

## **Temporary Compliance Waiver Notice**

At the time of initial posting on January 23rd, 2014, the attached PDF document may not be fully accessible to readers using assistive technology. A fully accessible version of the document is in preparation and will be posted as soon as it is ready. We regret any inconvenience that this may cause our readers.

In the event you are unable to read this document or portions thereof, please contact Division of Drug Information in Office of Communications at 301-796-3634 or email [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov).



# Cardiovascular and Renal Drugs Advisory Committee Meeting

NDA 203202

Droxidopa

Clinical-Statistical Findings

January 14, 2014

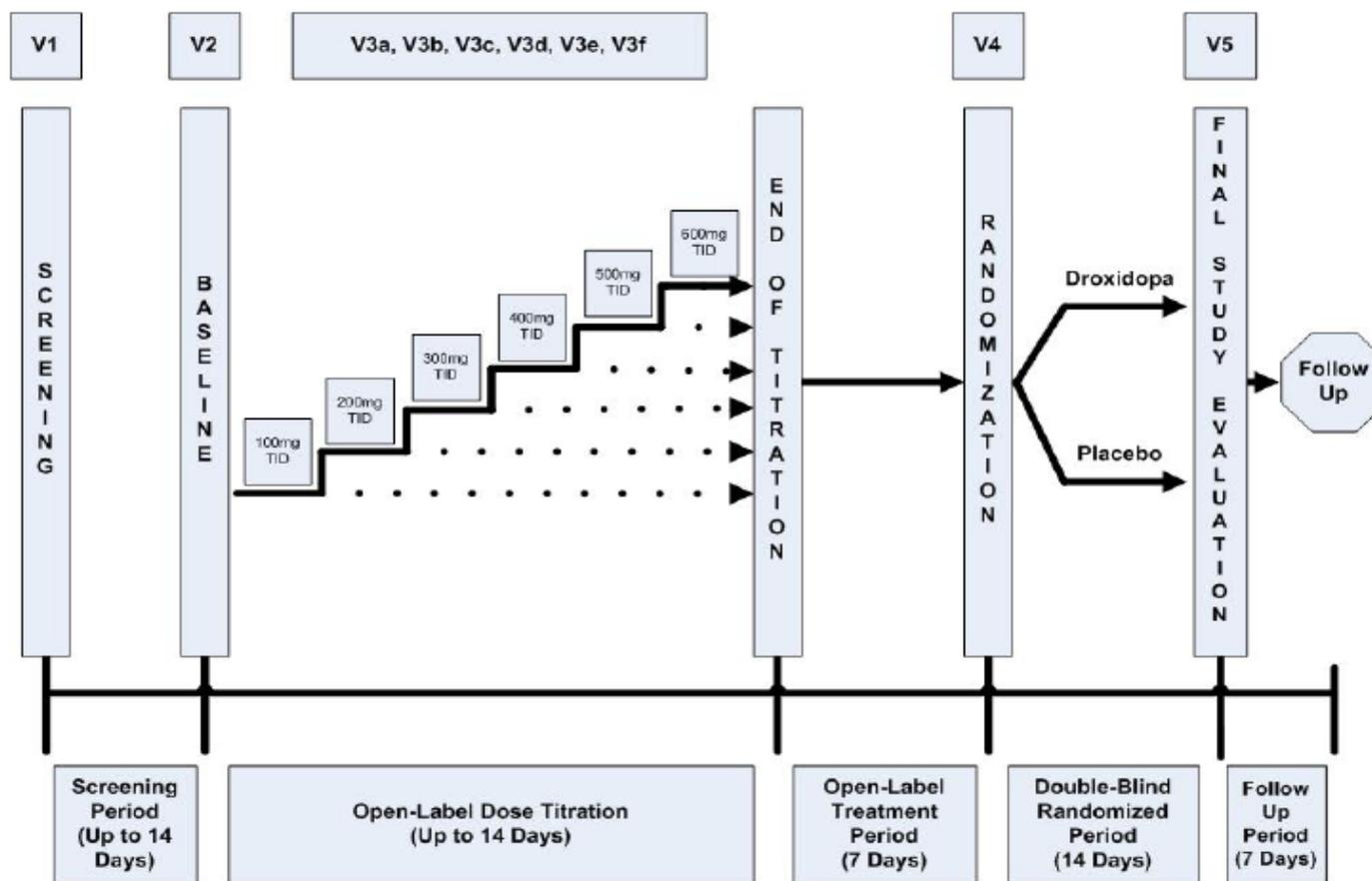
Shari L. Targum, M.D.

Jialu Zhang, Ph.D.

# Background

- Original application submitted 9/28/2011
- Discussed at Cardiovascular and Renal Drugs Advisory Committee meeting on 2/23/2012
- Sponsor submitted three efficacy studies:  
301, 302, 303
  - Multinational
  - Parkinson's disease, pure autonomic failure, multiple system atrophy, dopamine beta-hydroxylase deficiency, non-diabetic autonomic neuropathy

# Study 302 Design



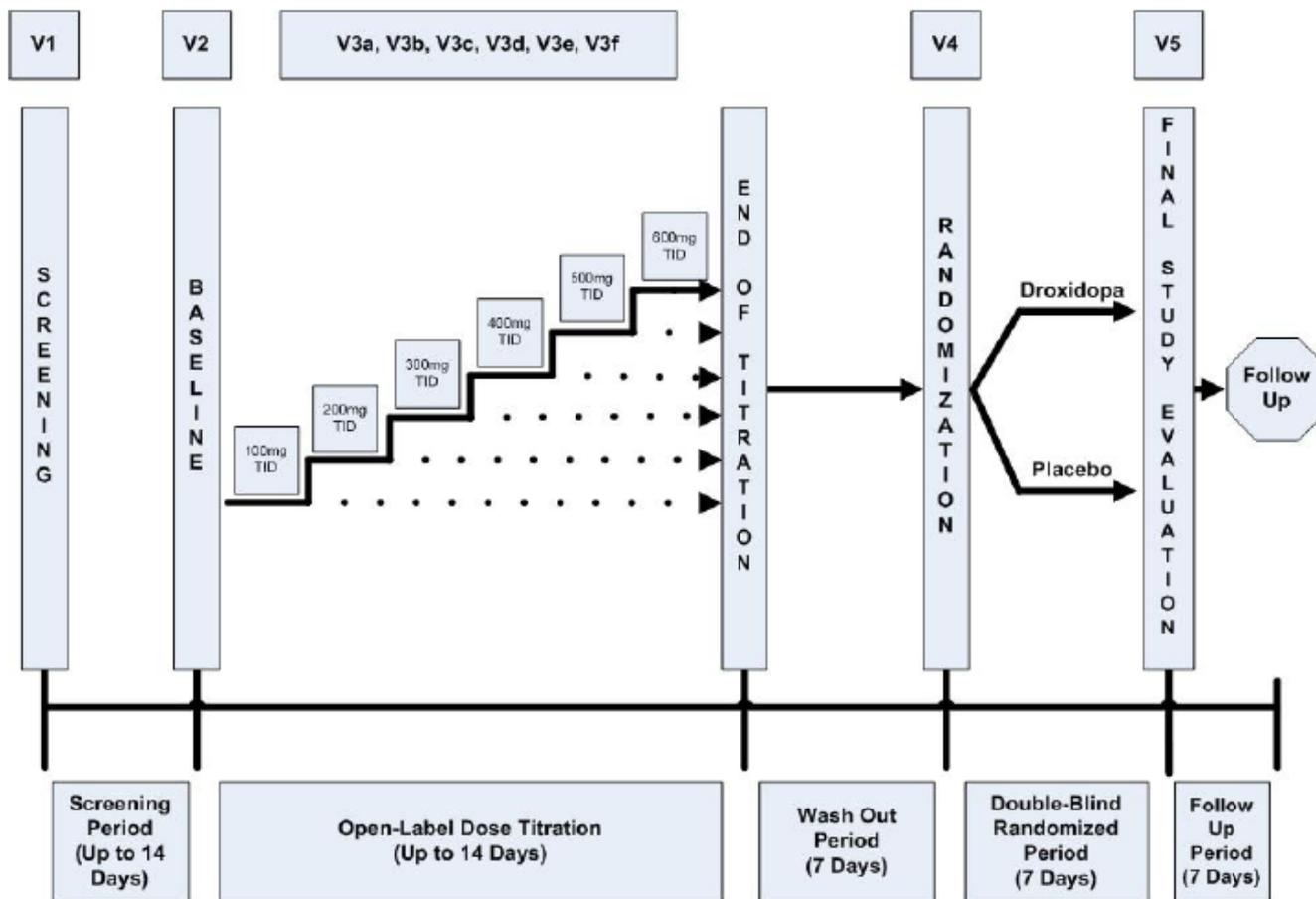
# Study 302 (N=101)

- Titrated until asymptomatic (OHSA item 1 +  $\uparrow$ SBP), maximum dose, intolerable side effects, BP criteria
- Randomized *only* if responders--improvement in SBP ( $\geq 10$  mm Hg) and OHSA item 1 (1 unit) with droxidopa
- 2 week randomized withdrawal period
  - Primary endpoint OHSA item 1, treatment effect -0.6 (p=NS): both groups showed worsening ( $\uparrow$ ) score
  - Exploratory analysis: nominally significant improvement in OHQ composite.

## Study 303 (N=75)

- Extension study
- Patients remained on their titrated droxidopa dose for 3 months
- Two-week randomized double-blind withdrawal period
  - Primary endpoint OHQ composite, effect -0.3 (p=NS)

# Study 301

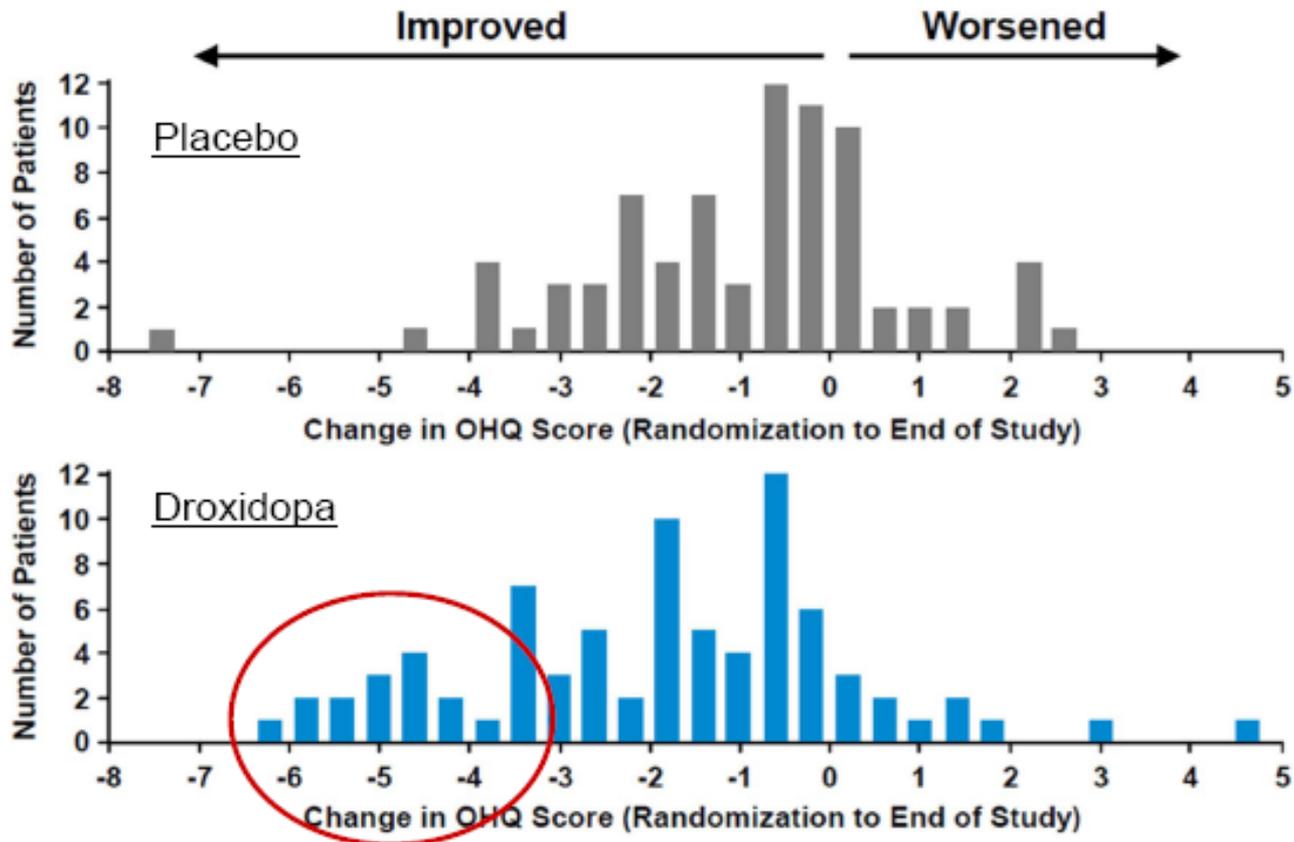


TID=Three times daily.

## Study 301 (N= 162)

- Similar enrichment strategy as 302, randomized responders to droxidopa
- Titration, washout period, randomized, double-blind period x 1 week
  - Primary endpoint: OHSA item 1, changed (following 302 results) to OHQ composite
  - Results statistically significant for OHQ composite (effect size 0.9) and OHSA item 1 (effect size 1.3), favorable for droxidopa
- Of three studies, *only* 301 showed statistically significant treatment effect

# Study 301: Distribution of the change in OHQ score



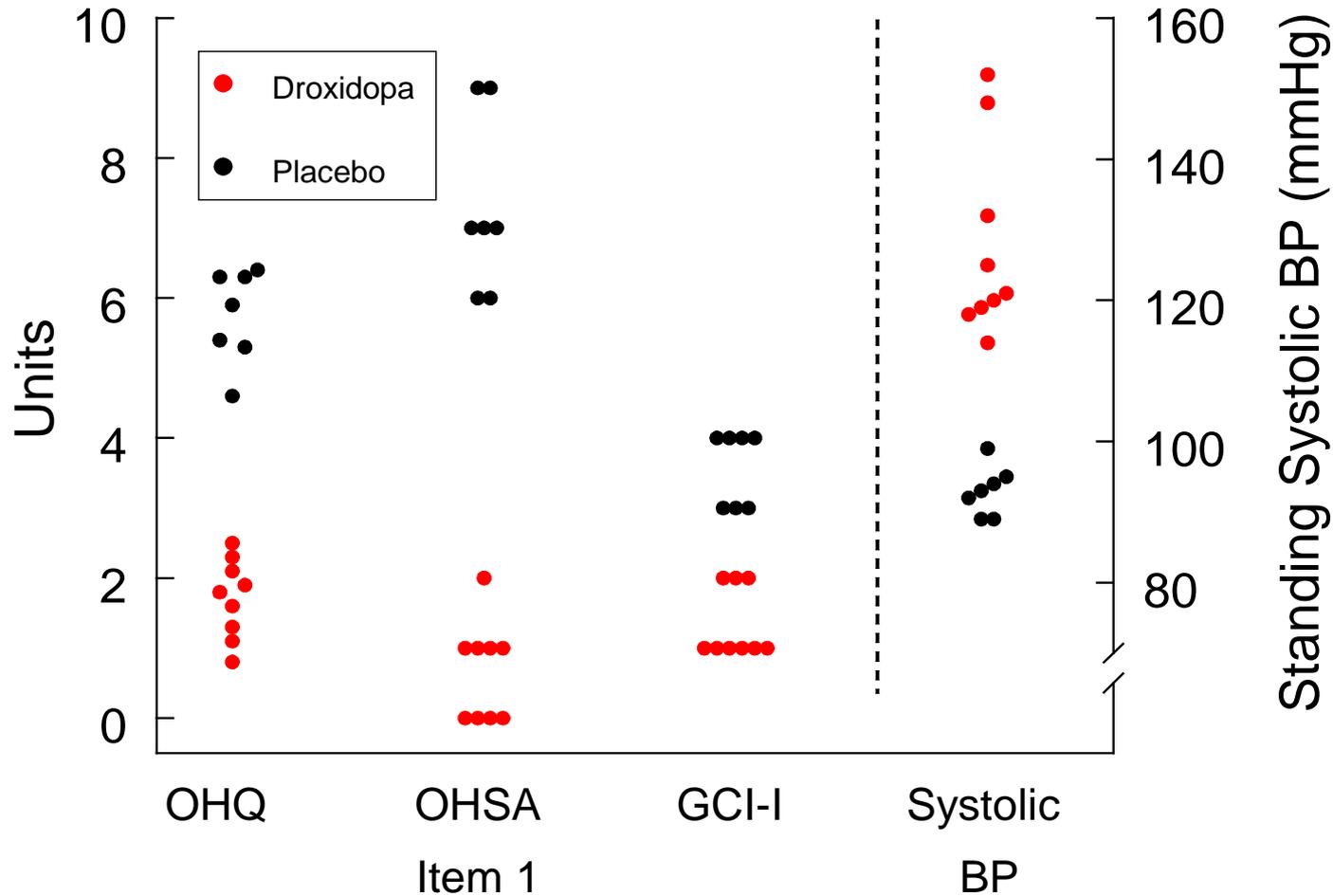
## Background (2)

- FDA further analyzed patients with high OHQ composite score response—6 of 15 patients from a single site (site 507).

# Site 507

- State Medical Academy in Ukraine
- Largest site in Study 301 (N=16)
- Fast enrollment (4 months)
- Large and homogeneous treatment effect

# Endpoints at the End of Study at Site 507



Source: Figure 5 in Decisional Memo by Dr. Unger



# Site 507 Endpoints

- Generally, in multicenter trials, effects can vary by site
  - Some sites can have large effects
- In this case (site 507), the low variance within treatment groups is unusual and concerning
  - No placebo SBP effect and lack of SBP variability

# Site 507 Findings

- Removal of Site 507 led to insignificant study results for the primary endpoint-- OHQ composite (p-value from 0.003 to 0.07)
- No significant inspection finding; site also audited by applicant

# Evidence of Effectiveness

- Agency may consider “data from one adequate and well-controlled clinical investigation” to constitute substantial evidence if FDA determines that such data and evidence are sufficient (Section 115a, FDAMA, 1997).
- If a single site is largely responsible for the overall effect seen in a multicenter trial, the credibility of the trial as sole support for effectiveness is diminished (FDA Effectiveness Guidance).
- Even without concerns about site 507
  - *The disproportionate contribution of Site 507 to the overall results of study 301 diminishes the persuasiveness of the study”* (FDA Decisional Memo).

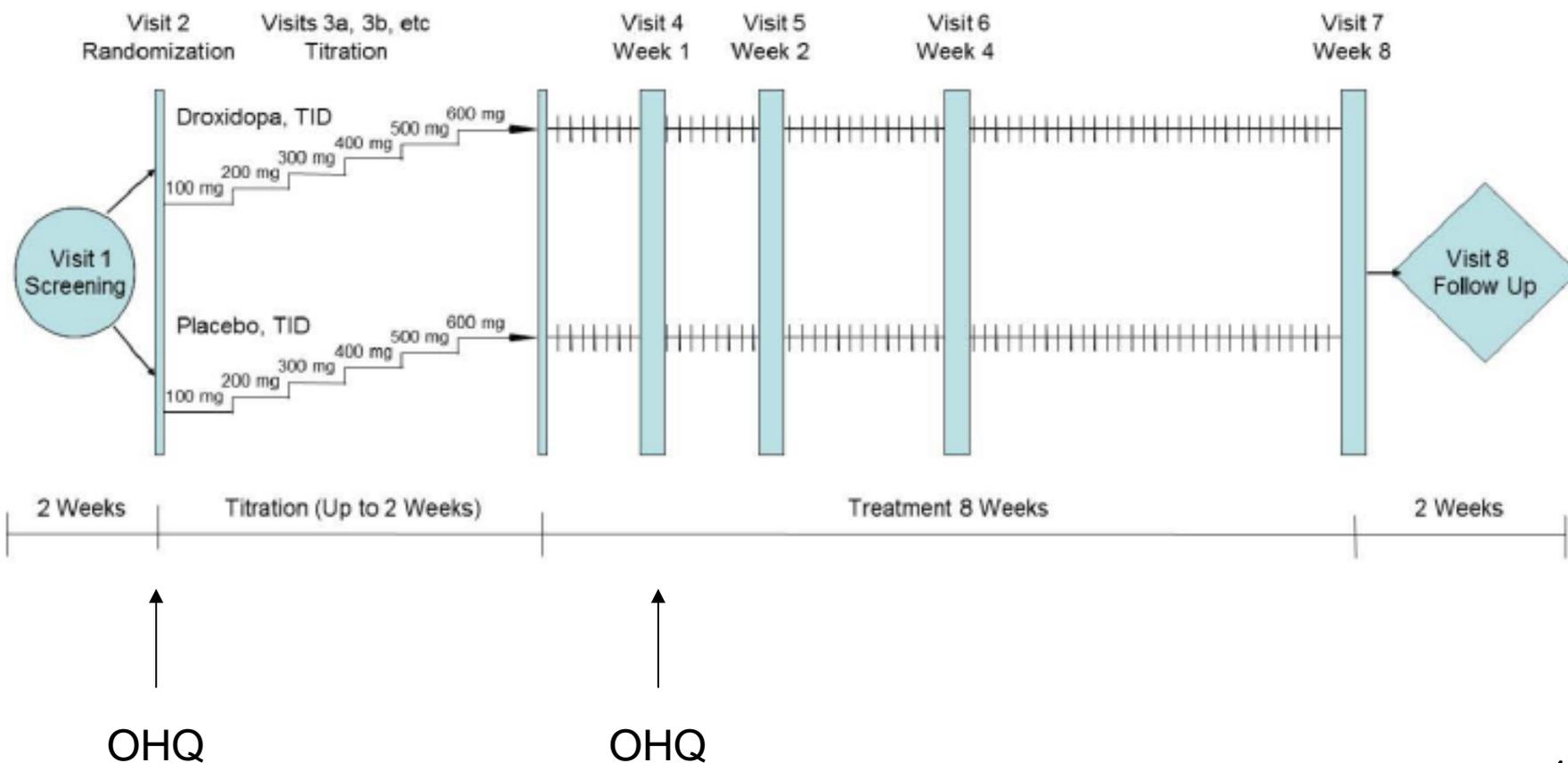


# Study 306

# 306 Study Population

- Parkinson's disease with symptomatic NOH
- At least 18 years old
- $\geq 3$  OHQ composite
- $\geq 3$  on clinician-reported CGI-S
- Fall  $\geq 20$  mm Hg SBP or 10 mm Hg DBP within 3 minutes of standing

# 306 Study Design



# 306: Study Drug Dosing

- Randomized to droxidopa 100 mg TID or placebo
- Treatments escalated in 100 mg increments until:
  - SBP  $\geq$  180 mm Hg or DBP  $\geq$  110 mm Hg supine
  - Clinician reported CGI-S = 1 (normal, no OH)
  - Intolerable side effects
  - Maximum dose of 600 mg TID



# **Statistical Review on Droxidopa**

## **Advisory Committee Meeting**

### **Droxidopa**

**NDA 203202**

**January 14, 2014**

# Timeline

Date	Event	306 N	306B N
Mar 10, 2010	Primary endpoint was OHQ composite score at Week 8 and planned sample size was 84 (protocol V1)		
Nov 19, 2010	Add an interim analysis at 60% information time (N=50), sample size may be increased up to a maximum of 192 (protocol V3)		
Dec 14, 2010	Cut-off date for interim analysis in Study 306	94	43
Jan 25, 2011	DMC met and recommended termination of Study 306	113	62

# Timeline

Date	Event	306 N	306B N
Feb 9, 2011	PPD informed Chelsea about improper access to randomization codes		
Feb 23, 2011	Enrollment resumed		
Mar 2, 2011	Access was revoked	118	67
May 12, 2011	protocol V4 with changed primary endpoint (patient reported falls at Week 8), sample size =160	143	92
Aug 10, 2012	Last patient enrolled in Study 306B	225	174
Nov 5, 2012	The primary endpoint was changed to OHSA Item 1 at Week 1 (protocol V5), sample size=200		

# Comparison of Efficacy Results at Different Time Points

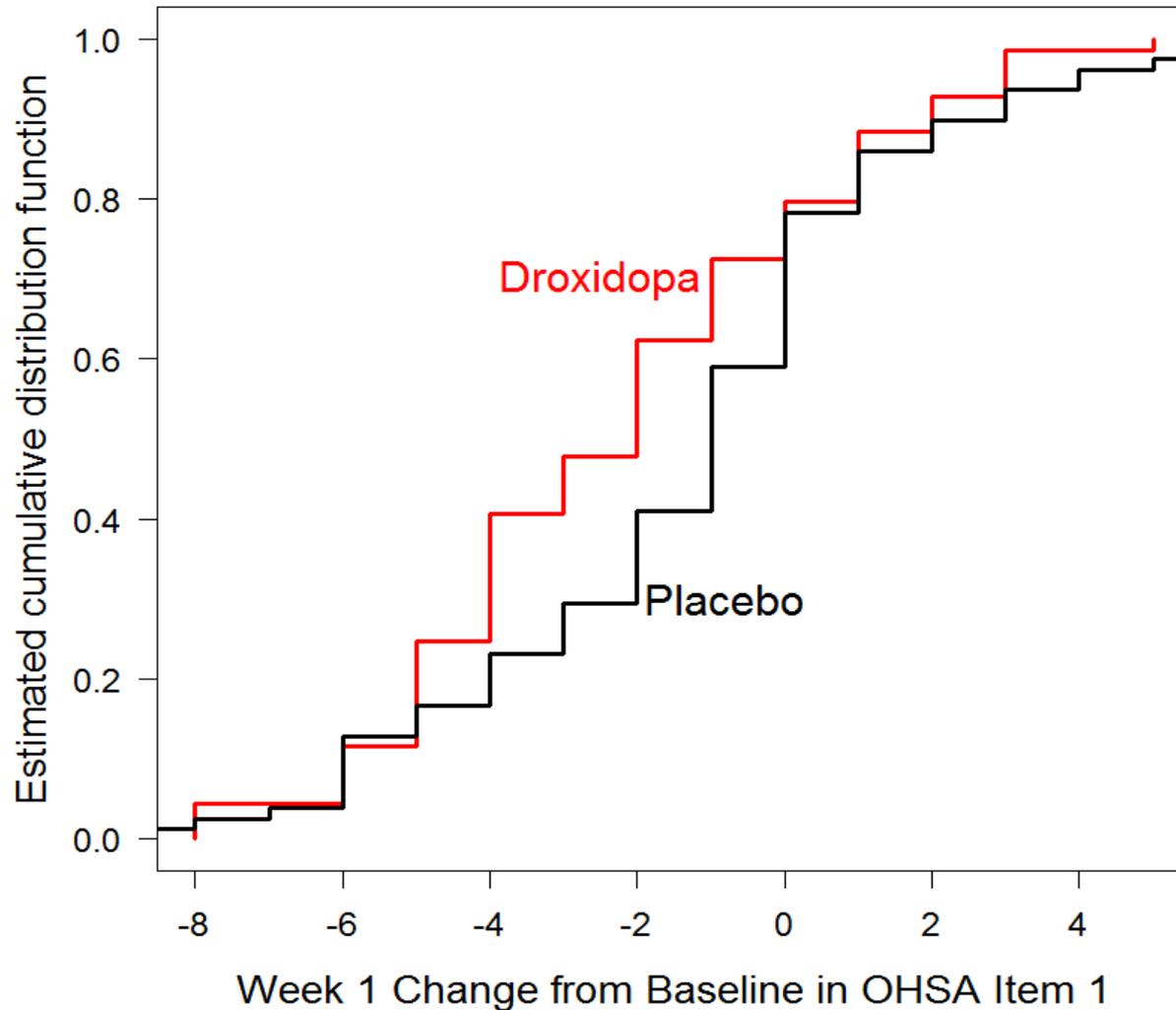
	Whole Study Population		Post Interim Analysis*		Revoking Access to Treatment Code		Changing Primary Endpoint	
	N=147		N=121		After March 2, 2011 N=93		After May 12, 2011 N=71	
	trt eff est	CI	trt eff est	CI	trt eff est	CI	trt eff est	CI
OHS Item 1: Mean change from baseline at Week 1	-0.9	(-1.8, 0.1)	-1.3	(-2.4, -0.1)	-0.6	(-1.7, 0.5)	-0.7	(-2.0, 0.6)
Lowest standing SBP between 0 to 3 minutes at Week 1	5.4	(-0.5, 11.3)	7.2	(-0.2, 14.6)	2.5	(-5.0, 10.0)	0.8	(-8.5, 10.1)
OHQ mean change from baseline at Week 1	-0.6	(-1.2, 0.1)	-0.7	(-1.5, 0.1)	-0.4	(-1.2, 0.4)	-0.3	(-1.3, 0.7)
Clinician-reported CGI-S at Week 1	-0.4	(-0.8, -0.05)	-0.4	(-0.9, -0.0)	-0.4	(-0.9, 0.03)	-0.2	(-0.7, 0.3)
Patient-reported CGI-S at Week 1	-0.4	(-0.8, 0.02)	-0.4	(-0.9, 0.2)	-0.4	(-1.0, 0.1)	-0.2	(-0.8, 0.4)
Clinician-reported CGI-I at Week 1	-0.5	(-0.9, -0.1)	-0.6	(-1.0, -0.2)	-0.5	(-1.0, -0.1)	-0.4	(-1.0, 0.1)
Patient-reported CGI-I at Week 1	-0.2	(-0.5, 0.1)	-0.3	(-0.7, 0.0)	-0.2	(-0.6, 0.2)	-0.2	(-0.7, 0.3)

\* sponsor's post-interim analysis

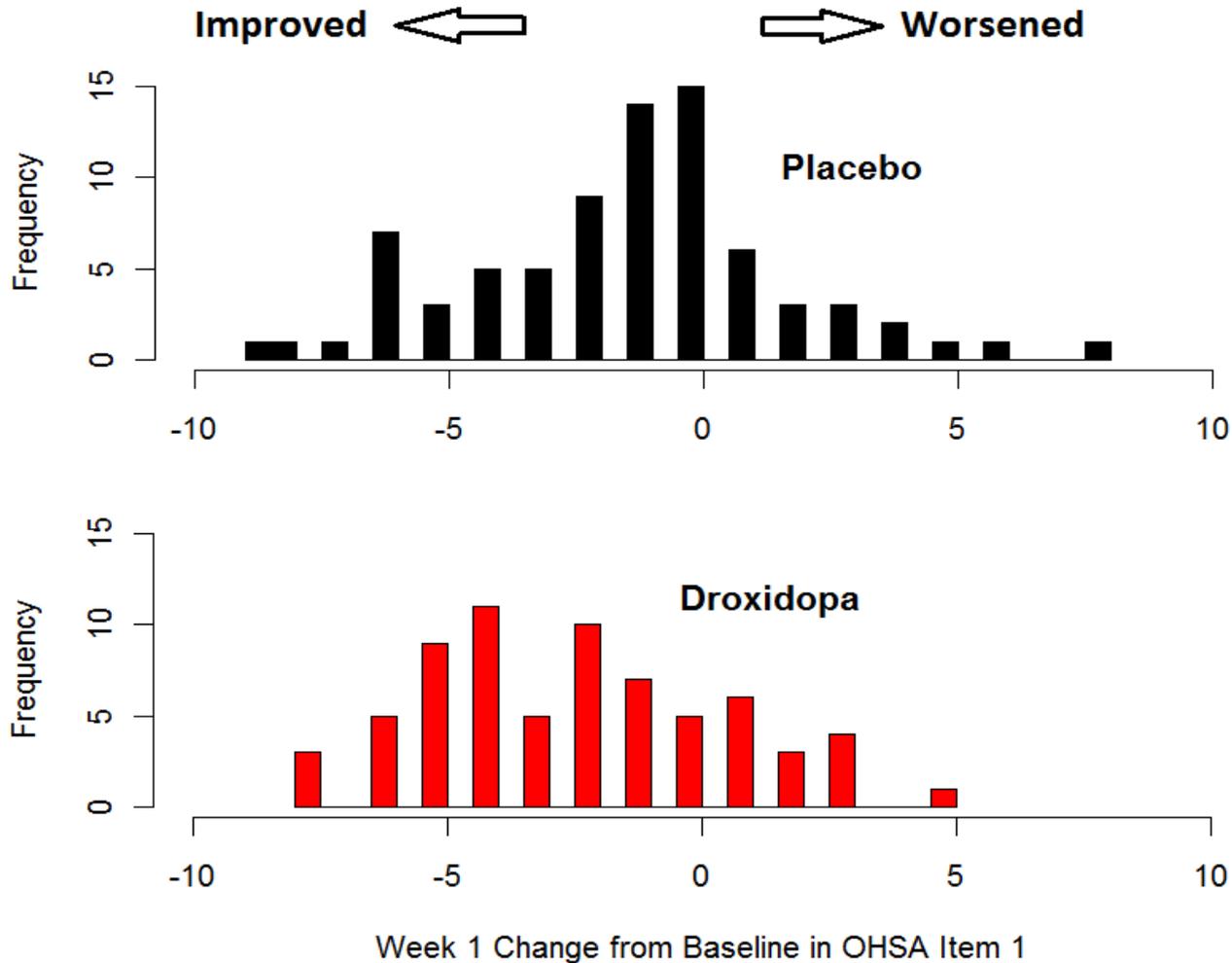
# Primary Analysis

	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
<b>Baseline</b>	69	5.1	2.0	78	5.1	2.3
<b>Week 1</b>	69	2.8	2.4	78	3.8	2.8
<b>Least square mean difference</b>	-0.94 with 95% CI (-1.8, -0.1)					
<b>p-value from ANCOVA model</b>	0.028					

# Cumulative Distribution on OHSA Item 1



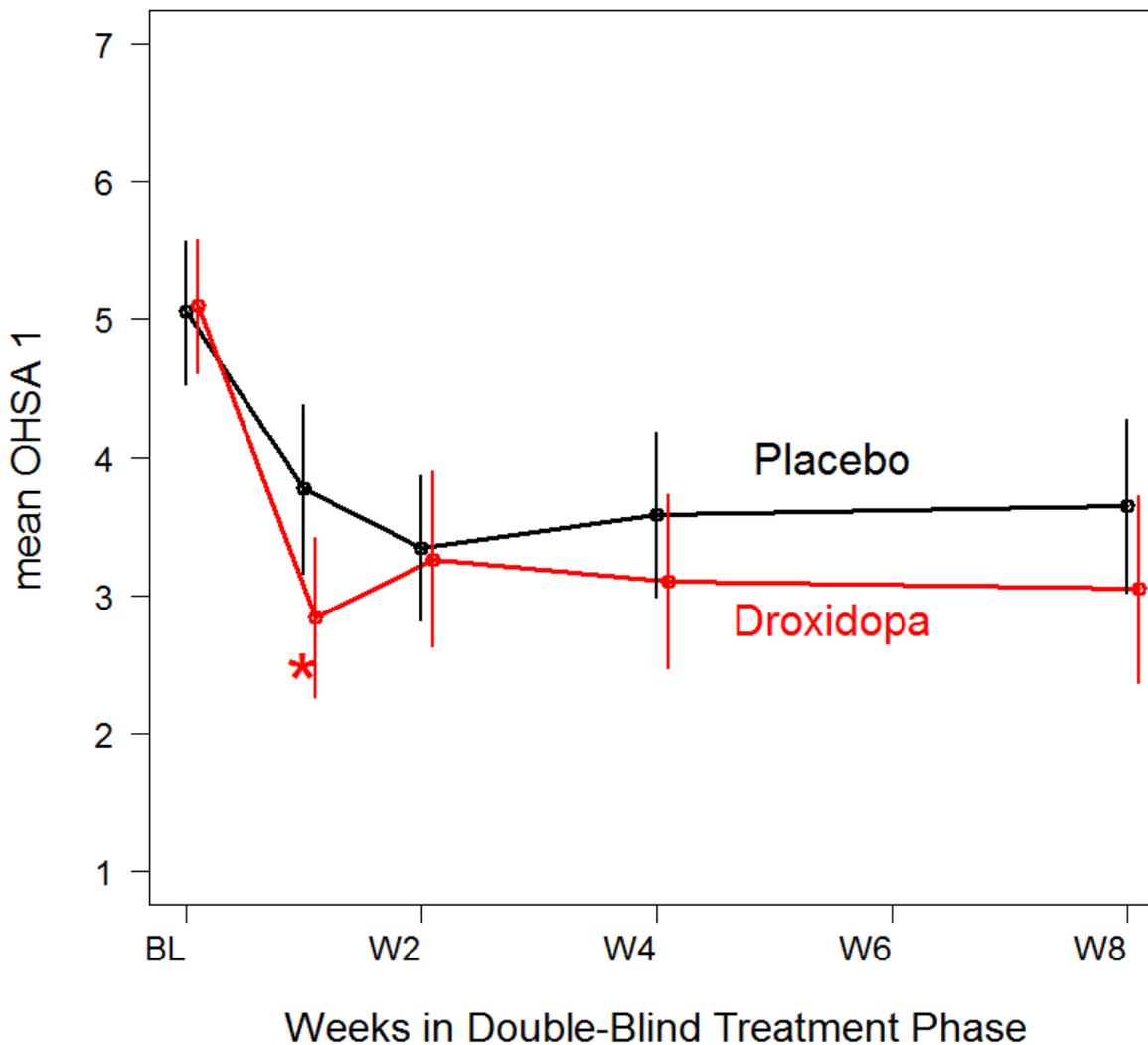
# Distribution of the Change in OHSA Item 1



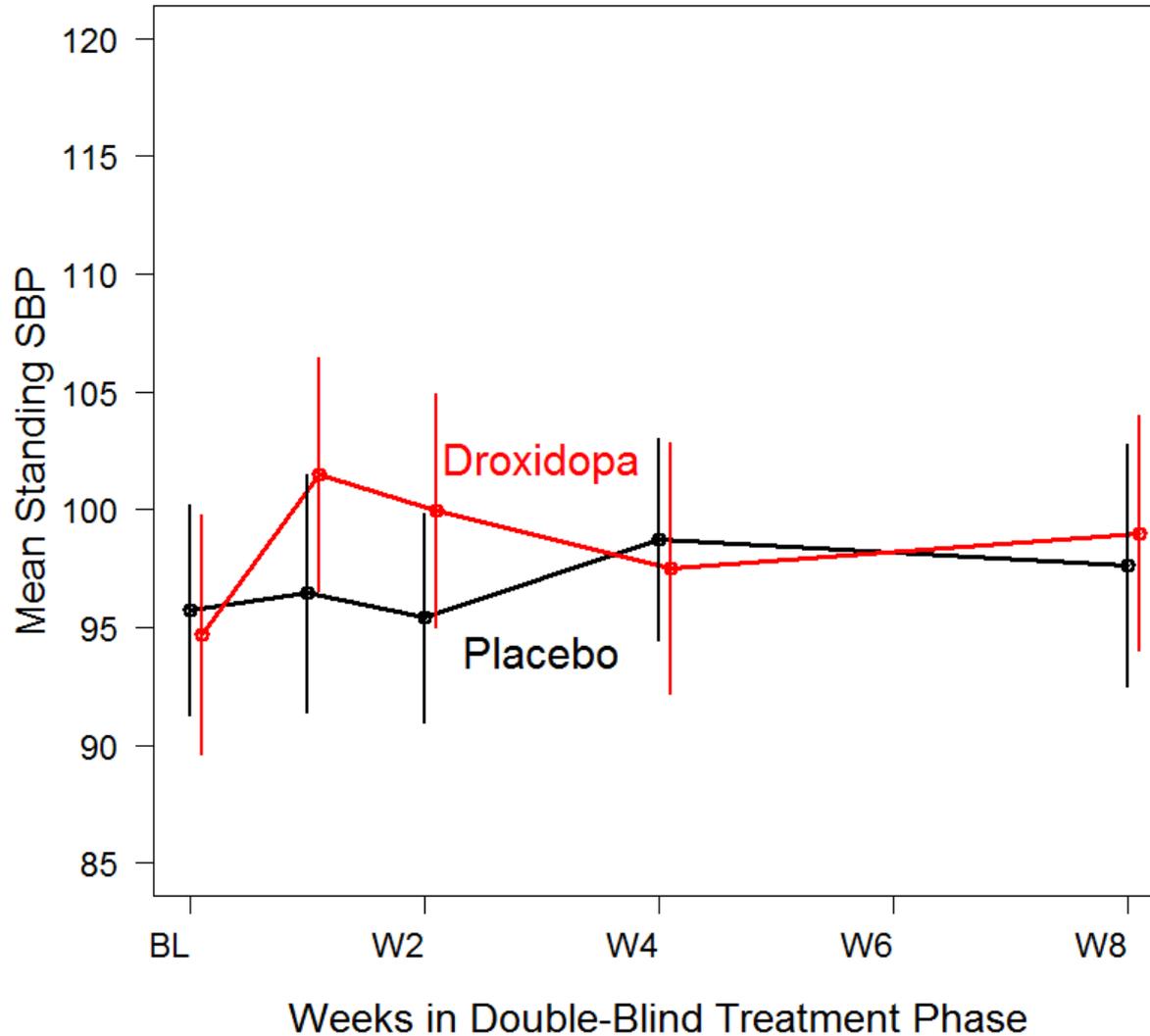
# Intra-Subject Variability

- The treatment effect is 0.94 unit in OHSA Item 1
- The intra-subject variability is 1.7 unit in OHSA Item 1 (based on all post-baseline data)
- The treatment effect is small compared with intra-subject variability

# Mean OHSA Item 1 Score by Week



# Mean Standing SBP by Week



# Patient Reported Falls

Analysis	Placebo (N=78)	Droxidopa (N=69)
Total Number of Falls	716	229
Percentage of Patients with $\geq 1$ Fall	47 (60%)	40 (58%)
Mean Patient Rate of Falls Per Patient-Week	2.0	0.4

- Placebo patient 122013 had 118 reported falls
- Placebo patient 146007 had 358 reported falls

# Patient Population

	Placebo (N=85)	Droxidopa (N=89)
Treated	84*	87
Never received study drug	1	2
Discontinued before Week 1	6	18
Full Analysis Set	78	69
Discontinued before interim cut-off date	1	7
Excluded from Full Analysis Set and dropped out after interim cut-off date	4**	12**

\* 2 patients were randomized to placebo but treated with droxidopa

\*\* based on actual treatment received

# Patients Discontinued before Week 1

Discontinuation reason	Placebo	Droxidopa
Not treated	1	2
Treatment failure	0	1
Adverse event	4	6
Lack of efficacy	0	3
Protocol violation	0	1
Patient withdrew consent	0	3
Investigator decision	0	2
Other	2	2
<b>Total</b>	<b>7</b>	<b>20</b>

# Fludrocortisone Imbalance

		Placebo	Droxidopa
<b>Baseline</b>	<b>With fludrocortisone</b>	16	30
	<b>No fludrocortisone</b>	69	59
	<b>Total</b>	85	89
<b>Discontinued before Week 1</b>	<b>With fludrocortisone</b>	1	11
	<b>No fludrocortisone</b>	5	7
	<b>Total</b>	6	18
<b>Week 1</b>	<b>With fludrocortisone</b>	15	19*
	<b>No fludrocortisone</b>	63	50
	<b>Total</b>	78	69

\* Patient 146012 and patient 132016 stopped fludrocortisone during titration

# Subgroup Analysis by Fludrocortisone Use

Fludrocortisone use	Placebo	Droxidopa	Treatment difference in OHSA 1	95% CI
Yes	15	19	-1.6	(-3.5, 0.4)
No	63	50	-0.8	(-1.8, 0.1)

# Summary

- Study 306B was successful, with a statistically significant amended primary endpoint (OHSA item 1)
- There is a baseline imbalance for concomitant fludrocortisone use, an off-label treatment of orthostatic hypotension.
  - How to interpret? Are the two treatment groups comparable?

## Summary (2)

- There is an imbalance of dropouts in the two treatment arms, with more droxidopa-treated patients dropping out
  - Concern about biasing the primary endpoint
- 306B primary treatment effect is small when compared with intra-subject variability
  - How to interpret?
- In a chronic condition such as NOH, 306B study results showed no durability of the treatment effect—

# Summary (3)

- Blinding cannot be verified but the study results were trending in the right direction in various time points.
- How to put together the efficacy study results, taking into account well-designed studies 302 and 303, with populations enriched for responders, that failed to show a statistically significant treatment effect?

# FDA Review Team/Contributors

- Anna Park
- Shari Targum
- Jialu Zhang
- Donald Jensen
- Lyudmila Soldatova
- Sreedharan Sabarinath
- Sharon Gershon
- Albert (Tien-Mien) Chen
- Elektra Papadopoulos
- Kenneth Bergmann
- Gerald Podskalny
- Melanie Blank
- James Hung
- Norman Stockbridge
- Ellis Unger
- Robert Temple



**Thank you**