteers [02, 05, 06, 09, 11, 12, 13, and 14, trial A] and one subject [10, trial B] fully adjusted to the OCOM and using the Akaike value as the adjustment criterion in five subjects [01, 04, 07, 08 and 10, trial A] and ten subjects [01, 03, 04, 05, 06, 07, 08, 12, 13 y 14, trial B] whose data were adjusted in both models, they remain at the OCOM. Thus, in this pharmacokinetic analysis and applying the principle of parsimony, the OCOM is chosen as the compartmental model for the pharmacokinetics of Nifedipine (Tables 2 and 3).

Table 2: Pharmacokinetic profiles of nifedipine after a single dose of 30-mg extended-release formulation at fasting state. Data are given as mean (SD).

Parameter	OCOM (n=13)	NCA (n=14)
C_{max} (ng/mL)	35.68 (10.979)	43.95 (16.082)
t_{max} (h)	6.5 (3.326)	7.2 (3.326)
$AUC_{0-\infty}$ (ng h/mL)	772.48 (311.174)	739.100 (224.436)
$t_{1/2}$ (h)	6.2 (3.111)	8.1 (2.081)
V_d/F (L)	515.37 (9.037)	526.46 (238.67)
CL/F (L/h)	45.94 (37.765)	44.49 (15.98)

Considering the classical guidelines expressed in the international scientific literature, we proceeded to use the plasma concentration vs. time data to determine the pharmacokinetic parameters of Nifedipine from the Non-Compartmental Model [NCA] analysis. To determine statistically significant differences between the pharmacokinetic parameters from the selected model of Nifedipine and those obtained with the non-compartmental analysis, a Student t-test was performed at a significance value of 0.05 and confidence of 95% from the arithmetic mean obtained from the volunteers who participated in the pharmacokinetic evaluation, no significant differences were found in the pharmacokinetic parameters [Study A], however, for $t_{1/2}$ and V_d/F parameters from Study B, statistically significant differences were found.

NCA Pharmacokinetic parameters obtained are mean [SD] C_{max} 43.95 [16.082] ng/mL and 100.71 [42.441] ng/mL, t_{max} 7.2 [3.326] h and 4.7 [2.343] h, $AUC_{0-\infty}$ 739.100 [224.436] ng h/mL and 676.605 [355.791] ng h/mL, $t_{1/2}$ 8.1 [2.081] h and 5.6 [2.174] h, V_d/F 526.46 [238.67] L and 434.35 [218.15] L and CL/F 44.49 [15.98] L/h and 56.97 [32.03] L/h for fasted (Study A, Table 2) and fed (Study B, Table 3) state, respectively.

Table 3: Pharmacokinetic profiles of nifedipine after a single dose of 30-mg extended-release formulation at fed state. Data are given as mean (SD).

Parameter	OCOM (n=11)	NCA (n=14)
C_{max} (ng/mL)	80.85 (38.494)	100.71 (42.441)
t_{max} (h)	3.4 (2.106)	4.7 (2.343)
$AUC_{0-\infty}$ (ng h/mL)	606.362 (377.097)	676.605 (355.791)
$t_{1/2}$ (h)	3.1 (2.51)	5.6 (2.174)
V_d/F (L)	249.12 (142.071)	434.35 (218.15)
CL/F (L/h)	67.40 (36.43)	56.97 (32.03)

Owing to the studies were carried out in a population of both sexes, sex pharmacokinetic parameters analysis was carried out. In Study A, statistically significant differences [$p<0.05$] were found in the values of Ke and $t_{1/2}$, with $t_{½}$ values of 6.9 [1.381] h and 9.6 [1.867] h in men and women, respectively. While in Study B statistically significant differences [$p<0.05$] were found in the C_{max} values, 82.36 [38.249] ng/mL and 133.74 [28.400] ng/mL in men and women, respectively.

Finally, due to the studies were made in both, fed and fasted state, food intake pharmacokinetic parameters analysis was performed. It was observed that the C_{max} values showed statistically significant differences [$p<0.05$] between studies, with the higher C_{max} values for the fed state [Study B].

Tolerability

Only two adverse events were reported in Study A, headache [4.16%]. In Study B, two AEs of headache [8.33%] were reported. All observed events have been previously described after exposure to nifedipine and were considered as probably related to the nifedipine dosing, they were mild [01 AEs] and moderate [03 AEs] severity, and no Serious Adverse Events [SAEs] were observed. According to AEs characteristics, the 30 mg- extended-release nifedipine tablet was considered well tolerated and safe for human use at both, fed and fasted.

DISCUSSION

The studies were conducted to evaluate the pharmacokinetic profile of 30-mg Extended-Release Nifedipine Tablets at fed and fasted state. After the fed vs. fasted analysis, (Figure 2) it was observed at fed state [trial B] a higher C_{max} values; 43.95 [16.082] ng/mL [trial A] and 100.71 [42.441] ng/mL [trial B] and faster t_{max}, results that correlate with the phenomenon described as "dose-dumping effect" [17], a pharmacokinetic event reported in several Extended-Release Nifedipine Tablets studies [18-20]. However, this modification did not represent an alteration in the safety aspects and efficacy of ANHITEN-A® [see below]. Finally, at fed and fasted state the literature-reported biphasic t_{max} peaks [3.0 h and 8.0 h [6,21] of the modified-release nifedipine systems, are appreciable.

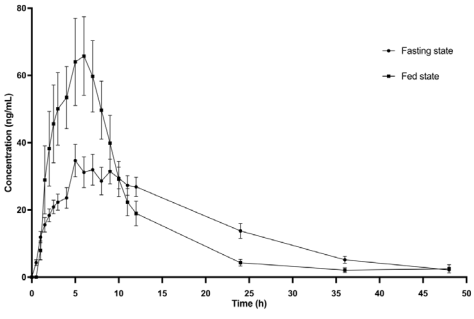

Figure 2: Mean (SD) Plasma concentration-time profiles of Nifedipine after single oral administration of 30-mg extended-release formulation in fed (square) or fasted state (circle) from 14 healthy volunteers (per study).

Despite nifedipine is highly permeable drug [BSC class II], its absorption is accelerated after food ingestion, an effect related to an accelerated release of the drug; secondary to an increase in gastric pH, between 4.0 and 5.0 [22,23]. Finally, nifedipine is a weak base drug [pk_a 5.33] [24] and a gastric pH elevation increase the non-ionized fraction of the drug and therefore enhances its absorption [25,26].

The pharmacokinetic modifications caused by "dose-dumping effect" [observed in Study B] may be therapeutically relevant; plasma concentrations at 24 hours in studies A and B, 13.75 ng/mL and 3.21 ng/mL, respectively, show that dosing after food intake decreases the maintained time of the Minimum Effective plasma Concentration [MEC], defined at 10 ng/mL [27,28], with a duration of 24 hours in Study A and 12 hours in Study B.

Regardless of "dose-dumping effect" is usually related to higher adverse events incidence [29], variations in the pharmacokinetic profile of nifedipine after dosing in the fed or fasted state did not significantly impact the safety of this nifedipine formulation. Minimum Toxic Concentration [MTC] of nifedipine, defined at ≥ 100 ng/mL [30], was achieved only in the fed Study, however, the duration of these concentrations was limited to 1.0 hours.

Variations in plasmatic concentrations associated with the dosage condition; higher C_{max} and faster t_{max} values for the fed state [Study B], did not impact the presence of adverse events, that was similar between studies. Several clinical trials have observed that after dosing nifedipine intravenously or in immediate-release oral systems; tachycardia occurs in response to fast hypotension [31-33], however, in studies A and B, vital signs values, especially heart rate and blood pressure, did not change substantially or exceed normal intervals, a fact probably related to maintenance of the prolonged-release formulation property. Hence the 30 mg extended-release nifedipine tablet was considered well tolerated and safe for human use at fed and fasted condition even between men and women.

Finally, plasma concentration variations associated with the sex of the subject; longer half-life and higher C_{max} in women, are probably related to slow, compared to men, renal clearance in women of calcium-blocking drugs, including nifedipine [34]. In fact, nifedipine clearance values in trial A are 37.35 [9.22] L/h and 47.14 [19.19] L/h and in trial B are 42.09 [32.10] L/h and 65.72 [37.41] L/h for women and men, respectively, data that corroborate a lower clearance in women. However, these results did not impact the presence of AEs, that was similar between both sexes. Additionally, the values of vital signs, especially heart rate, in men and women, did not change substantially or exceed the normal intervals.

CONCLUSION

The results obtained in the evaluated population show that 30-mg Extended-Release Nifedipine Tablets has the "dose-dumping effect" after a high-fat and high-calorie meal, a fact that at a single dose does not impact the safety of the research subjects. However, according to the food effect on ANHITEN-A® [decrease in the duration of the MEC and MTC presence] and that the drug is indicated for chronic degenerative diseases, dosing formulation is preferred to be under fasting conditions at 24-hour regimen, maintaining the CME during that time interval, avoiding MTC and keep the Extended-Release property, providing a safe and effective pharmaceutical product.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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