Statistical Analysis Plan

A double-blind single center, crossover, randomized controlled trial of antibacterial vs. placebo mouthwash to reduce the incidence of gonorrhea/chlamydia/syphilis in MSM taking HIV pre-exposure prophylaxis (PrEP) (Study Acronym: PReGo)

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1. Introduction

This Statistical Analysis Plan (SAP) provides a description of the main, pre-planned analyses for the study "A double-blind single center, crossover, randomized controlled trial of antibacterial vs. placebo mouthwash to reduce the incidence of gonorrhea/chlamydia/syphilis in MSM taking HIV pre-exposure prophylaxis (PrEP) (Study Acronym: PReGo)". The purpose of this study is to assess if there is a difference rate of gonorrhea (NG), chlamydia (CT) and syphilis detected at any site between MSM using Listerine Cool Mint (LCM) or a placebo mouthwash.

These planned analyses will be performed by the statistician at the Clinical Trials Unit of the Institute of Tropical Medicine (Antwerp) in collaboration with the coordinating investigator. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research. This document describes statistical methods for the primary, secondary and tertiary outcomes of the study as defined by protocol. Additional analyses may be performed but are not covered by the current analysis plan. Statistical methods for these additional analyses will be described together with the results.

All analyses described will be performed as soon as data from both study visits (month 3 and month 6) is collected and cleaned. An interim analysis will be performed to assess the efficacy of the study. Major changes in statistical methodology used for the main and pre-planned analyses from this SAP, which is finalized before database lock, will require detailed description and justification in the statistical analysis report. The final analysis datasets, programs, and outputs are archived following good clinical practice guidelines (ICH E9).

2. Study design and objectives

2.1. Study design

This is a double-blinded single center, cross-over, randomized controlled trial in MSM taking HIV Pre-exposure prophylaxis (PrEP). A total of 320 subjects was initially calculated to be recruited in the study. Due to unexpected high rates of drop-out, the sample size was further increase by 10%, to 352. This change which was approved by the IRB and EC will ensure that the requested number of participants complete the study according to the pre-specified significance level and power (for more details, see Protocol). Participants and randomized (1:1) to one of the following groups:

1. Listerine ® Coolmint (LCM) mouthwash: daily dose + before and after sex (n= 160)
2. Placebo mouthwash: daily dose + before and after sex (n= 160)

After 3 months, subjects will switch to the other study group for the next 3 months (until month 6). At the end of each period (month 3 and month 6), subjects will be screened for STIs and will be asked to complete a CASI (computer assisted self-interview) questionnaire on sexual behavior. During the whole duration of the study (enrollment – month 6 visit) participants will be asked to complete an online weekly diary with questions on adherence and acceptance.

Sixty-four participants will be selected for an enhanced detailed resistome/microbiome analysis. Because previous antibiotic exposure has a well-established effect on the

resistome and microbiome this sample will be stratified by history of antimicrobial exposure (32 individuals who report no antibiotics received in the 6 months prior to their enrollment visit and 32 individuals who report being treated at least once for Ng or Ct in the past 6 months). Allocation of the two arms will be balanced for this sub-group.

2.2. Study objectives and Hypotheses

Primary Objective

The primary objective of this study is to assess if there is a difference in the incidence rate of Ng plus Ct plus syphilis detected at any site whilst individuals are on LCM vs. placebo.

Secondary Objectives

The secondary objectives of the study are as follows:

1. Assess if there is a difference in incidence rate of pharyngeal Ng between periods on LCM vs. placebo
2. Assess if there is a difference in incidence rate of Ct (combined pharyngeal, urethral and rectal) between periods on LCM vs. placebo
3. Assess if there is a difference in incidence rate of syphilis between periods on LCM vs. placebo
4. Describe adherence to (1) daily mouthwash (2) pre/post sex mouthwash (3) pre sex mouthwash
5. Assess the difference in incidence rate of Ng plus Ct plus syphilis between LCM and placebo after controlling for adherence with daily and pre/post sex mouthwash
6. Assess if there is a difference in cumulative antibiotic use between periods on LCM vs. placebo

Safety Objective

To compare Serious Adverse Events (SAEs) occurring between the enrollment visit and the visit at month 6 between LCM and the placebo.

2.3. Variables of interest

Primary: An indicator variable counting the cumulative number of Ng, CT and syphilis infections in a 3 month period on LCM or placebo. Each participant can only contribute one diagnosis of each STI (Ct, Ng or syphilis) per visit - regardless of number of sites infected. Thus each participant can contribute up to 3 diagnoses (Ct/Ng/syphilis) at each visit.

Laboratory confirmed Ng, Ct or syphilis infections at the ITM or another center during their inclusion in the study (i.e. between visits), will be self-reported by the participants and will be included in the cumulative new number of Ct/Ng/syphilis diagnoses.

Secondary:

- Incidence rate of new pharyngeal Ng cases in each allocation arm (LCM and placebo)
- Incidence rate of new Ct cases in each allocation arm (LCM and placebo)

- Incidence rate of new syphilis cases in each allocation arm (LCM and placebo)
- Three ordinal variable indicating the percentage of compliance with the recommended dosage for every occasion (daily, pre- and post-sex)
- Cumulative number of antibiotics used between both groups (LCM and placebo) for each period
- Prevalence of LCM-resistance-associated mutations in the pharyngeal and rectal microbiome of the LCM group vs placebo-group (inter-individual comparison).
- Prevalence of LCM-resistance-associated mutations in those receiving LCM after 3 months vs before receiving LCM (intra-individual comparison).

Safety: the number of subjects reporting SAE's during the study period

3. Description of study population

3.1. Analysis populations

The primary and secondary efficacy endpoints will be analyzed using both an intention-to treat (ITT) as well as a Per-Protocol approach . The ITT approach assesses the superiority of LCM, taking into account the effects of non-compliance to the protocol guidelines and other possible effects. The ITT will be the primary analysis approach. However, non-compliance may bias results towards superiority, thus in accordance to ICH guidelines (CPMP, 2000), we will perform both ITT and PP analyses and asses if both approaches lead to similar conclusions. For the safety endpoints, an all-patient-treated approach will be used.

3.1.1. Intention to treat (ITT) analysis

To provide a pragmatic comparison of the different study arms, the principle of intention-to-treat will be the main strategy of analysis adopted for the primary and secondary efficacy endpoints. These analyses will be conducted on all patients assigned to the study arms as randomized, regardless of the study drug or non-study drug received.

Persons who were found to be HIV positive at inclusion, but have been randomized will be excluded from the all analyses, while persons who were found to be HIV positive during the study, will be excluded from further ITT analyses, but their data prior to that point will be used.

3.1.2. Per Protocol (PP) analysis

Subjects who do not comply with the inclusion/exclusion criteria and were wrongly included in the study, subjects that received the wrong treatment arm, discontinued the IP intake or performed visits outside the pre-specified window according to the protocol, will be included in the ITT but will be excluded from the PP analysis. In the following table, the protocol violations are classified as minor and major where minor violations can be included in the PP analysis population and major violations are excluded.

Protocol Violation	Major/Minor Violation	Comments
Inclusion criteria		
1. Men aged 18 or more	Major	
2. Enrolled in Belgian PrEP program at ITM	Major	
3. Has had sex with another man in the previous year	Major	
4. Has had a symptomatic or asymptomatic STI (Ct/Ng/syphilis) in the previous 2 years	Major	
5. Willing to be enrolled in the cohort for 6 months and attend 3 monthly follow up visits	Major	
6. Willing to comply with the mouthwash study schema and willing to ask their casual partners to mouthwash pre- and post-sex	Major	
7. Prepared to fill out the online diary once a week	Major	
8. Able and willing to provide written informed consent	Major	
Exclusion criteria		
1. Currently using a mouthwash and unwilling to cease use of this mouthwash	Major	
2. Enrolment in another interventional trial	Major	
3. Tests HIV positive at screening	Major	
Treatment violations		
1. Not taken the randomized treatment.	Major	
2. Discontinued IP intake	Major/Minor	Participants that have discontinued taking the IP, will not be included in PP analyses that statistics are calculated without controlling for adherence (e.g. primary outcome). In analyses where results will be presented controlling for adherence, then those participants will be included in the PP population.
3. Visit performed outside the pre-specified time window	Major	

3.2. Patient accounting

The number of patients screened, but not entered into the study is not contained in the main clinical database and will be described separately by the Coordination Investigator summarized according to reason for exclusion.

All patients who conform to all inclusion and exclusion criteria and are enrolled into the study will be tabulated. The number of patients discontinuing will be tabulated by reason for study discontinuation. This analysis will be performed at each study visit (Example Table 1). Differences between the ITT and the all-patients-treated populations, will also be noted in this table. These figures will be summarized in a CONSORT flow diagram.

3.3. Description of study population

Patients will be described with respect to baseline characteristics by allocation group. The description will be in terms of medians and interquartile ranges for continuous characteristics and using counts and percentages for categorical characteristics (Example Table 2). The clinical importance of any imbalance between the groups will be noted, but no formal statistical tests will be performed. Baseline characteristics will be presented separately for the subgroup analysis per treatment allocation and per prior antibiotic use (subgroup).

General characteristics from each study visit are presented and analyzed similarly to baseline characteristics. Those results are included in Example Table 3. Patient counts (and percentages) for STI cases and antibiotic use on every visit (CRF-visit questionnaire) will be presented by allocation group and by anatomical site in Example Table 4. An data check between STIs reported outside ITM in the CRF and the behavioral questionnaire will be performed.

4. Statistical Methods

4.1. Primary Objective

The primary hypothesis of this study is that LCM mouthwash used daily and pre/post sex is able to reduce the incidence rate of STIs (Ng, Ct, syphilis) in MSM over a 3 month period. This will be assessed using a mixed effects Poisson regression model. The sum of Ng, Ct and syphilis infections (0-3) occurring in one person between visits will be used as the outcome variable, **allocated treatment** (placebo or LCM), **time on LCM/placebo treatment** (number of days above or below the reference 90 days [3 months] on LCM or placebo) and **visit** as fixed effects and a random intercept for each participant. The primary objective will be addressed through the significance of the estimate of the treatment variable in the model. The results of the regression model will be summarized in Example Table 5.

The results of the Poisson mixed effects model will be in the form of an estimate for the treatment group (with 95% confidence interval) after adjusting for various sources of variability (visit and time on treatment). The results should be interpreted in the form of a multiplicative effect on counts for the treatment group on LCM compared to the placebo. For example, an estimate of 0.2 should be interpreted as "the counts of STIs on the patients on LCM is 80% lower compared to those on placebo".

4.2. Secondary Objectives

The secondary objective of incidence rate controlling for adherence levels will be analyzed using the same model as the primary objective, adding extra ordinal variables with percentage of adherence to LCM mouthwash (daily/pre and post sex, pre sex). The level of adherence will also be transformed into a binary/categorical variable with pre-specified cut-offs in case of sparse representation in the original categories.

The secondary objectives regarding the individual infections will be analyzed in a similar way as the primary analysis, using mixed effects logistic regression models instead of Poisson. The interpretation of these results are similar to the primary analysis.

The level of adherence to mouthwash use will be presented as counts and percentages of quartiles of adherence daily, pre- and post- sex. Any imbalance between the two groups will be noted, but no formal statistical test will be performed. The level of adherence will be treated as an ordinal variable in case of sparse representation in the different percentiles. All mouthwash and adherence related data are presented in Example Table 6. The objective regarding antibiotic use will be analyzed using mixed-effects Poisson model with treatment and time as covariates and a Chi-square test to compare the proportions in the two groups at different time points. A correction for the stratified randomization will be added.

The patient count with adverse events in the two groups will be compared using Fisher's exact test (Example Table 7).

4.3. Interim analysis

Due to the COVID-19 pandemic, since 17th March 2020 all non-essential health activities have stopped including PrEP consultations and PreGo visits, and all people are strongly advised to stay at home and self-isolate. During this period, we hypothesize that the sexual activities of our target population and as a consequence the exposure to STIs will decrease. This factor might prohibit us from making a clear inference regarding the effect of LCM.

For the above reasons, an interim analysis was decided to assess our study objectives up to this point in order to take an informed decision regarding the continuation of the study. The results of the primary and the first secondary objective will be used as a rule for discontinuation of the study. The boundaries that the produced test statistic will be compared to, will be adapted for the incomplete sample size and for the multiple testing (interim and final analysis). As a consequence, the level of significance that the analyses' p-values will be compared against, will change as well. We follow the methodology as described in Whitehead; Statistical Methods in Medical Research 2010; 20(6) 635 – 656. Given that 45% of the initially calculated sample size (131 participants) have completed all study visits, we calculate that the bounds the test

statistic will be compared against are lower = 0 (futility) and upper = 2.9265. If the test statistic of the covariate of interest is below the lower or above the upper bound then the study will be terminated. In the first case, no superiority can be established and in the second case, superiority can be established. If the test statistic is between the two bounds, then the status of the study will be further evaluated based on the results of the interim analysis and the status of the pandemic by the study investigators.
Given the above calculations, the adapted level of significance will be 0.0034 for two-sided tests and 0.0017 for one-sided tests. The primary outcome of the combination of the three STIs or pharyngeal NG alone will be the outcomes that will be of main focus in this interim analysis and decisions will be taken according to those results. Participants who have completed all study visits will be the primary population for this analysis. A second run of all analyses will include all available data.

The main objective on IP effect of the incidence of NG, CT or syphilis as well as secondary objectives 1-5 (effect of IP on specific STIs, describe and adjust results for adherence) will be included in the interim analysis. Safety results will be summarized and described in frequency tables, but no formal statistical testing will be performed.

4.4. Independence, Multiplicity and Missing Data

As every participant is measured 3 times, the measurements from the different visits within each participant cannot be regarded as independent. The differences among study subjects and within them in the different time points are corrected using mixed effects models. No adjustments for multiplicity are needed. We estimate that participants will miss 5% of their planned visits. Since we will not be able to assess for STIs at these visits, the respective data collected from these visits will be dropped from the analyses. An all-available data approach will be used in cases of missing values in the data.

5. Example Tables and Figures

Example Table 1: Patient Accounting

	Total	LCM	Placebo
Enrolled in the study	xx (xx %)	xx (xx %)	xx (xx %)
Did not complete visit at Month 3	xx (xx %)	xx (xx %)	xx (xx %)
- Did not meet eligibility criteria	xx	xx	xx
- Lost to Follow Up	xx	xx	xx
- Participant's decision	xx	xx	xx
- Investigator's decision	xx	xx	xx
- Serious Adverse Events related	xx	xx	xx
- HIV seroconversion	xx	xx	xx
- Death	xx	xx	xx
- Other	xx	xx	xx
Completed visit at Month 3	xx (xx %)	xx (xx %)	xx (xx %)
Did not complete visit at Month 6	xx (xx %)	xx (xx %)	xx (xx %)
- Did not meet eligibility criteria	xx	xx	xx
- Lost to Follow Up	xx	xx	xx
- Participant's decision	xx	xx	xx
- Investigator's decision	xx	xx	xx
- Serious Adverse Events related	xx	xx	xx
- HIV seroconversion	xx	xx	xx
- Death	xx	xx	xx
- Other	xx	xx	xx
Completed study	xx (xx %)	xx (xx %)	xx (xx %)

Example Table 2: Baseline Characteristics

	Total n (%)	LCM n (%)	Placebo n (%)
N	xx	xx	xx
Age (yr): median (IQR)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
STI history (last 24 months)			
- Any STI	xx (xx)	xx (xx)	xx (xx)
- Ct	xx (xx)	xx (xx)	xx (xx)
- Ng	xx (xx)	xx (xx)	xx (xx)
- Syphillis	xx (xx)	xx (xx)	xx (xx)
- Other	xx (xx)	xx (xx)	xx (xx)
Antibiotic use (last 6 months)	xx (xx)	xx (xx)	xx (xx)
Antibiotic categories			
[add categories]	xx (xx)	xx (xx)	xx (xx)

Example Table 3: Descriptive characteristics at each study visit

	Total n (%)	LCM n (%)	Placebo n (%)	p-value
Baseline	xx	xx	xx	
Number of main partners	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Number of casual partners (last 3 months)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Condom use with casual partners				0.xxx
- 0 – 24 %	xx (xx)	xx (xx)	xx (xx)	
- 25 – 49 %	xx (xx)	xx (xx)	xx (xx)	
- 50 – 74 %	xx (xx)	xx (xx)	xx (xx)	
- 75 – 100 %	xx (xx)	xx (xx)	xx (xx)	
Antibiotic use (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Diagnosed STI (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Chlamydia	xx (xx)	xx (xx)	xx (xx)	0.xxx
Gonorrhea	xx (xx)	xx (xx)	xx (xx)	0.xxx
Syphilis	xx (xx)	xx (xx)	xx (xx)	0.xxx
Other	xx (xx)	xx (xx)	xx (xx)	0.xxx
Month 3	xx	xx	xx	
Number of main partners	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Number of casual partners (last 3 months)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Condom use with casual partners				0.xxx
0 – 24 %	xx (xx)	xx (xx)	xx (xx)	
25 – 49 %	xx (xx)	xx (xx)	xx (xx)	
50 – 74 %	xx (xx)	xx (xx)	xx (xx)	
75 – 100 %	xx (xx)	xx (xx)	xx (xx)	
Antibiotic use (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Diagnosed STI (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Chlamydia	xx (xx)	xx (xx)	xx (xx)	0.xxx
Gonorrhea	xx (xx)	xx (xx)	xx (xx)	0.xxx
Syphilis	xx (xx)	xx (xx)	xx (xx)	0.xxx
Other	xx (xx)	xx (xx)	xx (xx)	0.xxx
Month 6	xx	xx	xx	
Number of main partners	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Number of casual partners (last 3 months)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	0.xxx
Condom use with casual partners				0.xxx
0 – 24 %	xx (xx)	xx (xx)	xx (xx)	
25 – 49 %	xx (xx)	xx (xx)	xx (xx)	
50 – 74 %	xx (xx)	xx (xx)	xx (xx)	
75 – 100 %	xx (xx)	xx (xx)	xx (xx)	
Antibiotic use (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Diagnosed STI (last 3 months)	xx (xx)	xx (xx)	xx (xx)	0.xxx
Chlamydia	xx (xx)	xx (xx)	xx (xx)	0.xxx
Gonorrhea	xx (xx)	xx (xx)	xx (xx)	0.xxx
Syphilis	xx (xx)	xx (xx)	xx (xx)	0.xxx
Other	xx (xx)	xx (xx)	xx (xx)	0.xxx

Example Table 4: Patient counts of STI cases at each visit (lab confirmed and STIs outside clinic)

	Total n (%)	LCM n (%)	Placebo n (%)
Baseline	xx	xx	xx
Any STI	xx (xx)	xx (xx)	xx (xx)
Any STI from ITM clinic	xx (xx)	xx (xx)	xx (xx)
Chlamydia (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Gonorrhea (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Syphilis	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Month 3	xx	xx	xx
Any STI	xx (xx)	xx (xx)	xx (xx)
Any STI from ITM clinic	xx (xx)	xx (xx)	xx (xx)
Chlamydia (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Gonorrhea (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Syphilis	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Month 6	xx	xx	xx
Any STI	xx (xx)	xx (xx)	xx (xx)
Any STI from ITM clinic	xx (xx)	xx (xx)	xx (xx)
Chlamydia (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Gonorrhea (total/pharynx/urethra/rectum)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)	xx/xx/xx/xx (xx/xx/xx/xx)
Syphilis	xx (xx)	xx (xx)	xx (xx)

Example Table 5: Summary of Primary and Secondary Analysis Results (regression models)

	Incidence Rate/Odds ratio (95 % CI)	**p-value**
Any STI	xx	
Chlamydia	xx (xx)	0.xxx
Pharyngeal Gonorrhea	xx (xx)	0.xxx
Syphilis	xx (xx)	0.xxx
Any STI (controlling for adherence)	xx (xx)	0.xxx
- Allocation group	xx (xx)	0.xxx
- Adherence levels	xx (xx)	0.xxx

Example Table 6: Mouthwash related and adherence descriptive characteristics at each study visit

	Total n (%)	LCM n (%)	Placebo n (%)
Baseline	xx	xx	xx
Wiling to ask main partners to mouthwash pre/post sex	xx (xx)	xx (xx)	xx (xx)
Proportion of main partners willing to ask to mouthwash pre/post sex	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Mouthwash use (ever)	xx (xx)	xx (xx)	xx (xx)
Mouthwash use (last month)	xx (xx)	xx (xx)	xx (xx)
Mouthwash use against STIs	xx (xx)	xx (xx)	xx (xx)
Mouth/teeth problems with mouthwash (last 3 months)	xx (xx)	xx (xx)	xx (xx)
Month 3/Month 6			
Main partner(s) asked to mouthwash pre/post sex (last 3 months)	xx (xx)	xx (xx)	xx (xx)
Mouthwash use with main partners before sex (last 3 months)			
0 – 24 %	xx (xx)	xx (xx)	xx (xx)
25 – 49 %	xx (xx)	xx (xx)	xx (xx)
50 – 74 %	xx (xx)	xx (xx)	xx (xx)
75 – 100 %	xx (xx)	xx (xx)	xx (xx)
Mouthwash use with casual partners after sex (last 3 months)			
0 – 24 %	xx (xx)	xx (xx)	xx (xx)
25 – 49 %	xx (xx)	xx (xx)	xx (xx)
50 – 74 %	xx (xx)	xx (xx)	xx (xx)
75 – 100 %	xx (xx)	xx (xx)	xx (xx)
Wiling to ask main partner to mouthwash pre/post sex	xx (xx)	xx (xx)	xx (xx)
Proportion of main partners willing to ask to mouthwash pre/post sex	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Mouthwash use with casual partners before sex (last 3 months)			
0 – 24 %	xx (xx)	xx (xx)	xx (xx)
25 – 49 %	xx (xx)	xx (xx)	xx (xx)
50 – 74 %	xx (xx)	xx (xx)	xx (xx)
75 – 100 %	xx (xx)	xx (xx)	xx (xx)
Mouthwash use with casual partners after sex (last 3 months)			
0 – 24 %	xx (xx)	xx (xx)	xx (xx)
25 – 49 %	xx (xx)	xx (xx)	xx (xx)
50 – 74 %	xx (xx)	xx (xx)	xx (xx)
75 – 100 %	xx (xx)	xx (xx)	xx (xx)
Mouthwash daily (last 3 months)			
0 – 24 %	xx (xx)	xx (xx)	xx (xx)
25 – 49 %	xx (xx)	xx (xx)	xx (xx)
50 – 74 %	xx (xx)	xx (xx)	xx (xx)
75 – 100 %	xx (xx)	xx (xx)	xx (xx)
Mouth/teeth problems with mouthwash (last 3 months)	xx (xx)	xx (xx)	xx (xx)

Example Table 7: Safety Analyses for the

	LCM	Placebo	P-value
Number of patients (%; 95% CI) with:			
Month 3	xx	xx	
- any serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx
- any drug-related non-serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx
Month 6	Xx	xx	
- any serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx
- any drug-related non-serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx
Complete study period	xx	xx	
- any serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx
- any drug-related non-serious adverse event	xx (xx; xx - xx)	xx (xx; xx - xx)	P=0.xxx