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Research Paper

96-week retention in treatment with extended-release subcutaneous buprenorphine depot injections among people with opioid dependence: Extended follow-up after a single-arm trial

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ABSTRACT

Background: The most recent formulation of buprenorphine treatment is extended-release depot injections (BUP-XR) that are administered subcutaneously by health care professionals. This study aimed to observe treatment outcomes of BUP-XR delivered in standard practice during a 96-week follow-up period in a community setting.
Methods: This study is an extension of the CoLAB study, a prospective single-arm, multicentre, open label trial (N=100, 7 sites in Australia) among people with opioid dependence who received monthly injections of BUP-XR to evaluate the retention in treatment. Participants were followed for 96 weeks, comprising 48 weeks of the CoLAB study followed by a 48-week extension.
Results: Of 100 participants at baseline, 47 were retained on BUP-XR at 96 weeks. The median time retained on monthly depot was 90 weeks. Heroin use (adjusted OR=0.19, P=0.012) in the month prior to baseline was associated with lower odds of retention on BUP-XR. Older age at first opioid use (adjusted OR= 1.08, P=0.009) and longer duration in OAT at baseline (adjusted OR= 1.12, P=0.001) were associated with increased retention. Prevalence of past four-weeks opioid use was estimated at 4% at 96 weeks of treatment (prevalence 0.04, 95%CI: 0.00-0.11) compared to 15% at baseline. Quality of life and medication treatment satisfaction improved over time for those retained in treatment.
Conclusion: This is one of the few studies to describe long term (96 week) retention in treatment with BUP-XR in a community setting. It displayed retention rates with 47% of participants completing 96 weeks of treatment with BUP-XR. Patient reported outcomes suggest improvements in client wellbeing.
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Introduction

Opioid dependence remains the leading cause of morbidity and mortality of all drug classes (Degenhardt et al., 2018; UNODC, 2022). Associated risks include overdose, injecting-related harms (e.g., injection related injuries and diseases such as blood-borne viruses), criminal activity, accidental injuries (such as road crash injuries, falls, drowning), interpersonal violence and suicide (Degenhardt et al., 2019).

Buprenorphine and methadone are evidence-based treatments for opioid dependence (Degenhardt et al., 2023; Mattick, Breen, Kimber, & Davoli, 2014) and both are listed in the World Health Organization's Model List of Essential Medicines (World Health Organization, 2021). Recently, extended-release depot formulations of buprenorphine maintenance treatment (BUP-XR), administered subcutaneously by healthcare professionals, have been approved in multiple countries. Two products of this formulation of buprenorphine are available in Australia which can be delivered monthly, Sublocade® (Therapeutic Goods Administration, 2022) and Buvidal® (Therapeutic Goods Administration, 2019a). Lower dose Buvidal® injections for weekly delivery are also available but this study is concerned primarily with monthly-delivered BUP-XR (Lintzeris, Dunlop, & Masters, 2019; Therapeutic Goods Administration, 2019b, 2023). Reduced frequency of dosing has the benefit of greater flexibility and freedoms for clients, particularly in settings where supervised dosing is a common model (as it is in Australia). Removing the requirement for regular clinic attendance for daily dosing allows for other lifestyle activities such as travel, work, and social engagements. Reduced clinic attendance might also reduce treatment stigma and related costs including appointment fees, dosing fees, and transport costs (Barnett et al., 2021; Tran et al., 2022; Treloar et al., 2022; Zahra et al., 2022).

Long-term observations of retention in treatment with the novel delivery of BUP-XR are needed to explore if this type of opioid dependence treatment can help improve outcomes for people with opioid use disorder (OUD). It is necessary to evaluate retention alongside other outcomes impacting quality of life in a real-world setting including a diverse range of community health care providers. Four randomised-control trials have published BUP-XR retention at 6 months with a pooled-estimate of retention in a recent systematic review and meta-analysis of 64% (47%, 82%) (Degenhardt et al., 2023; Haight et al., 2019; Ling et al., 2010; Lintzeris et al., 2021; Lofwall et al., 2018). Most studies of BUP-XR retention published to date have followed up participants for 18 months or less (Andorn et al., 2020; Boyett et al., 2023; Frost et al., 2019; Ling et al., 2020).

This study aimed to describe the outcomes from monthly injections of BUP-XR administered to trial participants of the Community Long-Acting Buprenorphine (CoLAB) trial over 96 weeks from the commencement of the study. Specifically, 1) quantifying the primary outcome of retention in treatment on either formulation of monthly BUP-XR during 96 weeks follow-up, and evaluating factors associated with retention in treatment, 2) describing changes in secondary outcomes, including opioid use, quality of life, medication satisfaction, depression and pain scores during the 96 week study period.

Method

Study design

The CoLAB study was a prospective single-arm, multicentre, open label trial. It followed 100 participants enrolled in seven sites (in three states) across Australia for a 48-week period. The CoLAB study investigational trial endpoint was at 48 weeks. At the end of week 48, all participants regardless of their treatment status were invited to reconsent to participate in the extended follow up with ongoing treatment for a further 48 weeks. During this extended follow-up period, clinicians were no longer required to follow an interventional trial protocol and treatment reverted to usual care, meaning participants could be transferred to other forms of OAT, or could remain on BUP-XR products (Fig. 1). The primary outcome of the study was retention in treatment, consistent with the original study, and secondary outcomes included opioid use, quality of life, medication satisfaction, depression and pain scores.

Data collection

This study included all participants from the original CoLAB trial. Details of the data collection for the original CoLAB study have been described previously (Farrell et al., 2022; Larance et al., 2020). After week 48, participants who provided informed consent for the extended study period were followed up for a further 48 weeks through telephone surveys conducted every eight weeks (weeks 56, 64, 72, 80, 88, and 96). Data on treatment retention including depot injection dates and dosages administered were collected retrospectively reviewing medical records. Participants were reimbursed $50 AUD per survey for their time during the first 48 weeks, as well as during the subsequent 48 to 96 weeks.

Ethics

Written informed consent for the extension study was obtained at the final clinical interview of the CoLAB study (week 48). The CoLAB study and its extension were approved by St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221) and conducted in compliance with Good Clinical Practice regulations and the ethical principles originated from the Declaration of Helsinki, the International Council for Harmonisation guidance, and all applicable local regulations. An independent data and safety monitoring board reviewed the progress of the study. The original CoLAB study is registered with ClinicalTrials.gov, number NCT03809143.

Procedures

Telephone interviews were scheduled to be completed by trained staff every eight weeks. The interviews included safety assessment components, substance use questionnaires and health, economic, and social outcome assessments. Assessment tools administered were the opioid craving visual analogue scale, the Australian Treatment Outcome Profile (ATOP) (Lintzeris et al., 2020; Ryan et al., 2014), Subjective Opiate Withdrawal Scale (SOWS) (Handelsman et al., 1987), Pain intensity, Enjoyment, General activity scale (PEG) (Krebs et al., 2009), Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001), Assessment of Quality of Life (AQoL-4D) (Hawthorne, Korn, & Richardson, 2013), World Health Organization's Health and Work Performance Questionnaire (HPQ) (Kessler et al., 2003), Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson et al., 2004), and Treatment perceptions questionnaire (TPQ) (Marsden et al., 2000). Questions regarding dose adequacy, overdose, and health service utilisation were also included.

Outcomes

Participants were considered to be retained in treatment while they received a monthly BUP-XR injection, either Sublocade® or Buvidal®, within 56 days of their previous dose, as re-induction is unnecessary if the interval between doses is less than 8 weeks (Lintzeris et al., 2019).

Patient reported outcomes were derived from survey responses. Responses to the AQoL-4D quality of life questionnaire were converted to utilities using Stata code available online (Assessment of Quality of Life., 2014). AQoL-4D utility is a health-related quality of life measure ranging from -0.04 to 1.0 with utilities of zero and one intended to indicate quality of life consistent with death and perfect health respectively (Hawthorne & Osborne 2005). Overall satisfaction with medication was based on the global satisfaction scale, derived from questions 12–14, from the TSQM questionnaire. Dichotomous variables were

defined for moderate or severe pain and moderate or severe depression. Moderate or severe pain was assumed for participants who responded to the PEG questionnaire with scores of 4 or above (Roldán-Majewski et al., 2022). Moderate or severe depression was assumed for participants who responded to the PHQ-9 questionnaire with an overall score of 10 or above (Kroenke, Spitzer & Williams, 2001).

Statistical analysis

The retention rate in treatment with monthly BUP-XR was estimated using survival analysis and the Kaplan–Meier curves were presented. Unadjusted logistic regression models were applied to determine the association of demographics, substance use and treatment history and other characteristics at baseline as well as the early outcomes of treatment in the first 12 weeks with retention on BUP-XR at 96 weeks. Odds ratios, confidence intervals, and p-values were reported for each model. A multiple variable logistic regression model was fitted to retention on treatment and baseline variables, utilising a significance level of $p<0.2$ to identify candidate predictors. Subsequently, adjusted odds ratios were estimated using stepwise logistic regression analysis to identify predictors that minimised the Akaike Information Criterion (AIC) value.

Participant reported outcomes were modelled using binomial generalised linear mixed models for dichotomous outcomes and Gaussian linear mixed models for numeric outcomes. Visit number was used as a categorical explanatory variable to enable change from baseline to be inferred as a fixed effect at each 12-weekly visit that these quantities were reported. Aside from the visit number explanatory variable, all models included participant as a random intercept we did not include a site effect or any other covariates. For the numeric outcomes, AQoL utility, global treatment satisfaction with medication and overall satisfaction with treatment, the raw visit number coefficients give the change in the measure from baseline. For the dichotomous outcomes fitted to binomial generalized linear mixed models (GLMMs), exponentiated visit number coefficients give odds ratios for the outcome relative to baseline.

Additionally, corresponding models were fitted with multiple imputation used to impute values for participants lost to follow-up. The chained equations approach to multiple imputation, or fully conditional specification, was used to impute outcomes (van Buuren & Groothuis-Oudshoorn, 2011). We assumed subjects lost to treatment or study follow up did not receive BUP-XR after dropping out. Cluster bootstrapping (Harden, 2011) was used to estimate prevalence of past four-week opioid use, and number of days of opioid use, conditional on use, by resampling subjects with replacement. We used cluster bootstrapping to estimate the sampling variability in these quantities while allowing for the complex data generating mechanism involving both retention and opioid use. Cluster bootstrapping was also used within each imputed dataset for past four-week opioid use from the multiply imputed datasets according to the "MI Boot" approach described by (Schomaker & Heumann, 2018). Analyses using multiple imputation are included in the Appendix only.

All analyses were performed using Stata version 17.0 (StataCorp, 2021) and R software version 4.2.2 (R Core Team, 2022).

Results

Retention in treatment with BUP-XR

A total of 100 participants were recruited in the CoLAB trial, with 77 consenting to stay in the study for an additional 48 months. After 48 weeks, 76 participants were retained on monthly Sublocade, and 47 participants were retained on monthly BUP-XR of either formulation for 96 weeks. All participants who were retained on treatment received Sublocade for 48 weeks, with seven individuals switching to monthly Buvidal at some point between weeks 48 and 96 (Figs. 1 and 2). A greater decline in retention was observed around the time of transitioning participants from the original CoLAB study to the extended follow up period. Out of the 29 dropouts observed after 48 weeks, 12 (41%) occurred during the 48-56 week period, with 5 (42%) of these attributed to a single site (Fig. 3). Median retention time was 90 weeks. Of the 29 participants that discontinued the study between 48 and 96 weeks, 11 received additional BUP-XR doses after being considered to have been not retained because of an interval between doses exceeding 56 days (Fig. 1) and had ongoing contact with the treatment services; three transferred to another form of opioid dependence treatment (one participant transferring to sublingual buprenorphine and two

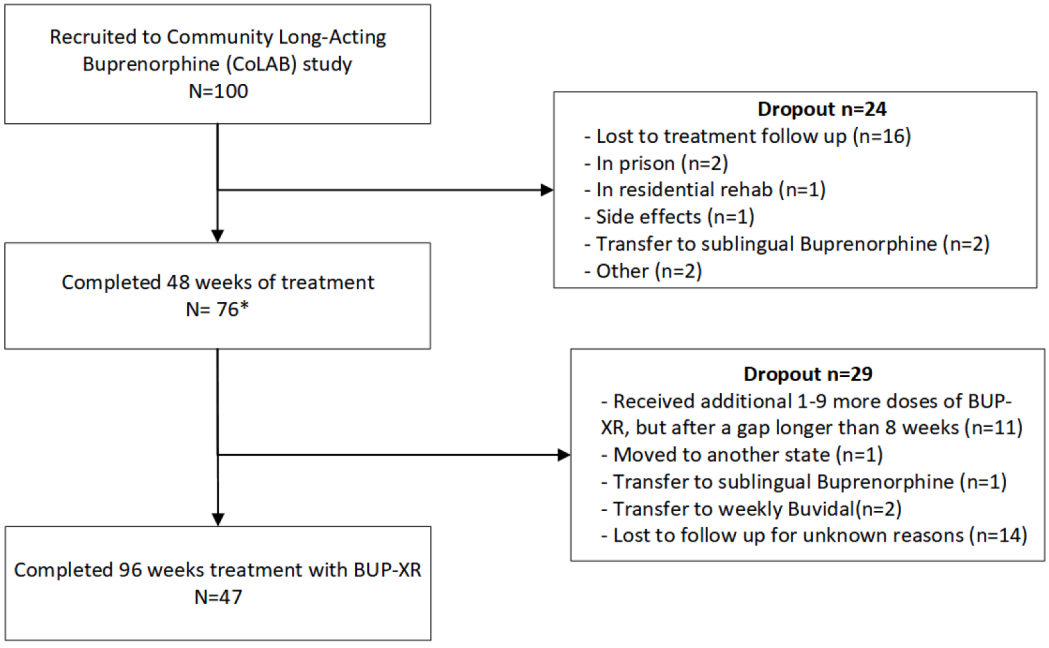

Fig. 1. Flow diagram of participants study involvement and treatment with extended-release buprenorphine BUP-XR
**Retention at 48 weeks reported as 75 in Farrell et al (2022). The difference is due to a different definition of retention used in the current study. Participants that transitioned to monthly injection of Buvidal were not considered as retained in treatment.*

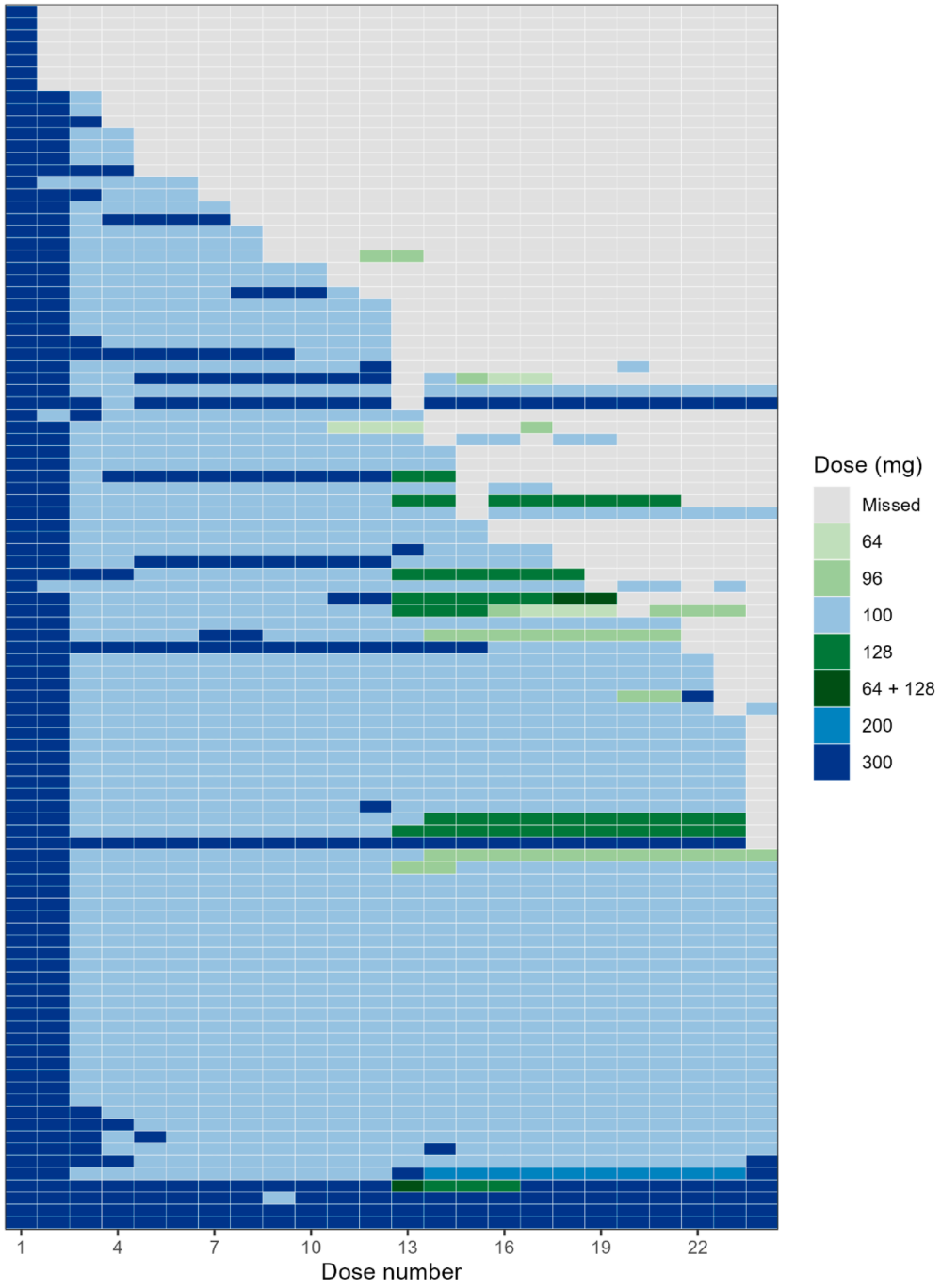

Fig. 2. Heat map showing depot buprenorphine doses received by each participant. The dosage received at each visit is depicted by the colour used to shade the corresponding cell. Sublocade® doses are depicted using a blue scale and Buvidal doses using a green scale. Intervals between doses exceeding 56 days are shaded grey, indicating a missed dose.
Note: One participant received 10 doses of approximately 200 mg by manipulating a 300 mg depot.

participants transferring to weekly Buvidal® injections); one participant moved to another state, and fourteen participants were lost to follow up for unknown reasons. Additional monthly BUP-XR doses are depicted as coloured cells to the right of the first grey cell on the same row in Fig. 2. a total of 11 doses of weekly depot buprenorphine were administered to six participants. Only one participant who switched to weekly Buvidal remained in treatment for 96 weeks but was considered a dropout based on the treatment retention definition.

Unadjusted logistic regression models showed that among the baseline characteristics, younger age, heroin and cannabis use in the past month, non-fatal overdose in the past year, fewer years in OAT prior to commencement of the CoLAB study had lower odds of treatment retention. Regarding the early outcomes of treatment in the first 12 weeks, any self-reported heroin us and injection of any drug had lower odds of treatment retention (Table 1).

The adjusted logistic regression model examined the association between baseline variables and 96 weeks retention in BUP-XR, and included a total sample size of 95 participants. The results revealed that heroin use in the past month (adjusted OR=0.19; 95%CI: 0.05- 0.70, P=0.012) was associated with lower odds of retention on BUP-XR. Older age at first opioid use (adjusted OR= 1.08; 95%CI: 1.02- 1.15, P=0.009) and longer duration in OAT at baseline (adjusted OR= 1.12; 95%CI:

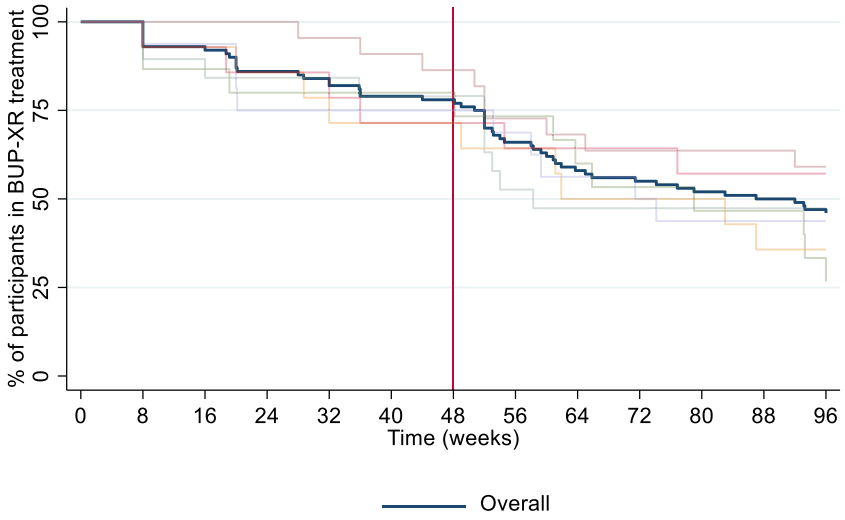

Fig. 3. Kaplan-Meier survival curve for dropout from treatment with extended-release buprenorphine injections, overall (dark) and separate curves for each of the six study sites (faint).

1.05- 1.20, *P*=0.001) were associated with increased retention (Table 2).

Past four-week opioid use

Bootstrapped prevalence of past four-week opioid use (heroin or other opioids) at baseline was estimated at 28 percent (point prevalence 0.28; 95%CI: 0.19-0.36) before declining after the first BUP-XR treatment (Fig. 4, circles). Among participants retained for the full 96 weeks, past four-week opioid use at baseline was 15 percent (point prevalence 0.15; 95%CI 0.09-0.21; Fig. 4, triangles). Over the course of the study, retained participants reported past-four-week opioid use on 135 occasions, including 28 at baseline. These 135 instances of reported past-four-week opioid use consisted of 82 reports of heroin use with no other opioids; 46 reports of no heroin use, but use of other opioids; and 7 reports of use of both heroin and other opioids. Where participants used both opioid categories in the same four-week period, it was unclear whether heroin and other opioids were used on the same days or on different days. Therefore, we assumed the number of days opioids were used was the maximum of heroin days used and other opioids days used. The bootstrapped mean days of use for participants that used opioids in the four weeks prior to baseline was 12 days (95% CI of mean: 8, 16 days). Among participants retained to treatment at 96 weeks, prevalence of opioid use in the final four weeks of the study was 4 percent (prevalence 0.04, 95% 0.00 – 0.11). Participants who used opioids in the four weeks prior to week 48 used on nine days on average (95% CI of mean 1, 21 days). Participants retained to BUP-XR that used opioids in the four weeks prior to week 96 used every day.

Assessment of quality of life

Models fitted to AQoL4D-based utility suggest that participants had significantly higher utility at the end of 48 weeks than at the commencement of the original study. The expected change at 48 weeks, based on survey responses of participants retained to BUP-XR, was 0.08 (95%CI: 0.02–0.13) on the -0.04–1 utility scale. The expected improvement in utility increased to 0.23 by 96 weeks (95%CI 0.16-0.30) (Fig. 5). The estimated increase in utility between baseline and week 96 among retained participants was again statistically significant. These improvements can be compared with an estimated minimal important difference for this measure (Hawthorne & Osborne, 2005) of 0.06.

Medication Satisfaction

Participants' global satisfaction with medication at the time of the first BUP-XR treatment were not considered. Therefore, changes are estimated relative to week 12, by which time participants opinions may have already been established. Mean Global dimension of TSQM at week 12 was 86. Nevertheless, significant increases in satisfaction with treatment from week 12 were estimated at weeks 80 and 96. The expected changes of people retained to treatment was 4.5 (95% CI 0.2, 8.7) at 80 weeks and 7.9 (95%CI 3.3 – 12.4) at 96 weeks (Fig. 5).

Pain

The prevalence of pain, based on a PEG score of four or above, was significantly lower than baseline (point prevalence = 0.46; 95%CI: 0.36 – 0.56) from weeks 24 onwards (Fig. 5). At 48 weeks, the odds that a given participant retained to BUP-XR was experiencing pain was reduced by around 73 percent (OR 0.27; 95%CI: 0.11-0.68) and by 96 percent after 96 weeks of treatment (OR 0.04; 95%CI: 0.01-0.21).

Depression

The prevalence of moderate or severe depression was 42 percent at baseline (point prevalence = 0.42; 95%CI: 0.33–0.52). The odds that a participant retained to BUP-XR treatment was experiencing moderate or severe depression at 48 weeks declined by 62 percent (OR 0.38; 95%CI 0.15-0.96) compared with baseline (Fig. 5). The odds of participants retained to BUP-XR at 96 weeks experiencing moderate or severe depression declined by 99 percent (OR 0.01, 95%CI 0.0–0.13) compared with baseline (Fig. 5).

Although the changes in participant outcomes summarised in Fig. 5 are fitted to retained participants which decline with increasing follow-up time, they summarise changes in individuals from baseline (or week 12 in the case of TSQM) and the fitted models include participant-level random effects which account for differences in scores among individuals for a given follow up time. The same models considering only participants retained for the full 96 weeks were fitted and gave similar results (see Appendix 1). Models for AQoL 4D-based utility, medication satisfaction, pain and depression incorporating multiple imputation for missing values, but otherwise identical to those described above were also fitted. These models were fitted with the intention of possibly providing some indication of bias resulting from loss to follow-up. However, the results obtained from models incorporating multiple

Table 1
Unadjusted logistic regression models for the association of baseline variables and early outcomes of treatment with 96 weeks retention on treatment with extended-release buprenorphine monthly injections (*N*=100).

	N (%)	Odds Ratio	95% CI	*P*-value
Baseline variables				
Demographics				
Age (mean)	44.4 (SD=9.3)	1.07	1.02– 1.12	**0.005**
Female	28 (28%)	0.65	0.27– 1.57	0.337
Born in Australia	88 (88%)	0.40	0.11– 1.42	0.156
Completed year 10 education or more	69 (69%)	1.34	0.57– 3.16	0.497
Main source of income pension or benefit	70 (70%)	0.57	0.24– 1.36	0.207
Present homelessness	27 (27%)	1.06	0.44– 2.58	0.889
Substance use and treatment history				
Age of first opioid use (mean)	23.6 (SD=8.2)	1.05	1.00–1.10	0.059
Past month's substance use				
Heroin use	20 (20%)	0.30	0.10– 0.91	**0.033**
Other non-prescribed opioids	11 (11%)	3.41	0.85– 13.74	0.083
Amphetamine use	23 (23%)	0.68	0.27–1.72	0.419
Cannabis use	35 (35%)	0.37	0.15– 0.88	**0.024**
Alcohol use	50 (50%)	1.08	0.49– 2.38	0.841
Daily tobacco smoking	73 (73%)	0.94	0.39– 2.27	0.889
Injected any drug in past month	28 (28%)	0.42	0.17– 1.06	0.067
Age of first treatment episode (mean)	34.1 (SD=10.1)	1.01	0.98– 1.06	0.346
Years in OAT prior to current study (mean)	8.5 (SD=8.1)	1.07	1.01– 1.13	**0.021**
Non-fatal overdose in the past year	20 (20%)	0.21	0.07– 0.70	**0.011**
Other characteristics				
Moderate to severe depression[1]	42 (42%)	0.66	0.29– 1.47	0.306
Pain[2] (mean)	3.37 (SD=3.0)	0.99	0.87– 1.14	0.944
Quality of Life[3] (mean)	0.53 (SD=0.3)	3.05	0.66– 14.01	0.152
Opioid Craving[4] (mean)	12.9 (SD=21.6)	0.98	0.96– 1.00	0.091
Subjective Opiate Withdrawal Scale (mean)	4.6 (SD=7.2)	0.95	0.88– 1.02	0.150
Mild Clinical Opiate Withdrawal[5]	10 (10%)	0.45	0.11– 1.84	0.266
The early outcomes of treatment in the first 12 weeks				
Any adverse events[6]	80 (80%)	0.40	0.14– 1.10	0.077
Any serious adverse events[7]	8 (8%)	0.65	0.14– 2.90	0.577
Treatment Perceptions[8] (mean score)	32.3 (SD=5.3)	1.01	0.94– 1.10	0.699
Medication Satisfaction[9] (mean score)	85.2 (SD=16.4)	1.03	1.00– 1.06	0.056
Any opioid use[10]	29 (29%)	0.47	0.19– 1.15	0.099
Heroin use[10]	15 (15%)	0.23	0.06– 0.88	**0.032**
Injected any drug[11]	26 (26%)	0.31	0.12– 0.83	**0.020**
Opioid craving (mean score)	8.5 (SD=15.3)	0.97	0.95– 1.01	0.102
Opioid craving (maximum score)	16.5 (SD=27.7)	0.99	0.97– 1.00	0.155
Subjective opiate withdrawal Scale [12]	2.9 (SD=4.0)	0.90	0.80– 1.02	0.091

[1] Assessed by Patient Health Questionnaire (PHQ)-9
[2] Assessed by Pain intensity, Enjoyment, General activity scale, higher score indicates more pain.
[3] Assessed by Assessment of Quality of Life -4 Dimensions (AQoL-4D), higher score indicates higher quality of life.
[4] Assessed by Visual Analogue Scale (VAS), higher score indicates more craving.
[5] Mild clinical opiate withdrawal (Score 5–12) versus no opiate withdrawal (Score <5). No observation of significant withdrawal (Score >12), Assessed by Clinical Opiate Withdrawal Scale (COWS).
[6] Withdrawal symptom, Injection site pain, Injection site itching, Headache, Injection site lump, Constipation, Lethargy, Nausea, Injection site redness, Product leakage due to faulty syringe
[7] Hospitalisation due to pneumonia, two occurrences of worsening COPD in one patient (pre-existing condition), hyperglycaemia (poor diabetes medication compliance), suicidal ideations, radial nerve palsy, exacerbation of pre-existing spinal canal stenosis, psychosis
[8] Assessed by Treatment Perceptions Questionnaire (TPQ), higher score indicates greater satisfaction with treatment.
[9] Assessed by Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction dimension, higher score indicates greater satisfaction.
[10] Based on self-report and urine tests in the first three months.
[11] Based on self-report in the first three months.
[12] Subjective opiate withdrawal scale in month 3 (visit 4), assessed by Subjective Opiate Withdrawal Scale (SOWS).

Table 2
Adjusted logistic regression model for the association of baseline with 96 weeks retention on treatment with extended-release buprenorphine monthly injections (*N*=100).

	Adjusted Model		
	OR	95% CI	*P*-value
Age of first opioid use	1.08	1.02– 1.15	0.009
Heroin use in past month	0.19	0.05– 0.70	0.012
Years in OAT prior to current study	1.12	1.05– 1.20	0.001

imputation were very similar to those fitted to retained participants. These results appear unlikely to provide a helpful indication of the influence of loss to follow up. Therefore, we have decided not to include the results of the multiple imputation analyses.

Discussion

This study found 47% of people who initiated BUP-XR were retained on a form of BUP-XR over 96 weeks in a real-world scenario. Opioid use decreased, and patient-centred outcomes were improved among those retained in treatment. The median retention time was 90 weeks. Previously reported retention rates at one year were between 49% (Ling et al., 2020) and 75% (Farrell et al., 2022; Frost et al., 2019). The main strengths of this study are the community-based context and length of follow-up period. We found that quality of life and treatment satisfaction improved over time, in alignment with the CoLAB 48 week trial (Farrell et al., 2022).

The adjusted logistic regression model that examined baseline characteristics revealed that heroin use, younger age at first opioid use, and fewer years in OAT prior to commencement of the CoLAB study, were associated with poorer treatment retention at 96 weeks. There is a lack of evidence on factors associated with retention in BUP-XR. Existing evidence on predictors of buprenorphine treatment retention suggests that female gender, older age, nicotine use disorder, and a diagnosis of mood disorder are associated with higher odds of retention. On the other hand, injection of drug in the past month at entry into the study, unemployment, additional substance use disorder, and hepatitis C are associated with higher dropout (Dayal & Balhara, 2017; Manhapra, Agbese, Leslie, & Rosenheck, 2018; Montalvo, Stankiewicz, Brochier, Henderson, & Borba, 2019; O'Connor, Cousins, Durand, Barry, & Boland, 2020; Stein, Cioe, & Friedmann, 2005; Weinstein et al., 2017). A cohort study of people receiving buprenorphine found that individuals with previous buprenorphine experience had better retention in treatment compared to individuals who had no buprenorphine treatment experience (Cunningham, Roose, Starrels, Giovanniello, & Sohler, 2013).

A substantial reduction in the past four-week opioid use among participants in this study was reported from the first BUP-XR dose. Fewer than one in twenty participants retained on BUP-XR at week 96

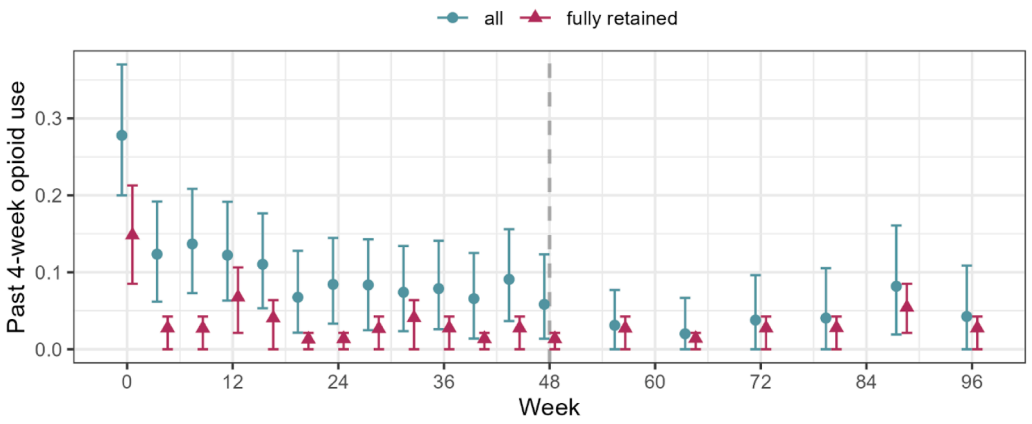

Fig. 4. Bootstrapped estimates of past 4-week opioid use in participants retained on monthly depot buprenorphine treatment (circles). The triangles are bootstrapped estimates at each stage using only the 47 participants retained at 96 weeks. Error bars are bootstrapped 95% confidence intervals.

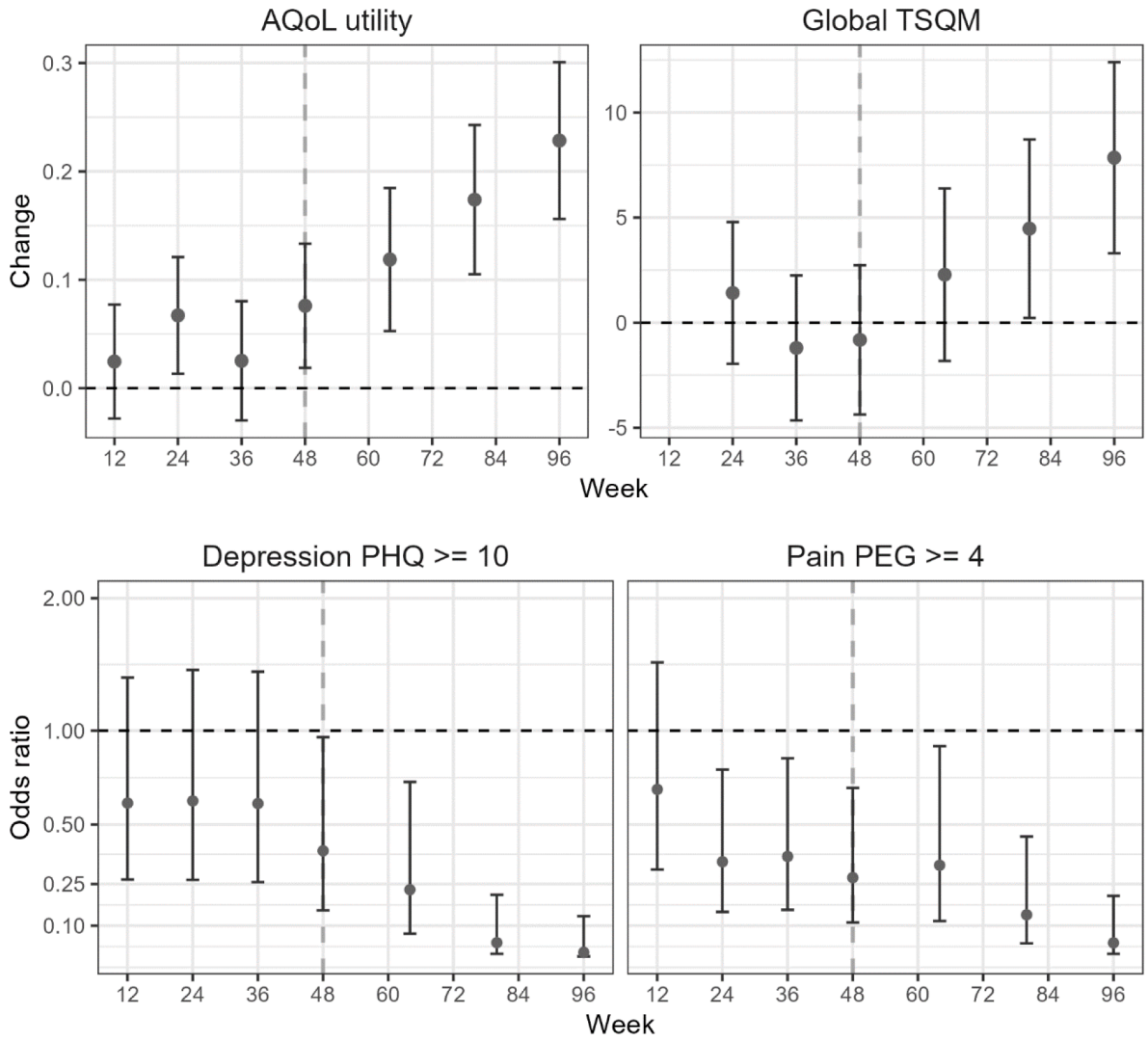

Fig. 5. Change in AQoL utility and TSQM global satisfaction from baseline and week 12 respectively predicted by linear mixed models (top) and odds ratios for moderate or severe depression and moderate or severe pain relative to baseline (bottom). Circles are estimated means from models fitted to participants retained to monthly buprenorphine. Error bars are 95 % confidence intervals.

reported past four-week opioid use. This reduced opioid use is consistent with findings from a recent systematic review and meta-analysis (Degenhardt et al., 2023), and 12-month observational studies (Frost et al., 2019; Ling et al., 2020).

Patient-reported outcomes such as quality of life and medication satisfaction provide an insight beyond opioid abstinence. This study

showed positive trends in these measures with both quality of life utility scores and medication satisfaction scores improving over the study period. The improvements in patient-reported outcomes are based on observations from retained participants only. Participants retained on BUP-XR for shorter periods will have experienced less improvement, on average. Nevertheless, an average improvement from baseline of around 0.2 in AQoL utility among the 47 percent of original participants retained is noteworthy.

Potential limitations of this study should be considered. The cohort of participants were engaged in opioid agonist treatment at the time of recruitment, and this may have influenced retention rates. Additionally, participants received financial reimbursements for completing the surveys, and survey data collection is subject to recall bias. We used multiple imputation using chained equations to impute outcomes of participants that were lost to follow up. Multiple imputation is unbiased when imputed values are missing at random conditional on observed data used for imputation. In this application missing values are likely to be missing not at random. This is a single arm observational and unblinded study. The planned follow-up period for the original CoLAB study was 48 weeks. Outcomes reported at follow up times beyond 48 weeks should be regarded as preliminary. The positive outcomes are reported in those who were retained in treatment. The baseline characteristics of participants of the study should be considered when interpreting the reported outcomes. Treatment outcomes differ among individuals, and the outcomes reported in this study will be most relevant for similar populations.

The data from this study may provide information to help guide national and international strategies to scale up access to and provision of this newest form of OAT. Further cohort and large scale follow up will help to clarify whether the reported benefits can be replicated in population based studies. The roll out of BUP-XR in Australia will enable such work to be undertaken in the near future.

Conclusions

This is one of the few studies to describe long term (96 week) retention in treatment with BUP-XR in a community setting. It displayed retention rates with 47% of participants completing 96 weeks of treatment with BUP-XR. Improvements in patient-centred outcomes and a low prevalence of past four-weeks opioid use were observed among participants retained to BUP-XR. These findings may inform provision of extended-release depot buprenorphine in Australia and internationally.

CRediT authorship contribution statement

Michael Farrell: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Jeyran Shahbazi:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Data curation. **Mark Chambers:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Marianne Byrne:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Data curation. **Jaleh Gholami:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Emma Zahra:** Writing – review & editing, Writing – original draft. **Jason Grebely:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Nicholas Lintzeris:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Briony Larance:** Writing – review & editing, Funding acquisition, Conceptualization. **Robert Ali:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Suzanne Nielsen:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Adrian Dunlop:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Gregory J. Dore:** Writing – review & editing, Funding acquisition, Conceptualization. **Michael McDonough:** Writing – review & editing, Investigation. **Mark Montebello:** Writing – review & editing, Investigation. **Rob Weiss:** Writing – review & editing, Investigation. **Craig Rodgers:** Writing – review & editing, Investigation. **Jon Cook:** Writing – review & editing, Investigation. **Louisa Degenhardt:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

This study was supported by an Externally Sponsored Collaborative Research grant from Indivior PLC (MF, BL, LD, NL, AD, RA, SN, GD, J Grebely). In the past three years, MF and LD have received funding from Indivior for studies of new opioid medications in Australia. J Grebely reports grants and personal fees from Abbvie, bioLytical, Camurus, Cepheid, Hologic, Indivior, and Gilead Sciences. NL has received reimbursement for participation in Advisory Boards for Mundipharma, Indivior and Chiesi Pharmaceuticals; he received funding from Camurus for a company-sponsored trial of BUP-XR. RA has received untied educational grants from Reckitt Benckiser and an untied educational grant from Mundipharma. AJD reports grants from Braeburn/Camurus AB, to conduct clinical studies with buprenorphine products and travel support to Hunter New England Local Health District, which employs AJD. GJD has received research grant funding from Gilead and Abbvie. MM has served as an honorary on advisory boards for Pfizer and AbbVie. MC, JS, MB, JG, and EZ have no conflicts to declare. SN has received untied research funding from Seqirus to conduct research on prescription opioid related harms.

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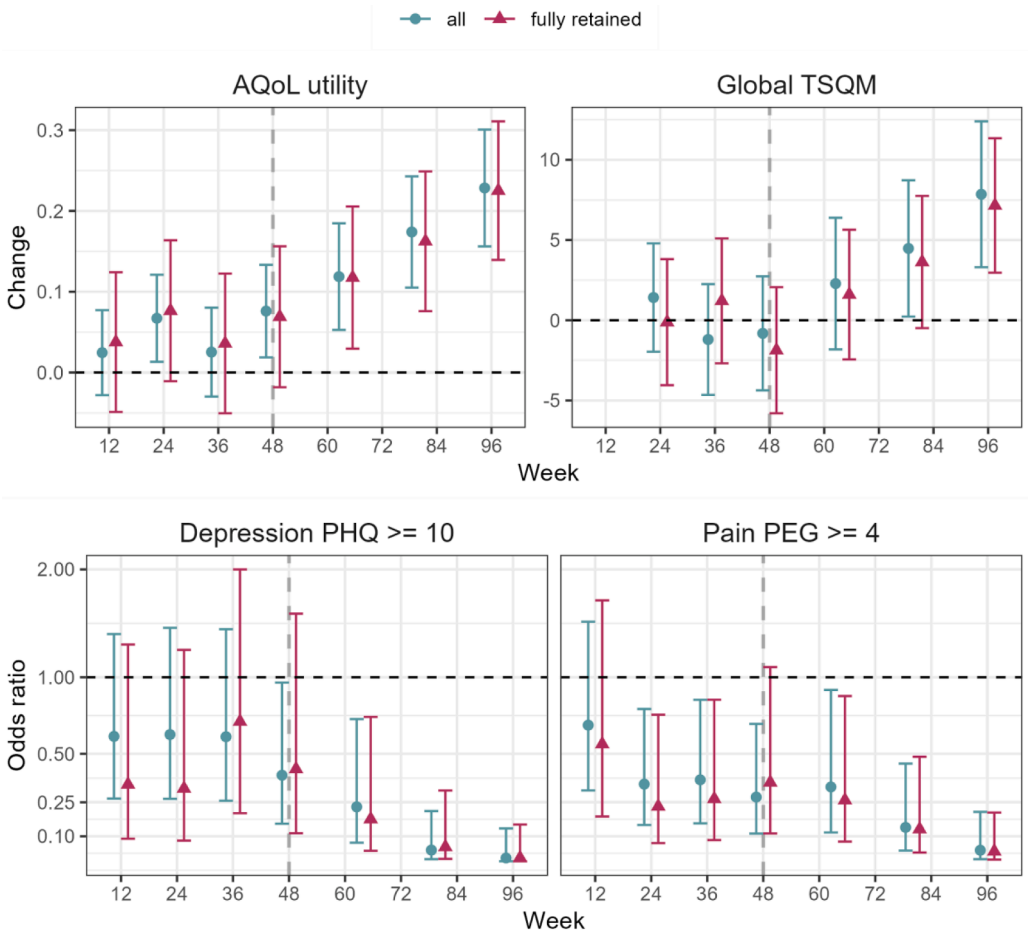
Appendix

Appendix 1: Change in AQoL utility and TSQM global satisfaction from baseline and week 12 respectively predicted by linear mixed models (top) and odds ratios for moderate or severe depression and moderate or severe pain relative to baseline (bottom). Circles are estimated means from models fitted to participants retained to monthly buprenorphine. The triangles depict estimates that result from fitting the same models only to participants that were retained at week 96. Error bars are 95 % confidence intervals



Appendix 2: Bootstrap estimated participant reported measures at quarterly visits with and without multiple imputation

	Retained	
	mean	95% CI
Quality of life utilities		
Visit 1	0.53	0.48, 0.58
Visit 4	0.56	0.49, 0.63
Visit 7	0.61	0.55, 0.67
Visit 10	0.57	0.51, 0.63
End of the 48 weeks	0.62	0.55, 0.69
Extension Follow up 2 (64 weeks)	0.68	0.59, 0.76
Extension Follow up 4 (80 weeks)	0.75	0.67, 0.82

(*continued on next page*)

(*continued*)

	Retained	
	mean	95% CI
Extension Follow up 6 (96 weeks)	0.81	0.72, 0.88
Treatment satisfaction for medication		
Visit 1	-	-
Visit 4	86	83, 89
Visit 7	87	84, 90
Visit 10	85	81, 89
End of the 48 weeks	85	81, 89
Extension Follow up 2 (64 weeks)	91	87, 95
Extension Follow up 4 (80 weeks)	94	89, 97
Extension Follow up 6 (96 weeks)	96	93, 99
Moderate to severe depression (PHQ-9>10+) (%)		
Visit 1	43	34, 53
Visit 4	34	24, 45
Visit 7	33	23, 44
Visit 10	33	24, 44
End of the 48 weeks	28	18, 39
Extension Follow up 2 (64 weeks)	20	9, 32
Extension Follow up 4 (80 weeks)	7	0, 16
Extension Follow up 6 (96 weeks)	3	0, 10
Pain (PEG>4+) (%)		
Visit 1	46	36, 56
Visit 4	39	29, 49
Visit 7	30	21, 40
Visit 10	33	23, 43
End of the 48 weeks	28	18, 40
Extension Follow up 2 (64 weeks)	30	17, 44
Extension Follow up 4 (80 weeks)	20	8, 33
Extension Follow up 6 (96 weeks)	8	0, 18

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