A Randomized Open-Label Study Comparing Rapid and Standard Inductions to Injectable Buprenorphine Extended-release (BUP-XR) Treatment

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Disclosures

Rajinder Shiwach: Member of study steering committee and principal investigator on several clinical trials for Indivior.

Bernard Le Foll: Participant in National Advisory Board for Indivior Canada; received funding and participated in steering committee for this Indivior trial; received funding to support projects for Indivior Canada, Canopy Growth Corporation, Pfizer, Bioprojet Pharma, Alcohol Countermeasure Systems, Alkermes and Universal Ibogaine; consultant for Shinogi; received in-kind donations of cannabis products, vareniciline for smoking cessation, and coil for Transcranial Magnetic Stimulation study for Aurora Cannabis Enterprises Inc, Pfizer Inc. Bioprojet Pharma, and Brainsway.

Kelly Dunn: Provided consult on protocols and/or steering committee participation for Indivior, Mind Med Inc., Cessation Therapeutics, and DemeRx; Site co-investigator for Phase I multi-site RCT of product with novel mechanism of action (no direct overlap with this work) for Indivior.

Hannu Alho: Member of steering committee for Indivior, and Key Opinion Leader board for Adial Pharma (honorarium received for the service).

Stephanie Strafford, Yue Zhao, Robert Dobbins: Employed by Indivior.

This study was sponsored by Indivior. These data address treatment regimens that are not currently part of the Prescribing Information for this product.

Background

- Buprenorphine (BUP) extended-release is a long-acting injectable formulation indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal (TM) buprenorphine containing product for a minimum of 7 days.[1,2]
- Patients who use intravenous drugs, very high doses of opioids, or highly potent synthetic opioids have an increased risk of treatment failure and opioid overdose.[3]
- In high-risk populations, rapid induction onto extended-release BUP in a single day might reduce barriers to treatment and improve patient retention.[4]

1. Prescribing Information for SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use, CIII. Revised August 2022.
2. Product monograph for SUBLOCADE (buprenorphine extended-release injection). July 5, 2022.
3. Lee, K. et al. Real-world evidence for impact of OAT on non-fatal overdose in patients with OUD during the COVID-19 pandemic. *J Addict Med*. 2023. EPub Aug 11.
4. Mariani, J. et al. Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl. *Am J Addict*. 2021;5:470-476.

Aim

Evaluate treatment retention using standard induction (SI) vs rapid induction (RI) onto BUP-XR injection in treatment-seeking participants who frequently inject opioids or use fentanyl or high doses of opioids (high-risk patients)

Methods

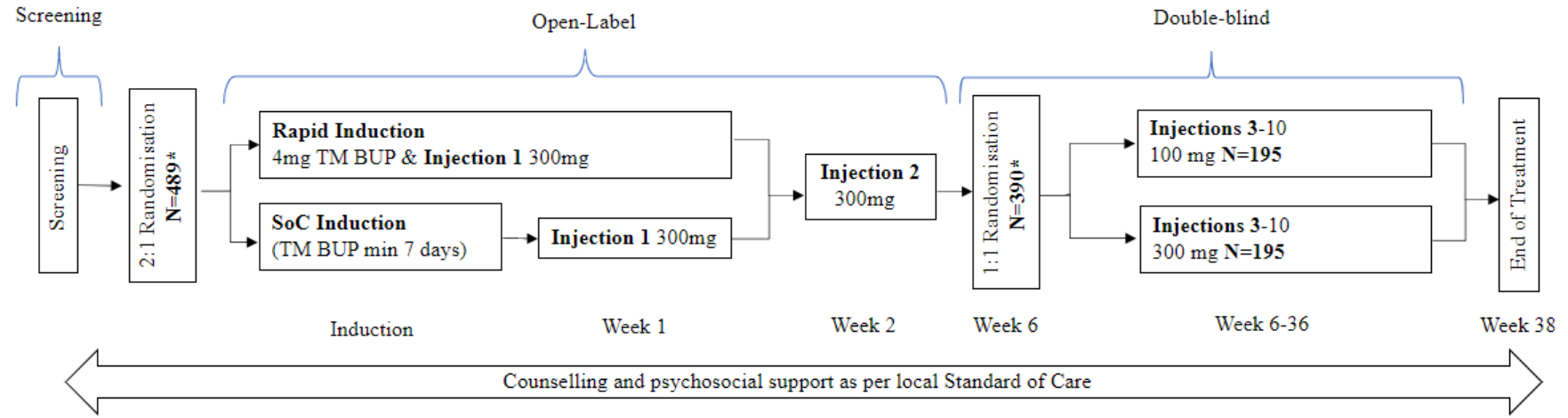
Inclusion criteria

- Age ≥18 years
- Diagnosis of moderate to severe OUD
- Meets at least 1 of these criteria for high-risk opioid use at the Screening visit:
  - using opioids via the injection route for an average of 5 or more days per week in the last 4 weeks
  - using at least 500 mg IV heroin equivalent or self-reported use of any dose of highly potent synthetic opioids (fentanyl and analogues excluding transdermal patches) for an average of 5 or more days per week in the last 4 weeks by any route
- Seeking treatment of OUD with medication
- Not pregnant and using highly effective methods of contraception

Randomization was stratified by the same-day urine drug screen fentanyl result (98/140 positive).

This is an interim analysis of a study that commenced October 26, 2021 (NCT04995029).

Study Design



** Assumes a 20% discontinuation rate after the 1st RBP-6000 injection and prior to the third injection of RBP-6000.*

BUP=buprenorphine; min=minimum; TM=transmucosal

Open-Label Objective: compare the treatment retention of all participants inducted onto BUP-XR using Standard (SI) vs Rapid Induction (RI)

At interim analysis (n=120), the criterion of Non-Inferiority was the probability of retention rate difference (RI – SI) > -10% being 96% or greater.

Demographics and Baseline Characteristics

	Fentanyl POS Subpopulation (N=96)			Fentanyl NEG Subpopulation (N=41)			Overall (N=137)		
	SI (N=35)	RI (N=61)	Total (N=96)	SI (N=13)	RI (N=28)	Total (N=41)	SI (N=48)	RI (N=89)	Total (N=137)
Age, years, Mean (SD)	42 (12)	44 (11)	44 (11)	44 (14)	45 (11)	45 (12)	43 (12)	44 (11)	44 (11)
Sex, Male, n (%)	13 (37)	42 (69)	55 (57)	9 (69)	19 (68)	28 (68)	22 (46)	61 (69)	83 (61)
Race, n (%)									
Black or African American	10 (29)	18 (30)	28 (29)	4 (31)	13 (46)	17 (42)	14 (29)	31 (35)	45 (33)
White	24 (69)	42 (69)	66 (69)	9 (69)	15 (54)	24 (59)	33 (69)	57 (64)	90 (66)
Other	1 (3)	1 (2)	2 (2)	0	0	0	1 (2)	1 (1)	2 (2)
Opioid Lifetime Use, years	13 (10)	18 (11)	16 (11)	18 (13)	16 (8)	17 (10)	15 (11)	17 (10)	17 (10)
Opioid Use Last 4 Weeks, days	27 (2)	28 (0)	28 (1)	28 (0)	27 (2)	28 (2)	28 (2)	28 (1)	28 (2)
Main Route Last 4 Weeks, n (%)									
Injection	11 (31)	15 (25)	26 (27)	9 (69)	14 (50)	23 (56)	20 (42)	29 (33)	49 (36)
Smoking	10 (29)	22 (36)	32 (33)	1 (8)	7 (25)	8 (20)	11 (23)	29 (33)	40 (29)
Oral	1 (3)	1 (2)	2 (2)	1 (8)	3 (11)	4 (10)	2 (4)	4 (5)	6 (4)
Snorting	13 (37)	23 (28)	36 (38)	2 (15)	4 (14)	6 (15)	15 (31)	27 (30)	42 (31)

Data are mean (SD) unless otherwise indicated.

Primary Endpoint: Treatment Retention at Injection 2

- RI is non-inferior to SI (prob of RI non-inferior to SI ≥98%).
- The observed treatment retention was numerically higher in the RI arm in both the overall population and among participants who were fentanyl positive on the day of induction.

	Fentanyl POS Subpopulation		Fentanyl NEG Subpopulation		Overall	
Category	SI (N=34)	**RI (N=60)**	SI (N=13)	**RI (N=25)**	SI (N=47)	**RI (N=85)**
Proportion of participants who received Injection 2 (n/N)	52.9% (18/34)	**65.0% (39/60)**	76.9% (10/13)	**72.0% (18/25)**	59.6% (28/47)	**67.1% (57/85)**
Difference on retention rate at Injection 2 - (RI - SI) (95% HPD)		**11.6% (-8.2, 31.7)**		**-2.8% (-30.1, 24.8)**		**7.5% (-8.7, 24.5)**
Probability of RI non-inferior to SI, ie, (RI – SI) > -10%		**98.2%**		**68.5%**		**98.2%**
Probability of RI superior to SI, ie, (RI – SI) > 0		87.0%		40.8%		80.9%

HPD=highest posterior density region; RI=rapid induction; SD=standard deviation; SI=standard of care.

Secondary Endpoint 2: Precipitated Opioid Withdrawal (POW) Up to Injection 2

- Percent of participants with POW was similar between RI and SI → RI does not increase POW.
- Most participants who reported POW were fentanyl positive (21/23) → POW appears to be a fentanyl issue.
- Most participants reported POW after TM BUP (RI: n=10 vs SI: n=7).

n (%)	Fentanyl Positive (N=96)		Fentanyl Negative (N=41)		Overall (N=137)		
Category (Participants with)	SI (N=35)	**RI (N=61)**	SI (N=13)	**RI (N=28)**	SI (N=48)	**RI (N=89)**	Total (N=137)
TEAE reported as opioid withdrawal symptom	9 (25.7)	**15 (24.6)**	1 (7.7)	**2 (7.1)**	10 (20.8)	**17 (19.1)**	27 (19.7)
TEAE reported as precipitated opioid withdrawal symptom	8 (22.9)	**13 (21.3)**	0 (0.0)	**2 (7.1)**	8 (16.7)	**15 (16.9)**	23 (16.8)

Concomitant Medication

A higher % of SI participants (100%) used medications to treat withdrawal symptoms vs RI (33.3%) on first day of induction.

- All participants who used concomitant medications were in the fentanyl positive subpopulation.
- The most common medications were clonidine, ondansetron, loperamide, and trazodone.

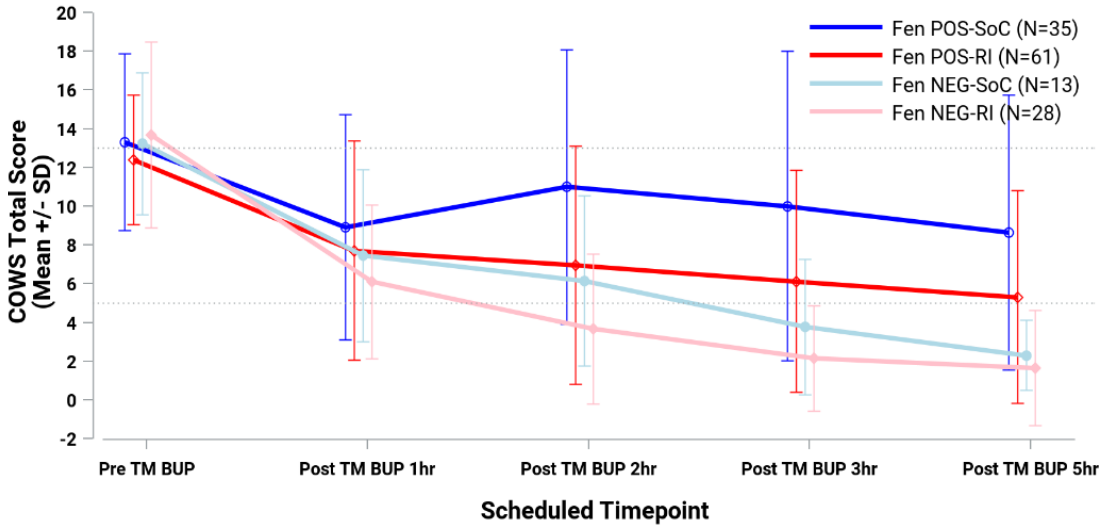
Retention After Precipitated Withdrawals (Overall, RI: n=15 vs SI: n=8)

Retention of participants after POW was higher for RI than SI

- Injection 1: RI 80.0% vs SI 37.5%
- Injection 2: RI 53.3% vs SI 37.5%
- Injection 3: RI 53.3% vs SI 37.5%

Secondary Endpoint 3: COWS Scores on Induction Day

- The response of opioid withdrawal symptoms was comparable for SI and RI overall.
- COWs scores tended to be lower in RI vs SI during induction.
  - RI received TM BUP, then BUP-XR at 1 hour.
  - SI received TM BUP (no BUP-XR).
- Fentanyl positive participants tended to have higher COWS scores during induction.



Secondary Endpoint 4: Treatment-Emergent Adverse Events (TEAEs) Up to Injection 2

The TEAE profile up to Injection 2 was comparable for RI and SI.

n (%)	Fentanyl POS subpopulation (N=96)		Fentanyl NEG subpopulation (N=41)		Overall (N=137)		
Category (Participants with)	SI (N=35)	**RI (N=61)**	SI (N=13)	**RI (N=28)**	SI (N=48)	**RI (N=89)**	Total (N=137)
Any TEAE up to Injection 2	14 (40.0)	**20 (32.8)**	4 (30.8)	**6 (21.4)**	18 (37.5)	**26 (29.2)**	44 (32.1)
TM BUP-related TEAEs	7 (20.0)	**8 (13.1)**	0 (0.0)	**2 (7.1)**	7 (14.6)	**10 (11.2)**	17 (12.4)
BUP-XR related TEAEs	6 (17.1)	**10 (16.4)**	3 (23.1)	**2 (7.1)**	9 (18.8)	**12 (13.5)**	21 (15.3)
Serious TEAEs	0 (0.0)	**1 (1.6)**	0 (0.0)	**0 (0.0)**	0 (0.0)	**1 (1.1)**	1 (0.7)
TEAEs leading to discontinuation	0 (0.0)	**2 (3.3)**	0 (0.0)	**2 (7.1)**	0 (0.0)	**4 (4.5)**	4 (2.9)

Secondary Endpoint 4: Treatment-Emergent Adverse Events (TEAEs) Up to Injection 3

In this study, Injection 2 was performed 1 week after the first injection (not 4 weeks).

Injection 2 one week after Injection 1 was well tolerated.

Similar exposure compared to standard dosing, supporting similar safety.

- **Adverse events:** There was a small decline in the number of participants reporting TEAEs after Injection 2 compared to before Injection 2.
  - TEAEs up to Injection 2 (32.1%)
  - TEAEs between Injections 2 and 3 (21.6%)

- **PK:** BUP plasma concentrations were consistent with PK predictions.

Conclusions

- Rapid induction was non-inferior to standard induction.
  - Precipitated opioid withdrawal was not more likely for rapid induction.
  - When POW occurred in rapid induction, events were not more serious, severe, or long-lasting, and did not result in an increased in discontinuation compared to standard induction.
- Administration of BUP-XR Injection 2 as soon as 1 week (rather than 4 weeks) after Injection 1 was well tolerated.

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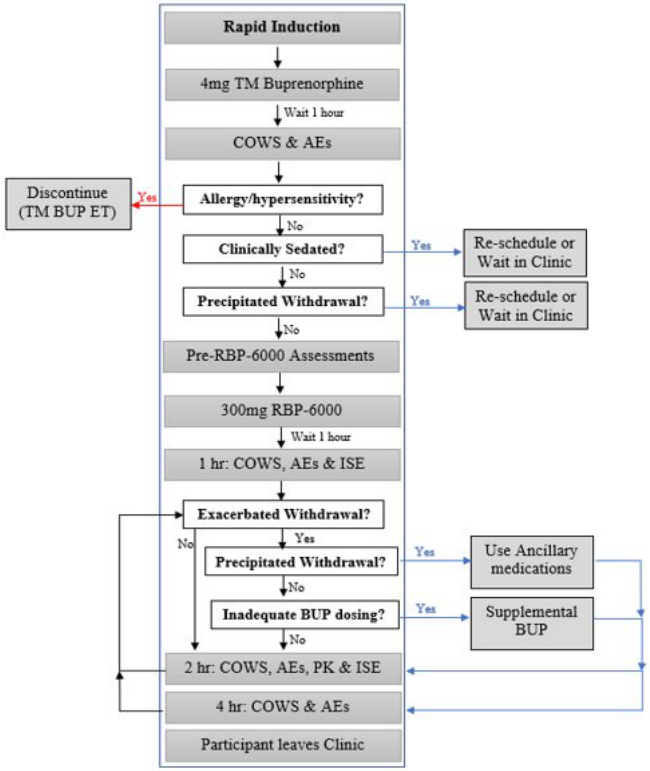
- others

Rapid Induction Dosing Day Procedures



AEs=Adverse Events; BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; ET=Early Termination; ISE=Injection Site Evaluation; PK=pharmacokinetic; TM=transmucosal;

- 4-mg TM buprenorphine dose
- 1 hour later: COWS & AEs
- 300 mg BUP-XR dosing criteria:
  - Does not display any allergic/hypersensitivity reaction
  - No precipitated withdrawal (PW)
  - No sedation
- If PW occurs, reschedule or re-dose later same day.
- Participants will be asked to remain in the clinic for at least 4 hours post-BUP-XR.
- The participant will be followed up via telephone the day after the first BUP-XR
- injection.