Statistical Analysis Plan (SAP)

Management of acute bronchitis in Switzerland with *Pelargonium sidoides* extract EPS®7630 *versus usual care* – a pragmatic, open-label, randomized controlled trial

PHYTOBRONCH

Administrative Information

Trial registration number:	NCT05916768
SAP version:	SAP version number with dates. 1 of 20.03.2025
Protocol version:	V3 of 24.10.2024

Abbreviations

ABSS	Acute Bronchitis Severity Score
AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BIHAM	Berner Institut für Hausarztmedizin
FAIR	Findable, Accessible, Interoperable and Re-usable
FAS	Full Analysis Set
GBTM	Group-Based Trajectory Modeling
ICE	Intercurrent Event
IML	Institut de Médecine de Famille
ITT	Intention To Treat
MAR	Missing At Random
MICE	Multiple Imputation with Chained Equations
PCP	Primary Care Physician
PP	Per Protocol
SAE	Severe Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan

Contents

1. Introduction

1.1 Background and rationale

Although most respiratory tract infections, including acute bronchitis, are caused by viruses, 53% of diagnosed patients receive antibiotics in Europe, representing one of the main reasons for prescribing antibiotics in adults. This inappropriate use is a major contributor to resistance to antibiotics and is therefore a global threat to public health. Furthermore, symptomatic treatments used in this indication have not yet shown convincing benefits. Therefore, there are no effective conventional medicines to treat acute bronchitis.

Phytotherapy could be a useful and promising resource for the development of candidate drugs for the treatment of acute bronchitis. A review of the literature identified one plant (*Pelargonium sidoides*), which has a standardized extract, EPs®7630 registered on the market in Switzerland under the name of Kaloba®, that may be effective as a symptomatic treatment in the management of acute bronchitis. The PHYTOBRONCH study aims to investigate the efficacy of Kaloba® in the management of acute bronchitis to find alternatives to the ineffective or inappropriate treatments that are currently used in the management of this disease.

1.2 Objectives

The primary objective is to assess the effectiveness of Kaloba® to treat acute bronchitis compared to usual care to reduce:

- Reduction of symptom severity
- Antibiotics use

Secondary objectives are:

- To assess the incidence of adverse events (AEs) and severe adverse events (SAEs)
- To estimate the proportion of primary care physicians (PCPs) who agree to participate in the study

1.3 Timing of SAP writing

This SAP version was written and finalized before enrollment of participants was finished.

2. Study Methods

2.1 Trial design

This is a pragmatic, open-label, superiority randomized controlled trial, which takes place in ~40 PCP in practices and 5 walk-in clinics. The intervention group receives Kaloba® for 7 days and up to 21 days. The control group receives usual care, with symptomatic treatments freely chosen by the PCP (phytotherapy excluded). Usual care is not standardized between PCPs. A delayed use of antibiotics can be used in both groups. Prescription of paracetamol is allowed, as well as any routine medication pre-reviewed by the PCP and not counter-indicated.

2.2 Randomization

Participants are randomized in a 1:1 ratio to either the intervention group or the control group, with stratification according to PCP. Randomization was performed using blocks of equal size (size=4). An independent statistician built the randomization table.

Study group allocation is done using the web-based system REDCap (hosted by the University of Fribourg), which also contains the electronic case report form (eCRF). The PCP uses the button “randomize” in REDCap to allocate each patient to a group.

2.3 Sample size

The sample size was calculated for each of the co-primary outcomes, using a Bonferroni correction for the significance level (.05 / 2 = .025). It was replicated in Stata 18 as follows:

- Reduction of symptom severity: Using a two-sample means test with power = 80%, a two-sided significance level = 2.5%, an allocation ratio 1:1, one day of difference between groups (Δ=1), and a standard deviation of 3 days assumed to be the same in both groups (1), we needed n=346 (173 in each group).
- Antibiotics use: Using a two-sample proportions test (Pearson’s chi-squared test) with power = 80%, a two-sided significance level = 2.5%, an allocation ratio 1:1, a proportion of 60% in the control group and 45% in the intervention group (Δ=15) (2), we needed n=420 (210 in each group).

The largest sample size estimation was selected: n=420. As this approach is rather conservative (e.g., it does not consider the fact that the co-primary outcomes may be correlated), we did not account for potential drop-out in the sample size calculation.

2.4 Framework

This is a superiority trial, comparing participants who receive Kaloba® to those who receive usual care.

2.5 Statistical interim analyses and stopping guidance

No interim analysis is planned.

2.6 Timing of final analysis

All outcomes will be analyzed after study completion, once the database is cleaned, validated, and locked.

2.7 Timing of outcome assessments

Participants answer daily a web-based questionnaire (from day 1 to 21, stopping at symptom resolution) and a phone call at days 4, 8, and 22. A paper version of the questionnaire is also available for participants who are unable to answer online.

2.8 Blinding

This study is not blinded.

3. Data Management

3.1 Data export

The database is hosted in the REDCap database system of University of Fribourg. It will be exported as a CSV file and imported in Stata 18 for analyses. Data will be stored on the server of the University of Bern for analyses.

3.2 Data validation

Central data monitoring is performed by the IMF at the University of Fribourg. Data will be cleaned and validated by the data manager of the University of Bern. We will check for outliers, implausible values, and missing data, as well as inconsistencies. We will particularly check outcomes.

3.3 Data preparation

Outcomes will be created as explained in section 6.

3.4 Data sharing (if applicable)

Once the statistical analysis completed, data will be prepared for sharing and storage. Documents will include database and metadata (e.g., SAP, codebook, and statistical code). They will be sent back to the University of Fribourg. They will be shared on FAIR data repository, if requested by the sponsor-investigator.

4. Statistical Principles

4.1 Confidence intervals and *P* values

Statistical tests will be two-sided with a 5% significance level, except for the co-primary outcomes, for which a 2.5% significance level is used. We will present 95% confidence intervals, used to assess the precision of the estimates. We will not calculate p-values for baseline comparisons.

4.2 Analysis populations

4.2.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized participants, regardless of protocol violations or discontinuation. Analyses will be conducted following the intention-to-treat (ITT) principle, with participants analyzed according to their assigned group.

For the secondary outcome on PCPs, the FAS will include all PCPs invited to participate in the trial, regardless their answer.

4.2.2 Per-protocol (PP)

Per-protocol (PP) analyses will be conducted in participants who do not have any intercurrent events (ICEs). ICEs include:

- ICE1: Non-respect of the treatment strategy, including cross-over (use phytotherapy in the control group or not used Kaloba® in the intervention group), non-adherence to treatment (adherence is defined as missing the treatment at least 50% over the period of symptoms (and maximum for 7 days), use of antibiotics at baseline, use medications other than those authorized (exclusion criteria 12, section 5.2), discontinuation of treatment in the intervention group (e.g., due to AEs or lack of efficacy), already using Kaloba® or Umckaloabo® in the control group (exclusion criteria 11, section 5.2).
- ICE2: Inclusion despite presence of an exclusion criterion (criteria 1 to 10, section 5.2) or lack of an inclusion criterion (criteria 1 to 3, section 5.2).
- ICE3: Terminal events, such as death.

4.2.3 Safety population (SAF)

The safety population (SAF) will be participants who received at least one medication (Kaloba® or usual care).

4.3 Estimands

We define the following estimands for the outcomes.

Estimand E1.1: This estimand quantifies the effectiveness of the treatment assessed with the reduction of symptom severity (co-primary outcome).

Outcome of interest: Number of days needed to achieve a 50% reduction on the Acute Bronchitis Severity Score (ABSS) after peak of symptoms, assessed at max. 22 days. The peak of symptoms is defined by the highest ABSS (or the initial score if there is no peak). This is a normally distributed count outcome (3).

Population-level summary measure of outcome: adjusted* mean difference.

Participant-set of interest: FAS.

Handling of intercurrent events: All participants are included.

Handling of missing data: Missing data will be multiple imputed (see section 6.4).

* 1) Adjusted for the type of recruitment (PCP/walk-in clinic) and 2) adjusted for the following factors at baseline: type of recruitment, age, sex, level of education, smoking status, beginning of symptoms (number of days), baseline ABSS, and prescriptions for corticosteroid containing oral medication or inhalers (yes/no), including Prednisone, Symbicort, and Vannair.

Estimand E1.2: This estimand quantifies the effectiveness of the treatment assessed with the reduction of symptom severity (co-primary outcome) in the PP population.

Outcome of interest: Same as estimand 1.1.

Population-level summary measure of outcome: same as estimand 1.1.

Participant-set of interest: PP.

Handling of intercurrent events: Participants with ICE1-3 are excluded from the analysis. The data will be weighted according to inverse probability weighting for ICE 1 and 2 (see section 6.2.2).

Handling of missing data: As ICE cannot be assessed in participants who drop out or are lost to follow-up, we will not use multiple imputation. We will use inverse probability of attrition weights to account for attrition and multiple imputation for missing baseline covariates (see section 6.4).

Estimand E2.1: This estimand quantifies the efficacy of the treatment assessed with the proportion of antibiotics use (co-primary outcome).

Outcome of interest: Use of antibiotics after the initial visit (binary).

Population-level summary measure of outcome: adjusted* risk ratio.

Participant-set of interest: FAS.

Handling of intercurrent events: All participants are included. Participants who took antibiotics at baseline will be considered as failures (having antibiotics).

Handling of missing data: Missing data will be multiple imputed (see section 6.4).

* Same adjustment as E1.1. If there are too few participants, we will use analyses adjusting separately for each covariate + type of recruitment.

Estimand E2.2: This estimand quantifies the efficacy of the treatment assessed with the proportion of antibiotics use (co-primary outcome) in the PP population.

Outcome of interest: same as estimand 2.1.

Population-level summary measure of outcome: same as estimand 2.1.

Participant-set of interest: PP.

Handling of intercurrent events: Participants with ICE1-3 are excluded from the analysis. The data will be weighted according to inverse probability weighting for ICE 1 and 2 (see section 6.2.2).

Handling of missing data: As ICE cannot be assessed in participants who drop out or are lost to follow-up, we will not use multiple imputation. We will use inverse probability of attrition weights to account for attrition and multiple imputation for missing baseline covariates (see section 6.4).

Estimand E3.1: This estimand quantifies the incidence of AEs and SAEs.

Outcome of interest: Presence of any adverse or severe adverse event (binary) during the follow-up (up to 22 days).

Population-level summary measure of outcome: adjusted* hazard ratio.

Participant-set of interest: SAF.

Handling of intercurrent events: All participants are included.

Handling of missing data: No missing data, participants are censored when the study ends (at day 22) or at the day of last contact.

* 1) Adjusted for the type of recruitment (PCP/walk-in clinic) and 2) adjusted for the following factors at baseline: type of recruitment, age, sex, level of education, smoking status, beginning of symptoms (number of days), and baseline ABSS. If there are too few participants, we will use analyses adjusting separately for each covariate + type of recruitment.

Estimand E3.2: This estimand quantifies the incidence of AEs and SAEs.

Outcome of interest: same as estimand 3.1.

Population-level summary measure of outcome: same as estimand 3.1.

Participant-set of interest: SAF without ICE2.

Handling of intercurrent events: Participants with ICE2 are excluded from the analysis. The data will be weighted according to inverse probability weighting for ICE 2 (see section 6.2.2). Participants will be censored when they deviate from the treatment strategy (ICE1) and when they have a terminal event (ICE3).

Handling of missing data: No missing data, participants are censored when the study ends (at day 22) or at the day of last contact.

Estimand E4: This estimand quantifies the proportion of PCPs who agree to participate in the study.

Outcome of interest: PCP agrees or declines to participate in the study (binary).

Population-level summary measure of outcome: Percentage.

Participant-set of interest: FAS PCPs.

Handling of intercurrent events: All PCPs are included.

Handling of missing data: No missing data (missing data are considered as refusal to participate in the study).

5. Trial Population

5.1 Screening data

Not available.

5.2 Eligibility

The target study participants are outpatients with acute bronchitis (with or without COVID-19).

Inclusion criteria are:

1. At least 18 years old
2. Consulting for the first time as part of this bronchial episode
3. Consulting for:
    a. Acute cough (≤ 8 days) as the main symptom
    b. Illness (≤ 8 days) in which cough is not the main symptom, but the PCP believes that acute bronchitis is the most likely diagnosis

Exclusion criteria are:

1. Infection requiring antibiotics
2. Pneumonia
3. Non-infectious causes (COPD, asthma, pulmonary embolism, heart failure, gastro-esophageal reflux, allergy)
4. Incapacity of judgment (dementia, psychosis or severe depression)
5. Important risk of bleeding (severe thrombocytopenia and anticoagulant intake)
6. Inability to complete the diary
7. Pregnancy or breastfeeding
8. Immunological deficiencies
9. Severe hepatic disease
10. Known hypersensitivity to Pelargonium sidoides extract or excipients of the trial medication
11. Currently taking Kaloba® or Umckaloabo® for this current episode of acute bronchitis
12. Taking anticoagulants, immunosuppressants, chemotherapy or immunotherapy

A CONSORT patient flow diagram will be drawn.

5.3 Baseline patient characteristics

Baseline parameters will be presented as means and standard deviations for continuous variables, or percentages and n for categorical variables.

The baseline table will include standardized mean/proportion differences to have an overview of the balance between groups, but no p-values or confidence intervals.

Relevant baseline covariates include:

- Socio-demographics: sex, age, level of education (primary, secondary, or university)
- Risk factors: smoking (yes/no), comorbidities (hypertension, diabetes, cardiovascular disease, cancer, obesity),
- Illness-related variables: number of days since the beginning of symptoms, baseline ABSS, medications already used (cough suppressant, expectorant, anti-inflammatory, febrifuge, other)
- Medical background: COVID-19 vaccination.

5.4 Adherence and protocol deviations

Protocol violations will be summarized by percentages and n in each group.

5.5 Withdrawal/follow-up

Withdrawal from the study and lost-to-follow-up will be summarized by percentage and n in each group.

6. Analysis

6.1 Outcome definitions

Reduction of symptom severity. The first co-primary endpoint uses the patient-reported outcome Acute Bronchitis Severity Score (ABSS), which quantifies the severity of 5 symptoms related to acute bronchitis for the previous 24 hours. It is assessed on a scale from 0 to 4, with the sum score ranging between 0 and 20 (see Table 1) (3). Participants will complete the ABSS daily on an online diary, until symptom resolution and up to 21 days. If the participant does not answer, the ABSS will be evaluated in phone interviews (days 4, 8, and 22).

Table 1. Acute Bronchitis Severity Score (ABSS)

Symptom	**0**	**1**	**2**	**3**	**4**
Overall severity of illness	Very mild	Mild	Moderate	Serious	Very serious
Day cough	1-2 times/day	3-5 times/day	6-10 times/day	11-20 times/day	>20 times/day
Night cough	1-2 times/night	3-5 times/night	6-10 times/night	11-20 times/night	>20 times/night
Limit daily activity	None	Mild	Moderate	Severe	Very severe
Subjective fever	None	Mild	Moderate	Severe	Very severe

The first co-primary is the number of days needed to achieve a 50% reduction in the ABSS after peak of symptoms (1). The peak of symptoms is defined as the highest ABSS observed during the study.

The procedure to calculate the first co-primary endpoint is the following:

- Calculate daily ABSS (sum score of the 5 symptoms)
- Calculate the peak (max. ABSS observed)
- Calculate daily percentage change in the ABSS after the peak
- Calculate which day corresponds to a 50% decrease
- Calculate the number of days between the peak and the 50% decrease

If there is no peak, the first day will be used as the peak. If the 50% decrease is not reached, we will set the number of days to the maximum (22 days). Imputation will be used for missing values on daily ABSS (see section 6.4). We will run a sensitivity analysis computing the primary outcome and using multiple imputation on the primary outcome.

Antibiotics use. The second co-primary endpoint is the proportion of participants who take antibiotics after the initial visit (≥ day 2). It is defined as 0=no antibiotics during the same illness episode and 1=antibiotics use during the same illness period. Antibiotics use is assessed daily in the diary (day 1 to 21) until symptom resolution and at the three phone calls at day 4, 8, and 22.

AEs and SAEs. The first secondary endpoint will include AEs, predefined according to the dictionary MedDRA and SAEs, defined according to the HRA. Assessments of severity (5 categories, from grade 0 to 5) and causality (5 categories, from “not related” to “definitely related”) will also be evaluated. We will compute a single endpoint with 0=no AE or SAE during the study and 1=at least one AE or SAE during the study period. We will also create separate endpoints for AEs and SAEs and types of AEs/AEs. The date of the (S)AEs will also be recorded, to capture the time until (S)AE.

PCP agreement to participate in the study. The second secondary endpoint will assess whether the PCP agrees to participate in the study. Participation will be defined as signing the agreement and enrolling participants. Non-participation will be defined as refusing or signing but not enrolling participants.

6.2 Analysis methods

6.2.1 Primary analysis

The primary analysis will be done according to the FAS (ITT) and PP sets specified in section 4.2, using the adjusted model (4, 5). The randomization group will be used as the main predictor, adjusting for the stratification factors and relevant predefined covariates. To account for the fact that participants are clustered in PCP practices, we will use bootstrapped standard errors (1000 reps). A random seed will be predefined for replicability. The intraclass coefficient is expected to be small. All effects will be shown using marginal point estimates (accounting for adjustment variables) and 95% confidence intervals.

For the first co-primary endpoint, *reduction in ABSS*, we will use a linear regression, e.g.:

```
bootstrap, reps(1000) seed(XXX): regress y x1 x2
```

This endpoint should be normally distributed, as observed in previous studies (3). However, if it is not normally distributed, we will use a log-transformation after adding the constant 1.

For the second co-primary endpoint, *proportion of antibiotics use*, we will use a logistic regression, e.g.:

```
bootstrap, reps(1000) seed(XXX): glm y x1 x2, fam(bin) link(log) eform
```

We will use multiple imputation to handle missing values on covariates and outcomes (see section 6.4). If there is collinearity between covariates, we will remove one colinear variable based on theoretical reasons.

6.2.2 Secondary analyses

The secondary analysis will be done according to the FAS (ITT) and PP sets specified in section 4.2. Models will also be adjusted for the stratification factor and relevant covariates, with bootstrapped standard errors, as described for the primary analysis. Effects will be shown using marginal point estimates (accounting for adjustment variables) and 95% confidence intervals.

For the first secondary endpoint, *AEs and SAEs*, we will use a Cox regression, e.g.:

```
stset timevar, failure(y) id(idvar)
bootstrap, reps(1000) seed(XXX): stcox x1 x2
```

We will use multiple imputation to handle missing values on covariates (see section 6.4). There won't be missing values on (S)AEs, as participants who drop out from the study will be right-censored. If there is collinearity between covariates, we will remove one colinear variable based on theoretical reasons. If the assumption of proportionality of hazard is not met, we will stratify on the problematic variable(s).

For the second secondary endpoint, *proportion of PCP who agree to participate*, we will calculate a percentage with a 95% confidence interval, using Wilson intervals which are superior for small samples without being overly conservative like exact methods (6), e.g.:

```
cci proportions n x, Wilson
```

For analyses on the PP set, we will run the same analyses as described in section 6.2.1. In addition, we will use inverse probability weighting for ICE1 and ICE2. We will derive stabilized weights separately and combined them by multiplying them. The covariates used to create weights are the following. For ICE1, we will use for GP/walk-in clinic, age, sex, education, beginning of symptoms (number of days), and baseline ABSS. For ICE2, we will use for GP/walk-in clinic. We will truncate weights at

the 99th percentile. The weights will then be used in the main adjusted model to re-balance randomization groups. We will check whether balance was achieved using standardized mean/proportion differences, which should be lower than .25 (7, 8). As balance may not be achieved using multiple imputation, we will use simple imputation in models using inverse probability weighting.

6.2.3 Sensitivity analyses

If the first co-primary endpoint (reduction in ABSS) is not normally distributed, we will run sensitivity analyses using negative-binomial regression (if data are positively skewed) or other transformations (i.e., square root transformation for positively-skewed data or square for negatively-skewed data).

6.2.4 Subgroup analyses

We will perform stratified analyses on the two primary endpoints for:

- Sex (men and women)
- Type of site (PCPs and walk-in clinics)
- Smoking status

While COVID-19 was a pre-planned analysis in the protocol, it is no longer possible since there is no testing for SARS-CoV-2 infection.

6.2.5 Additional analyses

In addition, we will explore:

Time to clinical improvement: We will test how long it takes to achieve symptom recovery using a Cox regression with the randomization group predicting time to complete resolution of symptoms (adjusted model with multiple imputation, as described in section 6.2.2).

Change in ABSS: We will test the trajectory of ABSS over time. In a first step, we will calculate a group-based trajectory model (GBTM) to identify trajectories of symptom severity over time, coding the score to 0 when symptom recovery is achieved. GBTM is kind of finite mixture modelling that identifies groups of individuals who share a similar trajectory based on a multinomial strategy with maximum likelihood estimation (9). The number of trajectories will be selected using usual fit indices: Akaike Information Criterion (AIC), Bayesian information criterion (BIC), loglikelihood, entropy, and the percentage of participants in each class (≥ 5%%). We will then test whether the group membership is associated with the randomization group using a multinomial regression with bootstrapped standard errors, adjusting for covariates. Odds-ratios will be reported.

Time to antibiotics use: We will test how long it takes to use antibiotics using a Cox regression, with the randomization group predicting time to antibiotics use (adjusted model with multiple imputation, as described in section 6.2.2).

6.2.6 Assessment of statistical assumptions

Statistical assumptions will be assessed using appropriate tools and diagnostic plots. Alternative models have been described above.

6.3 Interim analyses

No interim analyses are planned.

6.4 Missing data

For missing data on outcomes and covariates, we use multiple imputation by chained equations (MICE), under the assumption of missing at random (MAR). Ten imputation datasets will be created

and results pooled using Rubin's rule. The following auxiliary variables will be used to predict missingness: type of recruitment (PCP/walk-in clinic), age, sex, level of education, smoking status, beginning of symptoms (number of days), and baseline ABSS. Variables with missing values will be removed from the auxiliary list of variables. Terminal events such as death will be used as auxiliary variables. Technical issues (e.g., wrong email, reminder not sent) that cause missingness will also be used as auxiliary variables. For the PP analyses, we will also use inverse probability of attrition weights, which will be combined to inverse probability weights accounting for ICEs by a multiplication. We will use stabilized weights, truncated at the 99th percentile.

6.5 Safety evaluation

See section 6.2.2.

6.6 Subproject (if applicable)

Subprojects will be described in their own SAPs, where appropriate.

6.7 Statistical software

Statistical analysis will be performed with Stata 18. If required, some analyses will be performed in R (version 4.4.2 or more recent).

6.8 Quality control

An independent statistician will check the code of analyses described in sections 6.2.1 to 6.2.4.

7. Changes from the Protocol

Not applicable.

8. References

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