Introductory Remarks: Psychopharmacologic Drugs Advisory Committee March 27, 2018

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Outline

- Rationale for management of withdrawal syndrome (aka “detoxification treatment”)
- Historical context
- Development history
- Today’s focus

Clinical Relevance of Mitigation of Withdrawal Symptoms in OUD

- Goal of “detox” is to reach a state of not being physically dependent on opioids
- Clinical objective is to minimize unpleasant subjective experience while ceasing physical dependence on opioid to encourage patient to reach the goal
- If patient does not complete opioid discontinuation, then treatment goal has not been reached
- The clinical importance of a product’s ability to mitigate withdrawal symptoms (indication 1) is confirmed by patient’s success in completing opioid discontinuation (indication 2)

Need for Symptomatic Treatment of Withdrawal for Patients with OUD

- Obstacle to seeking treatment
- Obstacle to beginning antagonist treatment

Rationale for alpha agonists

- Clonidine 1974
- Oral naltrexone 1984
- Lofexidine
  - Putative benefit of lofexidine over clonidine

Development history

- IND opened 1995
- Pilot study
- Dose selection: 3.2 mg (vs previously-studied dose: 1.6 mg)
- Signs vs symptoms
- More dose-finding

Today’s focus

- Two claims, or just verification of one?
- Dose recommendations
- Available data vs data gaps

Clinical and Statistical Review of Lofexidine

NDA 209229

FDA Presentation
Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting
March 27, 2018

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Outline

- Introduction
- Therapeutic Context
- Clinical Relevance of Proposed Indications
- Efficacy
  - Phase 3 pivotal, Double-Blind (DB), Placebo-Controlled (PC) study (3002)
  - Phase 3 pivotal, Double-Blind (DB), Placebo-Controlled (PC), Dose-ranging study (3003-1)
- Safety
- Conclusions

Lofexidine Overview

- Lofexidine 0.18 mg (lofexidine HCl 0.2 mg) tablets
- Proposed Indication:
  - mitigation of symptoms associated with opioid withdrawal
  - facilitation of completion of opioid discontinuation treatment
- Proposed Dosing:
  - 0.72 mg (4 tablets) four times a day for seven days (equivalent to the 3.2 mg per day regimen)
- Marketed in the UK since 1992 as Britlofex; recommended maximum dose is 2.4 mg per day in 3 to 4 divided doses
  - Customary dose/regimen 1.6-2.2 mg per day

Pharmacokinetics

- Absorption: Tmax ~ 3 h, F ~ 72% (solution), dose proportional (1, 2, and 4 tablets), no food effect
- Metabolism: major contributor CYP2D6, with less contribution from 1A2 and 2C19
- Elimination: t1/2 11-20 h; primary route of elimination of the parent and its metabolites is via the kidney (93.5% of dose recovered in urine over 144 hr); renal elimination of unchanged drug accounts for ~ 15-20% of the administered dose

Physical Dependence on Opioids

- Expected physiological response to chronic exposure
- Down-regulation of endogenous endorphins and dynorphins
- Occurs in the setting of illicit use of unregulated opioid substances as well as prescribed use of regulated opioid products

Opioid Withdrawal

- DSM 5 criteria- cessation or reduction in opioid use and at least 3 of the following signs or symptoms:
  - Dysphoric moods
  - Nausea or vomiting
  - Muscle aches
  - Lacrimation or rhinorrhea
  - Pupillary dilation, piloerection, or sweating
  - Diarrhea
  - Yawning
  - Fever
  - Insomnia

Current Treatment Options

Product Name	Relevant Indication	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Methadone	For detoxification treatment of opioid addiction (heroin and other morphine-like drugs)	Oral, 40 mg per day in divided doses, gradual taper	Not described in product label	Respiratory depression, misuse and diversion, QT prolongation	Restricted to use in a certified opioid treatment program or inpatient setting
Buprenorphine /naloxone	Used off label for withdrawal management	Up to 8/2 mg to 16/4 mg SL per day (Suboxone and its generics), taper	Not approved for withdrawal management	Respiratory depression, misuse and diversion	
Clonidine	Used off label for withdrawal management	75-300 ug tid	Not approved for withdrawal management	Rebound hypertension, hypotension, bradycardia	

U.S. Outpatient Utilization of Clonidine IR

- According to office-based physician survey data*, approximately 75,000 drug use mentions‡ (3% of total mentions) for clonidine IR tablets were associated with opioid related disorders in 2017
- Prescribing of total clonidine IR was stable over 2013-2017^
- Data limited to outpatient retail pharmacy settings; does not cover clinics, addiction centers or hospitals

*Syneos HealthTreatment Answers™ 2017. Data extracted February 2018.
‡ The term " drug use mentions" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use mention" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
^Total prescriptions dispensed for any indication. IQVIA, National Prescription Audit (NPA) Enhanced. 2013-2017, Data Extracted February 2018.

Patient Selection: Non-opioid Withdrawal Management

- Are not candidates for agonist treatment
- Desire treatment with antagonist medications or other treatments (both existing and future)
- Are discontinuing agonist treatment

Clinical Relevance in Opioid Use Disorder Setting

- Proposed Indications
  - Mitigation of symptoms associated with opioid withdrawal
    - Mitigating a recognized condition
    - Benefit demonstrated on SOWS-Gossop
    - Clinical importance is contingent on patient's success in completing opioid discontinuation
  - Facilitation of completion of opioid discontinuation treatment
    - Not a disease or condition
    - Confirms/places into context the clinical benefit measured on the SOWS-Gossop
    - Information about completion rates could be included in the clinical studies section of the product label

Pivotal Studies

Study	Population	Treatment Arms	Treatment Period	Withdrawal Assessment Instrument	Protocol-specified Primary Endpoint	Protocol-specified Dropout/ Completer Endpoint	FDA Endpoints
3002	OUD and physical dependence to heroin or short-acting opioids	Placebo LFX 3.2 mg/day	5 days	SOWS	SOWS on Day 3	Time to dropout through Day 5	SOWS from Days 1 to 5, CS on Day 5
3003-1		Placebo LFX 2.4 mg/day LFX 3.2 mg/day	7 days		SOWS from Days 1 to 7	CS on Day 7	

OUD: Opioid use disorder
SOWS: SOWS-Gossop scores
CS: Completion status
LFX: Lofexidine

SOWS-Gossop

	Score[a]			
Condition	**None**	**Mild**	**Moderate**	**Severe**
Feeling sick	0	1	2	3
Stomach cramps	0	1	2	3
Muscle spasms/twitching	0	1	2	3
Feeling of coldness	0	1	2	3
Heart pounding	0	1	2	3
Muscular tension	0	1	2	3
Aches and pains	0	1	2	3
Yawning	0	1	2	3
Runny eyes	0	1	2	3
Insomnia/problems sleeping	0	1	2	3

[a] Possible score range = 0 to 30.

EFFICACY

Outline

- Study 3002
  - Overview of study design and analysis plan
  - Efficacy results
- Study 3003-1
  - Overview of study design and analysis plan
  - Efficacy results
- Impact of Missing Data
- Conclusions

Study 3002

Study	Population	Treatment Arms	Treatment Period	Withdrawal Assessment Instrument	Protocol-specified Primary Endpoint	Protocol-specified Dropout/ Completer Endpoint	FDA Endpoints
3002	**OUD and physical dependence to heroin or short-acting opioids**	**Placebo LFX 3.2 mg/day**	**5 days**	**SOWS**	**SOWS on Day 3**	**Time to dropout through Day 5**	**SOWS from Days 1 to 5, CS on Day 5**
3003-1		Placebo LFX 2.4 mg/day LFX 3.2 mg/day	7 days		SOWS from Days 1 to 7	CS on Day 7	

OUD: Opioid use disorder
SOWS: SOWS-Gossop scores
CS: Completion status
LFX: Lofexidine

Baseline Demographics

Characteristic	Placebo (N=130)	Lofexidine (N=134)
Sex, n (%)		
Male	99 (76)	101 (75)
Female	31 (24)	33 (25)
Age (years)		
Mean (SD)	38 (11)	36 (11)
Race, n (%)		
White	76 (59)	63 (47)
Black or African American	27 (21)	37 (28)
Hispanic	27 (21)	34 (25)
Baseline SOWS-Gossop Score (SD)	12 (6)	12 (6)

Subject Disposition

Number of Subjects	Placebo	Lofexidine
Screened		
Randomized	130	134
Completed study, n (%)	35 (27)	50 (37)
Discontinued, n (%)	95 (73)	84 (63)
Lack of efficacy	36 (28)	18 (13)
Adverse event	5 (4)	5 (4)
Evidence of contraband drug use	2 (2)	1 (1)
Therapy with exclusionary drug	1 (1)	0
Lack of compliance	4 (3)	1 (1)
Other	47 (36)	59 (44)
Subject request not related to withdrawal symptoms	45 (35)	54 (40)
Not covered above	2 (2)	5 (3)

Efficacy Analysis

	Applicant	FDA
Primary Endpoints	• SOWS on Day 3 • Time to dropout through Day 5	• SOWS from Days 1 to 5 • Completion status on Day 5
Analysis Methods	• ANCOVA with baseline SOWS and opioid dependence severity based on SCID (Structured Clinical Interview Axis I) • Log rank test	• MMRM with treatment, baseline SOWS, opioid dependence severity, study day, and treatment-by-day interaction • Fisher's exact test

ANCOVA: Analysis of covariance
MMRM: Mixed model repeated measures

Efficacy Analysis

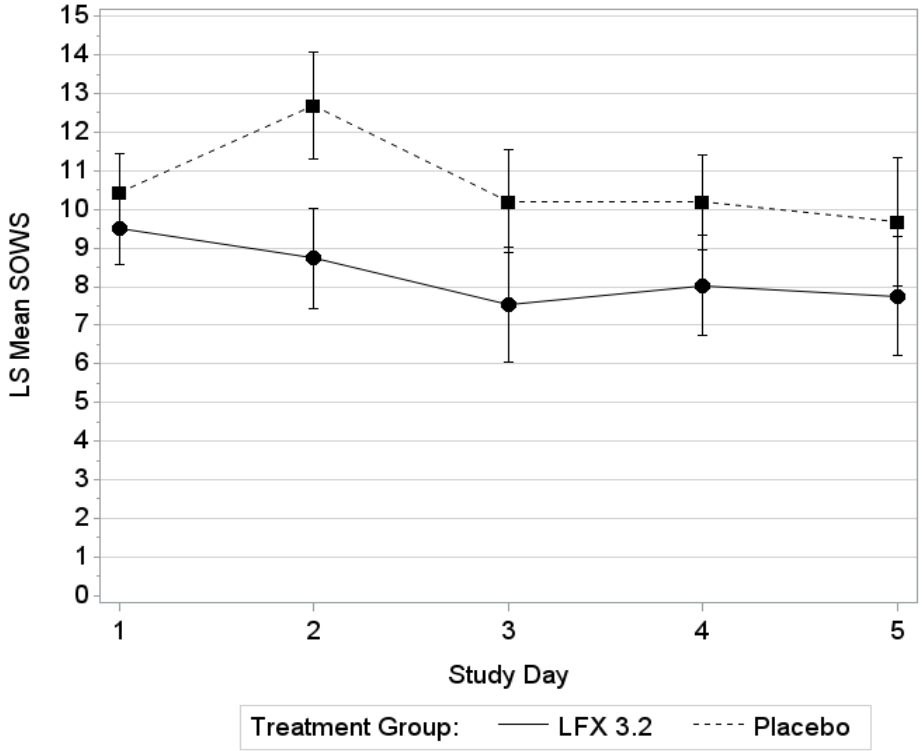
	Applicant	FDA
Missing Data Handling	Multiple imputation assuming missing at random (MAR)	Multiple imputation with placebo mean on Day 2 assuming missing not at random (MNAR)
Multiplicity Adjustment	Bonferroni-Holm method	Bonferroni-Holm method

Applicant Endpoint: SOWS on Day 3

	Placebo	Lofexidine
Mean (SD)	8.6 (5.4)	6.4 (4.7)
Estimated Difference (95% CI)		-2.2 (-3.9, -0.6)
P-value		0.009

SOWS-Gossop scores on Day 3 were analyzed using an ANCOVA model with baseline SOWS and pre-randomization opioid dependence severity.

FDA Endpoint: SOWS Days 1-5

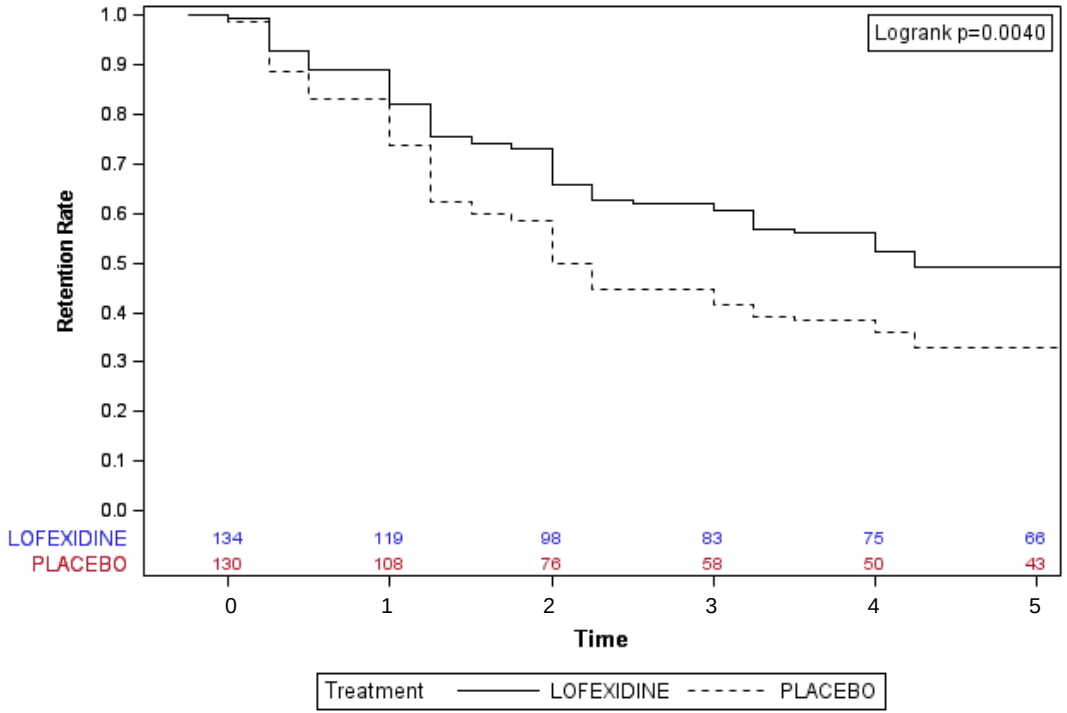


FDA Endpoint: SOWS Days 1-5

	Placebo	Lofexidine
Estimated Mean (95% CI)	10.6 (9.9, 11.4)	8.3 (7.6, 9.0)
Estimated Difference (95% CI)		-2.3 (-3.4, -1.3)
P-value		<0.001

SOWS-Gossop scores Days 1-5 were analyzed using an MMRM model with treatment, baseline SOWS, opioid dependence severity, study day, and treatment-by-day interaction.

Applicant Endpoint: Time to Dropout



FDA Endpoint: CS on Day 5

	Placebo (N=130)		Lofexidine (N=134)		P-value
	N	%	N	%	
Non-completer	87	67	68	51	
Completer	43	33	66	49	0.009

CS: Completion status, defined as a subject who completed the 5-day Treatment Phase and discharged in the first time quadrant of Day 6 or later.
P-value was based on the Fisher's exact test.

Study 3003-1

Study	Population	Treatment Arms	Treatment Period	Withdrawal Assessment Instrument	Protocol-specified Primary Endpoint	Protocol-specified Dropout/ Completer Endpoint	FDA Endpoints
3002	**OUD and physical dependence to heroin or short-acting opioids**	Placebo LFX 3.2 mg/day	5 days	**SOWS**	SOWS on Day 3	Time to dropout through Day 5	**SOWS from Days 1 to 5, CS on Day 5**
3003-1		**Placebo LFX 2.4 mg/day LFX 3.2 mg/day**	**7 days**		**SOWS from Days 1 to 7**	**CS on Day 7**	

OUD: Opioid use disorder
SOWS: SOWS-Gossop scores
CS: Completion status
LFX: Lofexidine

Baseline Demographics

Characteristic	Placebo (N=151)	Lofexidine 2.4 mg (N=229)	Lofexidine 3.2 mg (N=222)
Sex, n (%)			
Male	107 (71)	162 (71)	158 (71)
Female	44 (29)	67 (29)	64 (29)
Age (years)			
Mean (SD)	36 (12)	35 (11)	35 (11)
Race, n (%)			
White	117 (78)	169 (74)	158 (71)
Black or African American	26 (17)	54 (24)	48 (22)
Asian	1 (1)	1	3 (1)
American Indian or Alaska Native	2 (1)	0	2 (1)
Native Hawaiian or Other Pacific Islander	3 (2)	0	2 (1)
Other	2 (1)	5 (2)	9 (4)
Ethnicity, n (%)			
Hispanic or Latino	22 (15)	33 (14)	28 (13)
Not Hispanic or Latino	129 (85)	196 (86)	194 (87)
Baseline SOWS-Gossop Score (SD)	10 (7)	10 (7)	10 (7)

Subject Disposition

Number of Subjects	Placebo	Lofexidine	
		2.4 mg	3.2 mg
Randomized and treated	151	229	222
Completed DB phase, n (%)	42 (28)	95 (41)	88 (40)
Discontinued DB phase, n (%)	109 (72)	135 (59)	134 (60)
Lack of efficacy	53 (35)	44 (19)	30 (14)
Adverse event related to study drug	2 (1)	15 (7)	30 (14)
Adverse event unrelated to study drug	0	0	3 (1)
Evidence of contraband drug use	4 (3)	4 (2)	4 (2)
Therapy with exclusionary drug	0	1	1
Lack of compliance	5 (4)	7 (3)	3 (1)
Other	45 (30)	64 (28)	63 (28)
Withdrew consent	18 (12)	30 (13)	36 (16)
Subject request	15 (10)	14 (6)	17 (8)
Lack of efficacy (e.g. intensive craving)	1 (1)	10 (4)	2 (1)
Withdrew consent and left against medical advice	5 (4)	5 (2)	3 (1)
Adverse event	4 (3)	2 (1)	2 (1)
Completed detox	2 (1)	3 (1)	2 (1)
Lack of compliance	0	0	1

Reclassified Subject Disposition

Number of Subjects	Placebo	Lofexidine	
		2.4 mg	3.2 mg
Randomized	151	229	222
Completed DB phase, n (%)	42 (28)	95 (41)	88 (40)
Discontinued DB phase, n (%)	109 (72)	135 (59)	134 (60)
Lack of efficacy	54 (36)	54 (23)	32 (14)
Adverse event	6 (4)	17 (7)	35 (15)
Evidence of contraband drug use	4 (3)	4 (2)	4 (2)
Therapy with exclusionary drug	0	1	1
Lack of compliance	5 (4)	7 (3)	4 (1)
Other	40 (26)	52 (23)	58 (26)
Withdrew consent	18 (12)	30 (13)	36 (16)
Subject request	15 (10)	14 (6)	17 (8)
Withdrew consent and left against medical advice	5 (4)	5 (2)	3 (1)
Completed detox	2 (1)	3 (1)	2 (1)

Efficacy Analysis

	Applicant	FDA
Primary Endpoint	• SOWS from Days 1 to 7	• SOWS from Days 1 to 5
Secondary Endpoint	• Completion status on Day 7	• Completion status on Day 5
Analysis Methods	• MMRM with treatment, baseline SOWS, sex, study day, and treatment-by-day interaction • Logistic regression with treatment and sex	• MMRM with treatment, baseline SOWS, sex, study day, and treatment-by-day interaction • Fisher's exact test

Efficacy Analysis

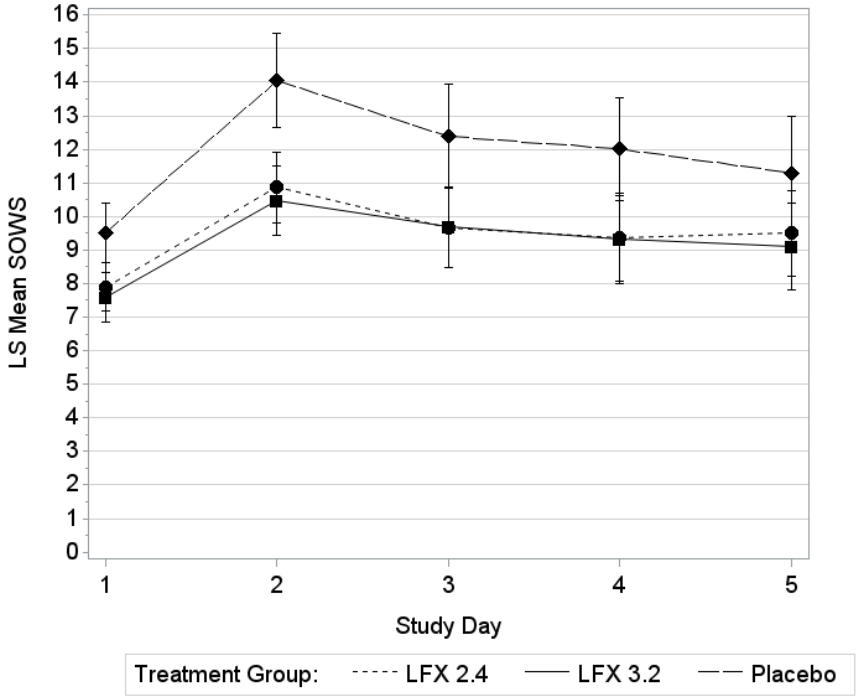
	Applicant	FDA
Missing Data Handling	Control-based pattern imputation assuming MNAR	Multiple imputation with placebo mean on Day 2 assuming MNAR
Multiplicity Adjustment	Sequential testing in the order of 1) primary, LFX 3.2 vs placebo 2) primary, LFX 2.4 vs placebo 3) secondary, LFX 3.2 vs placebo 4) secondary, LFX 2.4 vs placebo	Sequential testing in the order of 1) primary, LFX 3.2 vs placebo 2) primary, LFX 2.4 vs placebo 3) secondary, LFX 3.2 vs placebo 4) secondary, LFX 2.4 vs placebo

Applicant Endpoint: SOWS Days 1-7

	Placebo	LFX 2.4	LFX 3.2
Estimated Mean (95% CI)	1.8 (1.6, 2.0)	1.6 (1.5, 1.8)	1.6 (1.4, 1.7)
Estimated Difference (95% CI)		-0.2 (-0.4, -0.04)	-0.3 (-0.4, -0.1)
P-value		0.017	0.003

The estimates and p-values were based on the log scale using an MMRM model with treatment, baseline SOWS, sex, study day, and treatment-by-day interaction.

FDA Endpoint: SOWS Days 1-5



- Evidence of efficacy for both doses
- No statistically significant difference between doses

FDA Endpoint: SOWS Days 1-5

	Placebo	LFX 2.4	LFX 3.2
Estimated Mean (95% CI)	2.3 (2.2, 2.4)	2.0 (1.9, 2.1)	2.0 (1.9, 2.0)
Estimated Difference (95% CI)		-0.3 (-0.4, -0.1)	-0.3 (-0.4, -0.2)
P-value		<0.001	<0.001

The estimates and p-values were based on the log scale using an MMRM model with treatment, baseline SOWS, sex, study day, and treatment-by-day interaction.

Applicant Endpoint: CS on Day 7

	Placebo (N=151)		LFX 2.4 (N=229)		LFX 3.2 (N=222)	
	N	%	N	%	N	%
Non-completer	109	72	134	59	134	60
Completer	42	28	95	41	88	40
OR (95% CI)			1.9 (1.2, 2.9)		1.7 (1.1, 2.7)	
P-value			0.007		0.019	

CS: Completion status
P-values were based on a logistic regression model with treatment and sex.

FDA Endpoint: CS on Day 5

	Placebo (N=151)		LFX 2.4 (N=229)		LFX 3.2 (N=222)	
	N	%	N	%	N	%
Non-completer	102	68	124	54	118	53
Completer	49	32	105	46	104	47
P-value			0.010		0.007	

CS: Completion status
P-values were based on Fisher's exact test.

Impact of Missing Data

- Consistent results across studies
  - More subjects on lofexidine completed opioid discontinuation
    - Study 3002: 33% (placebo) vs 49% (LFX) completed through Day 5
    - Study 3003-1: 32% (placebo) vs ~46% (LFXs) completed through Day 5
  - Greater improvement on withdrawal symptoms compared to placebo
- Sensitivity analyses supported primary efficacy findings

Efficacy Conclusions

- Evidence of efficacy
  - Mitigation of withdrawal symptoms
  - Completion of opioid discontinuation
- No difference between doses in Study 3003-1

SAFETY

Pooling of Phase 3 Studies

- Controlled Period of Phase 3 Studies
  - Pivotal studies 3002 and 3003-1 and
  - Study 3001: R, DB, PC study of 3.2 mg lofexidine, N=35 and placebo, N=33
- All Phase 3 Studies
  - Studies 3002, 3003-1, 3001 and
  - 3003-2, an open-label safety study of 3.2 mg lofexidine for up to 7-14 days, N=286

Exposure

Safety Database for Lofexidine Individuals exposed to any Lofexidine dose in this development program for the indication under review N=1,276			
Clinical Trial Groups	**LFX 2.4 mg/day**	**LFX 3.2 mg/day**	**Placebo**
Controlled trials	229	390	313
All Phase 3 Studies	229	676	313
Day 1	229	676	312
Day 2	196	566	217
Day 3	148	456	152
Day 5	106	372	99
Day 7	96	258	-
Day 10	30	58	-
Day 14	7	24	-

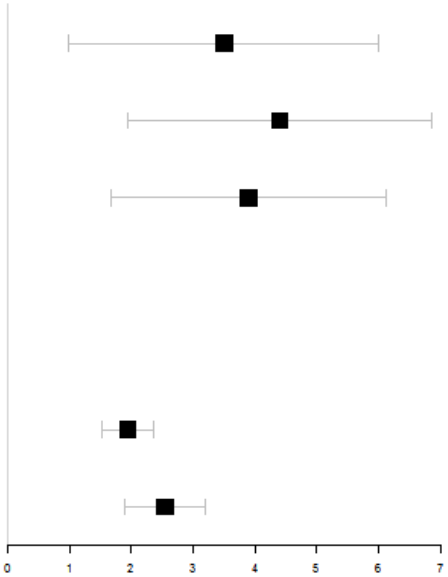
Exposure in Controlled Period of Phase 3 Studies

Exposure to Study Drug (days)

Treatment	Mean
Placebo	3.5
LFX 2.4	4.4
LFX 3.2	3.9

Average Daily Dose (mg)

Treatment	Mean
LFX 2.4	1.94
LFX 3.2	2.54



mean ± standard deviation

Fatal Serious Adverse Event (SAE)

- 34-year old female died of an overdose of heroin, cocaine and fentanyl 3 days after completing 7 days of lofexidine 3.2 mg in study 3003-1

Non-fatal SAEs

- No SAEs in 2.4 mg group
- In 3.2 mg group, 0.8% subjects had syncope, 0.8% bradycardia, 0.5% hypotension
- Bradycardia and hypotension events all classified as serious because of hospitalization for stabilization of vital signs
- One cerebrovascular accident and one manic episode with psychosis in OL study

Discontinuations Due to AE Controlled Period Phase 3 Studies

MedDRA PT	LFX 2.4 N= 229	LFX 3.2 N=390	Placebo N=313
	n subjects (%)	n subjects (%)	n subjects (%)
Any TEAE	45 (20%)	71 (18%)	61 (19%)
Hypotension	3 (1%)	10 (3%)	0
Bradycardia	0	13 (3%)	1 (<1%)
Dizziness	8 (3%)	7 (2%)	1 (<1%)
Insomnia	7 (3%)	7 (2%)	7 (2%)
Diarrhea	5 (2%)	6 (2%)	13 (4%)
Orthostatic hypotension	3 (1%)	7 (2%)	1 (<1%)
Pain	3 (1%)	6 (2%)	10 (3%)
Anxiety	4 (2%)	3 (1%)	10 (3%)
Myalgia	5 (2%)	3 (1%)	4 (1%)
Withdrawal Syndrome	2 (1%)	3 (1%)	5 (2%)
Drug Withdrawal Syndrome	2 (1%)	4 (1%)	4 (1%)
Syncope	1 (<1%)	4 (1%)	0
Somnolence	1 (<1%)	4 (1%)	1 (<1%)
Restlessness	1 (<1%)	4 (1%)	6 (2%)
Nausea	5 (2%)	1 (<1%)	12 (4%)
Vomiting	4 (2%)	2 (<1%)	14 (4%)

Discontinuations Due to AE Study 3003-1

MedDRA PT	LFX 2.4 mg % N= 229	LFX 3.2 mg % N=222
Bradycardia	0	5
Hypotension	1	3
Orthostatic Hypotension	1	3
Insomnia	2	3
Somnolence	<1	2
Syncope	<1	1
Myalgia	2	<1
Nausea	2	<1
Pain	1	2

Study 3003-1 Doses Withheld

		LFX 2.4 mg % N=229	LFX 3.2 mg % N=222	Placebo % N=151
Protocol-specified	Dose withheld	35	44	7
	Subject refusal	6	5	4
	TEAE	<1	3	0
	SBP [1]	9	9	0
	HR [2]	4	12	2
	Symptomatic hypotension or bradycardia [3]	9	13	0
	Orthostasis [4]	8	14	0

1 recumbent SBP <90 mmHg and >20% below screen value
2 <50 bpm and >20% below screen value
3 lightheadedness, dizziness, syncope
4 >25% below recumbent values

AEs Study 3003-1

Preferred Term	LFX 2.4 mg % N=229	LFX 3.2 mg % N=222	Placebo % N=151
Insomnia	51	55	48
Orthostatic Hypotension	29	42	5
Bradycardia	24	32	5
Hypotension	30	30	1
Dizziness	19	23	3
Somnolence	11	13	5
Sedation	13	12	5
Dry Mouth	10	10	0
Tinnitus	1	3	<1
Syncope	1	1	0

Vital Signs

- SBP and HR are lowered by 10 mmHg systolic and 4 bpm resting respectively
- Incidence of potentially clinically significant decreases in BP and HR higher in 3.2 mg compared to 2.4 mg group
- Rebound hypertension
  - only evaluated at 3.2 mg dose
  - peaks at day 2 (43% of subjects)
  - taper did not mitigate rebound

Clinically Significant Vital Signs

	LFX 2.4 mg % N = 229	LFX 3.2 mg % N = 390	Placebo % N = 313
Systolic BP < 70 mm Hg and > 20% below baseline	2	8	0
Diastolic BP < 40 mmHg and > 20% below baseline	1	3	1
Pulse rate < 40 bpm and > 20% below baseline	0	<1	0

Laboratory Values

- Higher incidence of shifts to increased prothrombin time (1-<3x upper limit of normal (ULN))
- Higher incidence of AST and ALT elevations (3-5X ULN)
- Very few subjects, clinical significance not established

Cardiac Electrophysiology

- Lofexidine prolongs the QTc interval
- No dose-response observed between 2.4 mg/day and 3.2 mg/day
- One PM torsade de pointes case after lofexidine administration
- Lofexidine and methadone
  - Further QTcF increase when coadministered with methadone
  - Three cases of clinically significant QTc prolongation when co-administered with methadone

Clinical Conclusions

- The efficacy data provide evidence that lofexidine mitigates symptoms of opioid withdrawal to a clinically relevant extent at both doses studied
- The risks of hypotension, bradycardia and syncope at the 3.2 mg dose exceed the 2.4 mg dose to a clinically important degree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