BMJ Open  LiMA: a study protocol for a randomised, double-blind, placebo controlled trial of lisdexamfetamine for the treatment of methamphetamine dependence

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ABSTRACT

Introduction Methamphetamine dependence is a growing public health concern. There is currently no pharmacotherapy approved for methamphetamine dependence. Lisdexamfetamine (LDX) dimesylate, used in the treatment of attention-deficit hyperactivity disorder and binge eating disorder, has potential as an agonist therapy for methamphetamine dependence, and possible benefits of reduced risk of aberrant use due to its novel formulation.

Methods and analysis A double-blind randomised controlled trial will be used to evaluate the efficacy of LDX in reducing methamphetamine use. The target sample is 180 participants with methamphetamine dependence of ≥2 years, using ≥14 days out of the previous 28, who have previously attempted but not responded to treatment for methamphetamine use. Participants will be randomly assigned to receive either a 15-week intervention consisting of induction (1 week of 150 mg LDX or placebo), maintenance (12 weeks of 250 mg LDX or placebo) and reduction (1 week of 150 mg LDX or placebo and 1 week of 50 mg LDX or placebo). All participants will be given access to four sessions of cognitive–behavioural therapy as treatment as usual and receive a 4-week follow-up appointment. The primary outcomes are efficacy (change from baseline in days of methamphetamine use by self-report for the last 28 days at week 13 and urinalyses confirmation of methamphetamine use) and safety (treatment-related adverse events). Secondary outcomes are total number of days of self-report methamphetamine use over the 12-week active treatment, longest period of abstinence during treatment period, percentage of achieving ≥21 days abstinence, craving, withdrawal, dependence, retention, bloodborne virus transmission risk behaviour, criminal behaviour, as well measures of abuse liability, physical and mental health, other substance use, cognitive performance, psychosocial functioning, treatment retention and satisfaction. Additionally, the study will assess the cost-effectiveness of LDX relative to the placebo control.

Strengths and limitations of this study

- The study design is a prospective, randomised controlled trial.
- Strength in methods includes allocation concealment, blinding, compliance measuring, drop-out measuring and analyses of results by intention to treat.
- The fixed-dose design is a limitation; if efficacious, further dose–response relationship studies may be indicated.
- The duration of active treatment is limited to 12 weeks; if efficacious, further studies will be needed to explore optimum duration of treatment and a reducing regimen.

BACKGROUND

Methamphetamine is a synthetic stimulant of growing global public health importance and an important contributor to the global burden of disease.1 There are an estimated 34 million people worldwide who use the drug, and an estimated 17 million who are dependent on methamphetamine.2

Australia has one of the highest documented rates of methamphetamine dependence in the world, with 160 000 people estimated to be dependent during 2013/2014.3 Methamphetamine dependence is estimated to cost Australia around $A5 billion a year, an economic impact which could be reduced by...
effective treatments. Methamphetamine dependence is associated with a range of negative health outcomes including psychosis, depression, anxiety, bloodborne virus transmission, sexually transmissible infections, and cardiovascular and cerebrovascular events. These problems are most prevalent among people who use methamphetamine on a heavy or regular basis, highlighting the need for effective treatments for this group.

There is no approved medication for the treatment of methamphetamine dependence. The standard treatment for methamphetamine dependence relies on psychosocial interventions, primarily cognitive–behavioural therapy (CBT)-based approaches. Such approaches produce small to medium reductions in methamphetamine use in controlled studies (d=0.538). However, CBT approaches require a substantial investment by trained therapists, there is often poor engagement with counselling by methamphetamine users, and cognitive impairment associated with severe methamphetamine dependence may limit CBT effectiveness. Poorer treatment outcomes are seen in methamphetamine users who use frequently (those using methamphetamine at least 15 days out of the previous 30 days at treatment entry), than in less frequent users, highlighting the need for more effective treatment approaches for such individuals.

Many authors have highlighted the potential role of substitution agonist treatment for methamphetamine dependence. The theoretical base for agonist substitution is consistent with the rationale for existing agonist substitution for nicotine and opioid dependence. Agonist substitution therapies aim to replace harmful drug use with safer alternatives in terms of dose, route of administration and adverse effects. Long-acting agonists can reduce amphetamine withdrawal, craving and decrease the euphoriant and reinforcing effects of extra (illicit) stimulant use due to cross-tolerance. Agonist treatment also provides a framework for regular ongoing healthcare and psychosocial interventions with this high-risk population, enabling patients to distance themselves from illicit drug networks and related crime.

Agonist therapies for methamphetamine dependence show promise. A number of ‘weak’ stimulant agonist therapies have been studied, including methylphenidate and modafinil. A recent systematic review showed no benefit over placebo for any of these medications, noting limitations in retention and power of published studies. Dexamphetamine (DXA), a more direct monoamine agonist that more closely mimics the effects of methamphetamine, has been used clinically for amphetamine and methamphetamine dependence in the UK (in doses ranging from 20 to 200 mg) for some time, and in New South Wales (NSW), Australia, since 2006, at doses up to 80 mg. This experience suggests DXA substitution treatment may be useful in retaining a difficult to engage group of severely dependent methamphetamine users who do not respond to stand-alone psychosocial interventions. Previous studies from methamphetamine dependent subjects found no serious consequences of DXA in doses from 30 to 110 mg/day.

While a statistically significant benefit on methamphetamine use has not been established with DXA pharmacotherapy, feasibility has been demonstrated with 60 mg DXA/day (equivalent to 150 mg lisdexamfetamine). Studies with sustained-release (SR)-DXA formulations have shown increased retention in treatment at up to 110 mg SR-DXA/daily (mean dose of 80 mg SR-DXA daily) and decreased craving and withdrawal symptoms in a study using 60 mg SR-DXA. This latter study (n=60) with a treatment duration of 8 weeks concluded that further studies should test a longer treatment duration, that higher doses of DXA could be warranted due to possible physiological tolerance, and that larger sample sizes are required.

Lisdexamfetamine, a pharmacologically inactive prodrug, is absorbed after oral administration and is hydrolysed to inactive l-lysine and active DXA by red blood cells. It has a slower onset, lower peak concentration and longer duration of action than DXA. It is metabolised rapidly to DXA: the peak plasma concentration occurs 3 hours after dosing. The plasma half-life (t½) of DXA is 10 hours, with plasma DXA concentrations reaching steady state at day 5 of once daily lisdexamfetamine dosing. There is no plasma accumulation of lisdexamfetamine. The conversion time from lisdexamfetamine to DXA results in a more blunted effect on brain dopamine than immediate release DXA and, as a consequence, it has a more moderate reinforcing effect in self-administration studies due to the slower onset of peak effects than other stimulant drugs.

Abuse liability studies of lisdexamfetamine with doses of up to 150 mg indicate it has significantly less propensity for abuse-related ‘liking’ when compared with DXA or diethylpropion. The lower abuse liability of lisdexamfetamine, due to its rate-limited hydrolysis, attenuated onset and intensity of amphetamine-like effects, and more moderate reinforcing properties thus reduce the need for supervised dosing.

There have been no published randomised controlled trials of lisdexamfetamine for methamphetamine dependence. Mooney et al. were unable to show a significant change in cocaine use, though the study used a lower dose of 70 mg lisdexamfetamine, and failed to reach its planned sample size. The maintenance dose of 250 mg lisdexamfetamine represents equivalence to current DXA regimens for methamphetamine dependence. This dose has also been tolerated by non-methamphetamine dependent volunteers in a pharmacokinetic study, as well as in a study in participants with schizophrenia receiving antipsychotic pharmacotherapy. A recent safety dose-escalating trial of methamphetamine dependent participants with high frequency of use successfully escalated 14 out of 16 participants to 250 mg lisdexamfetamine.
OBJECTIVES
The objective of the current trial was to test the efficacy of lisdexamfetamine for reducing methamphetamine use among people with methamphetamine dependence, who had not previously responded to psychosocial treatments.

We hypothesise that treatment with oral lisdexamfetamine will result in significantly reduced methamphetamine use at 13 weeks compared with placebo in people who are dependent on methamphetamine. The primary objectives of the study are efficacy and safety of 250 mg of lisdexamfetamine in reducing methamphetamine use after 13 weeks of treatment. Secondary objectives are to examine the changes in physical and mental health, cognitive and psychosocial functioning and well-being between lisdexamfetamine and placebo groups, as well as differences in retention rates, craving and withdrawal symptoms, and severity of dependence. Other secondary objectives are to examine differences in bloodborne virus transmission risk behaviour, criminality and in use of alcohol and other drugs between groups, as well as the abuse liability profile of lisdexamfetamine and the cost-effectiveness of lisdexamfetamine relative to the placebo control.

METHODS
Trial design
This project is a randomised double-blind placebo controlled fixed dose parallel design comparing a 12-week maintenance course of 250 mg lisdexamfetamine daily to placebo.

Sample size
The sample size calculation is based on data from the existing NSW Stimulant Treatment Program clients who meet the inclusion criteria. Such clients showed a reduction from a mean of 19 days of use out of 28 days at pretreatment to a mean of 9 days/28 days with SD of 9 days at 12 weeks post-treatment. To detect a mean difference of 4.5 days (9 days in control vs 4.5 days in the lisdexamfetamine group out of 28 days) at week 13 (12 weeks post-treatment), assuming a pooled SD of 9 days (ie, d=0.5, a median clinically relevant effect size), with over 80% power at two-sided significance level of 0.05, a sample size of 126 (63 per group) is required. Conservatively estimating a 30% attrition from research follow-up (previous trials have achieved follow-up of 81% at 12 weeks), 90 participants per group will be recruited—180 in total.

Participants
This study is being conducted in sites experienced in delivering and evaluating interventions in people who are dependent on methamphetamine. The participating sites are located in NSW and South Australia (SA).

The study population is treatment-seeking adults with long-standing (≥12 months) methamphetamine dependence who have failed to respond to previous methamphetamine treatment attempts. Participants will be aged 18–65 years, meet International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria for methamphetamine dependence and self-report methamphetamine use of ≥14 days out of the previous 28. Prior use of methamphetamine will be verified by urinalysis. Failure to respond to previous treatment is defined as relapse to dependent use within 1 month of completing treatment. Participants must be willing and able to comply with study requirements, be able to store study medications securely, and be able to provide written, informed consent.

Exclusion criteria are sensitivity or previous adverse reaction to lisdexamfetamine, concurrent use or use within the previous 14 days of medications with possible interaction with lisdexamfetamine. Known contraindications for lisdexamfetamine are also exclusion criteria. Individuals with severe medical disorders, including cardiovascular disease, untreated hypertension and peripheral vascular disease, will be ineligible, as will those with severe psychiatric disorders. Those currently in counselling for methamphetamine dependence or who have been prescribed DXA or modafinil (in the 4 weeks prior to assessment) will be ineligible. Other exclusion criteria are dependent use of alcohol or other drugs, exposure to another investigational drug within the 4 weeks prior to screening, unavailability for follow-up, pregnant or lactating women and receipt of current pharmacotherapy treatment for opioid dependence.

Four specialist outpatient stimulant treatment centres in NSW and SA will recruit participants. Potential participants will be prescreened in person or by telephone by a researcher, and if potentially eligible invited to attend for a formal eligibility assessment by a specialist in addiction medicine. The assessment schedule, including eligibility assessments, is outlined in table 1.

Randomisation
Eligible participants will be randomised to receive either the lisdexamfetamine or a placebo medication (see figure 1). A computer-generated randomisation schedule has been developed by an independent statistician and uploaded to the study database. Randomisation will be performed by the trial site pharmacist within the study database. The randomisation component of the database has been safe guarded with specific user rights allowing only the trial site pharmacist, the statistician and the chair of the Independent Data and Safety Monitoring Committee (IDSMC) to access randomisation allocations. Study participants, investigators, clinical and research staff will be blinded to the treatment condition allocated to reduce the risk of bias. Emergency unbinding will be permitted if required for safety of a participant, ongoing safe conduct of the trial or in the case of pregnancy.

Intervention
Oral lisdexamfetamine dimeisylate 50 mg capsules will be used to make up the prescribed study dose. Trial medications
On day 5, they will be provided with 2 days supply of study medication to take at home. For the remainder of the treatment period, participants will attend the clinic two times per week for supervised dosing, safety assessments, provision of urine sample and collection of take home doses. Research visits will occur every 4 weeks until week 19.

CBT, Cognitive behavioural therapy; MOCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Task; RVIP, Rapid Visual Information Processing; WTAR, Wechsler Test of Adult Reading.

will be obtained, prepacked in child resistant blister packs, stored and transported to participating sites by a contracted good manufacturing practice registered facility in accordance with the Poisons and Therapeutic Goods Act 1966 and the Poisons and Therapeutic Goods Regulation 2008.

The active drug (lisdexamfetamine dimesylate) and the placebo shall be provided in identical capsules to ensure the study blind.

### Table 1

**Assessments and procedures: eligible participants will be required to attend the clinic daily for the first 5 days of treatment**

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**Table 1 Continued**

| Depression Anxiety Stress Scales-21 | Weeks 1, 5, 9, 13, 19 |
| WHO Quality of Life-BREF           | Weeks 1, 5, 9, 13, 19 |
| Insomnia Severity Index38          | Weeks 1, 5, 9, 13, 19 |
| Neurocognitive testing batteries (combinations of the following): |  |
| MOCA, WTAR, RAVLT, RVIP, N-Back, trail making test, flankers, digit symbol | Screening and weeks 1, 5, 9, 13, 19 |

Measures of cravings, withdrawal and severity of dependence

| Amphetamine Withdrawal Questionnaire63 | Weeks 1, 5, 9, 13, 19 |
| Visual Analogue Scale for cravings64  | Weeks 1, 5, 9, 13, 19 |
| Severity of Dependence Scale65        | Weeks 1, 5, 9, 13, 19 |

Measures of abuse liability, other drug use, risk behaviour and crime

| Drug Evaluation Questionnaire-5       | Weeks 1, 5, 9, 13, 19 |
| Timeline followback (all drugs—past 28 days)42 | Screening and weeks 1–15 (two times per week) |
| Urine drug screen                     | Weeks 1–15 (two times per week) |
| Opiate Treatment Index-Injecting Practices (OTI-I) | Weeks 1, 5, 9, 13, 19 |
| OTI-Crime (OTI-C)                     | Weeks 1, 5, 9, 13, 19 |
| Substance Use and Sex Index           | Weeks 1, 5, 9, 13, 19 |

Measures for the cost-effectiveness analysis

| EuroQol-5 dimension66                 | Weeks 1, 5, 9, 13, 19 |
| Health service utilisation           | Weeks 1, 5, 9, 13, 19 |
| Work Productivity Questionnaire67    | Weeks 1, 5, 9, 13, 19 |
| OTI-C – additional questions         | Weeks 1, 5, 9, 13, 19 |
| Travel time and costs                | Week 5 |

On day 5, they will be provided with 2 days supply of study medication to take at home.
Eligible participants enrolled in the study will commence with 7 days of 150mg lisdexamfetamine or placebo daily (the induction phase). They will attend the clinic for the first 5 days for supervised administration of the study medication, recording of blood pressure, pulse and temperature, monitoring of adverse events and medication adherence counselling. On the fifth day, the participant will be provided with two additional doses self-administer orally once a day. If the induction phase is tolerated, the participant will progress to the 250mg lisdexamfetamine/placebo 12-week maintenance phase. During the maintenance phase, participants will visit the clinic two times per week for a nursing review where vital signs will be recorded, adverse events monitored and medication adherence counselling undertaken. On the visit days, the administration of the dose for that day will be observed by the study nurse and participants will be provided with 2 or 3 days supply of the lisdexamfetamine/placebo.
placebo to take home for self-administration until the next clinic visit. Participants will be required to return study medication packs for pill counts. A urine sample will be provided at each of the two times per week visits, one of which will be randomly selected according to a predetermined randomised schedule and sent for testing at the end of the study for the presence of methamphetamine, and the other stored for future use. Once each week study personnel will collect self-reported methamphetamine use for the previous week.

Participants will undergo a medical review every 4 weeks during the maintenance phase (weeks 5, 9 and 13), as well as neurocognitive testing and questionnaire completion as outlined in Table 1.

If the participant experiences a grade 2 or 3 adverse event at any time that is considered to be related to the study drug, the study doctor shall consult with the trial chairperson about the option of witholding one dose. If a dose is withheld the participant will be reviewed by the study doctor the following day, or sooner as clinically indicated. If the adverse event is resolved the following day, the dose can be recommenced and the participant will be reviewed the subsequent day. If the adverse event is not resolved or recurs after recommencing, the study doctor will then consult with the trial chairperson with regard to ceasing the medication and withdrawing the participant from the treatment component of the study.

During the reduction phase the dose will be tapered so as to minimise any drug discontinuation effects. The dose will be reduced to 150 mg lisdexamfetamine or placebo daily for 1 week, then 50 mg lisdexamfetamine or placebo daily for 1 week and then ceased.

Lisdexamfetamine will not be available for the management of methamphetamine dependence following completion of the study. However, ongoing treatment will be individualised to the participant and outlined in a treatment plan which will be developed at week 13 by the study doctor.

Subjects will have a follow-up visit 4 weeks after cessation of the reduction phase (week 19).

Participants will be reimbursed with a supermarket voucher (that cannot be spent on alcohol or cigarettes) at weeks 1, 5, 9, 13 and 19. Reimbursements will start at $20 and increase by $10 each month until the follow-up visit.

All participants will be offered counselling representing best practice treatment as usual. This will consist of four sessions of CBT of up to 1 hour per session, specially designed for and validated in the study population and delivered by trained therapist who will receive supervision monthly.

In addition to safety concerns (including acute psychosis, suicidal or homicidal ideation) or pregnancy, participants may be withdrawn from the study if they are absent from study treatment for more than two consecutive weeks. They will also be withdrawn from the study if they become subject to drug testing for legal or occupational reasons (due to the risk of unblinding to group allocation).

Participants who have discontinued protocol treatment will be offered the opportunity continue to participate in all remaining research interviews and assessments. For those participants who revoke their consent for the entire study, no further data will be collected from the participant.

**Statistical methods**

All efficacy analyses will use an intention-to-treat (ITT) approach. ITT will be defined as all randomised patients who received at least one dose of the prescribed medication. The primary efficacy measure is the change from baseline in days of methamphetamine use self-reported for the last 28 days at week 13. A likelihood-based mixed model of repeated measures (MMRM) approach will be used for the primary efficacy analysis. The difference between two groups at week 13 will be the primary comparison, and differences at week 5, 9 and 19 will also be examined. No imputation of missing data will be performed under MMRM approach, the MMRM analysis makes use of all available data and is reliable for effect and SE estimates under missing at random (MAR) assumption. Sensitivity analysis including baseline observation carried forward imputation will be performed to investigate the robustness of results to the departure from MAR assumption.

Secondary measures of the intervention effect will include total number of days of self-report MA use over the 12-week active treatment period; longest period of abstinence during treatment period; percentage of achieving ≥21 days abstinence; percentage of MA negative urines 4 weeks prior to week 12; craving, withdrawal, dependence, retention, bloodborne virus transmission risk behaviour, criminal behaviour, as well measures of abuse liability, physical and mental health, other substance use, cognitive performance, psychosocial functioning and treatment satisfaction. Statistical analysis strategies (t-test, Mann-Whitney U test, X2 test, linear/generalised linear regression and mixed-model analysis) will be used for secondary outcomes based on the type and distribution of the outcome measures. Kaplan-Merrier curve, log rank test and Cox proportional hazard model will be applied in the time to event data analysis.

Analysis of urine drug screen (UDS) results will follow established techniques for similar drug trials (Treatment Effectiveness Score), calculated as a proportion (%) of UDS negative for methamphetamine out of total of 12 possible UDS (with missing tests counted as positive). All patients enrolled in the study will be evaluated with respect to safety-related outcomes. Safety data will be analysed according to the treatment that the patients actually received. Safety analyses will include summaries of the incidence of all adverse events that are possibly or probably treatment related, that occur during the study treatment period or within 30 days of the last dose of study treatment.

Additionally, the study will assess the cost-effectiveness of lisdexamfetamine relative to the placebo control.
The primary outcome will be quality-adjusted life years measured by the five-level version of the EuroQol five-dimensional (EQ-5D) descriptive system (EQ-5D-5L). Costs will include clinical resources, other healthcare, crime, productivity and personal costs. The costs will be summed and combined with the outcome measure, and the incremental cost-effectiveness ratio calculated.

All tests of the treatment effect will be conducted at a two-sided alpha level of 0.05.

Interim analyses will be performed when the 50th patient has completed treatment or 6 months after the commencement of recruitment, whichever comes first.

An IDSMC will monitor the progress of the study with the aim of safeguarding trial participants by assessing the safety and efficacy of the drug being investigated in the trial. The IDSMC may recommend stopping the trial if the number and/or severity of adverse events justify discontinuation of the study; on the basis of a positive efficacy result only when the primary endpoint (methamphetamine use) data are truly compelling and the risk of a false positive conclusion is acceptably low (p<0.001 for primary endpoint); if accrual rates are too low and/or that non-compliance is too great to provide adequate power for identifying the specified benefit; it becomes clear that successful completion of the study is not feasible.

Data statement
Study data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Hunter New England Local Health District. REDCap is a secure, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for importing data from external sources.

Ethics and dissemination
Prior to an individual’s participation in the trial, he/she shall be fully informed about the research and given ample time and opportunity to inquire about details and decide whether or not to participate. If they agree to participate, they will be asked to sign the study-specific consent form. Participants will also be invited to consent for their urine samples to be stored for future research.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at the time of randomisation. Results arising from the main study will be published in peer-reviewed journals, and disseminated at international conferences. Results will be reported in such a manner that participants will not be identifiable in any way.

All data will be considered the property of the trial chairperson who, in consultation with the trial management committee, will be responsible for presentations and publications arising from this trial.

Patient involvement
The initial concept of investigating the use of lisdexamfetamine in reducing methamphetamine use in people who are dependent on methamphetamine was proposed by a patient who prefers to be unnamed. No other patients were involved in setting the research question or the outcome measures, nor have they been involved in developing plans for design or implementation of the study.

DISCUSSION
This is the first phase III trial of lisdexamfetamine for methamphetamine dependence. The strength of this study is in its proposed sample size, powered to detect a medium effect size in between group differences in the primary outcome (days of methamphetamine use), using a higher dose of agonist medication (more than triple) used typically for the treatment of attention-deficit hyperactivity disorder. Participants will be closely monitored with two times per week clinic visits and nursing reviews and monthly medical reviews. Two times per week, dispensing will promote retention in the study, and prevent high drop-out rates experienced in other studies. The study protocol proposes to deliver the medication in an outpatient setting allowing participants take-home dosing to more closely mimic the service delivery situations in which the medication may be used and provide some indication. Limitations of the study include the fixed-dose design, active treatment restricted to 12 weeks and two times per week observed dosing. If efficacious further dose–response relationship studies may be indicated to explore optimum duration of treatment and a reducing regimen. If successful the intervention will provide a much needed therapeutic adjunct for people who are dependent on methamphetamine.

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Contributors
The study was conceived and designed by NL, AD, NE and RA. Significant contribution to the development and conceptualisation of the protocol was made by NE, AD, NL, RA, MH, BC, RM, RB, NP, AC, JW, ZL, MS and ALB. KD
contributed to the design of the protocol. BC and MH wrote the first draft of the article with significant input from NE, RM, ZL, MS and ALB critically revised the article for intellectual content.

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**Competing interests** AC reports grants, personal fees and non-financial support from Gilead Sciences, grants, personal fees and non-financial support from ViV Healthcare, grants and personal fees from MSD and personal fees from Mayne Healthcare, outside the submitted work. RB has received investigator-initiated unied educational grants from Reckitt Benckiser/Indivior for the development of an opioid-related behaviour scale and a study of opioid substitution therapy uptake among chronic non-cancer pain patients and has received an untied educational grant from Mundipharma for a postmarket study of oxycodone. NL reports personal fees from Indivior, personal fees from Mundipharma, grants from Braeburn Pharmaceuticals outside the submitted work. AD reports grants from Braeburn Pharmaceuticals during the conduct of the study.

**Patient consent** Not required.

**Ethics approval** The study has been approved by the Human Research Ethics Committee of St Vincent’s Hospital, Sydney, Australia (HREC/16/SVH/222). Contact the corresponding author for the full trial protocol.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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