Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
Screening and baseline characteristics of the study participants have been published. Briefly, self-report data, administrative records, urine drug screens and a medical exam, occurring over a minimum of three successive screening visits, determined eligibility. The first screening visit collected self-reported data confirming participants had a minimum of five years of opioid dependence, regular injection of street acquired opioids (i.e., illicit heroin, morphine, hydromorphone, speedball) in the past year, and current injection of street acquired opioids (also confirmed by a positive urine drug screen and assessment of recent signs of injecting). Prior to the second screening visit, pharmaceutical dispensation records or other clinical records (e.g., detoxification treatments, residential treatments) were obtained to confirm participants had at least two prior addiction treatment episodes, including one opioid maintenance treatment. In the final screening visit, a study physician performed a full medical exam to verify Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition, criteria for opioid dependence (severe opioid use disorder in the DSM-5) and to exclude those with severe medical conditions contraindicated for diacetylmorphine or hydromorphone (e.g., stage II or greater hepatic encephalopathy), or those currently pregnant or planning on becoming pregnant.
**eAppendix 2. Summary of Changes in the SALOME Protocol**

SALOME was designed as a two-part trial. The first trial (denoted stage I, i.e., the subject of this manuscript) was a non-inferiority trial comparing injectable diacetylmorphine and hydromorphone. The second trial, denoted stage II and conducted after participants completed stage I, tested whether participants would equally benefit from oral formulations. Stage II was terminated early due to futility but this has no effect on the data from stage I which was collected prior to any treatment in stage II. For simplicity, the manuscript does not refer to stage II.

From Protocol Version 1.0 (June 2009) to Version 10.3 (August 2014), changes to the protocol included clarifications of procedures, revisions, and a change in the sample size.

No changes proposed by the investigators were based on any access to unblinded data. No changes in the protocol affected the randomization process.

All amendments were reviewed and approved by the relevant Research Ethics Board and Health Canada regulatory authorities prior to being implemented; the final version of the protocol was reviewed and approved prior to any unblinded data analysis. The change in the sample size was reviewed and recommended by the Data and Safety Monitoring Board of the trial who only had access to data named group A and group B (the investigators did not see data by group A or B before implementing any change).

1- **Clarifications of procedures**

Randomization process and procedures for communicating a participant’s randomization between the research, clinical and pharmacy teams was clarified.

Inclusion criteria were clarified (e.g., age was changed from 18 to 19, to reflect adult age in British Columbia) and their operationalization was made more specific to better reflect the criteria and avoid possible ambiguity.

Reasons for discontinuing participants’ therapy or assessment were clarified to reflect a less punitive approach and protect the safety of participants and health care staff.

Scenarios in which the randomization code may be broken were clarified to define all potential exceptional circumstances where this may occur and the procedures for reporting this.

Drug transport procedures were clarified to reflect the storage and safety procedures of the on-site pharmacy.

Titration protocols were clarified to ensure that study nurses and physicians could modify the titration protocol according to patient need and safety (e.g., prescribing two instead of three doses per day during titration).

Reductions in pre and post drug intake times were made to improve patient flow through the clinic.

Transition procedures from injectable to oral formulations were clarified to ensure that clinic nurses and physicians had flexibility to transition and titrate participants according to their needs and safety.

A methadone procedures section that was not relevant for the present study was deleted. Drug formulations expanded to include different lab and manufacturers used. Active pharmaceutical ingredient remained the same.

2- **Sample size change**

The original planned sample size was 322 participants, to be recruited in two study sites (Montreal and Vancouver). The Montreal site was unable to participate due to insufficient funding and lack of Provincial government approvals. As a result, a power of 0.95 as originally planned was considered too ambitious to accomplish with the Vancouver site only. The revised sample size utilizing a power of 0.90 was deemed acceptable by the DSMB.
The sample size was calculated using Laster and Johnson's formula (that yields a smaller sample size than Blackwelder's). However we have recently found a slight coding error in the formula we used to calculate the 202 sample. With the correct codes the sample size should have been 212 and not 202, as originally calculated (using the original expected decline from baseline of 20 days with a SD = 11.0 – obtained from data derived from the NAOMI results – and the original margin of 4 days).

Nevertheless, in the post hoc calculation of the power in our current analysis we obtain the following results using Blackwelder’s formula. For a sample size of 101 per group, a margin of 4 days, a one-sided alpha of 0.05, and a pooled standard deviation (SD) from both groups of 8.04 (diacetylmorphine group SD = 6.57; hydromorphone group SD=9.13) of the number of days of street heroin use, we obtain a power of 0.97. Using the larger SD from the hydromorphone group we obtain a power of 0.93.

The Laster’s formula calculates sample size based on comparing the group means as ratio (i.e. Mean DAM / Mean HDM) while the Blackwelder’s based on comparing the group means as mean difference (i.e. Mean DAM - Mean HDM). Since our analysis are mean differences with ANCOVA, the latter is the appropriated one for post-hoc power calculation.

3- Revision of assessments, secondary outcomes and addition of a follow-up visit

We added a 24th month follow-up visit to capture longitudinal data on participant’s post-trial outcomes.

Changes in the metabolites tested in research urine samples (papaverine and noscapine) were made to reflect street heroin markers.

The description of the secondary outcomes was reworded, specifically:

The original 'retention in treatment' definition was modified to better reflect the comprehensiveness of data available to the research team (i.e., provincial pharmacy dispensation database) and to ensure consistency in the time frame of data collected by all measures (i.e., using a 30 day time frame which is consistent with all variables, whereas the original definition was based on 14 day time frame).

Total days of all illicit opioids used was added as an outcome to reflect the inclusion criteria and the possibility that the number of days using illicit heroin (the POM) in the prior month might slightly underestimate total street opioid use if participants used other illicit opioids on days they could not access heroin. The DSMB approved this variable to complement the POM.

Data sources for criminal involvement were changed based on the protocol of the health economics sub-study.

Collection of urine for POM analysis was changed from weekly random samples in the last month of care to one sample taken the day the POM was assessed in the scheduled follow-up visit due to lack of feasibility. Random urine collections had to be done at the study’s clinical site, and the study clinic was already operating at full capacity making additional collection unmanageable. More scheduled collections were also not possible due to unanticipated increases cost of the test.

4- Changes in the analysis plan

For the primary outcome, instead of analyzing the “change from baseline”, we analyzed the POM at each end point, and we used ANCOVA to adjust for baseline.

The original protocol was not clear about the one or two-sidedness of the confidence intervals used in the analysis. Wording was added to clarify this.
Dichotomizing the POM in case it was not normally distributed was a recommendation from one member of the Data and Safety Monitoring Board. However, upon reflection, we realized there was no evidence to justify a non-inferiority margin for a proposed new variable. Therefore, we did not use it.

5- Health Economics sub-study

There were changes made by the Health Economics study team. Revisions were made in the protocol to reflect their modified analysis plan.

6- Success of the blinding sub-study

The testing of the success of the blinding was a sub-study added to the original protocol prior to the protocol being implemented.

7- Other changes

Other changes included investigators and roles, disambiguation of text, expansion of the study background and updates to the references list.
eAppendix 3. Details of Study Oversight

The study was conducted in Vancouver, Canada. All participants provided written informed consent prior to any administration of study medications or data collection. SALOME followed Good Clinical Practice Guidelines, and was approved by the Therapeutic Products Directorate of Health Canada and by the Providence Health Care/University of British Columbia Research Ethics boards. It also received an Exemption 56 from the Narcotics Control Act by the Office of Controlled Substances, Exemptions Division, of Health Canada. An independent Data and Safety Monitoring Board composed of experts in the fields of addiction medicine, biostatistics and ethics advised the investigators on patient safety and treatment efficacy during the study. External monitoring of the conduct of the study according to protocol and Good Clinical Practice was contracted.
eAppendix 4. Data Supplement

Analysis of Primary, Co-primary and Secondary Outcomes from Baseline to Six Months

Additional Analyses included in the supplement report the mean (standard deviation [SD]) for the primary, co-primary and secondary outcomes at baseline and six months by randomization as well as the change from baseline to six months follow-up (eTable 1).

eTable 1. Mean score and mean score change from baseline to six months for primary and co-primary efficacy variables by randomization group.

<table>
<thead>
<tr>
<th>Prior month variable</th>
<th>Intention to treat analysis</th>
<th>Per protocol analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDM (n=100)</td>
<td>DAM (n=102)</td>
</tr>
<tr>
<td></td>
<td>n  Baseline  n  Six months</td>
<td>n  Six months – baseline  n  Baseline  n  Six months</td>
</tr>
<tr>
<td>Days of street heroin use in the prior month</td>
<td>100</td>
<td>25.16 (7.50)</td>
</tr>
<tr>
<td>Days of any street opioid use in the prior month</td>
<td>100</td>
<td>27.28 (4.79)</td>
</tr>
<tr>
<td>MAP Physical Health</td>
<td>96</td>
<td>11.82 (8.57)</td>
</tr>
<tr>
<td>Days of crack cocaine use</td>
<td>100</td>
<td>11.56 (13.58)</td>
</tr>
<tr>
<td>Days of illegal activities</td>
<td>84</td>
<td>24.61 (7.97)</td>
</tr>
<tr>
<td>Days of any street opioid use in the prior month</td>
<td>84</td>
<td>27.05 (5.09)</td>
</tr>
<tr>
<td>MAP Physical Health</td>
<td>81</td>
<td>11.74 (8.57)</td>
</tr>
<tr>
<td>Days of illegal activities</td>
<td>84</td>
<td>12.38 (13.43)</td>
</tr>
<tr>
<td>Days of crack cocaine use</td>
<td>84</td>
<td>11.15 (12.90)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) for efficacy variables at baseline and six months follow-up and the mean change.

a. Includes street use of heroin, morphine, hydromorphone, and speedball (combined street opioids and stimulants). Non-injection use of street opioids was reported an average of 0.59 days ± 2.59 with no significant differences by group.

b. Maudsley Addiction Profile: Physical health scores range from 0 to 40, higher scores indicate poorer physical health.

c. Maudsley Addiction Profile: Psychological health scores range from 0 to 40, higher scores indicate poorer psychological health.
Post-hoc Analysis of Alternative Scenarios for Handling Missing Data

Missing values were imputed using multiple imputation, with the exception of the two participants who passed away. However, since six months data are missing from 4 participants, all in the diacetylmorphine group, ad-hoc sensitivity analysis of alternative approaches for handling missing data were estimated (eFigure 1).

eFigure 1. Sensitivity analysis of primary efficacy outcomes at six months.

Difference: DAM minus HDM (two-sided 90% CI)

Days of street heroin use in the prior month

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Difference (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.0</td>
<td>-2.34 (-4.14, -0.52)</td>
</tr>
<tr>
<td>S.1</td>
<td>-1.93 (-3.96, -0.12)*</td>
</tr>
<tr>
<td>S.2</td>
<td>-1.41 (-3.47, 0.48)*</td>
</tr>
<tr>
<td>S.3</td>
<td>-2.27 (-4.08, -0.36)</td>
</tr>
<tr>
<td>S.4</td>
<td>-1.81 (-3.70, 0.10)*</td>
</tr>
</tbody>
</table>

Days of street opioid use in the prior month, including heroin

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Difference (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.0</td>
<td>-0.85 (-2.97, 1.25)*</td>
</tr>
<tr>
<td>S.1</td>
<td>-0.51 (-2.69, 1.59)*</td>
</tr>
<tr>
<td>S.2</td>
<td>-0.03 (-2.23, 2.11)*</td>
</tr>
<tr>
<td>S.3</td>
<td>-0.76 (-2.87, 1.37)*</td>
</tr>
<tr>
<td>S.4</td>
<td>-0.36 (-2.44, 1.80)*</td>
</tr>
</tbody>
</table>

Proportion of urinalyses positive for street heroin metabolites in the 6th month visit urine sample

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Proportion (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.0</td>
<td>0.09 (-0.02, 0.19)*</td>
</tr>
<tr>
<td>S.1</td>
<td>0.10 (-0.00, 0.21)*</td>
</tr>
<tr>
<td>S.2</td>
<td>0.12 (0.01, 0.22)*</td>
</tr>
<tr>
<td>S.3</td>
<td>0.09 (-0.02, 0.19)*</td>
</tr>
<tr>
<td>S.4</td>
<td>0.10 (-0.00, 0.20)*</td>
</tr>
</tbody>
</table>

HDM = hydromorphone, injectable; DAM = diacetylmorphine, injectable; CI = confidence intervals; ITT = Intention to Treat.
S.0. ITT, excluding death, using multiple imputation in case of missing data (as presented in the manuscript)
S.1. ITT, excluding death, assuming worst outcomes in case of missing data.
S.2. ITT, assuming worst outcome for deaths and other missing data.
S.3. ITT, using multiple imputation for deaths and other missing data.
S.4. ITT, worst outcomes for deaths and using multiple imputation for other missing data.

Co-prescribed methadone

At any time, in consultation with the study physician, participants could add oral methadone to their care (e.g., to reduce overnight withdrawal symptoms) or transfer to methadone alone (e.g., in the event of travel, incarceration, preference) or any other available treatment (e.g., buprenorphine).

Per protocol, participants could add oral methadone to their treatment plan at any time, in consultation with the physician. Oral methadone could be dispensed on the same day participants were also receiving injectables. A total of 157 participants (81 in the HDM group and 76 in the DAM group) received injectables co-prescribed with methadone in the same day at least once. In the HDM group, the mean dose of methadone used on the days they also received injectables was 24.58 mg (SD=20.27) and in the DAM group was 23.64 (SD=18.04). On those days, the mean dose of injectables received was 495.14mg. (SD=214.00) and 494.59 mg (SD=218.38) in the HDM and DAM group respectively.
eAppendix 5. Outcome Measures

An independent, experienced and trained research team collected self-report research data and urine samples at baseline (prior to randomization and allocation to study medications), 3 and 6-months follow-up. Self-reported data were collected on the following topics: socio-demographics (e.g., age, gender, ethnicity, housing), illicit drug use, illegal activities and physical and psychological health. The European-version of the Addiction Severity Index measured the number of days in the prior 30 days of illegal activities and street drug use, including heroin, total days of any street opioids (e.g., from heroin, hydromorphone, morphine, speedball, etcetera), cocaine powder, and crack cocaine. Physical and psychological health symptoms were measured with the Maudsley Addiction Profile.

Street acquired opioids included heroin, speedball (combined opioids and stimulants, primarily heroin and cocaine), morphine, and hydromorphone. Although the main street opioid injected in the study setting is heroin, in recent years it has increasingly been supplemented with other street acquired opioids such as morphine or hydromorphone. Thus, the co-primary measure of total days of any street acquired opioids in the prior 30 days captures the full extent of this outcome in our particular setting.
eAppendix 6. Urinalyses

Urine specimens were collected from participants at each research visit using temperature strips at collection. Samples were stored in a freezer at -20 degrees Celsius until being transported to the British Columbia Provincial Toxicology Centre for analysis. Samples were analyzed for the detection of illicit heroin markers: papaverine, noscapine, acetylcodine, desmethylmeconine, desmethylpapaverine and di-desmethylpapaverine. The Provincial Toxicology Centre prepared the samples using standard liquid chromatography extraction techniques, a routine procedure for urine analysis of opioids. For each metabolite, the limit of detection was 1 ug/L. All stock solutions were certified reference standards from Cerilliant Corporation. Analysis was performed in multiple reaction monitoring mode using liquid chromatography mass spectrometry. Specimens which detected ≥ 1 ug/L for any of the six metabolites were considered to be positive for illicit heroin.

Testing for other opioids in this study posed methodological barriers with the interpretation of the meaning of the results in light of the research question. Since all participants were being prescribed opioids, positive tests would not be able to discriminate prescribed use from street use. It could be argued that the diacetylmorphine group be tested for hydromorphone metabolites and the hydromorphone group for diacetylmorphine ones, assuming they are mutually exclusive. However, the results could not be compared between groups, which is the purpose of this study.
eAppendix 7. Safety Measures

The nursing staff conducted pre-injection (i.e., observation for use of substances contraindicated for injectable opioid administration) and post-injection (i.e., observation for adverse or serious adverse events) assessments to ensure safety.

All possible AEs and serious AEs (SAEs) were documented. Events were followed up until resolved. The research office could also report possible SAEs (mainly hospitalizations) occurring in participants outside of the clinic. All SAEs were reviewed by the DSMB.

An adverse event was defined as any untoward medical occurrence in a participant administered a pharmaceutical product which did not necessarily have a causal relationship with the treatment. An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes:
- an event not present prior to drug administration;
- discovery of undiagnosed pre-existing condition after drug administration;
- exacerbation of pre-existing condition;
- increased frequency of an intermittent event;
- any change or worsening.

This does not include:
- continuous, pre-existing condition which does not change in nature or intensity;
- treatment failure.

A SAE included any adverse drug experience or adverse event occurring at any dose that:
- results in death;
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect;
- important medical event that may not be immediately life-threatening or result in death or hospitalization buy may jeopardize the patient or may require intervention to prevent one of the above outcomes.

All SAEs considered unexpected and related to study treatment were reported to Health Canada as well as the local ethics committee. Following appropriate clinical intervention and/or implementation of appropriate emergency protocols, an “SAE Report Form” was completed and systematic and standard procedures for registration, notification and follow-up were followed.

All study participants were assessed for adverse events (AEs), drug reactions or changes in health status during all visits to the clinic by clinic nurses, coordinators, physicians and/or other clinic workers. All AEs were documented in the electronic AE Case Report Forms in the SALOME database. The research office could also report possible SAEs (mainly hospitalizations) among participants not retained or not compliant with doctor appointments. Participants who received injection medications were assessed for AEs at every clinic study treatment dispensation visit during the 5 minute pre-injection assessment and 15 minute post-injection assessment periods and 30 minute titration post-injection periods, as applicable. SAEs were reported within 24 hours of knowledge of the event to the Clinical Trial Coordinator by email, phone, or by entering the event as an SAE in the SALOME database. The Clinical Trial Coordinator would report the event to the investigators responsible and to the Therapeutic Products Directorate and REB as required. Once an SAE was confirmed by the Clinical Trial Coordinator, it was added to the Case Report Form.
eAppendix 8. Analysis of Co-variance

For those outcomes that were also measured at baseline, analysis of covariance was used to adjust for the baseline values. Zero-inflated Poisson regression was used to model count data (number of days in the prior month) that had an excess of zero counts including street heroin use, any street acquired opioid use, crack cocaine use and other illegal activities. Based on the estimated coefficients from the zero-inflated Poisson model, we first computed the expected values for the two intervention groups respectively, while holding the model covariates at their mean value. Then we computed the difference in the expected values between the two intervention groups and its confidence intervals by the Bootstrap method. Linear regression models were used to estimate the mean difference and CI for physical and mental health scores. As for urinalyses and treatment compliance having binary outcomes, the proportions between the intervention groups were compared by the risk difference and the CIs for the risk difference were the Wald asymptotic confidence limits.