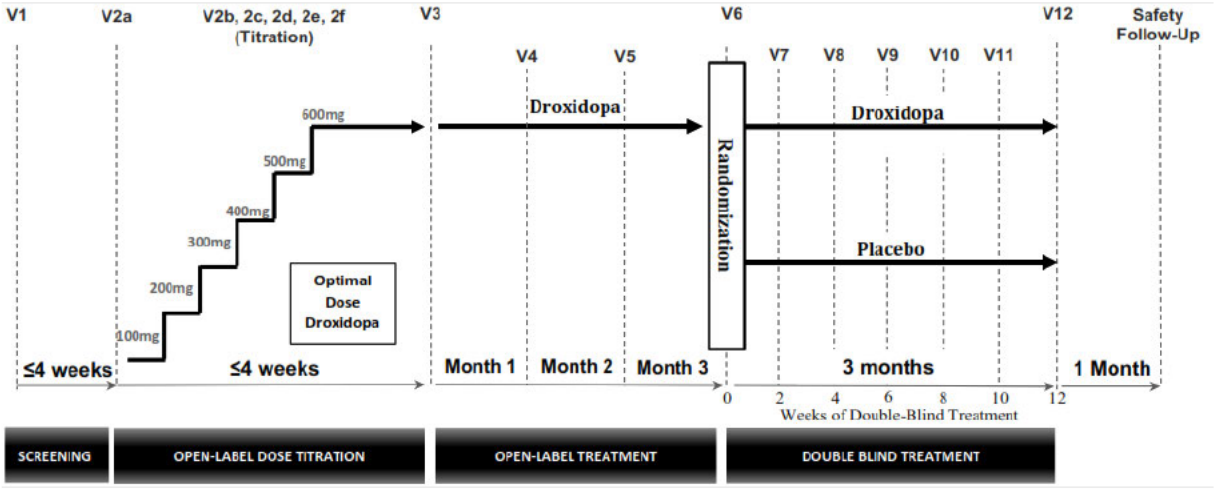
Synopsis – Study 16306A

Study Title RESTORE: A clinical study of patients with symptomatic neuRogenic orthostatic hypotEnsion to assess sustained effecTs of dRoxidopa thErapy	
Investigators 95 principal investigators (including former principal investigators) at 85 sites in 1 country	
Study Sites 85 sites in the United States	
Publications Hauser RA, Favit A, Hewitt LA, Lindsten A, Gorny S, Kymes S, et al. Durability of the Clinical Benefit of Droxidopa for Neurogenic Orthostatic Hypotension During 12 Weeks of Open-Label Treatment. Neurol Ther. 2022; 11(1): 459-469	
Study Period *First patient first visit* – 11 February 2016 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 9 September 2022 (the date of the last protocol-specified contact with any patient)	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • to evaluate the time-to-treatment intervention in patients with Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), non-diabetic autonomic neuropathy (NDAN) or dopamine-β-hydroxylase (DBH) deficiency who have been previously stabilized with droxidopa therapy for symptoms of neurogenic orthostatic hypotension (nOH) (dizziness, light-headedness, or feeling that they are about to black out)	Primary Endpoint: • time-to-intervention: need for intervention is defined as meeting ANY of the following criteria during the Double-Blind Treatment Period: – Orthostatic Hypotension Symptom Assessment (OHSA) Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the investigator; OR – OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR – OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR – patient stops investigational medicinal product (IMP) or withdraws from the study for patient-reported lack of efficacy
Secondary Objectives • to evaluate the long-term efficacy of droxidopa in patients with symptomatic nOH	Key Secondary Endpoint: • time to all-cause discontinuation Secondary Endpoints: • mean change in OHSA Item #1 score from Randomization (Visit 6; Week 0 of Double-Blind Treatment Period) to all post-randomization visits (Visits 7 to 12) • mean change in Orthostatic Hypotension Questionnaire (OHQ) composite score from Randomization (Visit 6; Week 0 of Double-Blind Treatment Period) to all post-randomization visits (Visits 7 to 12) • clinician-rated Clinical Global Impression – Severity (CGI-S) at all post-randomization visits (Visits 7 to 12) • patient-rated CGI-S at all post-randomization visits (Visits 7 to 12)

Objectives and Endpoints (continued)	
Objectives	**Endpoints**
	• proportion of patients who need intervention over the 12-week Double-Blind Treatment Period
Safety Objective • to evaluate the long-term safety and tolerability of droxidopa in patients with symptomatic nOH	Safety Endpoints: • adverse events • absolute values and changes from baseline in clinical safety laboratory test values and vital signs • potentially clinically significant (PCS) clinical safety laboratory test values and vital signs values

Study Methodology

• This was a multi-site, placebo-controlled, double-blind, randomized-withdrawal, time-to-intervention study with a duration of up to 36 weeks, consisting of 5 periods:



• During the Open-Label Titration Period, patients initially received droxidopa 100 mg three times daily (TID), which was increased by 100 mg TID increments until the patient reached the maximum allowed dose (600 mg TID) or when any of the titration stopping criteria were met.

• To enter the Open-Label Treatment Period, patients were required to have an Acute Dizziness score ≥2 units lower (improved) than the Visit 2a OHSA Item #1 score. Patients then received 12 weeks of open-label treatment (Visits 3 to 6).

• At the end of the Open-Label Treatment Period (Visit 6), patients with OHSA Item #1 scores ≥2 units lower (improved) than their Visit 2a (Baseline) OHSA Item #1 score proceeded to randomization for the 12-week, Double-Blind Treatment Period where they received either placebo or droxidopa (1:1 ratio). The randomized dose was the same dose the patient received at the end of the Open-Label Treatment Period and no dose changes were permitted during this period (Visits 7 to 12).

• Efficacy data were collected at the Baseline Visit (Visit 2a), during the Open-Label Treatment Period (Visits 3 to 6) and Double-Blind Treatment Period (Visits 7 to 12), and at withdrawal (if applicable); safety assessments were performed throughout the study.

• A safety follow-up visit was conducted 30 days (+5 days) after the final visit (Visit 12 or Early Termination Visit).

Number of Patients Planned

240 patients were planned for randomization into the Double-Blind Treatment Period: 120 in the droxidopa group and 120 in the placebo group.

Diagnosis and Main Selection Criteria

Adult patients diagnosed with symptomatic nOH associated with Primary Autonomic Failure (PD, MSA or PAF) or NDAN or DBH deficiency, who:

- were ≥18 years of age and able to stand (with or without limited assistance)
- had an OHSA Item #1 score ≥4 (measured at Screening [Visit 1] and the first Titration Visit [Visit 2a] prior to dosing)
- had a documented drop of ≥20 mmHg in systolic blood pressure (SBP), within 3 minutes of standing, documented either in the patient history or assessed during Screening prior to the first Titration Visit (Visit 2a)

Patients who were taking prescribed droxidopa therapy were eligible to participate if they fulfilled the above criteria, and if:

- they had been on a stable dose of prescribed droxidopa for ≥2 weeks prior to the Screening Visit. In addition, they had to meet either of the following at the Screening Visit:
  - had a Visit 1 OHSA Item #1 score ≥7 AND the prescribed dose was ≤300 mg TID; OR
  - had a Visit 1 OHSA Item #1 score ≤6 AND this score worsened by ≥2 units when retested after washing out of droxidopa for ≥3 days

Investigational Medicinal Product (IMP), Doses and Mode of Administration, Batch Numbers

Droxidopa (also known as L-threo-3,4-dihydroxyphenylserine, or L-DOPS) – 100, 200, 300, 400, 500, or 600 mg TID; capsules, orally

Batch numbers – 100 mg (CHCWZ, NWCY, SMKF, YFDK), 200 mg (CHCXC, NWDC, SMKH, YFFG) and 300 mg (PMCK, CHCWY, SMKK, YGNS, YGNP)

In the Open-Label Titration Period, doses were titrated in 100 mg TID increments until the optimal dose was achieved. Four dose changes were permitted within the first 2 months of the Open-Label Treatment Period. No dose changes were allowed after Visit 5 (that is, the end of the Open-Label Treatment Period).

Patients were randomized 1:1 to receive droxidopa or matching placebo (equal to their dose at the end of the Open-Label Treatment Period) at Randomization (Visit 6) and during the Double-Blind Treatment Period (Visits 7 to 12). No dose changes were permitted during the Double-Blind Treatment Period.

Control Product, Doses and Mode of Administration, Batch Numbers

Placebo – matching capsules, orally

Batch numbers – 100 mg (CHCXB, SFBW, YHKD), 200 mg (CHCWX, SFBX, WWCX) and 300 mg (CHCWW, SFBY, WWCZ)

Duration of Treatment

- Open-Label Titration Period: up to 4 weeks
- Open-Label Treatment Period: 12 weeks
- Double-Blind Treatment Period: 12 weeks

Statistical Analysis

- The following analysis sets were used:
  - *all-enrolled set* – all patients who were enrolled into the study (that is, patients who entered the Open-Label Titration Period at Visit 2a)
  - *safety set* – all patients who received at least one dose of IMP; this included patients who received IMP during the Open-Label Titration Period
  - *full-analysis set* – a modified intent-to-treat set, consisting of all randomized patients who took at least one dose of IMP in the Double-Blind Treatment Period. Patients were included in the analysis according to the treatment to which they were randomized
- Unless otherwise specified, all the efficacy analyses and data presentations are based on the *full-analysis set* and all the safety analyses and data presentation are based on the *safety set*.
- Descriptive statistics were used to summarize the data, with confirmatory statistical testing performed for the primary efficacy endpoint (time-to-intervention) and the key secondary endpoint (time to all-cause discontinuation).

Statistical Analysis (continued)

- The primary endpoint, time-to-intervention, was summarized using the Kaplan-Meier method. The primary analysis was the log-rank test to compare the two treatment groups on time-to-treatment intervention during the Double-Blind Treatment Period. In addition, a Cox regression model, including treatment as a factor and baseline OHSA Item #1 score (prior to initial titration dose) as a covariate, was used to estimate the hazard ratio. Furthermore, the following sensitivity analyses were conducted using both Kaplan-Meier and Cox regression analyses:
  - time-to-treatment intervention according to the treatment intervention criteria (as described above under endpoints) or OHSA Item #1 ≥2 units worsening from Randomization at the last visit of the Double-Blind Treatment Period (Visit 12)
  - the potential impact of the COVID-19 pandemic
- Time to all-cause discontinuation was the key secondary endpoint.
  - A gate keeping strategy was applied in the testing of the key secondary endpoint, that is, the log-rank test of this secondary endpoint was performed at the nominal alpha level of two-sided 0.05 only if the results for the primary endpoint were statistically significant in the primary analysis. This strategy ensured the overall type 1 error rate was preserved. The key secondary analysis was performed in the same way as the primary efficacy analysis (log-rank test of treatment difference, Kaplan-Meier plot, Cox regression analysis).
- The overall incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events leading to withdrawal were summarized separately for the Open-Label Titration Period, the Open-Label Treatment Period, and the Double-Blind Treatment Period. Clinical safety laboratory test values and vital signs were summarized for the entire open-label part of the study (Titration Period and Treatment Period) and the Double-Blind Treatment Period.

Patient Disposition and Analysis Sets

- Patient disposition in the Open-Label Titration and Open-Label Treatment Periods are summarized below:

	Droxidopa	
	Open-Label Titration Period	**Open-Label Treatment Period**
	n (%)	**n (%)**
Patients enrolled	453	379
Patients treated (Safety Set):	451[a]	366[b]
Patients completed	379 (84.0)	253 (69.1)
Patients withdrawn	72 (16.0)	113 (30.9)
Primary reason for withdrawal:		
Adverse event	30 (6.7)	23 (6.3)
Lost to follow-up	3 (0.7)	1 (0.3)
Non-compliance with IMP	2 (0.4)	2 (0.5)
Physician decision	5 (1.1)	6 (1.6)
Protocol violation	4 (0.9)	4 (1.1)
Withdrawal by patient	13 (2.9)	22 (6.0)
Did not meet open-label entry criteria	1 (0.2)	29 (7.9)
Did not meet randomization criteria	-	17 (4.6)
Other	14 (3.1)	9 (2.5)
Analysis sets:		
All-enrolled Set	451[a]	
Safety Set	451[a]	

a Patients 0419 and 0382 were excluded from all analysis sets due to incorrect signing of the ICF.
b This number includes 13 patients who withdrew after completing the Open-Label Titration Period and did not receive treatment in the Open-Label Treatment Period.

Patient Disposition and Analysis Sets (continued)

- Patient disposition in the Double-Blind Treatment Period is summarized below:

	Droxidopa n (%)	Placebo n (%)	Total n (%)
Patients randomized	127	126[a]	253
Patients treated (FAS):	126[b]	126	252
Patients completed	78 (61.4)	86 (68.3)	164 (64.8)
Patients withdrawn	49 (38.6)	40 (31.7)	89 (35.2)
Primary reason for withdrawal:			
Adverse event	6 (4.7)	4 (3.2)	10 (4.0)
Lost to follow-up	1 (0.8)	2 (1.6)	3 (1.2)
Non-compliance with IMP	1 (0.8)	1 (0.8)	2 (0.8)
Physician decision	0	1 (0.8)	1 (0.4)
Protocol violation	2 (1.6)	0	2 (0.8)
Withdrawal by patient	6 (4.7)	5 (4.0)	11 (4.3)
Met the need for intervention criteria	31 (24.4)	27 (21.4)	58 (22.9)
Did not meet randomization criteria	1 (0.8)	0	1 (0.4)
Other	1 (0.8)	0	1 (0.4)
Analysis sets:			
FAS	126[b]	126[a]	252

a Patient 0419 was excluded from all analysis sets due to incorrect signing of the ICF.
b 1 patient randomized to droxidopa did not receive IMP

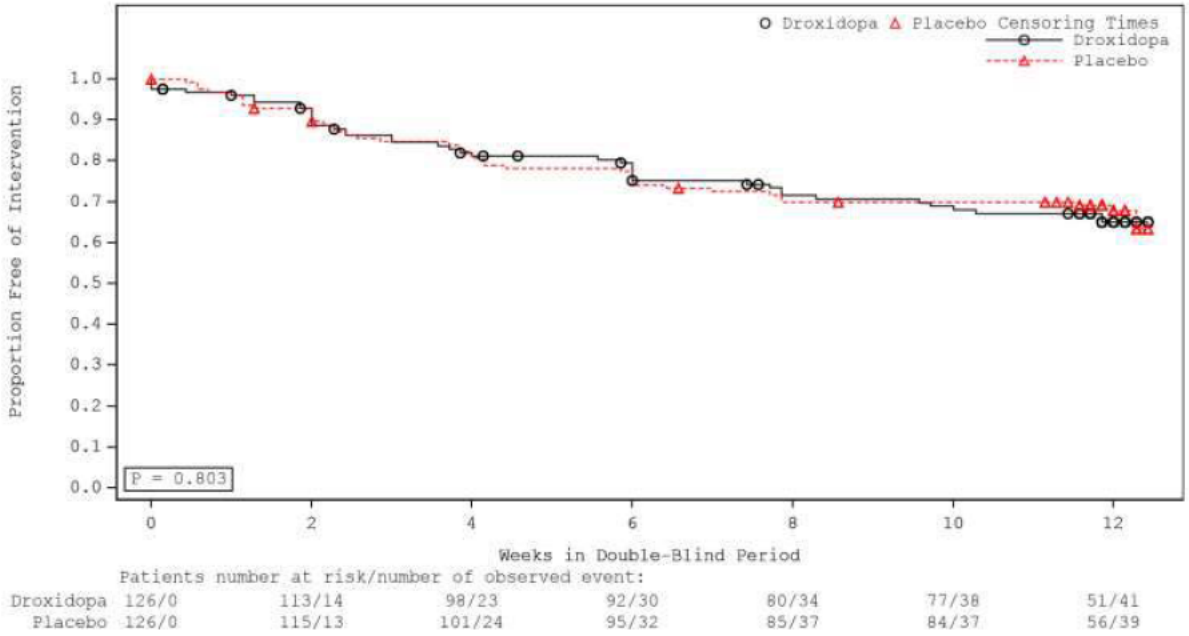
- The *safety set* included 451 patients and the *full-analysis set* included 252 patients (126 patients in each treatment group); 2 patients were excluded from all analysis sets due to incorrect signing of the ICF and 1 patient randomized to droxidopa did not receive IMP and was excluded from the *full-analysis set*.

Demographics and Baseline Characteristics of the Full-analysis Set

- Demographics were comparable between droxidopa- and placebo-treated patients: the mean age was 65 years; approximately 54% were men; and the majority (94%) were White.
- At Screening, the mean duration of nOH was longer for droxidopa-treated patients than for placebo-treated patients (34.0 months *versus* 22.8 months).
- The most common primary diagnosis was PD (droxidopa: 47.6%; placebo 54.8%), followed by NDAN (droxidopa: 24.6%; placebo 29.4%), PAF (droxidopa: 22.2%; placebo 11.1%), and MSA (droxidopa: 5.6%; placebo 4.8%). No patients had DBH deficiency.
- There were no marked differences between the droxidopa and placebo groups in the mean OHSA Item #1 score (2.8 *versus* 3.1), OHSA composite score (3.5 *versus* 3.7), Orthostatic Hypotension Daily Activity Scale (OHDAS) composite score (3.9 *versus* 4.3), or OHQ composite score (2.8 *versus* 3.1) at Randomization (that is, the baseline of the Double-Blind Treatment Period).
- The mean scores were similar between droxidopa-treated and placebo-treated patients for the clinician-reported CGI-S (3.0 *versus* 3.1) and the patient-reported CGI-S (3.2 *versus* 3.0). The mean scores indicate that patients and clinicians considered the severity of OH as *mild OH*.

Efficacy Results

- Droxidopa-treated patients were equally as likely to require treatment intervention as placebo-treated patients (log-rank test p=0.803, hazard ratio=1.04). The 25% Kaplan-Meier estimate of time-to-intervention was 52 days for droxidopa-treated patients and 42 days for placebo-treated patients. The results of the sensitivity analyses were in line with the results of the primary analysis.
- The results of the Kaplan-Meier and Cox regression analysis of time-to-intervention are presented below.



- The results of the analyses of the key secondary and secondary endpoints were similar to the results of the primary analysis.
- The mean change from Randomization in OHSA Item #1 scores in droxidopa-treated patients was minimal, with marginal increases (that is, worsening) observed. After withdrawal of droxidopa treatment at Randomization, OHSA Item #1 scores in placebo-treated patients had not considerably worsened at the time of withdrawal in the Double-Blind Treatment Period, and the mean changes (LOCF) from Randomization in OHSA Item #1 scores were in a similar range to those in droxidopa-treated patients during the Double-Blind Treatment Period. A similar finding was observed for the OHQ composite scores.
- At Randomization, the mean scores indicate that both clinicians and patients considered the severity of OH as *mild OH*. For both outcomes, minimal changes from Randomization were observed at each post-randomization visit, irrespective of treatment.
- The proportion of patients requiring treatment intervention during the Double-Blind Treatment Period was similar between treatment groups (32.5% of droxidopa-treated patients and 31.7% of placebo-treated patients).

Safety Results

- The incidence of adverse events in the Open-Label Titration and Open-Label Treatment Periods and in the Double-Blind Treatment Period is summarized below:

	Open-Label Titration Period	Open-Label Treatment Period	Double-Blind Treatment Period	
	Droxidopa	Droxidopa	Droxidopa	Placebo
	n (%)	n (%)	n (%)	n (%)
Number of patients	451	366	126	126
Any TEAE	233 (51.7)	189 (51.6)	62 (49.2)	52 (41.3)
Any TEAE related to IMP	158 (35.0)	86 (23.5)	20 (15.9)	15 (11.9)
Any severe TEAE	31 (6.9)	28 (7.7)	6 (4.8)	5 (4.0)
Any TEAE leading to IMP withdrawal	37 (8.2)	20 (5.5)	7 (5.6)	4 (3.2)
Any TEAE leading to death	3 (0.7)	3 (0.8)	1 (0.8)	0
Any SAEs	15 (3.3)	31 (8.5)	3 (2.4)	8 (6.3)
Any SAE related to IMP	5 (1.1)	8 (2.2)	1 (0.8)	1 (0.8)
Any SAE leading to IMP withdrawal	6 (1.3)	11 (3.0)	2 (1.6)	0

- A total of 9 patients died: 2 patients during the Screening Period and 7 patients during the study (3 patients in the Open-Label Titration Period; 3 patients in the Open-Label Treatment Period; and 1 patient in the Double-Blind Treatment Period). Only the events in 2 patients who died during the Open-Label Titration Period were considered *related* to droxidopa: *cerebral haemorrhage*; *cerebral haemorrhage* and *subdural haematoma*; these events led to confirmation of a stroke signal and subsequent updates to the package insert and the study protocol.
- The proportion of patients who reported TEAEs were similar during the Open-Label Titration and Open-Label Treatment Periods (approximately 52% each). The TEAEs with an incidence ≥5% during the Open-Label Periods were: *headache*, *fall*, *nausea*, and *dizziness*. The proportion of patients who had *severe* TEAEs during the Open-Label Periods was approximately 7%. The proportion of patients who reported SAEs was 3.3% during the Open-Label Titration Period and 8.5% during the Open-Label Treatment Period. The SAEs reported in >1 patient during this period were: *cerebral haemorrhage* (3 patients) and *fall* (2 patients) during the Open-Label Titration Period; *fall*, *syncope* (4 patients each), and *pneumonia aspiration* (3 patients) during the Open-Label Treatment Period.
- During the Double-Blind Treatment Period, the proportion of patients who had TEAEs was higher in the droxidopa than in the placebo group (49.2% versus 41.3%, respectively). The TEAEs with an incidence ≥5% in either the droxidopa or placebo groups during the Double-Blind Treatment Period were (droxidopa *versus* placebo): *urinary tract infection* (7.9% *versus* 4.0%); *fall* (6.3% *versus* 4.0%); *dizziness* (5.6% *versus* 4.0%); and *headache* (3.2% *versus* 5.6%). The proportion of patients who had *severe* TEAEs was similar between the droxidopa and placebo groups (4.8% *versus* 4.0%). The proportions of patients who had SAEs in the droxidopa and placebo group were 2.4% and 6.3%, respectively. The SAEs reported in >1 patient during this period were *syncope* (3 patients) and *pneumonia* (2 patients), both in the placebo group.
- Changes in clinical safety laboratory tests or vital signs from Baseline/Randomization during the Open-Label Periods or during the Double-Blind Treatment Period were small and considered not clinically relevant. The proportions of patients with post-baseline/randomization PCS shifts in laboratory or vital signs values were generally low and with no clinically relevant differences between treatment groups.

Conclusions

- The primary efficacy analysis failed to show durability of effect of droxidopa treatment; droxidopa-treated patients were equally as likely as placebo-treated patients to require treatment intervention during the 12-week Double-Blind Treatment Period.
- From the Baseline until the end of the Open-Label Treatment Period, patients demonstrated substantial improvements in efficacy scores while on droxidopa treatment. Minimal changes in efficacy scores were observed in both the droxidopa and placebo groups from Randomization to the time of withdrawal in the Double-Blind Treatment Period.

Conclusions (continued)

- The incidences of TEAEs ≥5% (*headache*, *nausea*, *fall*, *dizziness*, and *urinary tract infection*) are in line with those in previous clinical studies and post-marketing experience with droxidopa.
- A total of 7 droxidopa-treated patients died during the study. For 2 patients who died during the Open-Label Titration Period, the events of *cerebral haemorrhage* and *subdural haematoma* were considered *related* to droxidopa. This led to confirmation of a stroke signal and subsequent updates to the package insert and the study protocol.
- No other safety signals were identified during this study.
- In summary, continued review of the safety data from this study indicates that droxidopa was safe and well tolerated when administered to patients with nOH for up to 36 weeks.

Report Date

28 February 2023

This study was conducted in compliance with *Good Clinical Practice*.