Clinical Study Report	
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A BIOEQUIVALENCE STUDY OF AN ORAL DISSOLVABLE FILM FOR TRANSMUCOSAL NICOTINE DELIVERY WITH NICORETTE® PEPPARMINT ORAL NICOTINE SPRAY AS REFERENCE PRODUCT

Study duration (FPI-LPO) 14May2012-26Sep2012

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The clinical study was conducted, and essential study documentation archived, in compliance with company SOPs and standards, which incorporate the requirements of the EU Clinical Studies Directive 2001/20/EC and ICH Guideline for Good Clinical Practice.

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2 SYNOPSIS

Study Title: A bioequivalence study of an oral dissolvable film (ODF) for transmucosal nicotine delivery with Nicorette® peppermint oral nicotine spray as reference product	
Study code: FFT-01-11	**EudraCT No:** 2011-000930-12
Principal Investigator: Jon Enestig, MD	
Study centre: Capio S:t Görans Sjukhus Department of Medicine 112 81 Stockholm	
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Objectives

Primary objective: The primary objective was:

- to evaluate if Nicotine ODF achieved a comparable pharmacokinetic (PK) profile as compared to Nicorette® peppermint oral spray.

Secondary objectives: The secondary objectives were:

- to compare the overall subjective satisfaction between Nicotine ODF and Nicorette®.
- to evaluate the subjective urges to smoke following treatment with Nicotine ODF and Nicorette®.
- to evaluate nicotine withdrawal following treatment with Nicotine ODF and Nicorette®.

Safety objective: The safety objective was:

- to evaluate the safety and tolerability of Nicotine ODF when administered as a single dose.

Study design

This was an open, randomized, two-period, two-sequence, single dose, cross-over study to evaluate

the PK profile of Nicotine ODF when given as a single dose to Subjects with nicotine dependence. The Subjects served as their own controls thereby eliminating the impact of inter-subject variance. The study included three subject visits; one screening visit and two dosing visits. For Subjects with unresolved Adverse Events (AEs) at the end of the last visit, a follow-up safety contact was to be made 7±2 days after Visit 2. The screening was to take place within 21 days of the first dosing visit, Visit 1 (Day 0), the second dosing visit took place on Visit 2, which took place between 6 and 21 days after Visit 1. Subjects were sequentially randomized, as they became available for dosing, into two equally sized groups, one receiving first Nicorette® nicotine oral spray followed by the ODF and vice versa for the other group.

Methodology

A screening visit was conducted to assess the eligibility of the Subjects. Within 21 days of screening the first dosing visit was conducted, followed by the second dosing visit 6 to 21 days thereafter. During the dosing visits, a blood sample was taken pre-dose and a total of 10 blood samples were taken during six hours post-dose to analyze the PK profile. Questionnaires were used during the study to assess the Subjects 1) nicotine dependence, 2) satisfaction following use of the test and reference products respectively, 3) urges to smoke following use of the test and reference product respectively and 4) nicotine withdrawal following use of the test and reference product respectively. To assess safety, AEs and vital signs were collected and physical examination was performed during the dosing visits.

Number of subjects

40[1] ~~24~~ Subjects were randomized to receive the test product, Nicotine ODF, and the reference product, Nicorette® peppermint oral spray, in a cross over design. *20*[1] ~~12~~ Subjects were randomized to receive the test product first and *20*[1] ~~12~~ Subjects to receive the reference product first. The dose administrations were separated by 6 to 21 days.

Diagnosis and main eligibility criteria

Inclusion Criteria:

1. Healthy male and female smokers 18-55 years old.

Exclusion Criteria:

1. Physical or mental disorder that could impair the Subject's ability to participate in the study.
2. Ischemic Heart Disease, Cardiac infarction, or Cardiac arrhythmias in the medical history or signs of previous infarction on ECG from the screening visit.
3. Cerebrovascular disease in the medical history.
4. Uncontrolled hypertension, defined as Systolic Blood Pressure (SBP) ≥180 mm Hg and/or

[1] See section 9.8.2

Diastolic Blood Pressure (DBP) ≥110 mm Hg.

5. Moderate to severe liver or kidney disease, as judged by the Investigator.
6. Anaemia defined as haemoglobin <115g/L in women and <135g/L in men.
7. Known or suspected active hyperthyroidism.
8. Known or suspected phaeochromocytoma.
9. Active infection in the mouth or throat.
10. Pregnant or lactating females
11. Participation in any other clinical study within three months prior to enrolment or during the present study.
12. Known or suspected alcohol or illicit drug abuse.
13. History of alcohol or drug abuse.
14. Need for regular medication with prescription or over-the-counter drugs except contraceptives.
15. Dry mouth problems.
16. Has a nicotine level of ≥ *0.5* ~~2~~ ng/ml measured pre-dose at *either of* the ~~first~~ dosing visit*s were to be excluded from the bioequivalence calculations*.[2]
17. Known human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody positive status.
18. If the Investigator, for any other reason, judged that the Subject should not be included (e.g. if Subject was considered unlikely to comply with study procedures, restrictions, and requirement or if Subject was expected to withdraw from the study).

Investigational product, dosage and mode of administration, batch number

2.0 mg of Nicotine ODF administered to the oral mucosa. Batch numbers: 20120423-97:2/4 and 20120423-97:2/5.

Comparator product, dosage and mode of administration, batch number

Nicorette® peppermint oral spray, the dose was 2 mg given as two sprays administered into the mouth at close distance avoiding the lips. Batch numbers: ND132C.

Duration of treatment

The Subjects received a single dose of the test product and a single dose of the reference product with a 6 to 21 day interval.

Duration of subjects involvement in the study

The duration of the Subjects involvement in the study was four weeks including a three weeks screening period.

Efficacy and pharmacokinetic assessments

Blood samples were taken during the two dosing days for evaluation of the PK profile and calculation of Area Under the plasma concentration time Curve (AUC), t_{max} and C_{max}.

Subjects completed a questionnaire assessing their overall satisfaction of the test product and the reference product at the end of Visit 2.

Subjects completed the brief questionnaire on smoking urges (QSU brief) pre-dose, 30 minutes and 1

[2] See section 9.8.2

hour after the test product and reference product administration to assess the Subjects' urges to smoke.

Subjects completed a nicotine withdrawal questionnaire pre-dose and 30 minutes after administration of the test and reference products at Visits 1 and 2.

Subjects completed the Fagerström test for nicotine dependence (FTND) questionnaire, during the screening visit to assess the Subjects' dependence to nicotine.

Safety assessments

Safety and Tolerability will be assessed by collecting of AEs, vital signs and physical examination.

Statistical methods

Determination of sample size: Approximative formula of Hauschke for bioequivalence cross-over design.

Test for equivalence: CI of the AUC and C_{max} ratio between test and reference products. Descriptive statistics of t_{max}.

Analysis of variance (ANOVA) of log transformed data.

User satisfaction nicotine withdrawal and questionnaire on smoking urges: Results are presented descriptively in tables, listings, and graphs, as appropriate.

Safety and Tolerability: Results are presented descriptively in tables, listings, and graphs, as appropriate.

FTND questionnaire: Results are presented descriptively.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS

The pharmacokinetic analysis show that the 90% confidence intervals of the mean ratios are [0.91 – 1.11] for AUC and [0.83 -1.16] for C_{max}. For both variables the confidence intervals are contained within the equivalence region (0.8-1.25).

SAFETY RESULTS

In total, 70% of the subjects experienced at least one AE during the study. There were no major differences in the AEs reported between Nicotine ODF and Nicorette Spray.

The most frequently reported AEs were globus and nausea following treatment with both Nicotine ODF and Nicorette Spray. Nicotine ODF was found to be safe and well tolerated.

There were no deaths, SAEs or withdrawals due to AE.

CONCLUSION

This study was performed to test a new platform (/drug delivery system) for drug administration via the buccal mucosa using nicotine as a model substance. The study primary endpoint was to show

bioequivalence between Nicotine ODF and Nicorette Spray. The results show that 2mg Nicotine ODF is bioequivalent with 2mg of Nicorette spray.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
ANOVA	Analysis of Variance
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
C_V	Coefficient of Variance
DCF	Data Clarification Form
FTND	Fagerström Test for Nicotine Dependence
GCP	Good clinical practice
ICF	Informed Consent Form
DBP	Diastolic Blood Pressure
ICH	International conference on harmonization
IEC	Independent Ethics Committee
ITT	Intention-to-Treat
NRT	Nicotine Replacement Therapy
ODF	Oral Dissolvable Film
PIS	Patient Information Sheet
PK	Pharmacokinetic
QSU brief	Brief questionnaire on smoking urges
SAE	Serious adverse event
SD	Standard Deviation
SPB	Systolic Blood Pressure
SUSAR	Suspected Unexpected Severe Adverse Reaction
U-hCG	Urine human chorionic gonadotropin hormone
WHO	World Health Organisation

Term	Definition of term
Screening failure	Non eligible Subject
Enrolled Subject	Subject who signed Informed Consent Form
Included Subject	Subject who was randomized to receive study medication
Withdrawn Subject	Subjects who prematurely discontinued the study
Completed Subject	Subject who completed all study visit
End of Study	Last Subject last visit

5 ETHICS

5.1 Ethical review

The study protocol and protocol amendments were reviewed by the Independent Ethics Committee in Stockholm and necessary approvals were obtained.

IEC approvals are included in Appendix 16.1.3.

5.2 Ethical conduct of the study

The study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

5.3 Patient information and consent

It was the responsibility of the Investigator to give each potential study Subject adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before including the Subject in the study. The Subject was to be informed about the right to withdraw from the study at any time. The Subject was to be allowed sufficient time for consideration of the proposal.

Furthermore, it was the responsibility of the Investigator to obtain signed informed consent from all Subjects before including them in the study. The ICF was to be signed and dated before any study-specific procedures were performed, including screening procedures. The signed PIS and ICF was filed by the Investigator for monitoring and possible future audits and/or inspections, a copy was to be given to the Subject. The Investigator confirmed the receipt of the signed ICF for each Subject by signing the appropriate part of the Subject's Case Report Form (CRF).

The Final version of the PIS and ICF was submitted to the IEC and concerned Competent Authority and was not to be changed without permission from Sponsor and the local IEC.

The written patient information and informed consent form is included in Appendix 16.1.3.

5.4 Subject data protection

The Investigator filed a subject identification list, which includes sufficient information to link records, i.e. the CRF and clinical records. This list has been preserved for possible future inspections/audits but was not be made available to FFT Medical AB or delegate except for monitoring or auditing purposes.

The Subjects was informed that the data was to be stored and analyzed by computer, that Swedish and local regulations for the handling of computerized data were to be followed and that identification of individual Subject data would only be possible for the Investigator.

The potential study Subject was informed that by signing the ICF he/she approved that authorized representatives from FFT Medical AB or delegate, the IEC and the Competent

Authorities had direct access to his/her medical records for verification of clinical study procedures.

6 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

For the Investigator and study administrative structure, please see the title page of this Study Protocol.

Clinical study report signatures are included in Appendix 16.1.5.

7 INTRODUCTION

Globally about 1.3 billion people smoke tobacco [Shafey, Dolwick and Guindon 2003] and it has been estimated that 40% of the smokers will die prematurely from a disease associated with smoking [Peto et al. 1992]. Tobacco smoking has been identified as the single largest preventable cause of morbidity and premature death in the developed world [US Department of Health and Human Services 1988]. According to World Health Organisation (WHO), approximately 5.4 million deaths per year are attributable to tobacco-related disease [WHO, 2008]. A large body of scientific evidence supports a causal association between smoking and numerous diseases including respiratory diseases such as chronic obstructive pulmonary disease (COPD), one of the top five leading causes of death worldwide [SCB 2008] as well as different forms of cancer including lung cancer, the second leading cause of cancer deaths in Sweden [SCB 2008] and cardiovascular diseases.

Nicotine is an alkaloid that is present in and derived from the tobacco plant. It is widely accepted that cigarette smoking, to a large extent, is facilitated and driven by nicotine dependence.

Although most smokers quit without assistance, smokers who receive assistance are more likely to be successful [Fiore et al. 2008]. NRT remains the most widely used complement to behavioural interventions. The therapeutic benefit of NRT products are supported by results of 180 controlled studies demonstrating that patients receiving pharmacotherapy are approximately twice as likely to remain abstinent for more than 6 months [Stead et al 2008]. NRT products are available in a number of different formulations such as chewing gum, sublingual tablets, adhesive transdermal patches, nasal spray and oral mucosal inhalers as well as in different doses [FASS2010]. Most of these nicotine formulations, however, give a slow onset of action as compared to during tobacco smoking. After inhalation of cigarette smoke, the level of nicotine in the blood rises rapidly and reaches the brain within 10-20 seconds via the internal carotid arteries [C.K. Svensson 1987]. In the brain, the nicotine binds to nicotine receptors, which results in an increased in dopamine, which provide the smokers with the pleasurable sensation of smoking, the cognitive arousal and the rapid relief of the symptoms of nicotine abstinence. With nicotine delivered from chewing gum, sublingual tablets and oral mucosal inhalers, the resultant plateau blood nicotine levels are reached after 30 minutes. With transdermal adhesive patches it takes hours to reach a plateau [FASS 2010]. The only NRT products that provide a rapid absorption, reaching a plateau in about 5-10 minutes, which is similar to that of a cigarette puff are nasal and oral sprays [FASS2010, Hukkanen et al 2005]. Nicotine uptake depends on passive diffusion. The net rate of transportation through a membrane can be calculated by using the mathematical product of membrane permeability, surface area and the concentration difference. In the fast acting formulas, a relatively large surface area and a high concentration ratio is achieved through a “one hit” deposition of the

drug on a relatively large surface in the oral and nasal mucosa respectively. As has been found, this approach is complicated by adverse effects for many patients, reducing user satisfaction. Runny nose and nasal irritation are among the problems experienced by most users (Sutherland et al 1992, FASS2010). Another problem is that reactions in the mucosa may accelerate dilution from saliva and nasal secretions. When the drug is diluted, the concentration gradient decreases and hence the transmucosal transportation rate.

This study will evaluate a new formula for nicotine uniquely combining rapid transmucosal delivery with the convenience of an oral completely dissolving alginate film that will adhere to the mucosa and thus maintain the concentration gradient. Our own tests indicate a dissolution time for the film of approximately 1 minute (unpublished data). We accordingly expect a higher bioavailability and less adverse effects from swallowed nicotine. We believe our invention could benefit smokers not satisfied with the NRT available today. A fast acting, well tolerated, NRT alternative could be used alone or as a complement to slow release skin patches. Our hope is that the medication can provide new means for smokers, not satisfied with presently marketed NRT products, to quit or reduce their smoking.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective

The primary objective was to evaluate if Nicotine ODF achieved a comparable pharmacokinetic (PK) profile as compared to Nicorette® peppermint oral spray.

8.2 Primary endpoint

The primary endpoint was:

- to compare Area Under the plasma concentration time Curve (AUC), t_{max} and C_{max} for Nicotine ODF, as compared to Nicorette® peppermint oral spray.

8.3 Secondary objectives and endpoints

8.3.1 Secondary efficacy objectives

The secondary objectives were:

- to compare the overall subjective satisfaction following treatment with Nicotine ODF and Nicorette® peppermint oral spray.
- to evaluate the subjective urges to smoke following treatment with Nicotine ODF and Nicorette® peppermint oral spray.
- to evaluate nicotine withdrawal following treatment with Nicotine ODF and Nicorette® peppermint oral spray.

8.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints were:

- to assess the user satisfaction following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the User Satisfaction Questionnaire.
- to assess the urge to smoke following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the QSU brief questionnaire pre-dose, 30 minutes and 1 hour after the respective treatment.
- to assess signs of nicotine withdrawal following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the nicotine withdrawal questionnaire pre-dose and 30 minutes after each dose administration.

8.3.3 Safety objective

The safety objective was:

- to evaluate the safety and tolerability of Nicotine ODF when administered as a single dose.

8.3.4 Safety endpoints

The safety and tolerability endpoints were:

- to evaluate the nature, incidence and severity of Adverse Events (AE) and Serious Adverse Events (SAE)
- to evaluate physical examination findings
- to evaluate vital signs findings

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

This was a randomized, two-period, two-sequence, single dose, cross-over, non-blinded study. The Subjects were their own controls eliminating the impact of inter-subject variance. A total of 24 Subjects, male and female subjects aged 18 to 55 were to be included in the study.

A screening visit was conducted as within 21 days of Visit 1(Day 0), when the first dose administration occured. If the screening assessments provided proof of eligibility, the Subject was randomized into the study on Visit 1 (Day 0). The Subjects were to come back to the clinic on Visit 2 (Day 6-21) for the second dose administration.

The 24 Subjects were to be sequentially randomized, as they became available for dosing, into two equally sized groups, one receiving first Nicorette® nicotine oral spray followed by the ODF and vice versa for the other group (randomization scheme is included in Appendix 16.1.7).

During each dosing day, study assessments were performed by the Site Personnel and blood samples were to be taken. At the beginning of each dosing day, a peripheral venous catheter was inserted by a qualified nurse, for taking blood samples.

A baseline PK sample was taken before administration of the respective drug. PK blood samples were then to be taken post-dose, according to the protocol for evaluation of the PK

profile. Any AEs were to be thoroughly recorded for both groups from dose administration on Visit 1 until the end of Visit 2 or if applicable until the follow-up safety phone call seven days after Visit 2.

Four questionnaires were used in the study to assess the participating Subjects' nicotine dependence, how satisfying they found the test and reference products, to assess signs of nicotine withdrawal before and after dose administrations and to assess the Subjects' urges to smoke pre-dose, 30 minutes and 1 hour after treatment with the test and reference product respectively.

The study protocol and amendments A1 to A4 are included as Appendix 16.1.1 and a sample case report form (unique pages only) is included as Appendix 16.1.2.

9.2 Rationale for study design, doses and control group

The study was designed according to the bioequivalence guidelines [EMEA guideline 2010] to show bioequivalence between the test product and the reference product.

The normal dose of the reference product spray was 1-2 mg at each dosing occasion, corresponding to 1-2 sprays. The dose that was administered was 2mg of the reference product and 2mg of the test product. The ODF formulation was believed to have slightly faster and more reproducible absorption than oral spray. The rationale of having 2mg of the test product was to be able to show this and still have results bioequivalent to 2mg of the reference product.

The Subjects in the study were habitual smokers as it would have been unethical to administer nicotine to non-smokers, considering the addictive property of nicotine. Also the effects induced by a one-time use of nicotine would most likely have been unpleasant to non-smoking subjects.

9.3 Selection of study population

9.3.1 Inclusion criteria

A Subject was eligible for participation in the study if all of the following criteria were fulfilled:

1. Male or female smokers 18 to 55 years at the time of signing the ICF.
2. Body Mass Index between 18.5 and 30.0 kg/m².
3. Smoked on average at least 7 cigarettes per day, for at least the last two years.
4. Had signed the ICF.

9.3.2 Exclusion criteria

A Subject was eligibility for inclusion in the study if none of the following criteria were fulfilled:

1. Physical or mental disorder that could have impaired the Subject's ability to participate in the study.
2. Ischemic Heart Disease, Cardiac infarction, or Cardiac arrhythmias in the medical history or signs of previous infarction on ECG from the screening visit.
3. Cerebrovascular disease in the medical history.

4. Uncontrolled hypertension, defined as Systolic Blood Pressure (SBP) ≥180 mm Hg and/or Diastolic Blood Pressure (DBP) ≥110 mm Hg.
5. Moderate to severe liver or kidney disease, as judged by the Investigator.
6. Anaemia defined as haemoglobin <115g/L in women and <135g/L in men.
7. Known or suspected active hyperthyroidism.
8. Known or suspected phaeochromocytoma.
9. Active infection in the mouth or throat.
10. Pregnant or lactating females
11. Participation in any other clinical study within three months prior to enrolment or during the present study.
12. Known or suspected alcohol or illicit drug abuse.
13. History of alcohol or drug abuse.
14. Need for regular medication with prescription or over-the-counter drugs except contraceptives.
15. Dry mouth problems.
16. Had a nicotine level of ≥ *0.5* ~~2~~[3] ng/ml measured pre-dose *at either of* the ~~first~~ dosing visits *were to be excluded from the bioequivalence calculations*[4].
17. Known human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody positive status.
18. If the Investigator, for any other reason, judged that the Subject should not be included (e.g. if Subject was considered unlikely to comply with study procedures, restrictions, and requirement or if Subject was expected to withdraw from the study).

9.3.3 Restrictions

- The Subjects were instructed to abstain from use of any nicotine medication or tobacco product for at least 10 hours (5 nicotine elimination half-lives) before dosing on Visit 1 and Visit 2.
- The Subjects were instructed to fast for at least 8 hours prior to dose administration on Visit 1 and Visit 2, and no food was allowed until 1 hour post-dose. Water was allowed as desired except one hour before and one hour after drug administration.
- The Subjects were instructed to abstain from vigorous physical activity from at least 8 hours prior to the dose administration on Visit 1 and Visit 2.
- No concomitant drugs, herbal medicine, grapefruit juice or alcohol were allowed from 24 hours before and during Visit 1 and Visit 2, exception made only for contraceptives.

9.3.4 Removal of study subjects from treatment or assessments

A study Subject was withdrawn from the study treatment if, in the opinion of the Investigator, it was medically necessary, or if it is the expressed wish of the Subject.

[3] The level to be used was the detection limit of the analysis which after change of laboratory was 0.5 ng/ml

[4] It is clarified that subjects with nicotine level > 0.5ng/ml pre-dose at either of the dosing visits were excluded from the bioequivalence analysis

If a Subject did not return for a scheduled visit, every effort was made to contact the Subject to document the reason for the withdrawal. If a Subject was withdrawn due to an AE the Subject was followed up by a phone call one week after the withdrawal. The CRF was completed as far as possible and collected by the Monitor.

A Subject's participation in the study was to be discontinued if any of the following criteria applied:

- Consent withdrawn
- Subject experienced AEs or SAE that contraindicated continuing the study, as judged by the Investigator
- Subject's general condition contraindicated continuing the study, as judged by the Investigator
- Major protocol violations
- Non-compliance with the restrictions specified is section 9.3.3.

9.4 Treatments

9.4.1 Identity of test product

The test product was an ODF formulation manufactured by Vecura, Karolinska University Hospital. Each film contained 2.0mg nicotine which was the dose administered in this study. The test product was administered by the Investigator to the oral mucosa of the Subjects. The films are beige-white and have lemon flavour, the size of each film is 2x3 cm and the thickness is 0.07 mm.

9.4.2 Identity of Reference Product

The reference product was a clear oral spray with peppermint flavour manufactured by McNeil AB. Each bottle contained 13.2ml of liquid and allowed 150 sprays containing 1mg of nicotine. The dose given in this study was 2 mg administered by the Investigator as 2 sprays.

9.4.3 Packaging, labelling and storage of the test product

The labelling of the test product, including the reference product, followed the instructions given in Revised Annex 13, Manufacture of investigational medicinal products, Volume 4 of the rules governing medicinal products in the European Union.

The GMP unit at Huddinge Hospital was responsible for packaging and labelling of the test product.

The test product was packed separately in aluminium foil peel. Each foil peel was clearly labelled indicating the content of test product.

The reference product was provided as plastic spray bottles, one bottle for each dosing day. Each plastic bottle was clearly labelled indicating the content to be the reference product in the proposed clinical study.

The test and reference product were stored in a secure area with restrictive access during the entire study period. The test product was stored under dry conditions and both the test and the

reference products were stored in room temperature (no more than 25ºC). Any deviations from the recommended storage condition were to be reported immediately to Fredrik Sjöö at FFT Medical AB and the study medication was not to be used until authorisation had been given by FFT Medical AB.

9.4.4 Doses and treatment regimens

The Sponsor supplied the test product, Nicotine 2.0mg films. The film was administered by the Investigator to the oral mucosa of the Subject´s palate where it adhered and released the nicotine.

The reference product, Nicorette® peppermint oral nicotine spray was supplied by the Pharmacy. Nicorette® peppermint oral nicotine spray was administered by the Investigator in a dose of 2 mg, given as two sprays into the mouth.

All Subjects were to receive one dose of the test product and one dose of the reference product, separated with 6 to 21 days. The same doses were to be given to all Subjects.

9.4.5 Product accountability

The test product was released to the study site after approvals of the Study Protocol had been received from the IEC and the Competent Authority. The test product was dispensed to the study Subjects on Visit 1 and Visit 2 by the Investigator.

The Investigator was responsible for keeping detailed records, which showed the quantity of test product that was stored, delivered to and taken out from the place of storage. Any discrepancies between dispensed and returned test product were to be explained and documented.

Products deliberately and/or accidentally destroyed by the Investigator/ Hospital Pharmacy or the Subject, were also to be accounted for.

The Monitor performed test product accountability and made sure that all unused test product was adequately destroyed/returned and documented.

9.4.6 Method of assigning subjects to treatment groups

The *40* ~~24~~[5] Subjects were to be sequentially randomized, as they became available for dosing, into two equally sized groups, one receiving first Nicorette® peppermint oral nicotine spray followed by Nicotine ODF and vice versa for the other group. For practical reasons, a maximum of eight Subjects could be dosed on each dosing day.

9.4.7 Blinding

This was a non-blinded study.

9.4.8 Emergency decoding of blinded treatment

Not applicable.

[5] See section 9.8.2

9.4.9 Prior and concomitant therapy

All concomitant therapy used during and within 3 weeks prior to the study period was to be recorded in the CRF. No other drug under investigation could be used concomitantly with the study medication.

The Subjects could not participate concurrently in any other clinical study.

9.4.10 Continuation of treatment

Additional treatment with the test product, in addition to what was described in the protocol, was not administered.

9.4.11 Treatment compliance

The dosing of the test product was performed during visits at the site and was performed by the Investigator, who verified the treatment compliance

9.5 Study assessments

9.5.1 Demographics and other baseline characteristics

Subject demographic data (including date of birth and gender) and a complete medical history were obtained during the screening visit.

9.5.2 Efficacy assessments

A *user satisfaction questionnaire* (Appendix 16.1.1) was administered at the times indicated in the protocol. The questionnaire assessed the Subjects' overall satisfaction between the test and reference products respectively. The questionnaire was filled out by the Subjects themselves.

A questionnaire to assess the Subjects' urges to smoke, the *QSU brief questionnaire* (Appendix 16.1.1) was completed by the Subjects pre-dose and at 30 minutes and1hour after administration of the test and reference products, respectively. The questionnaire was filled out by the Subjects themselves.

A *nicotine withdrawal questionnaire* (Appendix 16.1.1), to assess the Subjects' signs of nicotine withdrawal symptoms, was completed by the Subjects pre-dose and 30 minutes after administration of the test and reference products, respectively. The questionnaire was filled out by the Subjects themselves.

The *FTND questionnaire,* a two question questionnaire (Appendix 16.1.1) was completed by the Subjects during the screening visit. The results indicate the Subjects degree of dependence to nicotine. The results might be used in explorative analyses to link degree of dependence on an individual level to other study results[6].

[6] Such analyses have not been performed.

9.5.3 Pharmacokinetic assessments

9.5.3.1 Sample collection and handling

A baseline sample was taken before administration of the respective drug.

Blood samples for evaluation of the pharmacokinetic profile were then taken after 2 minutes, 5 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours and 6 hours, respectively. The procedure was repeated when the Subject returned for the second treatment. Serum concentrations of nicotine were determined in blood, sampled and analysed according to Appendix 19.11 of the study protocol; Appendix 16.1.1. Each sample was divided into two tubes whereof the first was sent to ABS Laboratories in England for analysis and the second was stored in KI Biobank at Karolinska Institutet until 6 months after the end of the study if re-analysis was required. Samples were thereafter destroyed.

9.5.3.2 Pharmacokinetic analysis

Blood samples were analyzed using liquid chromatography.

AUC were estimated with a non-compartmental model using combined trapezoidal rule, linear until the peak concentration and beyond the peak concentration using log trapezoidal rule. The calculations were made using WinNonlin® 5.2 software from Pharsight Inc.

9.5.4 Laboratory assessments

Blood samples for determination of clinical chemistry and haematology were taken at the screening visit. A urine pregnancy test (u-hCG) was performed for all women of child bearing potential during screening.

The samples for clinical chemistry and haematology were analysed using routine methods at Unilabs Clinical Chemistry Laboratory, Sankt Görans Hospital, a SWEDAC accredited unit.

The collected specimens were stored at the Karolinska Institutet, Biobank according to an agreement between the Investigator and the sponsor. Blood samples were kept at the Department of Clinical Chemistry for six months after the end of the study and were thereafter to be destroyed.

9.5.5 Clinical safety assessments

9.5.5.1 Physical Examination

A physical examination was performed by the Investigator pre-dose and 6.5 hours post dose on the two dosing visits. The examination included cardiac and pulmonary auscultation, palpation of the abdomen and inspection of the oral mucosa in the palate and buccal area.

9.5.5.2 Vital Signs

Vital signs were assessed at time points indicated in the study protocol, Appendix 16.1.1. Vital signs measured included weight, height (on the screening visit only), SBP, DBP and heart rate.

9.5.5.3 Electrocardiogram (ECG)

A 12-lead paper ECG was obtained on the screening visit after the Subject had been sitting/lying down for at least 5 minutes. The Investigator evaluated the ECG as Normal/Abnormal Non-Clinically Significant/Abnormal Clinically Significant.

9.5.6 Adverse events

9.5.6.1 Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

An SAE is any untoward medical occurrence or effect that at any dose

- results in death
- is life-threatening
- requires patient's hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
- is regarded as medically important without meeting the above mentioned criteria.

9.5.6.2 Methods for eliciting adverse events

AEs were assessed from administration of the first dose on Visit 1 until the end of Visit 2 or if applicable until the safety follow-up phone call seven days after Visit 2.

An AE was either be reported spontaneously by the Subject, or reported in response to the questions "Have you experienced any unfavourable effects after the administration of the nicotine ODF/spray today?" and "Have you experienced any unfavourable effects since last visit?

All AEs, serious and non-serious, were recorded in the CRFs.

The following evaluations were made by the Investigator in connection with the AE:

- type of event
- seriousness
- degree of severity
- duration (start - end)
- action taken
- causality with study product
- outcome of the AEs

The Investigator rated the severity as follows:

Mild: The AE did not interfere with the Subject's usual function.

Moderate: The AE interfered to some extent with the Subject's usual function.

Severe: The AE interfered significantly with the Subject's usual function.

When assessing the causality to the study product, the following nomenclature was used:

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which could not be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) were to be clinically plausible. The event must have been definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable: A clinical event - including laboratory test abnormality - with a reasonable time sequence to use of the product, unlikely to have been attributed to concurrent disease or other drugs or chemicals, and which followed a clinically reasonable response on withdrawal (dechallenge). Rechallenge information was not required.

Possible: A clinical event - including laboratory test abnormality - with a reasonable time sequence to use of the product, but which could also have been explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may have been lacking or unclear.

Unlikely: A clinical event - including laboratory test abnormality - with a temporal relationship with use of the product which made a causal relationship improbable, and in which other drugs, chemicals or underlying disease provided plausible explanations.

Not assessable: A clinical event where the information received was too inadequate to allow a reasonable assessment.

For AE reporting purposes no distinction was made between the test or reference products.

9.5.6.3 Reporting of SAEs

All SAEs were to be reported by the Investigator using phone or fax within 24 hours of knowledge of the event to the Safety department at IRW Consulting AB, regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learned of it.

A SAE Report Form was also to be completed, signed by the Investigator and submitted to FFT Medical AB no later than five calendar days after the initial information was received.

No distinction was to be made between the test and the reference product regarding reporting of SAEs.

Only SAEs that were both unexpected and related to the test product, SUSARs, were subject to expedited reporting.

The Sponsor was responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of Subjects. The appropriate

IEC and Competent Authorities, as per local requirements, was to be informed by the Sponsor about SAEs associated with the use of the product (SUSARs).

9.5.6.4 Follow-up period after an AE

If a study Subject was withdrawn due to an AE, or if an AE persisted at the end of the study treatment period, this was to be followed up until the condition had ceased or until the Subject was under professional medical care and a potential causality between the investigational drug and the AE had been penetrated. An outcome assessment was to be performed when an AE persisted. In case of ongoing AEs at study termination they were to be followed up by a phone call one week after.

9.5.6.5 Procedures in case of pregnancy

All pregnancies (either through maternal exposure or transmission of a medicinal product via semen following parental exposure) were to be reported on a pregnancy notification form immediately within 24 hours after recognition. The pregnancy was to be followed up to determine outcome, including spontaneous or voluntary termination, details of birth and presence of any birth defects, congenital anomalies or newborn or maternal complication even if the Subject was discontinued from the study.

In case of pregnancy, the study treatment was to be stopped immediately, and the Subject discontinued from participation in the study.

9.5.6.6 Coding of AEs

All AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) by IRW after the CRFs had been collected from the study centre.

Periodic Safety Reporting

A safety report was to be sent to the Competent Authority and IEC within 90 days of the end of study together with the notification of the end of the study according to Article 10(c) of Directive 2001/20/EC. This report was to contain at least an analysis of the subjects' safety and line listings, and if appropriate aggregate summary tabulations.

9.6 Data Quality Assurance

The study was performed in compliance with Good Clinical Practice (GCP), applicable regulations and IRW Consulting SOPs.

A CRF was completed for each subject included. A sample of the CRF is included as Appendix 16.1.2.

The study sites were periodically visited by a monitor. The monitor had direct access to hospital records and original data.

All personnel involved in the study were listed on a signature and delegation list kept and updated by the Investigator.

Before inclusion of subjects into the study, a study initiation visit was performed by the monitor at each site in order to inform and train relevant study staff. The Investigator was thereafter responsible for providing appropriate study related training to new staff and to

forward any new information of relevance to the performance of this study to the staff involved.

No audit was performed during the study.

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Demographics and baseline data

Demographics and baseline data including the FTND, were presented in tabulations and listings. Descriptive statistics as mean, median, standard deviation, minimum and maximum were provided.

9.7.2 Analysis of efficacy

User satisfaction, urge to smoke and signs of nicotine withdrawal following treatment with Nicotine ODF and Nicorette®, were presented as tabulations and listings. Descriptive statistics as mean, median, standard deviation, minimum and maximum were provided.

9.7.3 Analysis of pharmacokinetic data

All individual concentration data and pharmacokinetic parameters were listed by formulation together with geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration/time curves were presented in linear/linear and log/linear scale.

The pharmacokinetic parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} and t_{max} were determined for the study formulation and for the reference formulation.

The assessment of bioequivalence was based upon 90% confidence intervals (CI) for the ratio of the geometric means (test/reference) for $AUC_{(0-t)}$ and C_{max}. If the 90% CI were contained within an interval of 0.8 and 1.25, the two formulations were to be considered bioequivalent.

$AUC_{(0-t)}$ and C_{max} was transformed using a logarithmic transformation and then subjected to analysis with an Analysis of Variance (ANOVA) fixed effects model using sequence, subject within sequence, period and formulation as sources for variance, in addition to residual error. A CI for the ratio study drug versus reference AUC and C_{max} was calculated from the data.

The CI was then back transformed to obtain the confidence interval geometric means for the ratio on the original scale.

WinNonlin® 5.2 software from Pharsight® was used for the statistical calculations as well as for the PK analyses.

9.7.4 Analysis of safety

AEs were collected from the first administration of the test or reference product until the end of Visit 2 or if applicable until the follow-up call after Visit 2.

All AEs were to be summarized and presented according to MedDRA system organ class and preferred term.

Descriptive statistics and individual listings were to be provided for AEs, laboratory data variables, vital signs and physical examination data. Depending on type, data were to be

tabulated in frequency tables or presented as mean, median, standard deviation, minimum and maximum values.

9.7.5 Statistical/analytical issues

9.7.5.1 Adjustments for covariates

No adjustments for covariates were made.

9.7.5.2 Handling of dropouts or missing data

No replacement of dropouts or withdrawn subjects was performed. No data imputations was made. Data points were considered missing at random.

9.7.5.3 Active-control studies intended to show equivalence

9.7.6 Analysis data sets

Safety Analysis Set: All Subjects who received at least one dose of the test product, were included in the safety analysis.

Intention-to-Treat (ITT) Analysis Set: All Subjects who receive at least one dose of the test product or reference product will be included in the description of the efficacy variables.

PK Analysis Set: Comprised all Subjects in the ITT Analysis Set who provided evaluable data for both treatment periods, i.e. no more than one missing data point from each treatment period for PK analysis and no pre-dose concentration greater than 5 percent of the C_{max} value for the subject in that period.

9.7.7 Determination of sample size

The number of subjects necessary for 90% power to prove the hypothesis of bioequivalence as previously described depends on intra-subject coefficient of variation (C_V) and actual difference between products. These factors were unknown. We estimated intra-subject log-transformed σ to approximately 15%, based on the fact that an inter-subject variability (30-50%) had been found in studies of similar products. We further estimated the actual difference between products to be no more than 5%.

Using the well-known approximate formula shown below for sample size in a cross-over design study for bioequivalence testing with log-transformed data the number of subjects for our study using the above assumptions was estimated to be 16 (15.73).

$$n \geq \frac{\sigma^2(t(\alpha, 2n-2) + t(\beta, 2n-2))^2}{(\log 1.25 - \log(\mu T/\mu R))^2}$$

α=level of significance

β=power

σ=intra subject standard deviation of log-transformed data

n=subjects per series (Total number of subjects=2*n*)

μT=Test formula mean result

μR=Reference formula mean result

(Adapted from Hauschke et al, J Pharmacokin Biopharm, Vol. 20, No. 5, 1992 pp 557-561)

We had chosen to calculate on a μT/μR>1. Due to asymmetry of the power curve on the original scale, the estimated sample size required was smaller than if we would have calculated on μT/μR<1. We, however, believed that it was more likely that the test formula had a slightly higher bioavailability than the reverse. Also, calculating with μT/μR<1 gave an estimate for need of subjects 2n=16.19. We accordingly concluded that the difference was not of any major importance.

From similar studies a drop-out frequency of approximately 30% has been reported (e g McRobbie et al. 2010) for included subjects. Accordingly we aimed to include 24 subjects for this study.

9.8 Changes in the conduct of the study or planned analyses

Four protocol amendments were made to the final study protocol. Amendments A1-A3 were approved and implemented before inclusion of the first study subject in the study. Therefore, the changes included in these amendments have been incorporated in the text of the report without being highlighted.

Changes included in Amendments A4 are presented below.

Protocol amendments No. A1-A4 are included in Appendix 16.1.1 to this report.

9.8.1 Amendment No.A4

Amendment No. A4, dated 20120903, was submitted to the MPA on 03SEP2012 for approval. Approval was received on 20120903. The amendment was not submitted to the IEC.

The final protocol was amended as follows:

Change 1

Extension of IMP shelf life to six months, i.e. for three additional months.

Reason for change

The study inclusion period was prolonged and therefore additional stability data was provided to support the use of the IMP for the entire duration of the trial.

Sections affected

No section of the protocol was affected by this change.

9.8.2 Changes not described in a formal protocol amendment

24 subjects had been planned to be included in the analysis however 40 subjects were included.

Due to a mistake, this change was not submitted to the competent authority or to the IEC for approval. When the 24 subjects planned to be included in the study had completed their participation, nicotine serum concentrations were analysed. It was discovered that 16 subjects had serum nicotine levels above above 0.5 ng/ml, the detection limit, despite having reported that they had not used any nicotine containing product s during the last 10 hours as specified in the protocol. According to the bioequivalence guideline (EMEA 2010) "*Subjects with non-zero baseline concentrations > 5% of C_{max}. Such data should be excluded from bioequivalence calculation*". Therefore, these subjects' nicotine concentration data were excluded from the bioequivalence analysis and 16 additional subjects were recruited into the study.

During the report writing period, when it was discovered that this change had not been submitted to or approved by the authorities the Sponsor contacted the competent authority and the IEC by phone and this issue was discussed. A letter was thereafter sent to the competent authority and the IEC respectively, formally informing them about the change in the study and the fact that the mistake of not seeking approval for this change had occurred. The letters are included in Appendix 16.1.13.

A clarification of exclusion criteria 16 was also made. During the protocol writing period a change of laboratory to analyse the nicotine levels was made. This change was made before finalising the study protocol and is therefore not shown herein. The change in laboratory also lead to a change in detection limit of nicotine from 2 to 0.5 ng/ml. Furthermore, since nicotine levels were not to be analysed until after the end of the study a clarification of exclusion criteria 16 was made as follows: Has a nicotine level of ≥ *0.5* ~~2~~ ng/ml measured pre-dose at *either of* the ~~first~~ dosing visit*s were to be excluded from the bioequivalence calculations*.

New text is shown in *italics* and deleted text is shown in ~~strikethrough.~~

The authorities were informed about this change after the end of the study, see Appendix 16.1.13.

9.8.3 Changes in the planned statistical analyses

It had been planned that no imputation of missing data was to be performed however imputation of one nicotine concentration value was performed for one subject. See section 11.1.2.2 for additional information.

10 STUDY SUBJECTS

10.1 Disposition of subjects

10.1.1 Number of subjects

In total 51 subjects were screened for participating in the study. Of those 40 subjects were randomised and included in the study. 20 subjects received Nicotine ODF and 20 received Nicorette during the first visit. Out of the 40 subjects that were included in the study 4 subjects were withdrawn, see Figure 1.

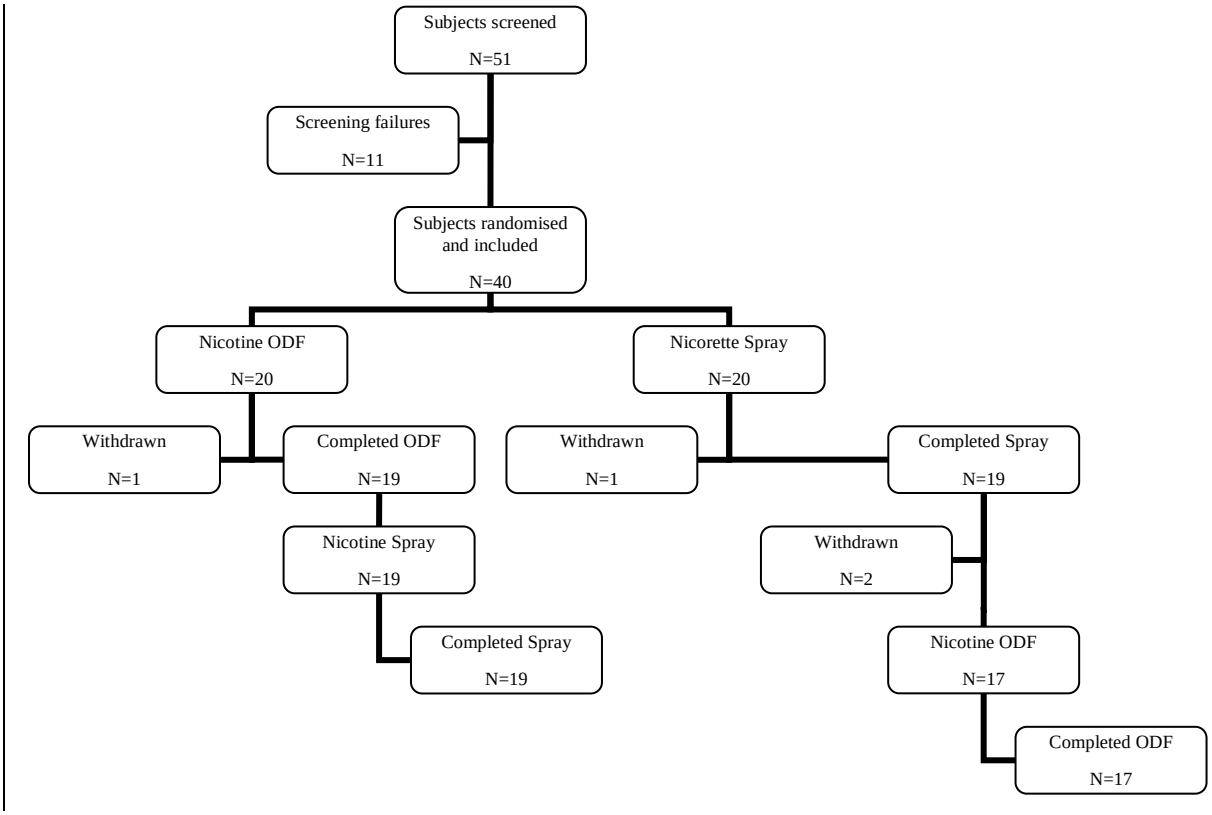

Figure 10.1 Flow chart of subjects participating in the study.

Eleven of the 51 subjects screened for participation in the study were found not to fulfil all eligibility criteria or did not show up to first visit and were therefore screening failures. A summary of reasons for screen failure is shown in Table 10.1.

Table 10.1 Screen failures, N=11

Reason for screen failure	No of subjects (%)
All eligibility criteria not fulfilled	4 (36.4)
Did not show up at first visit	7 (63.6)
Total no. of screening failures	**11 (100.0)**

10.1.2 Study discontinuations

Four randomised subjects discontinued their participation prematurely. Reasons for all post-randomisation discontinuations are shown in Table 10.2

Table 10.2 Reasons for discontinuation

Reason for discontinuation	No of subjects (%)
Lost to follow up	2 (50.0)
Other	2 (50.0)
Total number of withdrawals	**4 (100.0)**

At Visit 1, it was found that it was difficult to withdraw blood from two subjects (subject numbers PX2 and P#8) and they were therefore withdrawn from the study. Reason for withdrawal was recorded as "*other*". Two subjects (subject numbers PX14 and P#19) did not show up for the second treatment period and were recorded as "*lost to follow up*".

10.2 Protocol deviations

10.2.1 Major protocol deviations

Major protocol deviations were defined as any deviation from the inclusion and/or exclusion criteria, deviation in administration of the drugs administered in the study or other deviation affecting the primary efficacy variable and any deviation in the informed consent procedure.

One major protocol deviation (subject number PX11) was reported during the study. The deviation occurred while being treated with Nicotine ODF. See Table 10.3.

Table 10.3 Major protocol deviations

Deviation	Subjects in Safety analysis set N=40 n (%)	Subjects in PK analysis set N=13 n (%)
Incorrect dosing of IMP.	1 (2.5)	0 (0)
Total number of major protocol deviations	**1 (2.5)**	**0 (0)**

10.2.2 Minor protocol deviations

All protocol deviations not fulfilling the criteria for major deviations are considered as minor.

One minor protocol deviation was recorded during the study (subject P13 during treatment with Nicotine ODF), the nicotine blood sample to be taken at 360 minutes was taken before the stipulated time-point. The time-point at which the sample was taken was not recorded and is therefore not known. The result was included in the analysis for 360 minutes.

10.3 Data sets analyzed

Three analysis sets were defined in the study protocol.

Safety Analysis Set: All Subjects who received at least one dose of the test product, were included in the safety analysis.

Intention-to-Treat (ITT) Analysis Set: All Subjects who received at least one dose of the test product or reference product were included in the description of the efficacy variables. The ITT analysis set is identical to the Safety Analysis Set.

PK Analysis Set: All Subjects in the ITT Analysis Set who provided evaluable data for both treatment periods, i.e. no more than one missing data point from each treatment period for PK analysis and no pre-dose concentration greater than 5 percent of the C_{max} value for the subject in that period.

A listing of all subjects, visits and observations excluded from the efficacy analysis is provided in Appendix 16.2.3.

10.4 Demographics and other baseline characteristics

Individual subject demographic and baseline data for all subjects randomised is presented in individual listings in Appendix 16.2.4. Demographic data and baseline characteristics are shown below.

10.4.1 Demographics and vital signs

Demographic data (including gender and age) and vital signs (including height, weight, heart rate, systolic and diastolic blood pressure and ECG) was collected at the screening visit. Data is shown in Table 10.4.

Table 10.4 Demographic data and vital signs

Group			Kinetic	Safety
Gender				
	Male	n (%)	4(30.8)	14 (35.0)
	Female	n (%)	9(69.2)	26 (65.0)
Age (Years)				
	Mean		32	33
	SD		12.7	11.5
	Median		31	31
	min		18	18
	max		55	55
Values	n		13	40
Height (cm)				
	Mean		175	173
	SD		7.6	8.28
	Median		172	172
	min		166	160
	max		190	190
Values	n		13	40

Group			Kinetic	Safety
Weight (kg)				
	Mean		70	69
	SD		8.25	9.32
	Median		69.5	69.5
	min		56	50
	max		83	83
Values	n		13	40
Heart rate (bpm)				
	Mean		65	63
	SD		5.94	6.27
	Median		60	60
	min		60	50
	max		75	75
Values	n		13	40
Systolic (mmHg)				
	Mean		116	111
	SD		10.31	12.97
	Median		110	110
	min		110	90
	max		130	135
Values	n		13	40
Diastolic (mmHg)				
	Mean		72	68
	SD		7.25	8.24
	Median		70	70
	min		60	50
	max		85	85
Values	n		13	40
ECG				
	n		11	33
Normal	%		84.6	82.5
	n		2	7
Abnormal but not clinicly significan	%		15.4	17.5
	n		0	0
Abnormal and clinicly significant	%		0	0
Values	n		13	40

The demographic information shows that the mean age of the subjects participating in the study was 32 years at the time of inclusion in the study. Further, demographic data shows that a larger proportion of the subjects participating in the study were female, 65.0% and 69.2% in

the safety and kinetic populations respectively. Four male and nine female subjects were included in the kinetic analysis set.

Vital signs data show no notable findings or major differences between the safety and kinetic populations.

10.4.2 Physical examination

Physical examination was performed at the screening visit. No abnormal physical examination findings were reported in the study.

10.4.3 Medical history

Medical history was assessed at the screening visit. Results for the safety and kinetic analysis populations are shown in Table 10.5.

Table 10.5 Medical history

Group		Kinetic	Safety
Condition	Medical Abortion		
	n	0	1
	%	0	2.5
Condition	None		
	n	13	39
	%	100	97.5

One medical history event was reported in the study. One female subject (subject number PX8) in the safety analysis set reported a medical abortion.

10.4.4 Prior and concomitant medication

In total five subjects reported in summary seven prior or concomitant medications during the study. Four medications were prior medications used for the following diagnoses; two for medical abortion, one for pain and one for depression. Three medications were administered during the study; two hormonal contraceptive medications and one for dysthymia. For details see Appendix 16.2.4.

10.4.5 Fagerström test for nicotine dependence

The level of the participating subjects' nicotine dependence was assessed at the screening visit via two questions from the Fagerström test for nicotine dependence. Results are shown in Table 10.6. A listing of individual subjects' response is shown in Appendix 16.2.4.

Table 10.6 Fagerström test for nicotine dependence

Group		Kinetic	Safety
Q1: How soon after waking do you smoke your first cigarette?	Mean	0.77	1.43
	SD	0.93	1.03
within 6 min [3]	Median	0	2
6–30 min [2]	min	0	0
31–60 min [1]	max	2	3
more than 60 min [0]	n	13	40
Q2: How many cigarettes do you smoke per day?	Mean	0.23	0.53
	SD	0.44	0.51
less than 10 [0]	Median	0	1
11-20[1]	min	0	0
20-30 [2]	max	1	1
more than 30 [3]	n	13	40
Interpretation, total score:	Mean	1.00	1.95
	SD	1.15	1.32
0-1 = small nicotine addiction	Median	1	2
2 = moderate dependence	min	0	0
3 = strong dependence	max	3	4
4-6 = very strong nicotine addiction.	n	13	40

The results show that on average, subjects in the Safety analysis set had a higher total score, 1.95 than the subjects in the PK analysis set, 1.00, indicating that subjects in the Safety analysis set had a somewhat higher dependence to nicotine.

10.5 Measurements of treatment compliance

Administration of the test and reference products was performed by the Investigator during the subjects' visits at the site. The Investigator verified the treatment compliance. It was reported that drug administration failed for one subject (subject number PX11) while being treated with Nicotine ODF. Drug concentration of nicotine for this subject is shown in Appendix 16.2.6 together with listings of all individual subject nicotine plasma concentration data.

11 EFFICACY EVALUATION

11.1 Efficacy results and tabulations of individual subject data

Efficacy was assessed by measuring nicotine serum concentrations and questionnaires assessing; user satisfaction with the products, urges to smoke and signs of nicotine withdrawal.

11.1.1 Analysis of efficacy

11.1.1.1 Pharmacokinetic

Nicotine plasma samples were taken pre-dose and 2 minutes, 5 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours 4 hours and 6 hours post-administration of the test and reference products respectively. Samples were used to calculate the pharmacokinetic variables C_{max} and AUC to assess the bioequivalence between the two formulations. T_{max} was also determined for the two formulations.

The pharmacokinetic analysis show that the 90% confidence intervals of the mean ratios are [0.91 – 1.11] for AUC and [0.83 -1.16] for C_{max}. For both variables the confidence intervals are contained within the equivalence region (0.8-1.25).

Descriptive data of C_{max} and AUC following administration of Nicotine ODF and Nicorette Spray is shown in Table 11.1.

Table 11.1 Descriptive presentation of C_{max} and AUC, PK analysis set

		Spray N=13	ODF N=13
AUC	Mean	720.12	731.01
	Geometric mean	700.13	703.11
	Standard Deviation	190.79	211.68
	Coefficient of Variation	26.49	28.96
	Min	522.36	411.27
	Max	1238.69	1103.31
	Median	725.23	707.37
C_{max}	Mean	4.58	4.56
	Geometric mean	4.21	4.29
	Standard Deviation	2.27	1.71
	Coefficient of Variation	49.57	37.52
	Min	2.17	2.35
	Max	11.2	8.36
	Median	4.18	4.14

The mean AUC following administration of Nicotine ODF and Nicorette spray was 731.01 and 720.12 ng/ml, respectively. The mean C_{max} for Nicotine ODF and Nicorette spray was 4.56 and 4.38 ng/ml, respectively.

Descriptive data of t_{max} following administration of Nicotine ODF and Nicorette Spray respectively is shown in Table 11.2. T_{max} for individual subjects are shown in Appendix 16.2.6 and in Figure 11.1 and Figure 11.2.

Table 11.2 Descriptive presentation of T_{max}, PK analysis set

Group: Kinetic		
Visit 1 & 2		
T-Max (minutes) ODF	Mean	31
	SD	28,7
	Median	20
	min	10
	max	120
	n	13
T-Max (minutes) Spray	Mean	42
	SD	29,7
	Median	30
	min	5
	max	120
	n	13

Mean and median t_{max} values differed between Nicotine ODF and Nicotine Spray. Mean t_{max} was 31 minutes for Nicotine ODF and 42 minutes for Nicorette spray.

11.1.1.2 User satisfaction

Participating subjects' satisfaction with Nicotine ODF and Nicorette Spray was assessed at the end of the second dosing visit. Subjects responded to a questionnaire with eight questions regarding the two formulations, see Table 11.1.

A listing of all subject data is shown in Appendix 16.2.6.

Table 11.3 User satisfaction, Safety population

Group: Safety		
1. Which of the tested formulations, Spray or ODF, is the product you would choose for smoking cessation	Spray (n)	10
	Spray (%)	27.8
	ODF (n)	26
	ODF (%)	72.2
	Total (n)	36
2. Which of the products gives you the highest level of satisfaction?	Spray (n)	8
	Spray (%)	22.2
	ODF (n)	28
	ODF (%)	77.8
	Total (n)	36

3. Have you tried other products for smoking cessation?	Yes (n)	20
	Yes (%)	55.6
	No (n)	16
	No (%)	44.4
	Answers (n)	36
If yes specify	Inhaler (n)	2
	Spray (n)	2
	Champix (n)	3
	Lozenges (n)	8
	Patches (n)	12
	Chewing gum (n)	16
	Total (n)	43
4. If you answered yes to the above question (3): If the products had the same price, which product would you prefer to use for smoking cessation?	Spray (n)	3
	ODF (n)	14
	Chewing gum (n)	1
	Lozenges (n)	3
	Patches (n)	3
5. Do you perceive ODF as more discreet than Nicotine Gum?	Yes (n)	27
	Yes (%)	81.8
	No (n)	6
	No (%)	18.2
	Answers (n)	33
6. Do you perceive ODF as more discreet than Spray?	Yes (n)	27
	Yes (%)	81.8
	No (n)	6
	No (%)	18.2
	Answers (n)	33
7. Do you perceive ODF as more discreet than Lozenges	Yes (n)	17
	Yes (%)	53.1
	No (n)	15
	No (%)	46.9
	Answers (n)	32
8. Is it important to you that the product for smoking cessation is discreet?	Yes (n)	14
	Yes (%)	40
	No (n)	21
	No (%)	60

The results from the user satisfaction questionnaire show that 55.6% of the subjects participating in the study had previously used other smoking cessation aids. The smoking cessation aids most frequently reported were; chewing gum, patch and lozenges, reported by 16, 12 and 8 subjects respectively. Two subjects reported having used spray previously.

A larger proportion of the patients, 72.2%, reported that they would prefer the Nicoitne ODF formulation over Nicorette Spray for smoking cessation. Also, 77.8 % reported a higher level of satisfaction from the Nicoitne ODF formulation than from the Nicorette Spray formulation. A majority of the subjects reported that they perceived Nicotine ODF as more discrete than spray, chewing gum and lozenges.

11.1.1.3 Urge to smoke

A 10-question questionnaire on smoking urges was used to assess participating subjects' *urge to smoke* before dosing and at 30 and 60 minutes post-dosing with Nicotine ODF and Nicorette Spray respectively, see Table 11.1. Individual subjects' responses are shown in Appendix 16.2.6.

Table 11.4 Questionnaire on smoking urges, Safety population

Group: Safety					
Q: Please answer the questions below by circling the number that best matches your experience on a scale of 1 to 7, where 1 = strongly disagree, 7 = agree completely		Postdose 30min	Postdose 60min	Postdose 30min	Postdose 60min
Given drug		ODF	ODF	Spray	Spray
A. I have a desire for a cigarette right now	Mean	2.51	2.57	2.61	2.32
	SD	1.74	1.82	1.67	1.8
	Median	2.0	2.0	2.0	1.0
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38
B. Nothing would be better than smoking a cigarette right now	Mean	1.89	2.08	1.97	2.05
	SD	1.45	1.4	1.44	1.61
	Median	1	2	1	1
	min	1	1	1	1
	max	7	6	6	6
	n	37	37	38	38
C. If it were possible I would probably smoke now	Mean	3.84	3.70	3.95	4.21
	SD	2.24	2.15	2.14	2.29
	Median	3	3	4	4.5
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38

D. I could control things better right now if I could smoke	Mean	2.05	2.11	2.11	1.95
	SD	1.61	1.59	1.56	1.61
	Median	1	2	1.5	1
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38
E. All I want right now is a cigarette	Mean	2.0	2.22	1.95	2.11
	SD	1.41	1.70	1.41	1.59
	Median	1	1	1	1
	min	1	1	1	1
	max	6	7	6	6
	n	37	37	38	38
F. I have an urge for a cigarette	Mean	2.03	2.16	2.03	2.11
	SD	1.44	1.55	1.48	1.61
	Median	1	1	1	1
	min	1	1	1	1
	max	7	6	7	7
	n	37	37	38	38
G. A cigarette would taste good now	Mean	3.54	3.81	3.87	3.95
	SD	2.29	2.17	2.15	2.28
	Median	3	3	3	3.5
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38

H. I would do almost anything for a cigarette now	Mean	1.76	1.73	1.82	1.84
	SD	1.26	1.22	1.45	1.28
	Median	1	1	1	1
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38
I. Smoking would make me less depressed	Mean	1.78	1.73	1.82	1.71
	SD	1.67	1.61	1.5	1.37
	Median	1	1	1	1
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38
J. I am going to smoke as soon as possible	Mean	3.97	4.11	3.89	4.32
	SD	2.23	2.18	2.28	2.30
	Median	3	4	3	4
	min	1	1	1	1
	max	7	7	7	7
	n	37	37	38	38
Total score A-J	Mean	25.38	26.22	26.00	26.55
	SD	15.15	15.38	14.86	15.22
	Median	21	21	20	22
	min	10	10	10	10
	max	66	64	68	62
	n	37	37	38	38

There were no major differences in the mean responses to the questions in the urge to smoke questionnaire following treatment with Nicotine ODF and Nicorette Spray. The mean total score 60 minutes post dose was 26.22 and 26.55 for Nicotine ODF and Nicorette Spray, respectively.

11.1.1.4 Nicotine withdrawal

Signs of nicotine withdrawal were assessed before dosing and 30 minutes after dosing with Nicotine ODF and Nicorette Spray respectively, see Table 11.4. Individual subjects' responses are shown in Appendix 16.2.6.

Table 11.5 Nicotine withdrawal, Safety population

Group: Safety					
Q: Rate according to the options below, how you perceive yourself right now. Circle the option that best fits where 1 is least and 5 is most:		Pre dose	Postdose 30m	Pre dose	Postdose 30m
Given drug		ODF	ODF	Spray	Spray
Angry, irritable, frustrated	Mean (SD)	1.83(0.16)	1.38(0.72)	2.15(1.21)	1.37(0.71)
	Median	1	1	2	1
	min	1	1	1	1
	max	5	4	5	4
	n	36	37	40	38
Anxious, nervous	Mean (SD)	1.50(0.70)	1.24(0.49)	1.50(0.75)	1.13(0.41)
	Median	1	1	1	1
	min	1	1	1	1
	max	3	3	3	3
	n	36	37	40	38
Depressed mood, sad	Mean (SD)	1.39(0.73)	1.38(0.72)	1.65(0.89)	1,37(0,71)
	Median	1	1	1	1
	min	1	1	1	1
	max	4	4	4	4
	n	36	37	40	38
Total score	Mean (SD)	4.72(1.88)	4.00(1.60)	5.30(2.28)	3.87(1.49)
	Median	4	3	4	3
	min	3	3	3	3
	max	9	10	10	9
	n	36	37	40	38

There were no major differences in the subjects' signs of nicotine withdrawal between Nicotine ODF and Nicorette Spray pre-dose or 30 minutes after administration of the test or reference product respectively. The mean total scores at 30 minutes post-dose were 4.00 and 3.87 for Nicotine ODF and Nicorette Spray, respectively.

11.1.2 Statistical/analytical issues

11.1.2.1 Adjustments for Covariates

No adjustments for covariates were made.

11.1.2.2 Handling of Dropouts or Missing Data

No replacement for dropouts or withdrawn subjects was to be performed[7]. Data points were to be considered missing at random. No data imputations were to be performed. However, for one subject, one plasma concentration value was missing. The value was imputed using linear interpolation between the two adjacent values. Plasma concentration levels below the detection limit 0.5 ng/ml, were set to 0.25, the midpoint of the interval (0-0.5).

11.1.2.3 Interim Analyses and Data Monitoring

No interim analysis or data monitoring was planned to be performed however, see section 9.8.3.

11.1.2.4 Multi-centre Studies

Not applicable.

11.1.2.5 Multiple Comparison/Multiplicity

Not applicable.

11.1.2.6 Use of an "Efficacy Subset" of Subjects

Not applicable.

11.1.2.7 Active-Control Studies Intended to Show Equivalence

Please see sections 9.1 and 9.7.3.

11.1.2.8 Examination of Subgroups

Not applicable.

11.1.2.9 Tabulation of individual response data

Individual efficacy response data is included in Appendix 16.2.6.

11.1.3 Drug dose, drug concentration and relationships to response

Not applicable.

11.1.4 Drug-drug and drug-disease interactions

Not applicable.

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[7] See section 9.8.2

11.1.5 By-subject displays

Figures of individual subject nicotine concentration data over time for Nicotine ODF and Nicorette Spray are shown in Figure 11.1 and Figure 11.2.

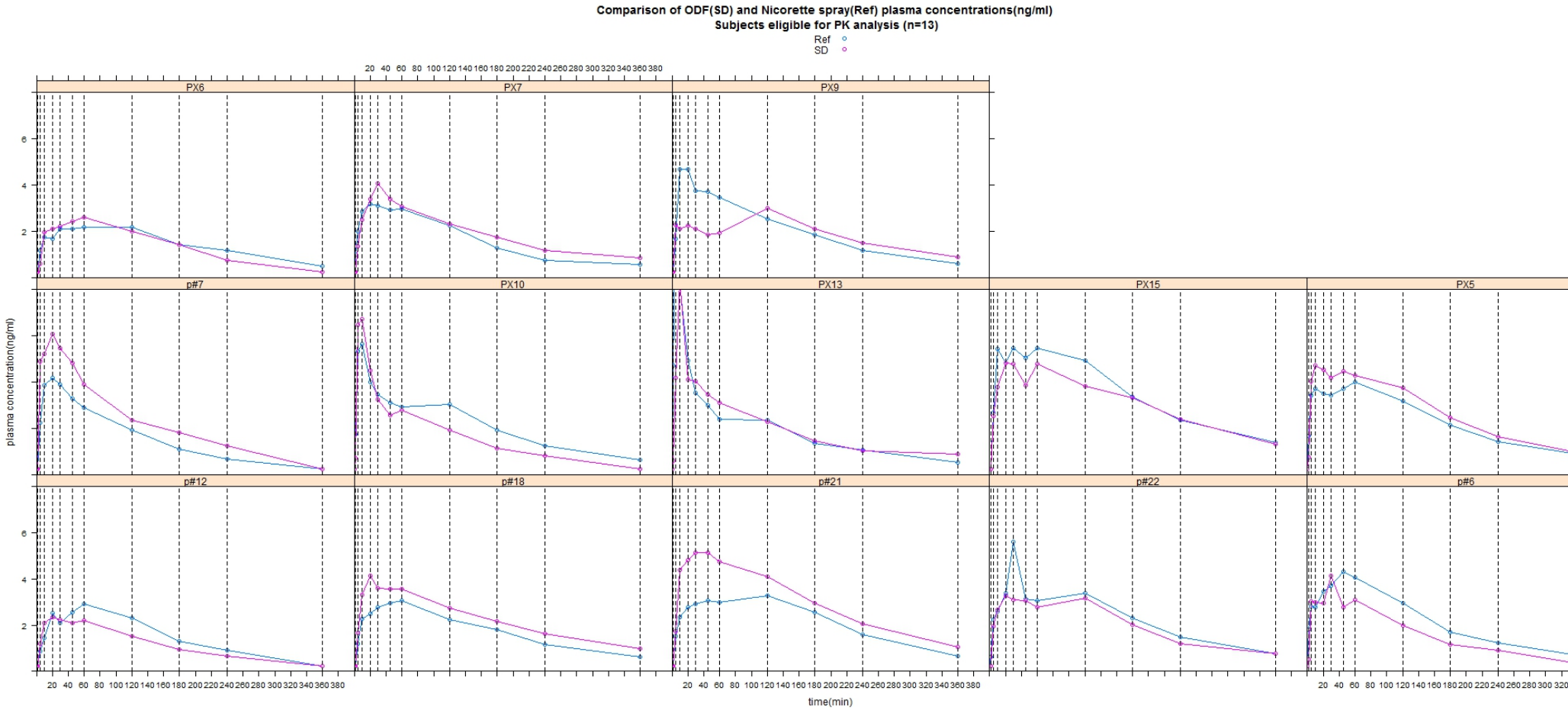

Figure 11.1 Shows individual nicotine concentration data per subject for all subjects in the PK analysis set. *Blue lines* show nicotine concentration data following administration of the reference drug, Nicorette Spray and *purple lines* show nicotine concentration data following administration of the study drug Nicotine ODF.

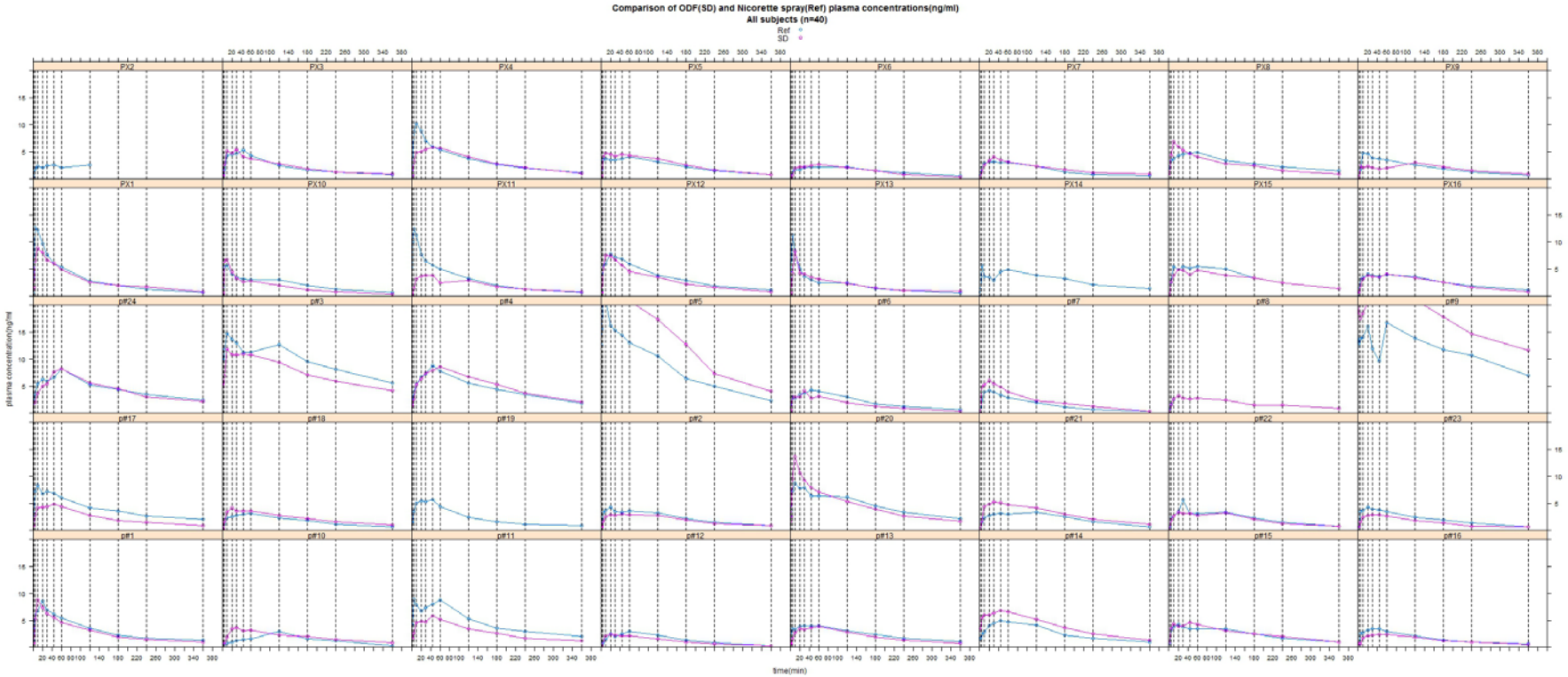

Figure 11.2 Shows individual nicotine concentration data per subject for all subjects in the Safety analysis set. *Blue lines* show nicotine concentration data following administration of the reference drug, Nicorette Spray and *purple lines* show nicotine concentration data following administration of the study drug Nicotine ODF.

11.1.6 Efficacy conclusions

Based on the pharmacokinetic results of this study, the two formulations are concluded to be bioequivalent.

A majority of the subjects reported that they found Nicotine ODF to be more satisfying than Nicorette Spray and further that they would prefer Nicotine ODF over Nicorette Spray as a smoking cessation aid. There were no difference in subjects' urges to smoke or signs of nicotine withdrawal following treatment with Nicotine ODF and Nicorette Spray.

12 SAFETY EVALUATION

The safety of Nicotine ODF and Nicorette Spray was evaluated by collecting information about adverse events, vital signs and physical examination. Blood samples for haematology and clinical chemistry was collected at the screening visit to verify eligibility for participating in the study but data was not collected in the database and analysed.

12.1 Extent of exposure

Thirty-six subjects (90%) were exposed to Nicotine ODF and 38 subjects (95%) were exposed to Nicorette Spray during the study.

The maximum dose subjects were exposed to in the study was 2 mg of the test and reference product, respectively.

12.2 Adverse events (AEs)

Severity of any AE (including changes in vital signs or physical examination findings) was graded using a categorical scale (mild to severe) as defined by ICH.

12.2.1 Brief summary of adverse events

A summary of AEs is presented and in Table 12.1 and the number of AEs per subject is shown Table 12.1.

Table 12.1 Summary of Adverse Events. Safety population

Group Safety		N	Total patient with AE	
ODF	n	37	19	
	%		51	
Spray	n	39	22	
	%		56	

Nineteen subject (51%) experienced AEs following treatment with Nicotine ODF and 22 subjects (56%) experienced AEs following treatment with Nicorette Spray.

There were no SAEs, deaths or withdrawals due to AEs reported during the study.

Table 12.2 Number of adverse events per subject, Safety population

Number of Adverse Events	Number of subjects (%)
0	12 (30.0)
1	10 (25.0)
2	10 (25.0)
3	5 (12.5)
4	2 (5.0)
6	1 (2.5)

In total 28 subjects (70%) in the safety population experienced at least one AE during the study. A majority of the subjects (22 subjects, 55%) experienced no or one AE during the study. Three subjects (7.5%) experienced more than three AEs.

Table 12.3 Number of adverse events per subject per treatment, Safety population

Number of Adverse Events per subject	Treatment	Number of subjects
0		12
1	ODF	14
2	ODF	5
4	ODF	1
1	Spray	13
2	Spray	9

There were no major difference in number of adverse events experienced by the subjects during treatment with Nicotine ODF and Nicorette Spray. In total 20 subjects experienced at least one adverse event in relation to treatment with Nicotine ODF and 22 subjects reported at least one adverse event in relation to treatment with Nicorette Spray.

12.2.2 Display of adverse events

All AEs experienced during the study are tabulated according to MedDRA by treatment, subject number, severity and causality classifications in Appendix 16.2.7.

The incidence of AEs by MedDRA preferred term and study treatment is shown in Table 12.2.

Table 12.4 Incidence of Adverse Events by MedDRA preferred term, Safety population

Group: Safety		Chest pain Mild	Cough (drug-induced) Mild	Coughing Mild	Dizziness Mild	Globus Mild	Headache Mild	Hiccups Mild	Nausea Mild	Pain throat Mild	Palpitation Mild	Vasovagal reaction Moderate	Vertigo Mild
MedDRA		10008479	10058276	10011232	10013573	10051180	10019218	10020039	10028813	10033494	10033556	10047166	10047340
Drug: ODF	n	0	1	1	0	13	2	0	7	1	1	1	1
Safety group	%	0	2,7	2,7	0	35,1	5,4	0	18,9	2,7	2,7	2,7	2,7
ODF in Safety	n	37	37	37	37	37	37	37	37	37	37	37	37
Drug: Spray	n	1	1	0	2	12	0	5	10	0	0	0	0
Safety group	%	2,6	2,6	0	5,1	30,8	0	12,8	25,6	0	0	0	0
Spray in Safety	n	39	39	39	39	39	39	39	39	39	39	39	39

The most frequently reported AEs following both Nicotine ODF and Nicorette Spray were globus and nausea. Globus was reported by 35.1 and 30.8% of the subjects following Nicotine ODF and Nicorette Spray, respectively. Nausea was reported by 18.9% of the subjects following Nicotine ODF and by 25.6% of the subjects following Nicorette Spray. Other AEs reported at least twice following administration of Nicorette Spray were hiccups and dizziness. For Nicotine ODF the only AE that was reported at least twice apart from globus and nausea was headache. It can be noted that hiccups were more frequently reported following treatment with Nicorette Spray (n=5) as compared to Nicotine ODF (n=0).

One AE was assessed to be of moderate severity, this event (vasovagal reaction), was experienced by a subject following administration of Nicorette ODF. All AEs were judged to be related to the treatment administered.

12.2.3 Analysis of adverse events

There were no clear differences between Nicotine ODF and Nicorette Spray with regards to reported AEs.

12.2.4 Listing of adverse events by subject

A listings of all AEs divided per subject is included in Appendix 16.2.7.

12.3 Deaths, other serious adverse events and other significant adverse events

12.3.1 Listing of deaths, other serious adverse events and other significant adverse events

No deaths, SAEs or other significant AE occurred during the study.

12.4 Clinical laboratory evaluation

At screening laboratory blood samples were taken and results were used to verify that all eligibility criteria were fulfilled. Apart from nicotine, clinical laboratory data were not collected or analysed.

12.5 Evaluation of clinical safety variables (vital signs and physical examinaition findings)

12.5.1 Vital signs

Vital signs, diastolic and systolic blood pressure and pulse were assessed pre-dose and at 30, 60, 90, 120, 180, 240, 300 and 360 minutes post-dose following Nicotine ODF and Nicorette Spray. The mean and median values per treatment at the respective time-points are shown in Table 12.3.

Table 12.5 Vital signs, safety population

Group: Safety		Pre dose	Post dose 30min	Post dose 60min	Post dose 90min	Post dose 120min	Post dose 180 min	Post dose 240min	Post dose 300min	Post dose 360min
Diastolic (mmHg)	Mean	72.41	72.11	70.68	72.43	71.76	70.03	70.22	70.62	71.17
	SD	7.79	9.18	8.19	7.72	7.55	8.57	8.13	8.52	7.94
	Median	72.5	75	70	75	72.5	72.5	75	75	75
ODF	min	60	55	60	55	60	50	60	60	58
	max	85	90	90	90	86	87	82	90	85
	n	37	37	37	37	37	37	37	37	36
Diastolic (mmHg)	Mean	71.03	71.55	70.71	70.68	69.68	70.89	69.95	69.63	71.53
	SD	8.18	8.34	8.30	9.09	8.33	7.27	8.98	7.81	8.95
	Median	70	75	70	70	70	75	70	70	70
Spray	min	50	51	55	55	50	60	50	60	55
	max	90	85	85	90	80	85	85	85	90
	n	40	38	38	38	38	38	38	38	38
Group: Safety		Pre dose	Post dose 30min	Post dose 60min	Post dose 90min	Post dose 120min	Post dose 180 min	Post dose 240min	Post dose 300min	Post dose 360min
Systolic (mmHg)	Mean	117.43	113.05	112.32	113.27	114.32	113.08	111.38	113.32	113.19
	SD	10.84	11.44	11.12	11.14	9.55	9.97	10.57	10.74	9.65
	Median	120	115	115	115	115	115	115	115	115
ODF	min	100	85	85	90	90	90	90	90	90
	max	140	140	140	140	130	130	130	140	130
	n	37	37	37	37	37	37	37	37	36
Systolic (mmHg)	Mean	113.58	113.71	111.76	115.34	114.66	113.00	111.03	112.32	113.89
	SD	9.82	10.00	9.23	10.12	8.81	9.90	10.08	10.59	10.74

	Median	115	120	110	120	115	115	115	115	120
Spray	min	95	95	90	95	95	95	90	90	90
	max	140	140	130	145	130	140	130	140	140
	n	40	38	38	38	38	38	38	38	38
Group: Safety		Pre dose	Post dose	Post dose	Post dose	Post dose	Post dose	Post dose	Post dose	Post dose
			30min	60min	90min	120min	180 min	240min	300min	360min
Pulse (beats/minute)	Mean	64.35	64.11	63.57	63.43	64.41	64.22	62.54	62.19	62.08
	SD	9.99	8.33	8.16	8.54	9.39	9.60	9.48	8.51	7.25
	Median	66	65	66	68	70	66	64	64	64
ODF	min	50	50	50	50	50	50	50	50	48
	max	92	82	84	84	82	86	86	85	75
	n	37	37	37	37	37	37	37	37	36
Pulse (beats/minute)	Mean	62.05	62.76	60.42	61.92	62.00	60.76	62.34	60.89	62.08
	SD	7.10	7.32	7.70	7.43	7.39	6.47	7.43	7.46	8.23
	Median	63.5	64	60	62	64	60	60	60	62
Spray	min	50	46	46	48	46	48	48	48	48
	max	80	78	80	80	78	74	80	78	80
	n	40	38	38	38	38	38	38	38	38

There were no notable differences in any of the vital signs parameters at any time-point between Nicotine ODF and Nicorette Spray.

12.5.2 Physical examination

Physical examination was assessed pre-dose and 6.5 hours post-dose at the two dosing visits. No abnormal physical examination findings were recorded during the study.

12.6 Safety conclusion

No deaths or SAEs occurred during the study and no subjects were withdrawn due to AEs. In total, 70% of the subjects experienced at least one AE during the study. There were no major differences in the AEs reported between Nicotine ODF and Nicorette Spray. However, it can be noted that hiccups occurred more frequently following administration of Nocirette Spray as compared to Nicotine ODF.

The most frequently reported AEs were globus and nausea following treatment with both Nicotine ODF and Nicorette Spray. Nicotine ODF was found to be safe and well tolerated.

13 DISCUSSION AND OVERALL CONCLUSIONS

This study was performed to test a new platform (/drug delivery system) for drug administration via the buccal mucosa using nicotine as a model substance. The study primary endpoint was to show bioequivalence between Nicotine ODF and Nicorette Spray. The results show that 2mg Nicotine ODF is bioequivalent with 2mg of Nicorette spray.

In this platform the drug is administered via a bioadhesive film which is attached to the inside of the mouth. The release can be controlled by changing the size of the film. The area of the film is used to control the dose of the drug. In the present study the film used was 3*2 cm and contained 2 mg nicotine. The film is homogenous and the dosing is therefore linearly in relation to area. Dose can thereby be easily controlled. This platform can be used for other drugs that are readily absorbed via the buccal mucosa including e.g. Zolmitriptan, Sumatriptan, Zolpidem and Lorantadine. There are several advantages with administering drugs via this route; administration bypass the first passage metabolism, a rapid onset is achieved and a lower dose may be required due.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Not applicable.

15 REFERENCE LIST

1. FASS2010 (Pharmaceutics Specialities In Sweden) 2010. Available at http://www.fass.se
2. Fiore MC , Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ et al.: Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guidelines, U S Department of Health and Human Services, Rockville, MD.

3. GOLD (Global initiative for chronic Obstructive Lung Disease) Global Strategy for the Diagnosis, Management and Prevention of COPD, 2009. Available at http://www.goldcopd.com
4. Hauschke D, Steinijans VW, Diletti E, Burke M (1992). Sample size Determination for Bioequivalence Assessment Using a Multiplicative Model. J Pharmacokin Biopharm, Vol. 20 (5): 557-561
5. Hukkanen J, Jacob P 3rd, Benowitz NL (2005). Metabolism and disposition kinetics of nicotine. Pharmacol Rev 57(1):79-115.
6. McRobbie H, Thornley S, Bullen C, Lin RB, Senior H, Laugesen M, Whittaker R, Hajek P (2010): A randomized trial of the effects of two novel nicotine replacement therapies on tobacco withdrawal symptoms and user satisfaction. Addiction 105: 1290-1298.
7. Peto P, Lopez AD, Boreham J, Thun M, Heath C (1992). Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 339: 1268-1278.
8. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P et al (2007). GOLD executive summary. Am J Respir Crit Care Med 176: 532-555
9. SCB Statistiska Central Byrån(Statistics Sweden), Data from 2008
10. Shafey O, Dolwick S, Guindon GE (2003). Tobacco control country profiles (2nd ed.) America Cancer Society, Atlanta , GA
11. Stead LF, Perera R, Bullen C, Mant D and Lancaster T.: Nicotine Replacement Therapy for Smoking Cessation. Cochrane Database Syst Review CD000146 (2008)
12. Sutherland G, Stapleton JA, Russel MAH, Jarvis MJ, Hajek P, Belcher M, Feyerabend C (1992): Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 340: 324-329.
13. Svenssom Craig K: Clinical Pharmacokinetics of Nicotine (1987). Clinical Pharmacokinetics 12(1): 30-40.
14. US department of Health and Human Services (1988). The health consequences of smoking: Nicotine addiction. A report of the surgeon general. DHHS: 88-8406.

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16 APPENDICES

16.1 Study information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 IEC approval including list of IEC (or IRB) members. Representative written information for subject and sample consent forms

16.1.4 List and description of Investigators and other important participants in the study, including brief (1 page) CVs *(or equivalent summaries of training and experience relevant to the performance of the clinical study).*

16.1.5 Signatures of the Sponsor, Project Manager/author of the report, Medical Director, Statistician and Coordinating/Principal Investigator

16.1.6 Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

16.1.7 Randomization scheme and codes (subject identification and treatment assigned)

16.1.8 Audit certificates *Not applicable*

16.1.9 Documentation of statistical methods *(Statistical Analysis Plan) Not applicable-included in study protocol*

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used. *Single laboratory QA statement included.*

16.1.11 Publications based on the study *Not applicable*

16.1.12 Important publications referenced in the report *Not applicable*

16.1.13 Correspondence authorities regarding changes to the study

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16.2.2 Protocol deviations *Not applicable*

16.2.3 Subjects excluded from the efficacy analysis

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16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject, when required by regulatory authorities *Not applicable*

16.3 Case report forms

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE *Not applicable*

16.3.2 Other CRFs submitted *Not applicable*

Clinical Study Protocol

EudraCT No.: 2011-000930-12
Study Product: Nicotine Oral Dissolvable Film
Study code: FFT-01-11
Protocol Version: Final 1.1
Date: 19 December 2011

A BIOEQUIVALENCE STUDY OF AN ORAL DISSOLVABLE FILM FOR TRANSMUCOSAL NICOTINE DELIVERY WITH NICORETTE® PEPPARMINT ORAL NICOTINE SPRAY AS REFERENCE PRODUCT

Development phase Bioequivalence study

Test product and dosage Nicotine Oral Dissolvable Film (ODF), 2.0mg, lemon

Duration of treatment Single Dose Study

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Signature pages found in appendix 19.1

2 PROTOCOL SYNOPSIS

Study Title: A bioequivalence study of an oral dissolvable film (ODF) for transmucosal nicotine delivery with Nicorette® peppermint oral nicotine spray as reference product	
Study code: FFT-01-11	**EudraCT No:** 2011-000930-12
Coordinating Investigator: Jon Enestig, MD Capio S:t Görans Sjukhus Department of Medicine 112 81 Stockholm Sweden	
Study period: Estimated date of first subject enrolled: Feb 2012 Estimated date of last subject completed: April 2012	**Phase of development:** Bioequivalence study

Objectives

Primary objective: The primary objective is:

- to evaluate if Nicotine ODF achieves a comparable pharmacokinetic (PK) profile as compared to Nicorette® peppermint oral spray.

Secondary objectives: The secondary objectives are:

- to compare the overall subjective satisfaction between Nicotine ODF and Nicorette®.
- to evaluate the subjective urges to smoke following treatment with Nicotine ODF and Nicorette®.
- to evaluate nicotine withdrawal following treatment with Nicotine ODF and Nicorette®.

Safety objective: The safety objective is:

- to evaluate the safety and tolerability of Nicotine ODF when administered as a single dose.

Number of subjects planned

24 Subjects will be randomized to receive the test product, Nicotine ODF, and the reference product, Nicorette® peppermint oral spray, in a cross over design. 12 Subjects will receive the test product first and 12 Subjects will receive the reference product first. The dose administrations will be separated by 6 to 21 days.

Diagnosis and main eligibility criteria

Inclusion Criteria:

1. Healthy male and female smokers 18-55 years old.

Exclusion Criteria:

1. Physical or mental disorder that could impair the Subject's ability to participate in the study.
2. Ischemic Heart Disease, Cardiac infarction, or Cardiac arrhythmias in the medical history or signs of previous infarction on ECG from the screening visit.
3. Cerebrovascular disease in the medical history.
4. Uncontrolled hypertension, defined as Systolic Blood Pressure (SBP) ≥180 mm Hg and/or

Diastolic Blood Pressure (DBP) ≥110 mm Hg.
5. Moderate to severe liver or kidney disease, as judged by the Investigator.
6. Anaemia defined as haemoglobin <115g/L in women and <135g/L in men.
7. Known or suspected active hyperthyroidism.
8. Known or suspected phaeochromocytoma.
9. Active infection in the mouth or throat.
10. Pregnant or lactating females
11. Participation in any other clinical study within three months prior to enrolment or during the present study.
12. Known or suspected alcohol or illicit drug abuse.
13. History of alcohol or drug abuse.
14. Need for regular medication with prescription or over-the-counter drugs except contraceptives.
15. Dry mouth problems.
16. Has a nicotine level of ≥ 2 ng/ml measured pre-dose at the first dosing visit.
17. Known human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody positive status.
18. If the Investigator, for any other reason, judge that the Subject should not be included (e.g. if Subject is considered unlikely to comply with study procedures, restrictions, and requirement or if Subject is expected to withdraw from the study).

Study design:

This is an open, randomized, two-period, two-sequence, single dose, cross-over study to evaluate the PK profile of Nicotine ODF when given as a single dose to Subjects with nicotine dependence. The Subjects will serve as their own controls thereby eliminating the impact of inter-subject variance. The study includes three subject visits; one screening visit and two dosing visits. For Subjects with unresolved Adverse Events (AEs) at the end of the last visit, a follow-up safety contact will be made 7±2 days after Visit 2. The screening visit will take place within 21 days of the first dosing visit, Visit 1 (Day 0), the second dosing visit will take place on Visit 2, which could take place between 6 and 21 days after Visit 1. Subjects will be sequentially randomized, as they become available for dosing, into two equally sized groups, one receiving first Nicorette® nicotine oral spray followed by the ODF and vice versa for the other group.

Methodology:

A screening visit will be conducted to assess the eligibility of the Subjects. Within 21 days of screening the first dosing visit will be conducted, followed by the second dosing visit 6 to 21 days thereafter. During the dosing visits, a blood sample will be taken pre-dose and a total of 10 blood samples will be taken during six hours post-dose to analyze the PK profile. Questionnaires will be used during the study to assess the Subjects 1) nicotine dependence, 2) satisfaction following use of the test and reference products respectively, 3) urges to smoke following use of the test and reference product respectively and 4) nicotine withdrawal following use of the test and reference product respectively. To assess safety, AEs and vital signs will be collected and physical examination will be performed during the dosing visits.

Investigational product, dosage and mode of administration:

2.0 mg of Nicotine ODF administered to the oral mucosa.

Comparator product, dosage and mode of administration:

Nicorette® peppermint oral spray, the dose will be 2 mg given as two sprays administered into the mouth at close distance avoiding the lips.

Duration of treatment:

The Subjects will receive a single dose of the test product and a single dose of the reference product with a 6 to 21 day interval.

Duration of subjects involvement in the study

The duration of the Subjects involvement in the study is four weeks including a three weeks screening period.

Efficacy assessments:

Blood samples will be taken during the two dosing days for evaluation of the PK profile and calculation of Area Under the plasma concentration time Curve (AUC) and t_{max} and C_{max}.

Subjects will complete a questionnaire assessing their overall satisfaction of the test product and the reference product at the end of Visit 2.

Subjects will complete the brief questionnaire on smoking urges (QSU brief) pre-dose, 30 minutes and 1 hour after the test product and reference product administration to assess the Subjects' urges to smoke.

Subjects will complete a nicotine withdrawal questionnaire pre-dose and 30 minutes after administration of the test and reference products at Visits 1 and 2.

Subjects will complete the Fagerström test for nicotine dependence (FTND) questionnaire, during the screening visit to assess the Subjects' dependence to nicotine.

Safety assessments:

Safety and Tolerability will be assessed by collecting of AEs, vital signs and physical examination.

Statistical methods

Determination of sample size: Approximative formula of Hauschke for bioequivalence cross-over design.

Test for equivalence: CI of the AUC and C_{max} ratio between test and reference products. Descriptive statistics of t_{max}

Analysis of variance (ANOVA) of log transformed data.

User satisfaction nicotine withdrawal and questionnaire on smoking urges: Results will be presented descriptively in tables, listings, and graphs, as appropriate.

Safety and Tolerability: Results will be presented descriptively in tables, listings, and graphs, as appropriate.

FTND questionnaire: Results will be presented descriptively.

Results might also be evaluated exploratively to link individual Subjects' experience of the test and reference products to other study results obtained.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
ANOVA	Analysis of Variance
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
C_V	Coefficient of Variance
DCF	Data Clarification Form
FTND	Fagerström Test for Nicotine Dependence
GCP	Good clinical practice
ICF	Informed Consent Form
DBP	Diastolic Blood Pressure
ICH	International conference on harmonization
IEC	Independent Ethics Committee
ITT	Intention-to-Treat
NRT	Nicotine Replacement Therapy
ODF	Oral Dissolvable Film
PIS	Patient Information Sheet
PK	Pharmacokinetic
QSU brief	Brief questionnaire on smoking urges
SAE	Serious adverse event
SD	Standard Deviation
SPB	Systolic Blood Pressure
SUSAR	Suspected Unexpected Severe Adverse Reaction
U-hCG	Urine human chorionic gonadotropin hormone
WHO	World Health Organisation

Term	Definition of term
Screening failure	Non eligible Subject
Enrolled Subject	Subject who signed Informed Consent Form
Included Subject	Subject who was randomized to receive study medication
Withdrawn Subject	Subjects who prematurely discontinued the study
Completed Subject	Subject who completed all study visit
End of Study	Last Subject last visit

5 ETHICS

5.1 Ethical review

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki (Appendix 19.1). Necessary approval of the Study Protocol, the Patient Information sheet (PIS) and Informed Consent Form (ICF) must be obtained before enrolment of any Subject into the study. Furthermore, it is the responsibility of the Sponsor, FFT Medical AB, to keep the Independent Ethics Committee (IEC) informed of any Suspected Unexpected Serious Adverse Reactions (SUSARs) and any applicable substantial amendments to the protocol during the study period. The written approval from the IEC, including a study identification and the date of review will be filed at FFT Medical AB and at the study site together with a list of the IEC members, their titles or occupation, and their institutional affiliations. All correspondence with the IEC should be filed both at the Sponsor and at the study site.

5.2 Ethical conduct of the study

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

The Declaration of Helsinki is included as Appendix 19.2 to the Protocol.

5.3 Patient information and consent

It is the responsibility of the Investigator to give each potential study Subject adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before including the Subject in the study. The Subject must be informed about the right to withdraw from the study at any time. The Subject should be allowed sufficient time for consideration of the proposal.

Furthermore, it is the responsibility of the Investigator to obtain signed informed consent from all Subjects before including them in the study. The ICF must be signed and dated before any study-specific procedures are performed, including screening procedures. The signed PIS and ICF should be filed by the Investigator for monitoring and possible future audits and/or inspections, a copy should be given to the Subject. The Investigator will confirm the receipt of the signed ICF for each Subject by signing the appropriate part of the Subject's Case Report Form (CRF).

The Final version of the PIS and ICF is submitted to the IEC and concerned Competent Authority and must not be changed without permission from Sponsor and the local IEC.

5.4 Subject data protection

The Investigator must file a subject identification list, which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to FFT Medical AB or delegate except for monitoring or auditing purposes.

The Subjects will be informed that the data will be stored and analyzed by computer, that Swedish and local regulations for the handling of computerized data will be followed and that identification of individual Subject data will only be possible for the Investigator.

The potential study Subject should be informed that by signing the ICF he/she approves that authorized representatives from FFT Medical AB or delegate, the IEC and the Competent Authorities have direct access to his/her medical records for verification of clinical study procedures.

5.5 Risk / benefit analysis

In general, the presently marketed Nicotine Replacement Therapy (NRT) products are not entirely satisfactory and the need for a comfortable NRT product with rapid delivery used alone or as supplement to more slow release NRT products is needed. To aid smoking cessation, an improved formulation that provides a convenient and comfortable administration route in combination with a rapid release and absorption of nicotine would be therapeutically advantageous.

Nicotine Oral Dissolvable Film (ODF) is a new formula, combining rapid transmucosal delivery of nicotine with the convenient administration of an oral, completely dissolving film. Nicotine ODF contains no new substances not already proved to be safe from years of therapeutic use in other commercially available registered drugs. All Subjects participating in the study will all be habitual smokers, daily exposed to nicotine in doses that are reasonably much higher than in this study. Therefore, the risks associated with participating in the study are limited and relate primarily to the risk associated with the blood sampling procedure. Although, the Subjects might not benefit personally from participating in the study, a new NRT product with improved formulation could help smokers give up smoking. Reduced smoking would have a benefit for the society in general and for the smokers in particular. The risk/benefit analysis for the present study may therefore be considered to be favourable.

6 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

For the Investigator and study administrative structure, please see the title page of this Study Protocol.

Clinical study protocol signatures are provided in appendix 19.1.

7 INTRODUCTION

Globally about 1.3 billion people smoke tobacco [Shafey, Dolwick and Guindon 2003] and it has been estimated that 40% of the smokers will die prematurely from a disease associated with smoking [Peto et al. 1992]. Tobacco smoking has been identified as the single largest preventable cause of morbidity and premature death in the developed world [US Department of Health and Human Services 1988]. According to World Health Organisation (WHO), approximately 5.4 million deaths per year are attributable to tobacco-related disease [WHO, 2008]. A large body of scientific evidence supports a causal association between smoking and numerous diseases including respiratory diseases such as chronic obstructive pulmonary disease (COPD), one of the top five leading causes of death worldwide [SCB 2008] as well as different forms of cancer including lung cancer, the second leading cause of cancer deaths in Sweden [SCB 2008] and cardiovascular diseases.

Nicotine is an alkaloid that is present in and derived from the tobacco plant. It is widely accepted that cigarette smoking, to a large extent, is facilitated and driven by nicotine dependence.

Although most smokers quit without assistance, smokers who receive assistance are more likely to be successful [Fiore et al. 2008]. NRT remains the most widely used complement to behavioural interventions. The therapeutic benefit of NRT products are supported by results of 180 controlled studies demonstrating that patients receiving pharmacotherapy are approximately twice as likely to remain abstinent for more than 6 months [Stead et al 2008]. NRT products are available in a number of different formulations such as chewing gum, sublingual tablets, adhesive transdermal patches, nasal spray and oral mucosal inhalers as well as in different doses [FASS2010]. Most of these nicotine formulations, however, give a slow onset of action as compared to during tobacco smoking. After inhalation of cigarette smoke, the level of nicotine in the blood rises rapidly and reaches the brain within 10-20 seconds via the internal carotid arteries [C.K. Svensson 1987]. In the brain, the nicotine binds to nicotine receptors, which results in an increased in dopamine, which provide the smokers with the pleasurable sensation of smoking, the cognitive arousal and the rapid relief of the symptoms of nicotine abstinence. With nicotine delivered from chewing gum, sublingual tablets and oral mucosal inhalers, the resultant plateau blood nicotine levels are reached after 30 minutes. With transdermal adhesive patches it takes hours to reach a plateau [FASS 2010]. The only NRT products that provide a rapid absorption, reaching a plateau in about 5-10 minutes, which is similar to that of a cigarette puff are nasal and oral sprays [FASS2010, Hukkanen et al 2005]. Nicotine uptake depends on passive diffusion. The net rate of transportation through a membrane can be calculated by using the mathematical product of membrane permeability, surface area and the concentration difference. In the fast acting formulas, a relatively large surface area and a high concentration ratio is achieved through a “one hit” deposition of the drug on a relatively large surface in the oral and nasal mucosa respectively. As has been found, this approach is complicated by adverse effects for many patients, reducing user satisfaction. Runny nose and nasal irritation are among the problems experienced by most users (Sutherland et al 1992, FASS2010). Another problem is that reactions in the mucosa may accelerate dilution from saliva and nasal secretions. When the drug is diluted, the concentration gradient decreases and hence the transmucosal transportation rate.

This study will evaluate a new formula for nicotine uniquely combining rapid transmucosal delivery with the convenience of an oral completely dissolving alginate film that will adhere to the mucosa and thus maintain the concentration gradient. Our own tests indicate a dissolution time for the film of approximately 1 minute (unpublished data). We accordingly expect a higher bioavailability and less adverse effects from swallowed nicotine. We believe our invention could benefit smokers not satisfied with the NRT available today. A fast acting,

well tolerated, NRT alternative could be used alone or as a complement to slow release skin patches. Our hope is that the medication can provide new means for smokers, not satisfied with presently marketed NRT products, to quit or reduce their smoking.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective

The primary objective is to evaluate if Nicotine ODF achieves a comparable pharmacokinetic (PK) profile as compared to Nicorette® peppermint oral spray.

8.2 Primary endpoint

The primary endpoint is:

- to compare Area Under the plasma concentration time Curve (AUC), t_{max} and C_{max} for Nicotine ODF, as compared to Nicorette® peppermint oral spray.

8.3 Secondary objectives and endpoints

8.3.1 Secondary efficacy objectives

The secondary objectives are:

- to compare the overall subjective satisfaction following treatment with Nicotine ODF and Nicorette® peppermint oral spray.
- to evaluate the subjective urges to smoke following treatment with Nicotine ODF and Nicorette® peppermint oral spray.
- to evaluate nicotine withdrawal following treatment with Nicotine ODF and Nicorette® peppermint oral spray.

8.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- to assess the user satisfaction following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the User Satisfaction Questionnaire.
- to assess the urge to smoke following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the QSU brief questionnaire pre-dose, 30 minutes and 1 hour after the respective treatment.
- to assess signs of nicotine withdrawal following treatment with Nicotine ODF and Nicorette® peppermint oral spray as assessed by the total score of the nicotine withdrawal questionnaire pre-dose and 30 minutes after each dose administration.

8.3.3 Safety objective

The safety objective is:

- to evaluate the safety and tolerability of Nicotine ODF when administered as a single dose.

8.3.4 Safety endpoints

The safety and tolerability endpoints are:

- to evaluate the nature, incidence and severity of Adverse Events (AE) and Serious Adverse Events (SAE)
- to evaluate physical examination findings
- to evaluate vital signs findings

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

This is a randomized, two-period, two-sequence, single dose, cross-over, non-blinded study. The Subjects will be their own controls eliminating the impact of inter-subject variance. A total of 24 Subjects, male and female subjects aged 18 to 55 will be included in the study.

A screening visit will be conducted as, outlined in Table 1, within 21 days of Visit 1(Day 0), when the first dose administration will occur. If the screening assessments provide proof of eligibility, the Subject will be randomized into the study on Visit 1 (Day 0). The Subjects will come back to the clinic on Visit 2 (Day 6-21) for the second dose administration.

The 24 Subjects will be sequentially randomized, as they become available for dosing, into two equally sized groups, one receiving first Nicorette® nicotine oral spray followed by the ODF and vice versa for the other group. For practical reasons, a maximum of eight Subjects will be dosed on each dosing day, which is the dosing scenario shown in **Fel! Hittar inte referenskälla.**. If for some reason, less than eight Subjects would be dosed on a dosing day, an additional dosing day will be added.

During each dosing day, study assessments will be performed by the Site Personnel and blood samples will be taken as described in 9.5 and Table 1. At the beginning of each dosing day, a peripheral venous catheter will be inserted by a qualified nurse, for taking blood samples.

A baseline PK sample will be taken before administration of the respective drug. PK blood samples will then be taken post-dose, as outlined in Table 1, for evaluation of the PK profile. Any AEs will be thoroughly recorded for both groups from dose administration on Visit 1 until the end of Visit 2 or if applicable until the follow-up safety phone call seven days after Visit 2.

Four questionnaires will be used in the study to assess the participating Subjects' nicotine dependence, how satisfying they find the test and reference products, to assess signs of nicotine withdrawal before and after dose administrations and to assess the Subjects' urges to smoke pre-dose, 30 minutes and 1 hour after treatment with the test and reference product respectively.

Table 1.Schedule of events

Event	Screening	Visit 1 (Day 0) Pre-dose	Visit 1 (Day 0) Post-dose	Visit 2 (Day 6+15) Pre-dose	Visit 2 (Day 6+15) Post-dose	Tel. F-U[f] 7±2 days after Visit 2
Informed consent	X					
Demographics	X					
Medical history	X					
Physical examination	X	X[a]	X[a]	X[a]	X[a]	
Vital signs[b]	X	X[c]	X[c]	X[c]	X[c]	
ECG	X					
Prev. and concom. Medication	X	X	X	X	X	
Eligibility	X	X				
Randomization		X				
Time point of last cigarette		X				
PK Blood sampling[d]		X	X	X	X	
Clinical Chemistry/Haematology	X					
Blood Sample for Nicotine level	X					
Test/reference product administration		X		X		
Adverse Events		X	X	X	X	X[f]
Pregnancy test (female Subjects)	X	X				
Health Declaration Questionnaire	X					
User satisfaction questionnaire[e]					X	
Fagerström questionnaire	X					
QSU brief[h]			X		X	
Nicotine withdrawal questionnaire[g]		X	X	X	X	
End of study					X	

a) A Physical Examination performed pre-dose and 6.5 h post-dose.
b) Vital Signs include systolic/diastolic blood pressure and pulse. On the screening visit, weight and height is also included.
c) Vital Signs will be assessed pre-dose and 30 min, 1h, 1.5h, 2h, 3h, 4h, 5h and 6h
d) Blood samples for evaluation of PK profile will be taken pre-dose and after 2, 5, 10, 20, 30, 45 min, 1, 2, 3, 4, and 6h after administration of the test product and reference product

e) The Subjects will complete a user satisfaction questionnaire (appendix 19.7) 5h ±1h after the second dose administration.
f) A telephone follow-up call will be performed in case of ongoing AEs at study termination, i.e. the end of Visit 2.
g) The Subjects will complete a nicotine withdrawal questionnaire (appendix 19.10) pre-dose (-15 to -1 minutes before administration) and 30 min post-dose
h) The Subjects will complete a questionnaire on smoking urges (appendix 10) pre-dose (-15 to -1 minutes before administration), 30 minutes and 1 hour post-dose

9.2 Rationale for study design, doses and control group

The study is designed according to bioequivalence guidelines [EMEA guideline 2010] to show bioequivalence between the test product and the reference product.

The normal dose of the reference product spray is 1-2 mg at each dosing occasion, corresponding to 1-2 sprays. The dose that will be administered is 2mg of the reference product and 2mg of the test product. The ODF formulation is believed to have slightly faster and more reproducible absorption than oral spray. The rationale of having 2mg of the test product is to be able to show this and still have results bioequivalent to 2mg of the reference product.

The Subjects in the study will be habitual smokers as it would be unethical to administer nicotine to non-smokers, considering the addictive property of nicotine. Also the effects induced by a one-time use of nicotine would most likely be unpleasant to non-smoking subjects.

9.3 Selection of study population

9.3.1 Inclusion criteria

For a Subject to be eligible for participation in the study, all of the following criteria must be fulfilled:

1. Male or female smokers 18 to 55 years at the time of signing the ICF.
2. Body Mass Index between 18.5 and 30.0 kg/m².
3. Smoking on average at least 7 cigarettes per day, for at least the last two years.
4. Has signed the ICF.

9.3.2 Exclusion criteria

For the Subject to be eligibility for inclusion in the study, none of the following criteria should be fulfilled:

19. Physical or mental disorder that could impair the Subject's ability to participate in the study.
20. Ischemic Heart Disease, Cardiac infarction, or Cardiac arrhythmias in the medical history or signs of previous infarction on ECG from the screening visit.
21. Cerebrovascular disease in the medical history.
22. Uncontrolled hypertension, defined as Systolic Blood Pressure (SBP) ≥180 mm Hg and/or Diastolic Blood Pressure (DBP) ≥110 mm Hg.
23. Moderate to severe liver or kidney disease, as judged by the Investigator.
24. Anaemia defined as haemoglobin <115g/L in women and <135g/L in men.
25. Known or suspected active hyperthyroidism.
26. Known or suspected phaeochromocytoma.
27. Active infection in the mouth or throat.
28. Pregnant or lactating females

29. Participation in any other clinical study within three months prior to enrolment or during the present study.
30. Known or suspected alcohol or illicit drug abuse.
31. History of alcohol or drug abuse.
32. Need for regular medication with prescription or over-the-counter drugs except contraceptives.
33. Dry mouth problems.
34. Has a nicotine level of ≥ 2 ng/ml measured pre-dose at the first dosing visit.
35. Known human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody positive status.
36. If the Investigator, for any other reason, judge that the Subject should not be included (e.g. if Subject is considered unlikely to comply with study procedures, restrictions, and requirement or if Subject is expected to withdraw from the study).

9.3.3 Restrictions

- The Subjects will be instructed to abstain from use of any nicotine medication or tobacco product for at least 10 hours (5 nicotine elimination half-lives) before dosing on Visit 1 and Visit 2.
- The Subjects will be instructed to fast for at least 8 hours prior to dose administration on Visit 1 and Visit 2, and no food is allowed until 1 hour post-dose. Water is allowed as desired except one hour before and one hour after drug administration.
- The Subjects will be instructed to abstain from vigorous physical activity from at least 8 hours prior to the dose administration on Visit 1 and Visit 2.
- No concomitant drugs, herbal medicine, grapefruit juice or alcohol are allowed from 24 hours before and during Visit 1 and Visit 2, exception made only for contraceptives.

9.3.4 Removal of subjects from therapy or assessment

A study Subject should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the expressed wish of the Subject.

If a Subject does not return for a scheduled visit, every effort should be made to contact the Subject to document the reason for the withdrawal. If a Subject is withdrawn due to an AE the Subject should be followed up by a phone call one week after the withdrawal. The CRF should be completed as far as possible and collected by the Monitor.

A Subject's participation in the study will be discontinued if any of the following criteria applies:

- Consent withdrawn
- Subject experiences AEs or SAE that contraindicate continuing the study, as judged by the Investigator
- Subject's general condition contraindicates continuing the study, as judged by the Investigator

- Major protocol violations
- Non-compliance with the restrictions specified is section 9.3.3.

9.3.5 Screening and enrolment log

The clinic will keep a log of all Subjects screened and included. The reason for screen failure should be stated for all Subjects screened but not included. The reason for withdrawal should be stated for all Subjects included but not completed.

9.3.6 Recruitment

The study Subjects will be recruited by an announcement (Appendix 19.5) on placards placed on strategic public places at Campus Huddinge, Campus Solna, Sankt Görans Hospital and Karolinska, Huddinge. Announcement will also be made on the intranets of Karolinska University Hospital and Capio S:t Görans Hospital.

9.4 Treatments

9.4.1 Identity of test product

The test product is an ODF formulation manufactured by Vecura, Karolinska University Hospital. Each film contains 2.0mg nicotine which will be dose administered in this study. The test product will be administered by the Investigator to the oral mucosa of the Subjects. The films are beige-white and have lemon flavour, the size of each film is 2x3 cm and the thickness is 0.07 mm.

9.4.2 Identity of Reference Product

The reference product is a clear oral spray with peppermint flavour manufactured by McNeil AB. Each bottle contains 13.2ml of liquid and allows 150 sprays containing 1mg of nicotine. The dose given in this study will be 2 mg administered by the Investigator as 2 sprays.

9.4.3 Packaging, labelling and storage of the test product

The labelling of the test product, including the reference product, will follow the instructions given in Revised Annex 13, Manufacture of investigational medicinal products, Volume 4 of the rules governing medicinal products in the European Union.

The GMP unit at Huddinge Hospital is responsible for packaging and labelling of the test product.

The test product will be packed separately in aluminium foil peel. Each foil peel will be clearly labelled indicating the content to be the test product. For samples of the labelling see Appendix 19.3.

The Pharmacy at Huddinge hospital is responsible for packaging and labelling of the reference product.

The reference product will be provided as plastic bottles, one bottle for each dosing day. Each plastic bottle will be clearly labelled indicating the content to be the reference product in the proposed clinical study. For samples of the labelling see Appendix 19.3.

The test and reference product will be stored in a secure area with restrictive access during the entire study period. The test product should be stored under dry conditions and both the test and the reference products should be stored in room temperature (no more than 25ºC). Any deviations from the recommended storage condition should immediately be reported to Fredrik Sjöö at FFT Medical AB and the study medication should not be used until authorisation has been given by FFT Medical AB.

9.4.4 Doses and treatment regimens

The Sponsor will supply the test product, Nicotine 2.0mg films. The film will be administered by the Investigator to the oral mucosa of the Subject´s palate where it will adhere and release the nicotine.

The reference product, Nicorette® peppermint oral nicotine spray will be supplied by the Pharmacy. Nicorette® peppermint oral nicotine spray will be administered by the Investigator in a dose of 2 mg, given as two sprays into the mouth.

All Subjects will receive one dose of the test product and one dose of the reference product, separated with 6 to 21 days. The same doses will be given to all Subjects.

9.4.5 Product accountability

The test product will be released to the study site after approvals of the Study Protocol have been received from the IEC and the Competent Authority. The test product will be dispensed to the study Subjects on Visit 1 and Visit 2 by the Investigator.

The Investigator is responsible for keeping detailed records, which show the quantity of test product that is stored, delivered to and taken out from the place of storage. Any discrepancies between dispensed and returned test product must be explained and documented.

Products deliberately and/or accidentally destroyed by the Investigator/ Hospital Pharmacy or the Subject must also be accounted for.

The Monitor will perform test product accountability and make sure that all unused test product is adequately destroyed/returned and documented.

9.4.6 Method of assigning subjects to treatment groups

The 24 Subjects will be sequentially randomized, as they become available for dosing, into two equally sized groups, one receiving first Nicorette® peppermint oral nicotine spray followed by Nicotine ODF and vice versa for the other group. For practical reasons, a maximum of eight Subjects can be dosed on each dosing day. If, for some reason, there would be less than eight Subjects dosed on a dosing day, an additional dosing day will be added.

9.4.7 Blinding

This is a non-blinded study.

9.4.8 Emergency decoding of blinded treatment

Not applicable.

9.4.9 Prior and concomitant therapy

All concomitant therapy used during and within 3 weeks prior to the study period must be recorded in the CRF. No other drug under investigation may be used concomitantly with the study medication.

The Subjects must not participate concurrently in any other clinical study.

9.4.10 Continuation of treatment

Additional treatment with the test product, in addition to what is described in this protocol, will not be administered.

9.4.11 Treatment compliance

The dosing of the test product will be performed during visits at the site and will be performed by the Investigator, who will verify the treatment compliance.

9.5 Study assessments

9.5.1 Demographics and other baseline characteristics

Subject demographic data (including date of birth and gender) and a complete medical history will be obtained during the screening visit.

9.5.2 Clinical efficacy assessments

A *user satisfaction questionnaire* (Appendix 19.7) will be administered at the times indicated in the Table 1. The questionnaire will assess the Subjects overall satisfaction between the test and reference products respectively. The questionnaire will be filled out by the Subjects themselves.

A questionnaire to assess the Subjects' urges to smoke, the *QSU brief questionnaire* (Appendix 19.9) will be completed by the Subjects pre-dose and at 30 minutes and1hour after administration of the test and reference products, respectively. The questionnaire will be filled out by the Subjects themselves.

A *nicotine withdrawal questionnaire* (Appendix 19.10) to assess the Subjects' signs of nicotine withdrawal symptoms will be completed by the Subjects pre-dose and 30 minutes after administration of the test and reference products, respectively. The questionnaire will be filled out by the Subjects themselves.

The *FTND questionnaire,* a two question questionnaire (Appendix 19.8) will be completed by the Subjects during the screening visit. The results will indicate the Subjects degree of dependence to nicotine. The results might be used in explorative analyses to link degree of dependence on an individual level to other study results.

9.5.3 Pharmacokinetic assessments

9.5.3.1 Sample collection and handling

A baseline sample will be taken before administration of the respective drug.

Blood samples for evaluation of the pharmacokinetic profile will then be taken after 2 minutes, 5 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours 4 hours and 6 hours, respectively. The procedure will be repeated when the Subject returns for the second treatment. Serum concentrations of nicotine will be determined in blood, sampled and analysed according to Appendix 19.11. Each sample will be divided into two tubes whereof the first will be sent to ABS Laboratories in England for analysis and the second will be stored in KI Biobank at Karolinska Institutet until 6 months after the end of the study if re-analysis is required. Samples will thereafter be destroyed.

9.5.3.2 Pharmacokinetic analysis

Blood samples will be analyzed using liquid chromatography.

AUC are estimated with a non-compartmental model using combined trapezoidal rule, linear until the peak concentration and beyond the peak concentration using log trapezoidal rule. The calculations will be made using WinNonlin® 5.2 software from Pharsight Inc.

9.5.4 Laboratory assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the screening visit. The variables to be analysed are listed in Table 2. A urine pregnancy test (u-hCG) will be performed for all women of child bearing potential during screening.

Table 2. Laboratory Variables

Clinical Chemistry	Haematology	Urine
P/S-Sodium	B-Haemoglobin	Pregnancy test (U-hCG)
P/S-Potassium	Leukocyte count	
P/S-Calcium	Thrombocyte count	
P/S-Lactate Dehydrogenase		
P/S-Bilirubin		
P/S-Alanine Transaminase (ALT)		
P/S-Aspartat Transaminase (AST)		
P/S-PK-INR		
P/S-C reactive Protein		
P/S-Thyroid Stimulating Hormone		
P/S-Nicotine		

The samples for clinical chemistry and haematology will be analysed using routine methods at Unilabs Clinical Chemistry Laboratory, Sankt Görans Hospital, a SWEDAC accredited unit.

The collected specimens will be stored at the Karolinska Institutet, Biobank according to an agreement between the Investigator and the sponsor. Blood samples will be kept at the Department of Clinical Chemistry for six months after the end of the study and will thereafter be destroyed.

9.5.5 Clinical safety assessments

9.5.5.1 Physical Examination

A physical examination will be performed by the Investigator at time points specified in Table 1. The examination will include cardiac and pulmonary auscultation, palpation of the abdomen and inspection of the oral mucosa in the palate and buccal area.

9.5.5.2 Vital Signs

Vital signs will be assessed at time points indicated in Table 1. Vital signs to be measured include weight, height (on the screening visit only), SBP and DBP. Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.

9.5.5.3 Electrocardiogram (ECG)

A 12-lead paper ECG will be obtained on the screening visit after the Subject has been sitting/lying down for at least 5 minutes. The Investigator will evaluate the ECG as Normal/Abnormal Non-Clinically Significant/Abnormal Clinically Significant.

9.5.6 Adverse events

9.5.6.1 Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the product.

An SAE is any untoward medical occurrence or effect that at any dose

- results in death
- is life-threatening
- requires patient’s hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
- is regarded as medically important without meeting the above mentioned criteria.

9.5.6.2 Methods for eliciting adverse events

AEs will be assessed from administration of the first dose on Visit 1 until the end of Visit 2 or if applicable until the safety follow-up phone call seven days after Visit 2.

An AE can either be reported spontaneously by the Subject, or reported in response to the questions “Have you experienced any unfavourable effects after the administration of the nicotine ODF/spray today?” and “Have you experienced any unfavourable effects since last visit?

All AEs, serious and non-serious, should be recorded in the CRFs. If no AE has occurred during the study period, this should also be recorded in the CRF.

The following evaluations are to be done by the Investigator in connection with the AE:

- type of event
- seriousness
- degree of severity
- duration (start - end)
- action taken
- causality with study product
- outcome of the AEs

The Investigator should rate the severity as follows:

Mild: The AE does not interfere with the Subject’s usual function.

Moderate: The AE interferes to some extent with the Subject’s usual function.

Severe: The AE interferes significantly with the Subject’s usual function.

When assessing the causality to the study product, the following nomenclature should be used:

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable: A clinical event - including laboratory test abnormality - with a reasonable time sequence to use of the product, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

Possible: A clinical event - including laboratory test abnormality - with a reasonable time sequence to use of the product, but which could also

be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event - including laboratory test abnormality - with a temporal relationship with use of the product which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Not assessable: A clinical event where the information received is too inadequate to allow a reasonable assessment.

For AE reporting purposes no distinction should be made between the test or reference products.

9.5.6.3 Reporting of SAEs

All SAEs must be reported by the Investigator using phone or fax within 24 hours of knowledge of the event to the Safety department at IRW Consulting AB, regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. The Initial Report should contain as much information as possible, but a minimum the following information:

- Subject identification
- treatment specification (blinded information, if code not broken)
- AE diagnosis
- time specification for the medical event
- name of the original reporter

A SAE Report Form must also be completed, signed by the Investigator and submitted to FFT Medical AB no later than five calendar days after the initial information was received. Apart from the information above, this Follow-up Report should also contain the following information:

- assessment of severity
- assessment of causality

No distinction should be made between the test and the reference product regarding reporting of SAEs.

Only SAEs that are both unexpected and related to the test product, SUSARs, are subject to expedited reporting.

The Sponsor is responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of Subjects. The appropriate IEC and Competent Authorities, as per local requirements, should be informed by the Sponsor about SAEs associated with the use of the product (SUSARs).

9.5.6.4 Follow-up period after an AE

If a study Subject is withdrawn due to an AE, or if an AE persists at the end of the study treatment period, this should be followed up until the condition has ceased or until the Subject is under professional medical care and a potential causality between

the investigational drug and the AE has been penetrated. An outcome assessment should be performed when an AE persists. In case of ongoing AEs at study termination they can be followed up by a phone call one week after.

Serious AEs that occur after a Subject has completed the clinical study should possibly be reported to IRW by the Investigator. A causality assessment and a determination of expectedness are needed for a decision on whether or not reporting to the Competent Authorities is required.

9.5.6.5 Procedures in case of pregnancy

All pregnancies (either through maternal exposure or transmission of a medicinal product via semen following parental exposure) must be reported on a pregnancy notification form immediately within 24 hours after recognition. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth and presence of any birth defects, congenital anomalies or newborn or maternal complication even if the Subject was discontinued from the study.

In case of pregnancy, the study treatment must be stopped immediately, and the Subject discontinued from participation in the study.

9.5.6.6 Coding of AEs

All AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) by IRW after the CRFs have been collected from the study centres.

9.5.1 Periodic Safety Reporting

A safety report should be sent to the Competent Authority and IEC within 90 days of the end of study together with the notification of the end of the study according to Article 10(c) of Directive 2001/20/EC. This report should contain at least an analysis of the subjects' safety and line listings, and if appropriate aggregate summary tabulations.

9.6 Data quality assurance

9.6.1 Monitoring and auditing procedures

The study site will be visited by the Monitor and/or the Project Manager periodically at times agreed on by the Investigator and the Sponsor. It is the function of the Monitor to ascertain that all aspects of the Study Protocol are complied with and that the conduct of the study conforms to applicable regulatory requirements and established rules for Good Clinical Practice (GCP).

At the time of each monitoring visit, the Monitor will review the completed CRFs to ascertain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.

The Monitor will also check that the data in the CRF are consistent with the clinical records (Source Data Verification) and that study results are recorded completely and correctly. The Monitor will check on the reporting of SAEs and the procedures for test

product accountability and record keeping. For this purpose the Monitor must be given direct access to clinical records, original laboratory data, etc., as far as these relate to the study and without jeopardizing Subject integrity. CRFs for all included Subjects must be made available to the Monitor for review. Completed CRFs will be collected by the Monitor as soon as the data has been validated.

The study site may also be subject to quality assurance audit by the Sponsor or someone appointed for this task by the Sponsor. A Competent Authority may request to make an inspection of the study site. The procedures of such a visit would be similar to those of a monitoring visit, and data already checked by the Monitor may be checked again. The Investigator is required to inform the Sponsor immediately of an inspection requested by a Competent Authority.

9.6.2 Case Report Forms

CRFs of a design mutually agreed upon by FFT Medical and IRW will be supplied by IRW. A CRF must be completed and signed for each included Subject. All data and information on the CRFs are to be neatly and legibly recorded in black or blue ball-point ink to ensure legibility of self-copying and/or photocopied pages. Corrections on the CRFs must be made by one single line through the incorrect data, leaving the corrected data clearly visible. The revised entry should be made alongside, initialled and dated by a member of the Investigator's research team who is authorized to initial CRF changes for the Investigator. This authorization must be documented in writing. Correction fluids are not permitted.

The completed CRFs should be made available for checking of completeness and accuracy before collection by the Monitor as agreed in advance. The original CRFs are the sole property of the Sponsor and should not be copied or made available in any form to a third party, with the exception of authorized representatives of local Competent Authorities, without the written permission from the Sponsor".

The CRF should be completed as soon as the data are available or during the subject's evaluation.

The completed CRFs should be made available for checking of completeness and accuracy before collection by the Monitor as agreed in advance. The original CRFs are the sole property of the Sponsor and should not be copied or made available in any form to a third party, with the exception of authorized representatives of local Competent Authorities, without the written permission from the Sponsor.

9.6.3 Source Data

The Investigator ensures that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is CRFs and source documents, original documents, data and records including records kept at the laboratories, involved in the clinical study are complete, accurate, and kept in a secure area at the site with restricted access to Study Personnel.

Data recorded in the CRF should correspond to the data in the source documents, as applicable. Any discrepancies or notable omissions should be brought to the attention of the Investigator/ study staff. For protection of the confidentiality of study Subjects, only non-ambiguous subject identification numbers should be used for identification of all data reported in the CRF.

9.6.4 Training of study staff

It is the responsibility of the Investigator to ensure that all Personnel involved in the study are fully informed of all relevant aspects of the study, and have a detailed knowledge of and training in the procedures that are to be executed by them.

All Investigators and staff carrying out observations of primary or other major outcome variables involved in the study should provide a Curriculum Vitae (CV). The Investigator will keep a list of all Personnel involved in the study together with their function and study related duties delegated. He/she will ensure that appropriate study related training is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before inclusion of subjects the Monitor and/or Project Manager will perform a study initiation visit to inform and train relevant study staff.

9.7 Statistical methods and determination of sample size

9.7.1 Demographics and baseline data

Demographics and baseline data including the FTND, will be presented in tabulations and listings. Descriptive statistics as mean, median, standard deviation, minimum and maximum will be provided.

9.7.2 Analysis of efficacy

User satisfaction, urge to smoke and signs of nicotine withdrawal following treatment with Nicotine ODF and Nicorette® , will be presented as tabulations and listings. Descriptive statistics as mean, median, standard deviation, minimum and maximum will be provided.

9.7.3 Analysis of pharmacokinetic data

All individual concentration data and pharmacokinetic parameters will be listed by formulation together with geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration/time curves will be presented in linear/linear and log/linear scale.

The pharmacokinetic parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} and t_{max} will be determined for the study formulation and for the reference formulation.

The assessment of bioequivalence is based upon 90% confidence intervals (CI) for the ratio of the geometric means (test/reference) for $AUC_{(0-t)}$ and C_{max}. If the 90% CI are contained within an interval of 0.8 and 1.25, the two formulations will be considered bioequivalent.

$AUC_{(0-t)}$ and C_{max} will be transformed using a logarithmic transformation and then subjected to analysis with an Analysis of Variance (ANOVA) fixed effects model using sequence, subject within sequence, period and formulation as sources for variance, in addition to residual error. A CI for the ratio study drug versus reference AUC and C_{max} will be calculated from the data.

The CI will then be back transformed to obtain the confidence interval geometric means for the ratio on the original scale.

WinNonlin® 5.2 software from Pharsight® will be used for the statistical calculations as well as for the PK analyses.

9.7.4 Analysis of safety

AEs will be collected from the first administration of the test or reference product until the end of Visit 2 or if applicable until the follow-up call after Visit 2.

All AEs will be summarized and presented according to MedDRA system organ class and preferred term.

Descriptive statistics and individual listings will be provided for AEs, laboratory data variables, vital signs and physical examination data. Depending on type, data will be tabulated in frequency tables or presented as mean, median, standard deviation, minimum and maximum values.

9.7.5 Statistical/analytical issues

9.7.5.1 Adjustments for covariates

No adjustments for covariates will be made. All effects included in analysis model are specified in section 9.7.3 of this protocol.

9.7.5.2 Handling of dropouts or missing data

No replacement of dropouts or withdrawn subjects will be performed. No data imputations will be made. Data points will be considered missing at random.

9.7.5.3 Active-control studies intended to show equivalence

9.7.6 Analysis data sets

Safety Analysis Set: All Subjects who receive at least one dose of the test product, will be included in the safety analysis.

Intention-to-Treat (ITT) Analysis Set: All Subjects who receive at least one dose of the test product or reference product will be included in the description of the efficacy variables

PK Analysis Set: Comprise all Subjects in the ITT Analysis Set who provide evaluable data for both treatment periods, i.e. no more than one missing data point from each treatment period for PK analysis and no pre-dose concentration greater than 5 percent of the C_{max} value for the subject in that period.

9.7.7 Determination of sample size

The number of subjects necessary for 90% power to prove the hypothesis of bioequivalence as previously described depends on intra-subject coefficient of variation (C_V) and actual difference between products. These factors are unknown. We estimate intra-subject log-transformed σ to approximately 15%, based on the fact that an inter-subject variability (30-50%) has been found in studies of similar products. We further estimate the actual difference between products to be no more than 5%.

Using the well-known approximate formula shown below for sample size in a cross-over design study for bioequivalence testing with log-transformed data the number of subjects for our study using the above assumptions is estimated to be 16 (15.73).

$$n \geq \frac{\sigma^2(t(\alpha, 2n-2) + t(\beta, 2n-2))^2}{(\log 1.25 - \log(\mu T/\mu R))^2}$$

α=level of significance
β=power
σ=intra subject standard deviation of log-transformed data
n=subjects per series (Total number of subjects=2*n*)
μT=Test formula mean result
μR=Reference formula mean result

(Adapted from Hauschke et al, J Pharmacokin Biopharm, Vol. 20, No. 5, 1992 pp 557-561)

We have chosen to calculate on a μT/μR>1. Due to asymmetry of the power curve on the original scale, the estimated sample size required is smaller than if we would have calculated on μT/μR<1. We, however, believe that it is more likely that the test formula has a slightly higher bioavailability than the reverse. Also, calculating with μT/μR<1 gives an estimate for need of subjects 2n=16.19. We accordingly conclude that the difference is not of any major importance.

From similar studies a drop-out frequency of approximately 30% has been reported (e g McRobbie et al. 2010) for included subjects. Accordingly we aim to include 24 subjects for this study.

9.8 Data Management

CRFs will be filled in by the study Site Personnel. The CRF will be checked by the Monitor before being forwarded to a database. Copies of all CRFs will be stored at the clinic. The Sponsor will make sure that the entered data is validated, by logical checks, both computerized and manual, as well as proof reading of specified variables. In case there are any inconsistencies detected during these procedures, a Data Clarification Form (DCF) will be sent to the Investigator and resolved by the Monitor or Site Personnel. When filled in and signed, it will be returned to the Sponsor. A copy of the DCF will be filed with the CRF at the study site and the original DCF will be returned to the Sponsor. No changes will be done on the CRF copies at the centre.

9.9 Changes in the approved Study Protocol

Any proposed change to the approved Final Study Protocol (including appendices) will be documented in a written and numbered protocol amendment. All amendments

including substantial changes to the protocol must be submitted to appropriate IEC and/or Competent Authority for approval, according to applicable national regulations. A substantial protocol amendment should be signed and dated by the same parties who signed the Final Study Protocol, as applicable.

10 EMERGENCY PROCEDURES

10.1 Emergency contacts

If an emergency occurs, the Investigator will immediately be contacted and within 24 hours the Sponsor contact person should also be contacted.

Principal Investigator:
Jon Enestig
Department of Medicine
Capio S:t Görans Hospital
Stockholm, Sweden
Phone: +46 8 587 01 000 Mobile: +46 70 304 40 001.

Sponsor contact person:
Fredrik Sjöö, MD
FFT Medical AB
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10.2 Procedures in case of medical emergency

The Investigator is responsible for ensuring that there are procedures and expertise available to cope with medical emergencies during the study.

10.3 Procedures in case of overdose

Only regular smokers daily exposed to nicotine in relation to cigarette smoking will participate in the study. The nicotine exposure following administration of the reference products is comparable to the to the nicotine exposure following cigarette smoking. The test product is estimated to induce a similar nicotine exposure as compared to the reference product and to cigarette smoking. The site personnel will administer both the test product and the reference product to the Subjects during the two treatment visits to the site. Therefore, procedure in the case of overdose is not applicable for this study.

11 STUDY TIME TABLE

The estimated time for inclusion of the first subject is Q1 2012, the anticipated completion time for the last Subject is Q2 2012 and the estimated time for the final clinical study report is Q2 2012. The end of the study is defined as the last visit of the last Subject participating in the study.

12 DISCONTINUATION OF THE STUDY

The Sponsor reserves the right to discontinue the study at any time, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must inform all participating Subjects about the termination of the study, before their next visit to the study site. All delivered and unused study products and other study materials must be returned and all CRFs completed as far as possible.

The Investigator will be reimbursed for reasonable expenses incurred; in the event this becomes necessary.

13 FINAL STUDY REPORT AND PUBLICATION OF STUDY RESULTS

A Clinical Study Report, in compliance with International Conference on Harmonization (ICH) E3; Structure and content of Clinical Study Reports, will be prepared describing the conduct of the study, the statistical analysis performed and the results obtained.

It is agreed between the Investigator and the Sponsor that data from the study will be used in connection with the development of the test product. Information about the study may therefore be disclosed by the Sponsor to their Scientific Advisers and to Competent Authorities.

A summarizing report will be submitted to Competent Authorities and IEC within 12 months from end of study. The Final Study Report will be submitted to Competent Authorities when available and should also form the basis for a manuscript intended for publication in a medical journal.

Formal presentation or publication of data collected in this study should be considered as a joint publication by the Investigator and person appointed by the Sponsor. Authorship will be determined by mutual agreement.

Before any publication (oral or written) of the results the Sponsor will be given 30 days for review and comment on the manuscript. If the Investigator has not submitted the results for publication within six months after completion of the final Clinical Study Report, the Sponsor has the right to publish. In this event, the Investigator will be given 30 days to review and comment on the manuscript before it is submitted to a journal.

14 RECORD RETENTION

The Investigator must arrange for retention at the investigational site of a list of the subjects and their identifying code, subject files and other study documents, in accordance with ICH GCP and regulatory requirements. The archiving period must be adapted to regulations in force and should not be shorter than ten years after the termination of the study and the presentation of the final report.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

15 DISCLOSURE AND CONFIDENTIALITY

All unpublished information concerning the test product and research carried out by the Sponsor, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of the Sponsor. Disclosure to third parties must be limited to those undertaking legitimate peer review of the scientific and ethical aspects of the study and to those participating, including the recipients of drugs, so that customary medical care and informed consent can be achieved.

16 INSURANCE/INDEMNITY

The Sponsor agrees to indemnify (legal and financial coverage) and hold the Investigator free of harm from any claim, whether based on legal principles or on generally accepted liability standards within the pharmaceutical industry, made against him by reason of personal injury, including death, to any person arising out of or connected with the performance of the study to the extent that the injury is not caused by:

1. failure by the Investigator to adhere to the terms of the Protocol;
2. failure by the Investigator to comply with any applicable governmental regulations;
3. malpractice, negligence or willful malfeasance by the Investigator.

The Investigator agrees to notify the Sponsor whenever he/she becomes aware of a claim or action, and to co-operate with and to authorize the Sponsor to carry out sole management of such claim or action.

The Sponsor's responsibility there under is covered by insurance policy from LFF Service AB. The insurance also covers the Sponsor's liability under law and generally accepted liability standards within the pharmaceutical industry towards any third parties, including subjects, as Sponsor of the study.

17 STUDY AGREEMENTS

The Principal Investigator at the investigational site must comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CTA) for this study. In the event of any inconsistency between the Study Protocol and the CTA, the study agreement shall prevail.

A separate Financial Agreement between FFT Medical AB and the Principal Investigator and/or institution will be filed in the Investigator's File and the Study Master File.

18 REFERENCES

1. FASS2010 (Pharmaceutics Specialities In Sweden) 2010. Available at http://www.fass.se
2. Fiore MC , Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ et al.: Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guidelines, U S Department of Health and Human Services, Rockville, MD.
3. GOLD (Global initiative for chronic Obstructive Lung Disease) Global Strategy for the Diagnosis, Management and Prevention of COPD, 2009. Available at http://www.goldcopd.com
4. Hauschke D, Steinijans VW, Diletti E, Burke M (1992). Sample size Determination for Bioequivalence Assessment Using a Multiplicative Model. J Pharmacokin Biopharm, Vol. 20 (5): 557-561
5. Hukkanen J, Jacob P 3rd, Benowitz NL (2005). Metabolism and disposition kinetics of nicotine. Pharmacol Rev 57(1):79-115.
6. McRobbie H, Thornley S, Bullen C, Lin RB, Senior H, Laugesen M, Whittaker R, Hajek P (2010): A randomized trial of the effects of two novel nicotine replacement therapies on tobacco withdrawal symptoms and user satisfaction. Addiction 105: 1290-1298.
7. Peto P, Lopez AD, Boreham J, Thun M, Heath C (1992). Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 339: 1268-1278.
8. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P et al (2007). GOLD executive summary. Am J Respir Crit Care Med 176: 532-555
9. SCB Statistiska Central Byrån(Statistics Sweden), Data from 2008
10. Shafey O, Dolwick S, Guindon GE (2003). Tobacco control country profiles (2nd ed.) America Cancer Society, Atlanta , GA
11. Stead LF, Perera R, Bullen C, Mant D and Lancaster T.: Nicotine Replacement Therapy for Smoking Cessation. Cochrane Database Syst Review CD000146 (2008)
12. Sutherland G, Stapleton JA, Russel MAH, Jarvis MJ, Hajek P, Belcher M, Feyerabend C (1992): Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 340: 324-329.
13. Svenssom Craig K: Clinical Pharmacokinetics of Nicotine (1987). Clinical Pharmacokinetics 12(1): 30-40.
14. US department of Health and Human Services (1988). The health consequences of smoking: Nicotine addiction. A report of the surgeon general. DHHS: 88-8406.

19 APPENDICES

19.1 Signature pages

19.2 Declaration of Helsinki

19.3 Labelling of Study Medication

19.4 Patient Information Sheet and Inform Consent Form

19.5 Subject Advertisement

19.6 Case Report Form

19.7 User Satisfaction Questionnaire

19.8 Fagerström Questionnaire

19.9 Questionnaire on smoking urges

19.10 Nicotine withdrawal questionnaire

19.11 Pharmacokinetic Analysis Method and Certificate of destruction of samples

FFT Medical

2011-12-19

Läkemedelsverket
Kliniska prövningar
Box 26,
751 03 Uppsala

Amendment" (FFT-01-11-A3) av ansökan med EudraCT 2011-000930-12

I tillägg till ansökan med EudraCT nr 2011-000930-12 har förut två Amendments skickats in och godkänts:

- FFT-01-11-A1 berörde införande av Kaliumdivätefosfat såsom ingrediens.
- FFT-01-11-A2 berörde byte av referensprodukt i studien (Zonnic Pepparmint byttes här ut mot Nicorette Pepparmint).

I den godkända ansökan hade referensläkemedlet Zonnic Pepparmint Spray angivits som referensläkemedel. I förut presenterat amendment (FFT-01-11-A2) valdes en annan referensprodukt på grund av att referensprodukten måste vara godkänd i enlighet med en komplett ansökan vilket ju är fallet med "Nicorette Pepparmint 1mg/spray oromucosal spray" som har ett läkemedelsgodkännande baserat på en "line extension" av Nicorette tuggummi.

Analyser av referensprodukten visar att halten nikotin i det undersökta läkemedlet (Nicotine Oral Dissolvable Film (ODF), lemon) bör ändras för att kunna påvisa bioekvivalens. Dosjusteringen innebär en förändring av nikotinhalten från 1,6mg till 2,0mg för det undersökta läkemedlet.

Följande förändringar görs också:

- Ett kommersiellt laboratorium i England väljs för bestämmande av nikotinhalt i plasma. Detta säkrar tillgången på analyskapacitet. I samband med detta anges en uppdaterad analysmetod samt byte till KI Biobank för hantering av plasmaprover.
- En tidpunkt, 2 minuter, för bestämning av nikotinhalt i plasma har lagts till efter administrering av studieläkemedel respektive referensläkemedel.
- Gult färgämne (E100) har tagits bort från beredningen.
- Ingredienserna i beredningen av det undersökta läkemedlet har utökats med pepparmintolja (smak) och titandioxid för att lättare se testprodukten (ODF).
- Fosfatbuffert (Kaliumdivätefosfat) har tagits bort från beredningen (i princip ett återtag av Amendment FFT-01-11-A1)
- Listan över ingående ingredienser ser därför ut som följer: Nikotinbitartrat, Vatten, Natriumalginat (Protanal 5/60). Sorbitol, Glycerol, Natriumhydroxid, Citronolja, Pepparmintolja, Titandioxid.
- Förpackningen är fortfarande Alu/PET peel. Den nu valda leverantören av dessa har en något mindre förpackning i sitt standardsortiment och därav ändrats förpackningsmåtten från 70x40mm till 70x38mm.

Alla dokument skall nu återspegla denna bruttolista.
Tacksamt och med vänlig hälsning

Thomas Ekerborn (Tel 0705127009)

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FFT Medical

2012-09-03

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Kliniska prövningar
Box 26,
751 03 Uppsala

Följebrev väsentlig ändring (FFT-01-11-A4) med ansökan utökad hållbarhetstid för läkemedel i studie med EudraCT 2011-000930-12

Återkoppling till mig i ett email från Annika Ridell (2012-08-30), på en begärand om utökad hållbarhetstid, samt därtill övrig information, har jag tagits tillvara i innehållsförteckningen nedan och där hänvisade dokument.

1. Satsdata inkluderande upplösningstest för 4 satser återfinns i dokumentet *"Summary of batch data Nicotine ODF. 4 Batches.pdf".*
2. "Uniformity of dosage units" kom aldrig att ingå i specifikationsdokument av produkten men var med i planarbetet genom att utökat antalet analysdoser till 10st för både 0-provet och 14-dagarsprovet för stabstudien vid 25 grader. Värdena för Uniformity of dosage units finns att tillgå för samtliga satser i *"Stability data summary 20120902 25C.pdf".*
3. HPLC-metod med valideringsrapport framgår av dokumenten
    a. *"Toxicon Nikotinmetod 2012-02-23.pdf"*
    b. *"Toxicon Validering Nikotinmetod 2012-02-23.pdf"*
4. Summering av stabilitetsstudier, specifikationer och mätvärden för 4 satser och för tre lagringsbetingelser.
    a. *" Stability data summary 20120902 25C.pdf"*
    b. *" Stability data summary 20120902 40C.pdf"*
    c. *" Stability data summary 20120902 60C.pdf"*
5. Method suitability test (MST) framgår av fyra dokument i
    a. *"Method Suitability Test – TAMC.pdf"*
    b. *"Method Suitability Test – TYMC.pdf"*
    c. *"Method Suitability Test - Staphylococcus aureus.pdf"*
    d. *"Method Suitability Test - Pseudomonas aeruginos.pdf"*

Förslag på hållbarhetstid är 6 månader (dvs tre månader utöver dagens hållbarhetstid).

Då studien fortsatt inkluderat patienter, är planen att snarast frisläppa doser ur karantän från sats 20120423-97:2/5 för att kunna fullgöra studien.

Tacksamt och med vänlig hälsning

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Case Report Form

FFT-01-11

A bioequivalence study of an oral dissolvable film (ODF) for transmucosal nicotine delivery with Nicorette® Pepparmint oral nicotine spray as reference product

General Instructions for completion of the Case Report Form

GENERAL
Complete the CRF in **English.**
Avoid abbreviations and acronyms as far as possible.
Use only abbreviations/acronyms that are clear and in standard medical use.
Use **black or blue ink** for all entries and press firmly.
Fill in all pages completely and legibly.
Do not write in shaded areas unless requested.

Corrections:
Cross out the incorrect entry with one single line, so that it remains legible.
Place the correct entry next to the one stroked out.
Date and initialise the correction.
The Investigator can confirm an extreme value by giving **sic** ("so is correct") next to the extreme value. Example: Weight:

SCREENING
If the Subject is judged as a Screen failure no further assessments should be performed but all data obtained so far should be entered.

BOX ENTRIES
All numbers and letters are to be written **within the boxes.**
Numbers and letters are to be arranged **to the right** in the data entry field
Initials must be consistent throughout the CRF.
Fill in empty positions with "0" (missing number) or "-" (missing letter).

TEXT ENTRIES
Write in allocated spaces only.

DATES and TIME
Time shall be recorded as HH:MM, using 24 hours.
Dates shall be recorded as day MON year; e.g. 19 MAR 2011
If the month and/or day of the month are unknown, enter UNK for the respective field.
The 4-digit year must be entered in all date fields.
The Subject should estimate the year if the year is not documented.

MISSING DATA
Use the following abbreviations for missing information:
NA Not Applicable
ND Not Done
UNK Unknown

Screening Visit

Screening

1. Date Of Visit	
1. Date of visit (dd-MMM-yyyy)	Date Month Year

2. Informed Consent		
1. Did the patient sign the informed consent?	☐ Yes	☐ No
2. Date of informed consent signed (dd-MMM-yyyy)	Date Month Year	

3. Demographics		
1. Gender information	☐ Male	☐ Female
2. Date of birth (dd-MMM-yyyy)	Date Month Year	

Site Number		E- Code		Subject Number			Subject Initials		
0	1								

FFT-01-11

Screening

4. Medical History			
1. Does the Subject have any relevant medical or surgical history?	☐ Yes	☐ No	
If yes, specify below:			
Diagnosis/Surgical procedure & MedDRA	**Start Date**	**End Date**	**Ongoing**
			☐
			☐
			☐
			☐
			☐
			☐
			☐

5. Concomitant Medication		
1. Is the Subject taking any medication regularly and/or within 3 weeks prior to the date of screening visit?	☐ Yes	☐ No
If YES, please specify on the Concomitant Medication page.		

Screening

6. Physical Examination		
Body system	**Status**	**Finding (symptom/diagnosis) and MedDRA code**
General appearance	☐ Without remarks ☐ Abnormal ⇨	
ENT (Ear,Nose,Throat)	☐ Without remarks ☐ Abnormal ⇨	
Heart	☐ Without remarks ☐ Abnormal ⇨	
Lungs	☐ Without remarks ☐ Abnormal ⇨	
Abdomen	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	

7. Vital Signs	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Height (cm)	
4. Weight (Kg)	
5. Heart Rate	

8. ECG	
1. Date of ECG (dd-MMM-yyyy)	Date Month Year

☐ Normal

☐ Abnormal, but not clinically significant; specify

☐ Abnormal and clinically significant; specify

9. Laboratory Assessments	
1. Have routine Hematology samples been taken?	☐ Yes ☐ No
2. Have routine Clinical Chemistry samples been taken?	☐ Yes ☐ No
3. Have Nicotine level samples been taken?	☐ Yes ☐ No

10. Urine dipstick pregnancy test	
1. Specify Urine Dipstick Result	☐ Positive ☐ Negative ☐ NA

11. HÄLSODEKLARATION

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date Month Year

1. Vilka mediciner äter du regelbundet?.	
2. Hur många cigaretter röker du ungefär i genomsnitt per dag?	
3. Hur många gånger ungefär röker du pipa en vanlig dag?	
4. Har du problem med muntorrhet?	☐ Ja ☐ Nej
5. Har du någon gång drabbats av hjärtinfarkt eller stroke	☐ Ja ☐ Nej
6. Har du problem med kärlkramp i hjärtat (angina pectoris)?	☐ Ja ☐ Nej
7. Har du problem med hjärtrytmrubbningar	☐ Ja ☐ Nej
8. Är du gravid?	☐ Ja ☐ Nej ☐ NA
9. Har du problem med överaktiv sköldkörtel?(Hyperthyreos)	☐ Ja ☐ Nej
10. Har du problem med överaktiv binjure?(Pheochromocytom)?	☐ Ja ☐ Nej
11. Har du missbrukat alkohol eller narkotika?	☐ Ja ☐ Nej
12. Har du eller misstänker du att du har någon blodsmitta?	☐ Ja ☐ Nej

12. FAGERSTRÖMS TEST FOR NICOTINE DEPENDENCE	
FRÅGOR TILL FÖRSÖKSPERSONERNA **Subject Questionnaire**	
Date ☐☐ Month ☐☐☐ Year ☐☐☐☐	
Markera det svar för de respektive frågorna som bäst överensstämmer med din rökning.	
13. Hur snabbt efter uppvaknandet röker du din första cigarett?.	☐ inom 6 min [3] ☐ 6–30 min [2] ☐ 31–60 min [1] ☐ mer än 60 min [0]
14.Hur många cigaretter röker du per dag?	☐ färre än 10 [0] ☐ 11–20 [1] ☐ 21–30 [2] ☐ fler än 30 [3]
Tolkning, poängsumma: 0-1= litet nikotinberoende, 2 = moderat beroende, 3 = starkt beroende, 4-6 = mycket starkt nikotinberoende.	

Site Number	E- Code	Subject Number	Subject Initials
0 1			

FFT-01-11

Screening

13. Inclusion Criteria		
1. Male or female smokers 18 to 55 years at the time of signing the ICF.	☐ Yes	☐ No
2. Body Mass Index between 18.5 and 30.0 kg/m^2.	☐ Yes	☐ No
3. Smoking on average at least 7 cigarettes per day, for at least the last two years.	☐ Yes	☐ No
4. Has signed the ICF.	☐ Yes	☐ No

14. Exclusion Criteria		
1. Physical or mental disorder that could impair the Subject's ability to participate in the study.	☐ Yes	☐ No
2. Ischemic Heart Disease, Cardiac infarction, or Cardiac arrhythmias in the medical history or signs of previous infarction on ECG from the screening visit.	☐ Yes	☐ No
3. Cerebrovascular disease in the medical history.	☐ Yes	☐ No
4. Uncontrolled hypertension, defined as Systolic Blood Pressure (SBP) ≥180 mm Hg and/or Diastolic Blood Pressure (DBP) ≥110 mm Hg.	☐ Yes	☐ No
5. Moderate to severe liver or kidney disease, as judged by the Investigator.	☐ Yes	☐ No
6. Anaemia defined as haemoglobin <115g/L in women and <135g/L in men.	☐ Yes	☐ No
7. Known or suspected active hyperthyroidism.	☐ Yes	☐ No
8. Known or suspected phaeochromocytoma.	☐ Yes	☐ No
9. Active infection in the mouth or throat.	☐ Yes	☐ No
10. Pregnant or lactating females	☐ Yes	☐ No
11. Participation in any other clinical study within three months prior to enrolment or during the present study.	☐ Yes	☐ No
12. Known or suspected alcohol or illicit drug abuse.	☐ Yes	☐ No

Exclusion Criteria Contd.		
13. History of alcohol or drug abuse.	☐ Yes	☐ No
14. Need for regular medication with prescription or over-the-counter drugs except contraceptives.	☐ Yes	☐ No
15. Dry mouth problems.	☐ Yes	☐ No
16. Has a nicotine level of ≥ 2 ng/ml measured pre-dose at the first dosing visit.	☐ Yes	☐ No
17. Known human immunodeficiency virus (HIV), hepatitis B surface antigen or hepatitis C antibody positive status.	☐ Yes	☐ No
18. If the Investigator, for any other reason, judge that the Subject should not be included (e.g. if Subject is considered unlikely to comply with study procedures, restrictions, and requirement or if Subject is expected to withdraw from the study).	☐ Yes	☐ No

15. Eligibility Check	
1. Does the Subject fulfill all inclusion criteria and none of the exclusion criteria?	☐ Yes ☐ No
2. If NO, give number of first failed criterion and tick whether inclusion or exclusion criterion	☐ Inclusion ☐ Exclusion

Visit 1 – Day 0

Visit 1 (Day 0) - Pre-dose

16.	**Date Of Visit**		
1. Date of visit (dd-MMM-yyyy)	Date	Month	Year

17.	**Concomitant Medication**	
1. Has there been any change(s) in the Subject's concomitant medication(s) since previous visit?	☐ Yes	☐ No
If YES, please specify on the Concomitant Medication page.		

18.	**Last Cigarette**		
1. Date of Subjects Last Cigarette?	Date	Month	Year
2. Time of Subjects Last Cigarette?	:		

19.	**Urine dipstick pregnancy test**
1. Specify Urine Dipstick Result	☐ Positive ☐ Negative ☐ NA

20.	**Vital Signs**
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 1 (Day 0) – Pre-dose

21. Physical Examination		
Body system	**Status**	**Finding (symptom/diagnosis) and MedDRA code**
General appearance	☐ Without remarks ☐ Abnormal ⇨	
ENT (Ear,Nose,Throat)	☐ Without remarks ☐ Abnormal ⇨	
Heart	☐ Without remarks ☐ Abnormal ⇨	
Lungs	☐ Without remarks ☐ Abnormal ⇨	
Abdomen	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	

Visit 1 (Day 0) – Pre-dose

22. **Eligibility Check**	
1. Does the Subject fulfill all inclusion criteria and none of the exclusion criteria?	☐ Yes ☐ No
2. If NO, give number of first failed criterion and tick whether inclusion or exclusion criterion	☐☐ ☐ Inclusion ☐ Exclusion

23. **Randomization**	
1. Will the Subject be included in the study?	☐ Yes ☐ No
2. If YES, give Randomization Number	☐☐☐

24. **PK blood sampling**	
1. Have a pre-dose PK sample been taken?	☐ Yes ☐ No
2. Time of PK samples taken	☐☐ : ☐☐

Visit 1 (Day 0) - Pre-dose

25. NICOTINE WITHDRAWAL QUESTIONNAIRE

The Subjects will complete the nicotine withdrawal questionnaire 15 to 1 minutes before administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Dos 1 före dos

Date	Month	Year	Time
			:

Bedöm enligt nedanstående alternativ hur du uppfattar dig själv just nu. Ringa in det alternativ som passar bäst där 1 är minst och 5 är mest

1. Arg, irriterad, frustrerad				
1	**2**	**3**	**4**	**5**

2. Nervös				
1	**2**	**3**	**4**	**5**

3. Ledsen, nedstämd.				
1	**2**	**3**	**4**	**5**

Visit 1 (Day 0) – Drug Administration

26. 1st Administration of drug	
1. Which drug will be administered to the subject?	☐ study drug- ODF ☐ Nicorette® pepparmint Spray
The Subject should be fasted for at least 8 hours prior to administration of the study drug- oral dissolvable film / Nicorette® pepparmint oral nicotine spray, and no food is allowed until 1 hour post-dose. Water is allowed as desired except one hour before and one hour after drug administration	
2. Date of Subjects Last meal	Date Month Year ☐☐ ☐☐☐ ☐☐☐☐
3. Time of Subject's latest meal	☐☐ : ☐☐
4. Time of Study Drug administration	☐☐ : ☐☐
5. Has the Study Drug been administered according to the protocol?	☐ Yes ☐ No
6. If No, please specify the reason	

Visit 1 (Day 0) – Post-dose

27. PK blood sampling - 2 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

28. PK blood sampling - 5 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

29. PK blood sampling - 10 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

30. PK blood sampling - 20 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

31. Vital Signs - 30 minutes after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

32. PK blood sampling - 30 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 1 (Day 0) – Post-dose

33. NICOTINE WITHDRAWAL QUESTIONNAIRE

The Subjects will complete the nicotine withdrawal questionnaire 30 minutes after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Dos 1 efter dos

Date	Month	Year	Time
			:

Bedöm enligt nedanstående alternativ hur du uppfattar dig själv just nu. Ringa in det alternativ som passar bäst där 1 är minst och 5 är mest

1. Arg, irriterad, frustrerad				
1	**2**	**3**	**4**	**5**

2. Nervös				
1	**2**	**3**	**4**	**5**

3. Ledsen, nedstämd.				
1	**2**	**3**	**4**	**5**

Visit 1 (Day 0) – Post-dose

34. QUESTIONNAIRE ON SMOKING URGES – 30 MINUTES AFTER DRUG ADMINISTRATION

The Subjects will complete the questionnaire on smoking urges 30 minutes after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date	Month	Year	Time
			:

Vänligen besvara nedanstående frågor genom att ringa in den siffra som bäst överensstämmer med din upplevelse på en skala mellan 1 och 7 där: 1=stämmer inte alls, 7=stämmer helt

A.	Jag skulle vilja ha en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
B.	Inget vore bättre än att röka en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
C.	Om det vore möjligt skulle jag troligen ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
D.	Jag skulle ha bättre kontroll om jag kunde ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
E.	Den enda jag vill nu är att röka en cigarett.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
F.	Jag har ett trängande behov av en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
G.	En cigarett skulle smaka fint nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
H.	Jag skulle göra nästan vad som helst för en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
I.	Att röka skulle göra mig mindre deprimerad.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
J.	Jag kommer att ta en cigarett så fort det är möjligt.						
	1	**2**	**3**	**4**	**5**	**6**	**7**

Visit 1 (Day 0) – Post-dose

35. PK blood sampling - 45 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

36. Vital Signs – 1 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

37. PK blood sampling – 1 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

38. QUESTIONNAIRE ON SMOKING URGES – 1 HOUR AFTER DRUG ADMINISTRATION

The Subjects will complete the questionnaire on smoking urges 1 hour after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date	Month	Year	Time
			:

Vänligen besvara nedanstående frågor genom att ringa in den siffra som bäst överensstämmer med din upplevelse på en skala mellan 1 och 7 där: 1=stämmer inte alls, 7=stämmer helt

A.	Jag skulle vilja ha en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
B.	Inget vore bättre än att röka en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
C.	Om det vore möjligt skulle jag troligen ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
D.	Jag skulle ha bättre kontroll om jag kunde ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
E.	Den enda jag vill nu är att röka en cigarett.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
F.	Jag har ett trängande behov av en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
G.	En cigarett skulle smaka fint nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
H.	Jag skulle göra nästan vad som helst för en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
I.	Att röka skulle göra mig mindre deprimerad.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
J.	Jag kommer att ta en cigarett så fort det är möjligt.						
	1	**2**	**3**	**4**	**5**	**6**	**7**

Visit 1 (Day 0) – Post-dose

39. Vital Signs – 1.5 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

40. Vital Signs – 2 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

41. PK blood sampling – 2 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

42. Vital Signs – 3 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 1 (Day 0) – Post-dose

43. PK blood sampling – 3 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	__ __ : __ __

44. Vital Signs – 4 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

45. PK blood sampling – 4 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	__ __ : __ __

46. Vital Signs – 5 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 1 (Day 0) – Post-dose

47. Vital Signs – 6 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

48. PK blood sampling – 6 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 1 (Day 0) – Post-dose

49. Physical Examination		
Body system	**Status**	**Finding (symptom/diagnosis) and MedDRA code**
General appearance	☐ Without remarks ☐ Abnormal ⇨	
ENT (Ear,Nose,Throat)	☐ Without remarks ☐ Abnormal ⇨	
Heart	☐ Without remarks ☐ Abnormal ⇨	
Lungs	☐ Without remarks ☐ Abnormal ⇨	
Abdomen	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	

Visit 1 (Day 0) – Post-dose

50. Concomitant Medication		
1. Has there been any change(s) in the Subject's concomitant medication(s) since previous visit?	☐ Yes	☐ No
If YES, please specify on the Concomitant Medication page.		

51. Adverse Events		
1. Has the Subject experienced any Adverse Event(s) since the study drug administration?	☐ Yes	☐ No
If YES, please specify on the Adverse Event page.		

Visit 2 – Day 6+15

Visit 2 (Day 6+15) – Pre-dose

52. Date Of Visit			
1. Date of visit (dd-MMM-yyyy)	Date	Month	Year

53. Concomitant Medication		
1. Has there been any change(s) in the Subject's concomitant medication(s) since previous visit?	☐ Yes	☐ No
If YES, please specify on the Concomitant Medication page.		

54. Adverse Events		
1. Has the Subject experienced any Adverse Event(s) since the previous visit?	☐ Yes	☐ No
If YES, please specify on the Adverse Event page.		

55. Last Cigarette			
1. Date of Subjects Last Cigarette?	Date	Month	Year
2. Time of Subjects Last Cigarette?		:	

56. Vital Signs	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 2 (Day 6+15) – Pre-dose

57. Physical Examination		
Body system	**Status**	**Finding (symptom/diagnosis) and MedDRA code**
General appearance	☐ Without remarks ☐ Abnormal ⇨	
ENT (Ear,Nose,Throat)	☐ Without remarks ☐ Abnormal ⇨	
Heart	☐ Without remarks ☐ Abnormal ⇨	
Lungs	☐ Without remarks ☐ Abnormal ⇨	
Abdomen	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	

58. PK blood sampling	
1. Have a pre-dose PK sample been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 2 (Day 6+15) – Pre-dose

59. NICOTINE WITHDRAWAL QUESTIONNAIRE

The Subjects will complete the nicotine withdrawal questionnaire 15 to 1 minutes before administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Dos 1 före dos

Date	Month	Year	Time
			:

Bedöm enligt nedanstående alternativ hur du uppfattar dig själv just nu. Ringa in det alternativ som passar bäst där 1 är minst och 5 är mest

1. Arg, irriterad, frustrerad				
1	**2**	**3**	**4**	**5**

2. Nervös				
1	**2**	**3**	**4**	**5**

3. Ledsen, nedstämd.				
1	**2**	**3**	**4**	**5**

Visit 2 (Day 6+15) – Drug Administration

60. 2nd Administration of drug	
1. Which drug is administered to the Subject?	☐ study drug- ODF ☐ Nicorette® pepparmint Spray
The Subject should be fasted for at least 8 hours prior to administration of the study drug- oral dissolvable film / Nicorette® pepparmint oral nicotine spray, and no food is allowed until 1 hour post-dose. Water is allowed as desired except one hour before and one hour after drug administration	
2. Date of Subjects Last meal	Date Month Year
3. Time of Subject's latest meal	:
4. Time of Study Drug administration	:
5. Has the Study Drug been administered according to the protocol?	☐ Yes ☐ No
6. If No, please specify the reason	

Site Number	E- Code	Subject Number	Subject Initials
0 1			

Visit 2 (Day 6+15) – Post-dose

61. PK blood sampling - 2 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

62. PK blood sampling - 5 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

63. PK blood sampling - 10 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

64. PK blood sampling - 20 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

65. Vital Signs - 30 minutes after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

66. PK blood sampling - 30 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 2 (Day 6+15) – Post-dose

67. NICOTINE WITHDRAWAL QUESTIONNAIRE

The Subjects will complete the nicotine withdrawal questionnaire 30 minutes after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Dos 2 efter dos

Date	Month	Year	Time
			:

Bedöm enligt nedanstående alternativ hur du uppfattar dig själv just nu. Ringa in det alternativ som passar bäst där 1 är minst och 5 är mest

1. Arg, irriterad, frustrerad				
1	**2**	**3**	**4**	**5**

2. Nervös				
1	**2**	**3**	**4**	**5**

3. Ledsen, nedstämd.				
1	**2**	**3**	**4**	**5**

Visit 2 (Day 6+15) – Post-dose

68. QUESTIONNAIRE ON SMOKING URGES – 30 MINUTES AFTER DRUG ADMINISTRATION

The Subjects will complete the questionnaire on smoking urges 30 minutes after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date	Month	Year	Time
			:

Vänligen besvara nedanstående frågor genom att ringa in den siffra som bäst överensstämmer med din upplevelse på en skala mellan 1 och 7 där: 1=stämmer inte alls, 7=stämmer helt

A.	Jag skulle vilja ha en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
B.	Inget vore bättre än att röka en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
C.	Om det vore möjligt skulle jag troligen ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
D.	Jag skulle ha bättre kontroll om jag kunde ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
E.	Den enda jag vill nu är att röka en cigarett.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
F.	Jag har ett trängande behov av en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
G.	En cigarett skulle smaka fint nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
H.	Jag skulle göra nästan vad som helst för en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
I.	Att röka skulle göra mig mindre deprimerad.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
J.	Jag kommer att ta en cigarett så fort det är möjligt.						
	1	**2**	**3**	**4**	**5**	**6**	**7**

Site Number	E- Code	Subject Number	Subject Initials
0 1			

Visit 2 (Day 6+15) – Post-dose

69. PK blood sampling - 45 minutes after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

70. Vital Signs – 1 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

71. PK blood sampling – 1 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 2 (Day 6+15) – Post-dose

72. QUESTIONNAIRE ON SMOKING URGES – 1 HOUR AFTER DRUG ADMINISTRATION

The Subjects will complete the questionnaire on smoking urges 1 hour after administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date	Month	Year	Time
			:

Vänligen besvara nedanstående frågor genom att ringa in den siffra som bäst överensstämmer med din upplevelse på en skala mellan 1 och 7 där: 1=stämmer inte alls, 7=stämmer helt

A.	Jag skulle vilja ha en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
B.	Inget vore bättre än att röka en cigarett nu omedelbart.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
C.	Om det vore möjligt skulle jag troligen ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
D.	Jag skulle ha bättre kontroll om jag kunde ta en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
E.	Den enda jag vill nu är att röka en cigarett.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
F.	Jag har ett trängande behov av en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
G.	En cigarett skulle smaka fint nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
H.	Jag skulle göra nästan vad som helst för en cigarett nu.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
I.	Att röka skulle göra mig mindre deprimerad.						
	1	**2**	**3**	**4**	**5**	**6**	**7**
J.	Jag kommer att ta en cigarett så fort det är möjligt.						
	1	**2**	**3**	**4**	**5**	**6**	**7**

Visit 2 (Day 6+15) – Post-dose

73. Vital Signs – 1.5 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

74. Vital Signs – 2 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

75. PK blood sampling – 2 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

76. Vital Signs – 3 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 2 (Day 6+15) – Post-dose

77. PK blood sampling – 3 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	__ __ : __ __

78. Vital Signs – 4 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

79. PK blood sampling – 4 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	__ __ : __ __

80. Vital Signs – 5 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

Visit 2 (Day 6+15) – Post-dose

81. USER SATISFACTION QUESTIONNAIRE

The Subjects will complete the user satisfaction questionnaire 5h ±1h after the second dose administration

FRÅGOR TILL FÖRSÖKSPERSONERNA

Subject Questionnaire

Date	Month	Year	Time
			:

1. Vilket av de testade preparaten, Spray eller ODF, är den produkt du skulle välja för rökavvänjning.	☐ Spray ☐ ODF
2. Vilken av produkterna ger dig högst tillfredställelse	☐ Spray ☐ ODF
3. Har du prövat andra läkemedel för rökavvänjning?	☐ Ja ☐ Nej
Om Ja, Specifera	
4. Om du svarat Ja på ovanstående fråga: Om produkterna har samma pris, vilken produkt skulle du helst använda för rökanvändning?	☐ Spray ☐ ODF ☐ Tuggummi ☐ Sugtabletter ☐ Plåster
5. Uppfattar du ODF som mer diskret än Nikotintuggummi?	☐ Ja ☐ Nej
6. Uppfattar du ODF som mer diskret än Spray?	☐ Ja ☐ Nej
7. Uppfattar du ODF som mer diskret än Sugtablett?	☐ Ja ☐ Nej
8. Är det viktigt med en diskret produkt för rökavvänjning för dig?	☐ Ja ☐ Nej

USER SATISFACTION QUESTIONNAIRE Contd.	
9. Beskriv med egna ord hur du uppfattar ODF?	
10. Ta ställning till följande påstående på skalan 1-5, där 1 står för lite och 5 står för mycket.	
a. Det är viktigt att rökavvänjningsprodukten är diskret	☐1 ☐2 ☐3 ☐4 ☐5
b. ODF ger en snabb effekt för att minska röksuget	☐1 ☐2 ☐3 ☐4 ☐5
c. ODF har en behaglig smak	☐1 ☐2 ☐3 ☐4 ☐5
d. ODF har en tillfredställande effekt	☐1 ☐2 ☐3 ☐4 ☐5
11. Anser du att ODF är en attraktiv produkt inom rökavvänjningsområdet?	☐ Ja ☐ Nej
Oavsett svar, kommentera gärna:	

Site Number	E- Code	Subject Number	Subject Initials
0 1			

Visit 2 (Day 6+15) – Post-dose

82. Vital Signs – 6 hour after drug administration	
Blood pressure and heart rate will be measured after the Subject has been sitting/lying down for at least 5 min.	
1. Blood pressure - systolic (mmHg)	
2. Blood pressure - diastolic (mmHg)	
3. Heart Rate	

83. PK blood sampling – 6 hour after drug administration	
1. Have PK blood samples been taken?	☐ Yes ☐ No
2. Time of PK samples taken	:

Visit 2 (Day 6+15) – Post-dose

84. Physical Examination		
Body system	**Status**	**Finding (symptom/diagnosis) and MedDRA code**
General appearance	☐ Without remarks ☐ Abnormal ⇨	
ENT (Ear,Nose,Throat)	☐ Without remarks ☐ Abnormal ⇨	
Heart	☐ Without remarks ☐ Abnormal ⇨	
Lungs	☐ Without remarks ☐ Abnormal ⇨	
Abdomen	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	
Other	☐ Without remarks ☐ Abnormal ⇨	

Visit 2 (Day 6+15) – Post-dose

85. Concomitant Medication		
1. Has there been any change(s) in the Subject's concomitant medication(s) since previous visit?	☐ Yes	☐ No
If YES, please specify on the Concomitant Medication page.		

86. Adverse Events		
1. Has the Subject experienced any Adverse Event(s) since the study drug administration?	☐ Yes	☐ No
If YES, please specify on the Adverse Event page.		

87. Adverse Events

No Adverse Events Reported ☐ | AE Page No

No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			

Action Taken*	**Outcome****	**Causality****
1 Study drug dosage adjusted	**1** Complete Recovery	**1** Certain
2 Study drug treatment discontinued	**2** Recovered with sequelae	**2** Probable
3 Medication taken to treat event	**3** Not recovered / Ongoing	**3** Possible
4 No action taken	**4** Death	**4** Unlikely
	5 Unknown	**5** Not Assessable

If serious complete SAE report form and contact IRW (fax number + 46 735 274 441) within 24 Hours

88. Adverse Events

No Adverse Events Reported ☐ | AE Page No

No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
	MedDRA Code	- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			

Action Taken*	**Outcome****	**Causality****
1 Study drug dosage adjusted	**1** Complete Recovery	**1** Certain
2 Study drug treatment discontinued	**2** Recovered with sequelae	**2** Probable
3 Medication taken to treat event	**3** Not recovered / Ongoing	**3** Possible
4 No action taken	**4** Death	**4** Unlikely
	5 Unknown	**5** Not Assessable

If serious complete SAE report form and contact IRW (fax number + 46 735 274 441) within 24 Hours

89. Adverse Events

No Adverse Events Reported ☐ | AE Page No

No.	Adverse Events	Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)	Severity	Serious	Action Taken*	Outcome**	Causality***
		- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
	MedDRA Code	- -					
No.	**Adverse Events**	**Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)**	**Severity**	**Serious**	**Action Taken***	**Outcome****	**Causality*****
		- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
	MedDRA Code	- -					
No.	**Adverse Events**	**Start Date (DD-MON-YYYY) / End Date (DD-MON-YYYY)**	**Severity**	**Serious**	**Action Taken***	**Outcome****	**Causality*****
		- -	☐Mild ☐Moderate ☐Severe	☐ Yes ☐ No			
	MedDRA Code	- -					

Action Taken*	**Outcome****	**Causality*****
1 Study drug dosage adjusted	**1** Complete Recovery	**1** Certain
2 Study drug treatment discontinued	**2** Recovered with sequelae	**2** Probable
3 Medication taken to treat event	**3** Not recovered / Ongoing	**3** Possible
4 No action taken	**4** Death	**4** Unlikely
	5 Unknown	**5** Not Assessable

If serious complete SAE report form and contact IRW (fax number + 46 735 274 441) within 24 Hours

Site Number	E- Code	Subject Number	Subject Initials	
0 1				**FFT-01-11**

90. Concomitant Medication

No concomitant Medication Reported ☐					Page No	
If yes, specify below:						
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		- -	- -		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		- -	- -		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		- -	- -		☐	

Final Date: 19-December-2011

Site Number	E- Code	Subject Number	Subject Initials	
0 1				**FFT-01-11**

91. Concomitant Medication

No concomitant Medication Reported ☐	Page No	

If yes, specify below:

No.	Medication (Brand Name)	Indication	Dose	Unit	Frequency	Route of Admin
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	

Site Number	E- Code	Subject Number	Subject Initials	
0 1				**FFT-01-11**

92. Concomitant Medication

No concomitant Medication Reported ☐					Page No	
If yes, specify below:						
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	
No.	**Medication (Brand Name)**	**Indication**	**Dose**	**Unit**	**Frequency**	**Route of Admin**
						☐ ih ☐ inj ☐ r ☐ im ☐ iv ☐ top ☐ in ☐ po ☐ vag
	ATC Code	**Start Date (DD-MON-YYYY)**	**End Date(DD-MON-YYYY)**		**Ongoing**	
		__ - ___ - ____	__ - ___ - ____		☐	

Telephone Follow -Up

Telephone Follow Up - 7±2 days after Visit 2

93. Telephone Follow Up		
1. Was a telephone follow-up done?	☐ Yes	☐ No
2. If Yes, date of follow-up call:	Date ☐☐	Month ☐☐☐ Year ☐☐☐☐

94. Adverse Events		
1. Has the Subject experienced any Adverse Event(s) since the previous visit?	☐ Yes	☐ No
If YES, please specify on the Adverse Event page.		

Site Number		E- Code		Subject Number			Subject Initials		
0	1								

FFT-01-11

Study Termination

95. Date Of study termination/withdrawal	
1. Date of study termination/withdrawal (dd-MMM-yyyy)	Date ☐☐ Month ☐☐☐ Year ☐☐☐☐
2. Did the subject complete the study?	☐ Yes ☐ No
If NO, tick one box for primary reason for discontinuation	☐ Adverse Event ☐ Withdrawn consent ☐ Lost to follow-up ☐ Other; please specify __________

Investigator's Signature Page

Investigator' Signature

I hereby confirm that all entries on each CRF page are correct and complete to the best of my knowledge.

AE Page No.	0 1	to		
CM Page No.	0 1	to		

Investigator' Signature

Date	Month	Year

Utdrag ur protokollet från sammanträdet den 4 maj 2011 i avdelning 1.

Nya ärenden

Diarienummer:
2011/592-31/1
Föredragande:
Elisabeth Faxelid

Sökande: Capio S:t Görans Sjukhus AB
Behörig företrädare: Lennart Wennerström
Projekt: En jämförande studie för att mäta nikotin i blodet efter intag av dels en ny form av nikotinersättningsmedel dels en på marknaden befintlig produkt. Projektnummer/id: FFT01-11. Version nr: Final 1.0. EudraCT-nr: 2011-000930-12
Forskare som genomför projektet: Jon Enestig

BESLUT
Nämnden godkänner forskningen.

Beslut expedierat till: behörig företrädare, ansvarig forskare och sponsor FFT Medical AB, Danderyd, Thomas Ekerborn.

Att utdraget stämmer med originalet intygar:

Eja Fridsta
Administratör

PROTOKOLL 2011/1:5
2011-05-04

Sammanträde i Stockholm

Avdelning 1

Ordförande
Olof Forssberg

Ledamöter med vetenskaplig kompetens
Pierre Lafolie, vetenskaplig sekreterare *(klinisk farmakologi)*
Milita Crisby *(geriatrik, neurologi)*
Elisabet Faxelid *(vårdvetenskap)*
Yigael Finkel *(barnmedicin)*
Christina Hultman *(psykiatri, epidemiologi), deltar inte i ärende 2011/528*
Nina Kyrklund Blomberg *(kvinnosjukdomar)*
Bernt Lindelöf *(dermatologi)*
Sven Lindskog *(odontologi)*
Christer Paul *(medicin, blodsjukdomar)*
Henryk Wilczek *(transplantationskirurgi)*

Ledamöter som företräder allmänna intressen
Majvi Andersson
Elisabeth Dingertz
Stig Johnell
Åsa Öckerman

Administrativ sekreterare
Lena Creutzer Waldersten

Övriga
Erik Eliasson, *(klinisk farmakologi) ersättare*

---

§ 1 Ordföranden förklarar sammanträdet öppnat.

§ 2 Den administrativa sekreteraren anmäler att den vetenskaplige sekreteraren sedan föregående möte den 6 april 2011 fattat beslut i 17 ärenden som avser ändring av godkännande.

§ 3 Ansökningar om etisk granskning av forskningsprojekt, se **Bilaga.**

§ 4 Ordföranden meddelar att nästa sammanträde i avdelning 1 äger rum tisdagen den 31 maj 2011.

§ 5 Ordföranden förklarar mötet avslutat.

Olof Forssberg
Ordförande

Pierre Lafolie
Protokollförare

Adress FE 289 171 77 Stockholm | **Besöksadress** Nobels väg 9 Solna | **Telefon** 08-524 800 00 | **Fax** 08-524 866 99 | **E-post** kansli@stockholm.epn.se | **Hemsida** www.epn.se

FFT Medical

2011-07-29

Regionala etikprövningsnämnden i Stockholm
FE 289
Karolinska Institutet
171 77 STOCKHOLM

"Amendment" (FFT-01-11-A1) och (FFT-01-11-A2)

Bifogat finner ni två "Amendments"

Mvh

Thomas Ekerborn
Tel 0705127009

GODKÄNNES Dat. 2011 -08- 08

Hans Glaumann
Vetenskaplig sekreterare
Regionala etikprövningsnämnden
i Stockholm

Kopians överensstämmelse
med originalet intygas

Anne Manninen
Administratör

Postadress:
FFT Medical AB
Nora Strand 1A
182 38 DANDERYD

Bankgiro:
666 - 0039

Bankkonto:
SHB *6158 445 055 618*

Org.nr:
556818-7214

FFT Medical

GODKÄNNES Dat.
2011-12-19 2012 -01- 09
Pierre Lafolie
Regionala etikprövningsnämnden
i Stockholm

Regionala etikprövnings-
nämnden i Stockholm
2011 12 27
2011/2125-32

Regionala etikprövningsnämnden i Stockholm
FE 289
Karolinska Institutet
171 77 STOCKHOLM

Amendment" (FFT-01-11-A3) av ansökan med EudraCT 2011-000930-12

I tillägg till ansökan med EudraCT nr 2011-000930-12 har förut två Amendments skickats in och godkänts:

- FFT-01-11-A1 berörde införande av Kaliumdivätefosfat såsom ingrediens.
- FFT-01-11-A2 berörde byte av referensprodukt i studien (Zonnic Pepparmint byttes här ut mot Nicorette Pepparmint).

I den godkända ansökan hade referensläkemedlet Zonnic Pepparmint Spray angivits som referensläkemedel. I förut presenterat amendment (FFT-01-11-A2) valdes en annan referensprodukt på grund av att referensprodukten måste vara godkänd i enlighet med en komplett ansökan vilket ju är fallet med "Nicorette Pepparmint 1mg/spray oromucosal spray" som har ett läkemedelsgodkännande baserat på en "line extension" av Nicorette tuggummi.

Analyser av referensprodukten visar att halten nikotin i det undersökta läkemedlet (Nicotine Oral Dissolvable Film (ODF), lemon) bör ändras för att kunna påvisa bioekvivalens. Dosjusteringen innebär en förändring av nikotinhalten från 1,6mg till 2,0mg för det undersökta läkemedlet.

Följande förändringar görs också:

- Ett kommersiellt laboratorium i England väljs för bestämmande av nikotinhalt i plasma. Detta säkrar tillgången på analyskapacitet. I samband med detta anges en uppdaterad analysmetod samt byte till KI Biobank för hantering av plasmaprover.
- En tidpunkt, 2 minuter, för bestämning av nikotinhalt i plasma har lagts till efter administrering av studieläkemedel respektive referensläkemedel.
- Gult färgämne (E100) har tagits bort från beredningen.
- Ingredienserna i beredningen av det undersökta läkemedlet har utökats med pepparmintolja (smak) och titandioxid för att lättare se testprodukten (ODF).
- Fosfatbuffert (Kaliumdivätefosfat) har tagits bort från beredningen (i princip ett återtag av Amendment FFT-01-11-A1)
- Listan över ingående ingredienser ser därför ut som följer: Nikotinbitartrat, Vatten, Natriumalginat (Protanal 5/60). Sorbitol, Glycerol, Natriumhydroxid, Citronolja, Pepparmintolja, Titandioxid.
- Förpackningen är fortfarande Alu/PET peel. Den nu valda leverantören av dessa har en något mindre förpackning i sitt standardsortiment och därav ändrats förpackningsmåtten från 70x40mm till 70x38mm.

Alla dokument skall nu återspegla denna bruttolista.
Tacksamt och med vänlig hälsning

Thomas Ekerborn (Tel 0705127009)

Kopians överensstämmelse med originalet intygas:
Eja Fridstå
REGIONALA ETIKPRÖVNINGSNÄMNDEN EPN STOCKHOLM
FE 289
SE-171 77 STOCKHOLM

Postadress:
FFT Medical AB
Nora Strand 1A
182 38 DANDERYD

Bankgiro:
666 - 0039

Bankkonto:
SHB *6158 445 055 618*

Org.nr:
556818-7214

Patient Information för studien FFT-01-11

En studie för att jämföra en oralt löslig film (ODF) som nikotinersättningsmedel med Nicorette Pepparmint 1 mg/spray, munhålespray.

Vi tillfrågar dig om du vill delta i en vetenskaplig studie, vid S.t Görans sjukhus. Du tillfrågas att delta eftersom du är rökare mellan 18-55 år. Läs igenom informationen noggrant innan du bestämmer dig för om du vill delta. Deltagande är helt frivilligt. Du kommer även att få muntlig information om studien och möjlighet att ställa frågor om det är något du funderar över. Om du vill delta i studien ska du skriva på samtycket på sista sidan. Tveka inte att fråga om det är något ord eller delar av informationen som du inte förstår.

1. Bakgrund och syfte med studien

Rökning är ett stort global hälsoproblem som orsakar bland annat lungcancer, kronisk obstruktiv lungsjukdom (KOL) och hjärt-kärl problem. Många som vill sluta röka har ofta svårt att lyckas, bland annat beroende på nikotinets vanebildande effekt. Studier har visat att läkemedel, som nikotinersättningsmedel, ökar chanserna att lyckas med ett rökstopp. Med nikotinersättningsmedel tillförs nikotin till kroppen men inte de cancerframkallande och luftvägsirriterande beståndsdelarna i tobak och tobaksrök. De flesta nikotinersättningsmedel som finns på marknaden idag ger ett betydligt långsammare tillslag av nikotinet än rökning, som till exempel nikotinplåster och tuggummi. Många rökare upplever att känslan blir annorlunda när nikotinet tar sig in i blodet långsamt och att medlen då inte fungerar tillfredsställande. Det finns också näsown och munhålespray som ger snabbare nikotinfrisättning till blodet och mer liknar effekten av att röka en cigarett. Dessa produkter kan dock upplevas som mindre diskreta och bekväma. FFT Medical AB har därför tagit fram ett annat medel i form av en liten oralt löslig film (ODF). Den är gjord för att placeras innanför kinden där den fastnar och sedan löser upp sig på några minuter. Den ger under den tiden ifrån sig nikotin som snabbt tas upp genom slemhinnan.

Syftet med den här studien är att utvärdera om ODF ger jämförbara nikotinnivåer i blodet som munhålespray. Vi kommer att använda Nicorette Pepparmint 1 mg/spray, munhålespray som jämförelseprodukt, denna finns idag tillgänglig i handeln. Syftet är också att utvärdera effekt och säkerhet av ODF.

2. Hur går det till?

Om du väljer att delta i studien kommer du först att genomgå en allmän undersökning för att se om du har några sjukdomar eller andra tillstånd som gör att du inte kan vara med i studien. Du kommer då att få svara på frågor om din hälsa och om du har haft några tidigare sjukdomar. En läkarundersökning kommer att genomföras och blodtryck, puls och EKG kommer också att mätas. Dessutom kommer blodprover som motsvarar en vanlig hälsoundersökning att tas, om du är kvinna i fertil ålder kommer ett urinprov för graviditetstest att tas. Du kommer också att få svara på ett frågeformulär med frågor om dina nikotinvanor.

Om du är fullt frisk och inte använder några andra mediciner än p-piller kan du inkluderas i studien som består av två besök på Sankt Görans Sjukhus, förutom den inledande undersökningen. Det första besöket kommer att ske inom 21 dagar från den inledande undersökningen och det andra besöket 1-3 veckor därefter. De är planerat att upp till 24 personer skall deltaga i studien, de kommer slumpvis delas upp i två lika stora grupper, den ena gruppen kommer att doseras med ODF på det första besöket och Nicorette Pepparmint 1 mg/spray, munhålespray vid det andra, och vice versa för den andra gruppen.

Varje besök tar ca 8 timmar och kommer att genomföras på Sankt Görans Sjukhus, Medicinsk Dagavdelning av erfarna sjuksköterskor och en legitimerad läkare med specialistkompetens i internmedicin.

Under varje besök kommer du, förutom att få nikotinersättningsmedel, på morgonen, att genomgå läkarundersökning vid tre tillfällen, dessutom kommer blodtryck och puls att mätas vid flera tidpunker under dagen. Blodprov (5ml venprov) för att mäta nikotinnivåerna i blodet kommer att tas vid elva tillfällen under varje besök. Blodproverna kommer att tas genom en så kallad Perifer Ven Kateter (PVK), som kommer att sättas i ett blodkärl i din arm på morgonen av varje besök. En PVK är en liten plastslang som skall användas för att ta blodprover under doseringsbesöken utan att behöva sticka flera gånger. Vid två tillfällen kommer du också få besvara ett frågeformulär med frågor som behandlar eventuella abstinensbesvär du upplever, och vid tre tillfällen kommer du att få besvara ett frågeformulär med frågor som behandlar ditt begär efter rökning. Vid slutet av det andra besöket kommer du också att besvara ett frågeformulär med frågor om hur du tycker att ODF och Nicorette Pepparmint 1 mg/spray, munhålespray fungerar och dina övriga erfarenheter av nikotinersättningsmedel.

Under hela studien samlas data in om förändringar i din hälsostatus, eventuella biverkningar och obehag. Om en biverkarn är pågående vid slutet av den andra doseringsbesöket kommer du att bli kontaktat en vecka efter besöket för att säkerhetsställa att du mår bra.

Vi ber dig att under studien följa vissa restriktioner:

- fasta från kvällen före båda besöken, vatten är tillåtet. Du kommer att få gratis lunch på sjukhuset och en lättare middag under besöken. Däremot får du får inte äta någon medhavd mat då det kan störa resultatet
- avstå från rökning under åtminstonde 10 timmar innan båda besöken och fram tills alla blodprover för analys av nikotinnivåer i blodet är tagna
- avstå från hård fysisk träning inom 8 timmar innan båda besöken
- avstå från att ta några läkemedel, både receptbelagna och receptfria, naturläkemedel, grapefruktjuice och alkohol 24 timmar innan och under varje doseringsbesök, undantag gäller för preventivmedel

3. Vilka risker/nackdelar kan studien medföra

Alla läkemedel kan innebära risker som är okända och oförutsedda. Om något biverkar skulle uppstå kommer du att mottaga lämplig och adekvat behandling för detta.

Det är inte något nytt ämne som provas i denna studie. Riskerna med nikotin från nikotinersättningsmedel är desamma som med nikotin från cigaretter, men utan rökningens andra skadliga effekter. ODF består huvudsakligen av ett algextrakt. Samma algextrakt används sedan många år bland annat i en magsårsmedicin som heter Gaviscon®.

Att sätta en PVK är ett mycket vanligt och rutinmässigt ingrepp på sjukhus och riskerna är små. I studien kommer vana sjuksköterskor, som dagligen sätter PVK på sjukhus att utföra ingreppet. I vissa fall kan ett lokalt blåmärke uppstå och i mer ovanliga fall kan en kärlirritation (tromboflebit) uppstå. Båda dessa tillstånd går oftast över av sig själv efter några dagar.

Då nikotin kan orsaka fosterskador, kan kvinnor i fertil ålder endast deltaga i studien om de använder preventivmedel såsom spiral, p-piller, eller barriärmetoder såsom kondom, eller pessar med spermiedödande medel.

4. Vilka fördelar kan studien medföra

Om du väljer att delta i studien kommer det troligen inte medföra någon direkt fördel för dig personligen. Förhoppningen är att information från studien ska komma personer som vill sluta röka till nytta i framtiden.

5. Ny information

Om någon ny information om studieläkemedlet framkommer under studietiden, som skulle kunna påverka ditt beslut att deltaga i studien, så kommer du att omedelbart få reda på det.

6. Hantering av data och sekretess

Under studiens gång kommer uppgifter om dig att samlas in på speciella studieformulär. På dessa anges inte ditt namn och personnummer utan endast initialer och födelsedatum och ett för studien specifikt patientnummer. Listan med den information som kopplar samman numret med din identitet finns endast på kliniken och kommer att sparas så tillsammans med din medicinska journal i upp till 15 år. De data som samlas in kommer att granskas av behörig personal från FFT Medical AB och/eller samarbetspartner samt eventuellt av forskningsetiska nämnder och tillsynsmyndigheten. Studieformulären kommer också att jämföras med för studien relevanta uppgifter i dina journalhandlingar, för att säkerställa att insamlade data är fullständiga och korrekta, samt att studien är riktigt genomförd. All sådan granskning kommer att ske under sekretess. Ingen obehörig kommer att få tillgång till dina data.

Data från studieformulären samlas in, lagras och bearbetas manuellt och elektroniskt hos FFT Medical AB och/eller samarbetspartner inom eller utanför EU. Studiens resultat kommer att sammanställas i en rapport som är utformad enligt läkemedelsmyndighetens krav och rapporteras då i kodad form vilket innebär att din identitet inte kan spåras i rapporten. Om studieresultaten publiceras i t.ex. en vetenskaplig tidskrift kommer det även att göras utan att någon enskild individ kan identifieras.

Det är personuppgiftsansvarig för sjukhuset som är ansvarig för dina personuppgifter. Enligt personuppgiftslagen har du rätt att begära information om vilka uppgifter om dig som registrerats. Om du skulle upptäcka att någon felaktig information registrerats har du rätt att få denna korrigerad.

7. Hantering av biologiska prover

Proverna som tas vid första besöket motsvarar de prover som tas vid en vanlig hälsoundersökning. Dessa kommer att analyseras av Unilabs Laboratorie på Sankt Görans Sjukhus och kommer där att sparas upp till 6 månader efter det att studien har avslutats..

De prover som tas för att mäta nikotinnivåer i blodet kommer att delas upp i två delar. Den ena delen analyseras av ett laboratorium i England, ABS Laboratories Ltd, där proverna kommer att destrueras efter analys. Den andra delen sparas i upp till 6 månader efter det att studien har avslutats. Proverna kommer endast att användas på det sätt som du givits ditt samtycke till och i enlighet med Biobankslagen (SFS 2002:297). Om några ytterligare analyser skall utföras kommer vi att be om ditt samtycke för detta.

Alla dina prover kommer att kodas och en ‘kodnyckel’ kommer att behövas för identifiering.

8. Information om studieresultat

Studiens resultat kan komma att presenteras vid vetenskapliga möten och i medicinska tidskrifter. Någon identifierbar individuell data kommer inte att presenteras. Din identitet kommer att behandlas konfidentiellt.

9. Ersättning och försäkring

Deltagandet i studien och all studierelaterade undersökningar är kostnadsfria och du kommer att få studieläkemedlet gratis. Om du slutför alla studiebesök kommer du att kompenseras för obehag och eventuella intrång med 2000 SEK. Denna ersättning är skattepliktig.

Patientskadelagen och läkemedelsförsäkringen gäller i studien på samma sätt som vid all annan behandling inom sjukvården. Utöver detta har sponsorn, FFT Medical AB, en produktansvarsförsäkring som täcker eventuella skador orsakade av produkten. Vid eventuella skador ges behandling inom ramarna för ordinarie sjukvård och om du drabbas av en studierelaterad skada ber vi dig kontakta kliniken. Deltagande i studien och alla studierelaterade undersökningar är kostnadsfria och du kommer att få studieläkemedlet gratis.

10. Vad händer om jag väljer att inte delta?

Ditt deltagande i studien är helt frivilligt och du kan när som helst, utan att ange någon anledning välja att avbryta ditt deltagande. Om du väljer att inte delta, kommer din nuvarande eller framtida medicinska vård inte påverkas på något sätt. Om du deltar, men beslutar att avsluta deltagande kommer inga nya uppgifter eller prover att samlas in från dig. För din egen säkerhet ber vi dig att komma på ett avslutande besök.

Studieläkaren eller FFT Medical AB kan också besluta att avbryta ditt deltagande om:

- Du inte följer anvisningarna från studieläkaren
- Du utvecklar en allvarlig sjukdom som omöjliggör fortsatt deltagande i studien
- Din läkare beslutar att denna behandling inte passar dig
- FFT Medical AB, tillsynsmyndigheterna eller oberoende etisk kommitté beslutar att avsluta studien
- Du blir gravid, planerar att bli gravid eller ammar ett barn.

Denna forskningsstudie har granskats och godkänts av Läkemedelsverket och oberoende etisk forskningskommitté**.**

Om du har några frågor, tveka inte att kontakta någon av oss på kliniken.

Jon Enestig, Ansvarig Läkare Tel:

XXXXX, Ansvarig Sjuksköterska Tel:

Huvudansvarig för studien är:

Jon Enestig

Capio S.T Görans Sjukhus

Medicinska Avdelningen

112 82 Stockholm

Patient/Subject study code: _____ Initials: _____ Centre No.: _____

Samtyckesformulär för studie FFT-01-11

Genom min underskrift försäkrar jag att jag muntligen har informerats om studien samt tagit del av ovanstående skriftliga information. Jag har haft tillräckligt med tid för att tänka igenom mitt beslut, ställa frågor och få dem besvarade.

Jag är medveten om att min medverkan är frivillig och att jag när som helst kan avbryta min medverkan i studien utan att lämna någon förklaring. Om jag avbryter mitt deltagande kommer detta inte att påverka min fortsatta medicinska behandling eller vård.

Jag samtycker till:

- deltagande i studien FFT-01-11
- att personliga uppgifter om mig, inklusive medicinska uppgifter, får samlas in, behandlas och användas för de ändamål och på det sätt som beskrivs i informationen jag tagit del av.
- mina medicinska journaler och data om mig som insamlas under studien granskas av behörig personal från sponsorn och/eller dennes sammarbetspartner och tillsynsmyndigheter.
- Att mina blodprover omhändertas som beskrivet i informationen ovan

Datum (ifylles av forskningpatienten)	Forskningspersonens underskrift
	Patient/Subject name (printed)

Jag har mottagit detta signerade samtycke från patienten, givit både muntlig och skriftlig information om studien. Patienten kommer att få en kopia av den skriftliga informationen och detta medgivande.

Datum	Läkarens underskrift
	Läkarens namn (textat)

CV - JON ENESTIG

Erfarenhet

Vikarierande underläkare *1998-1999*
ÖNH-kliniken Länssjukhuset Halmstad

AT-läkare *1999-2000*
Länssjukhuset Halmstad

Vikarierande läkare och bemanningsläkare *2000-2002*
Bland annat Getinge VC, Bollnäs sjukhus, KS Solna
Arbete framför allt inom primärvården och internmedicin. Även inom psykiatrin.

ST-läkare Allmänmedicin *2002-2004*
Tranebergs VC Bromma, Stockholm

ST-läkare Internmedicin och Hematologi *2004-2010*
Medicinkliniken Capio Sankt Görans sjukhus
Bevis om specialistkompetens Internmedicin 30/4 2009,
Hematologi 1/5 2010

Specialistläkare Internmedicin och Hematologi *2010-2012*
Medicinkliniken Capio Sankt Görans sjukhus

Överläkare Internmedicin och Hematologi *2012-*
Medicinkliniken Aleris Bollnäs Sjukhus

Utbildning

Uppsala Universitet *1990 och 1992*
National- och Företagsekonomi

Linköpings tekniska högskola *1990-1992*
Civilingenjörsprogrammet Datateknik

Uppsala Universitet *1993-1998*
Läkarlinjen

Övriga meriter

Forskning vid institutionen för Medicinsk Cellbiologi Uppsala Universitet *1995-98*
Gästforskare vid Mass General Hospital Harvard Med School Boston US apr-jun *1996*
Good Clinical Practice Course Stockholm *nov 2009*
Medskribent Populationsbaserad Myelomstudie (Abstract 2970 presenteras ASH dec 2012)

Referenser

Robert Lindberg Öl Cardiologisektionen Capio Sankt Görans Sjukhus 08-58701000
Bengt Bäckström Öl Sektionen för Internmedicin Capio Sankt Görans Sjukhus
Geir Falck Öl Verksamhetschef Medicinkliniken Aleris Bollnäs Sjukhus 0278-38000

Jon Enestig (691101)
Adress: Hedåsvägen 4, 821 30 Bollnäs, Tel: 0730-440001

16.1.5 Signatures of the Sponsor, Project Manager/author of the report, Medical Director, Statistician and Coordinating/Principal Investigator

TBD

16.1.6 Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.

Patient_ID	Number	Initials	Visit1Drug	Visit1Batch#	Visit2Drug	Visit2Batch#
p#1	A46	YS	ODF	20120419-97:2/4	Spray	ND132C
p#10	A13	CL	ODF	20120419-97:2/4	Spray	ND132C
p#13	A23	TG	ODF	20120419-97:2/4	Spray	ND132C
p#15	A14	TO	ODF	20120419-97:2/4	Spray	ND132C
p#17	A21	AV	ODF	20120419-97:2/4	Spray	ND132C
p#2	A44	NC	ODF	20120419-97:2/4	Spray	ND132C
p#20	A22	OZ	ODF	20120419-97:2/4	Spray	ND132C
p#21	A31	RH	ODF	20120419-97:2/4	Spray	ND132C
p#3	A42	SK	ODF	20120419-97:2/4	Spray	ND132C
p#5	A32	JA	ODF	20120419-97:2/4	Spray	ND132C
p#7	A12	JR	ODF	20120419-97:2/4	Spray	ND132C
p#8	A24	IM	ODF	20120419-97:2/4	Spray	ND132C
px1	X1	RR	ODF	20120423-97:2/5	Spray	ND132C
px11	X11	MV	ODF	20120423-97:2/5	Spray	ND132C
px13	X13	JH	ODF	20120423-97:2/5	Spray	ND132C
px15	X15	LN	ODF	20120423-97:2/5	Spray	ND132C
px3	X3	LO	ODF	20120423-97:2/5	Spray	ND132C
px5	X5	EB	ODF	20120423-97:2/5	Spray	ND132C
px7	X7	VO	ODF	20120423-97:2/5	Spray	ND132C
px9	X9	JC	ODF	20120423-97:2/5	Spray	ND132C
p#11	B41	RS	Spray	ND132C	ODF	20120419-97:2/4
p#12	B33	AE	Spray	ND132C	ODF	20120419-97:2/4
p#14	B32	MS	Spray	ND132C	ODF	20120419-97:2/4
p#16	B31	AO	Spray	ND132C	ODF	20120419-97:2/4
p#18	B43	JB	Spray	ND132C	ODF	20120419-97:2/4
p#19	B22	DL	Spray	ND132C	NULL	NULL
p#22	B12	FG	Spray	ND132C	ODF	20120419-97:2/4
p#23	B21	SM	Spray	ND132C	ODF	20120419-97:2/4
p#24	B11	MR	Spray	ND132C	ODF	20120419-97:2/4
p#4	B45	MJ	Spray	ND132C	ODF	20120419-97:2/4
p#6	B23	JL	Spray	ND132C	ODF	20120419-97:2/4
p#9	B13	PI	Spray	ND132C	ODF	20120419-97:2/4
px10	X10	MB	Spray	ND132C	ODF	20120423-97:2/5
px12	X12	ACP	Spray	ND132C	ODF	20120423-97:2/5
px14	X14	HF	Spray	ND132C	NULL	NULL
px16	X16	MO	Spray	ND132C	ODF	20120423-97:2/5
px2	X2	LN	Spray	ND132C	NULL	NULL
px4	X4	RF	Spray	ND132C	ODF	20120423-97:2/5
px6	X6	DB	Spray	ND132C	ODF	20120423-97:2/5
px8	X8	FL	Spray	ND132C	ODF	20120423-97:2/5

*) “NULL” means that no drug was administrated

16.1.7 Randomization scheme and codes (subject identification and treatment)

Number	Patient_ID	Group	DrugDate1	Drug1	DrugDate2	Drug2
A13	p#10	Safety	2012-05-26	ODF	2012-06-02	Spray
A14	p#15	Safety	2012-05-26	ODF	2012-06-02	Spray
B12	p#22	Kinetic And Safety	2012-05-26	Spray	2012-06-02	ODF
A23	p#13	Safety	2012-05-27	ODF	2012-06-09	Spray
A12	p#7	Kinetic And Safety	2012-05-26	ODF	2012-06-02	Spray
A21	p#17	Safety	2012-05-27	ODF	2012-06-10	Spray
A22	p#20	Safety	2012-05-27	ODF	2012-06-03	Spray
A24	p#8	Safety	2012-05-27	ODF	2012-06-09	Spray
A32	p#5	Safety	2012-06-03	ODF	2012-06-10	Spray
A46	p#1	Safety	2012-06-09	ODF	2012-06-17	Spray
A44	p#2	Safety	2012-06-09	ODF	2012-06-17	Spray
B23	p#6	Kinetic And Safety	2012-05-27	Spray	2012-06-09	ODF
A42	p#3	Safety	2012-06-10	ODF	2012-06-17	Spray
X1	px1	Safety	2012-09-08	ODF	2012-09-16	Spray
B33	p#12	Kinetic And Safety	2012-06-03	Spray	2012-06-10	ODF
X3	px3	Safety	2012-09-08	ODF	2012-09-16	Spray
X11	px11	Safety	2012-09-09	ODF	2012-09-16	Spray
A31	p#21	Kinetic And Safety	2012-06-03	ODF	2012-06-17	Spray
B11	p#24	Safety	2012-05-26	Spray	2012-06-02	ODF
B13	p#9	Safety	2012-05-26	Spray	2012-06-09	ODF
B22	p#19	Safety	2012-05-27	Spray	NULL	NULL
B21	p#23	Safety	2012-05-27	Spray	2012-06-17	ODF
B43	p#18	Kinetic And Safety	2012-06-10	Spray	2012-06-17	ODF
B41	p#11	Safety	2012-06-02	Spray	2012-06-09	ODF
B32	p#14	Safety	2012-06-03	Spray	2012-06-10	ODF
B31	p#16	Safety	2012-06-03	Spray	2012-06-10	ODF
B45	p#4	Safety	2012-06-09	Spray	2012-06-17	ODF
X2	px2	Safety	2012-09-08	Spray	NULL	NULL
X5	px5	Kinetic And Safety	2012-09-08	ODF	2012-09-15	Spray
X6	px6	Kinetic And Safety	2012-09-08	Spray	2012-09-15	ODF
X7	px7	Kinetic And Safety	2012-09-08	ODF	2012-09-15	Spray
X4	px4	Safety	2012-09-08	Spray	2012-09-15	ODF
X10	px10	Kinetic And Safety	2012-09-09	Spray	2012-09-16	ODF
X8	px8	Safety	2012-09-08	Spray	2012-09-16	ODF
X12	px12	Safety	2012-09-09	Spray	2012-09-16	ODF
X13	px13	Kinetic And Safety	2012-09-09	ODF	2012-09-15	Spray
X14	px14	Safety	2012-09-09	Spray	NULL	NULL
X15	px15	Kinetic And Safety	2012-09-09	ODF	2012-09-15	Spray
X16	px16	Safety	2012-09-09	Spray	2012-09-15	ODF
X9	px9	Kinetic And Safety	2012-09-09	ODF	2012-09-16	Spray

*) “NULL” means that no drug was administrated

ABS Laboratories Ltd
BioPark
Broadwater Road
Welwyn Garden City
Herts AL7 3AX
United Kingdom
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Tel: +44 (0) 1707 358666
Fax: +44 (0) 1707 358667

Analytical Report

Study Number: ABS/32/12

Determination of Nicotine in Plasma Samples from FFT Medical AB Clinical Protocol No. FFT-01-11

Sponsor: FFT Medical AB
Nora Strand 1A
182 38 Danderyd
Sweden

Study Number: FFT-01-11

Report Issue Date: 26 November 2012

Title:	**Determination of Nicotine in Plasma Samples from FFT Medical AB Clinical Protocol No. FFT-01-11**
ABS Report No:	**ABS/32/12**
ABS Study No:	**ABS/32/12**
Electronic filename:	**ABS_32_12 report.docx**
Sponsor Study No:	**FFT-01-11**
Analytical Laboratory:	**ABS Laboratories Ltd BioPark Broadwater Road Welwyn Garden City Herts AL7 3AX**
Sponsor:	**FFT Medical AB Nora Strand 1A 182 38 Danderyd Sweden**
Clinical Study Site	**Capio S:t Gorans Sjukhus Medicine Department 112 81 Stockholm Sweden**
Study Director:	**Paul Baker**
Bioanalyst	**Colin Feyerabend**
Report Author	**Colin Feyerabend**
Sponsor's Study Monitor:	**Thomas Ekerborn**
Experimental Phase Began:	**25 June 2012**
Experimental Phase Ended:	**3 October 2012**
No of samples analysed:	**912**

STUDY DIRECTOR'S STATEMENT

This study was conducted to the standards described in the United Kingdom Good Laboratory Practice Regulations (SI 1999 No. 3106 as amended SI 2004 No. 994) and the OECD Principles of Good Laboratory Practice 1997 (ENV/MC/CHEM(98)17).

This study was also conducted in compliance with the United Kingdom "The Medicines for Human Use (Clinical Trials) Regulations", (SI 2004 No. 1031 and subsequent amendments).

I declare that this report fully reflects the raw data generated during this study.

Signature: ..... Date: 26 Nov 2012

Paul Baker
(Study Director)

QA STATEMENT

I have examined the raw data related to the analysis of the samples from study protocol number ABS/32/12 and reported my findings to the Study Director on the following dates:

Dates of Audit	Date findings reported to Principal Investigator and Management	Audit description
19-Jun-12	20-Jun-12	Review of draft analytical protocol
20-Jun-12	20-Jun-12	Review of final analytical protocol
21-Jun-12	22-Jun-12	Review of draft & final analytical protocol amend 01
03-Jul-12	03-Jul-12	Experimental audit of the sample preparation of Batch 9
23-Jul-12	24-Jul-12	Review of raw data to final results
1-Nov-12	02-Nov-12	Sponsor query on sample receipt
07 to 08-Nov-12	08-Nov-12	Review of draft report to raw data

In addition to the detailed study-based inspections a series of routine facility and processed-based inspections were also being conducted and reported to management during the course of this study. A full facility audit is conducted once a year whilst specified facilities are audited on an 18 month rolling schedule.

The raw data and the study report have been audited and the report accurately reflects the raw data.

Signature: ..... Date: 26-Nov-2012
Mira Doig
(QA Manager)

2012/1942-39

FFT Medical

2012-11-03

Prof. Hans Glaumann
Regionala etikprövningsnämnden I Stockholm
FE 289
Karolinska Institutet
171 77 STOCKHOLM

Förfrågan om godkännande i efterhand av förfarande vid studie FFT-01, EudraCT 2011-000930-12, EPN Dnr 2011/1252-32.

Vi hänvisar till tidigare telefonkontakt angående det beklagliga misstag som har begåtts under studiens gång varvid vi har försummat att be om godkännande för att inkludera ett ökat patientantal.

Det rör sig således om en studie där rökare har fått pröva en ny beredningsform av nikotin vid ett tillfälle och ett redan registrerat nikotinersättningsprodukt vid ett annat tillfälle. Blodprov har tagits för att jämföra nikotinnivåerna i blodet under de första 6 timmarna efter administrering.

Som en absolut nödvändighet krävs avhållsamhet från rökning under 10 timmar (5 halveringstider) före administrering av läkemedlet för att nikotinnivåerna skall vara under detektionsgränsen (0,5ng/ml i blod) vid noll prov.

Vi planerade för att inkludera 24 patienter med förhoppningen att 17 patienter skulle fullfölja studien på korrekt sätt. 22 patienter, av 24 som startade, fullföljde provtagning som planerat både efter referens och efter ny beredningsform. Tyvärr visade det sig när vi analyserade proverna från dem, att endast 6 personer hade nikotinnivåer under detektionsgränsen. Detta trots att de i samband med nollprovet skriftligen fick intyga att de hade följt instruktionerna om avhållsamhet från rökning.

Med en tidigare formulering, som dock av misstag hade strukits i protokollet från draft till final version, hade vi haft möjlighet att ersättningsrekrytera i fall som dessa. Beklagligt nog förbisågs att detta förfarande inte hade stöd i det slutgiltiga protokollet. Sammantaget inkluderades ytterligare 16 patienter varvid vi erhöll användbara data från ytterligare 7 personer och således totalt 13 som kan användas i PK analys. Därefter stängdes studien.

Vi är självfallet medvetna om att det egentligen är oacceptabelt att meddela en ändring av detta slag i efterhand och har diskuterat igenom det i gruppen och med huvudprövaren. Jag intygar på heder och samvete att inget annat än den mänskliga faktorn och omedvetet misstag kan skyllas detta.

Med förhoppning om att trots allt kunna få acceptans för det här vill vi nämna att vi inte har haft några allvarliga biverkningar under studiens gång. Försökspersonerna i denna studie utsätts för minimala risker och obehag endast i form av blodprovstagning vid ett par tillfällen. Vi är också självklart beredda att vidta alla de åtgärder som ni anser kunna gottgöra eller mildra det inträffade.

FFT Medical

2012-11-03

Prof. Hans Glaumann
Regionala etikprövningsnämnden i Stockholm
FE 289
Karolinska Institutet
171 77 STOCKHOLM

Vi har hela tiden satt försökspersonernas säkerhet och komfort i första rummet och vi har absolut inte haft uppsåt att på något vis bryta etiska regler eller GCP. Tvärtom har vi haft ambitionen att hålla en hög etisk standard och med gällande regelverk som absoluta baskrav.

Huvudprövaren, en specialistläkare med GCP utbildning, har själv utfört alla studierelaterade uppgifter och hela tiden var närvarande vid studiens gång. Prövaren har avbrutit vid ett par tillfällen med anledning av att försökspersonen var svårstucken eftersom upprepade försök att sätta nål bedömdes vara besvärligt för försökspersonen. De försökspersonerna fick ändå full ersättning för sitt deltagande.

Under screeningförfarandet har upptäckts ett par fall av tidigare okänd hypothyreos. Dessa personer har genom prövaren fått en "gräddfil" till klinikens endokrinologer och i princip omedelbart omhändertagande som en liten bonus, trots att de inte kunde ingå i studien.

Med detta vill jag visa att vi genom hela studien har försökt hålla en hög etisk standard och att detta beklagliga misstag inte på något sätt är orsakat av bristande respekt för etiska regler.

Jag vill slutligen nämna att vi parallellt har haft kontakt med läkemedelsverket och Arzu Günes Granberg i detta ärende och fått ett förhandsbesked att de har för avsikt att se med förståelse på det inträffade.

Med Vänliga Hälsningar

Fredrik Sjöö, Med Dr, Överläkare.
Medical adviser FFT

Jon Enestig, Specialistläkare,
Prövare FFT-01-11

Thomas Ekerborn,
Projektledare FFT-01-11

Kopians överensstämmelse med originalet intygas
Anne Manninen
Administratör

Inkommen handling föranleder ingen åtgärd av Etikprövningsnämnden

☒ **Ad acta** 2012 -11- 13

☐ **Gallras** **signatur**

Hans Glaumann

16.2.3 Subjects excluded from the efficacy analysis.

Patient_ID	Number	Initials	Kinetic_group_exl_reason
p#1	A46	YS	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#10	A13	CL	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#11	B41	RS	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#13	A23	TG	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#14	B32	MS	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#15	A14	TO	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#16	B31	AO	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#17	A21	AV	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#19	B22	DL	Discontinuation after visit 1
p#2	A44	NC	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#20	A22	OZ	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#23	B21	SM	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#24	B11	MR	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#3	A42	SK	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#4	B45	MJ	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#5	A32	JA	Pre-dose nicotine level not below 0,5ng/ml at both visits
p#8	A24	IM	Discontinuation during visit 2
p#9	B13	PI	Pre-dose nicotine level not below 0,5ng/ml at both visits
px1	X1	RR	Pre-dose nicotine level not below 0,5ng/ml at both visits
px11	X11	MV	Incorrect dosing of IMP
px12	X12	ACP	Pre-dose nicotine level not below 0,5ng/ml at both visits
px14	X14	HF	Discontinuation after visit 1
px16	X16	MO	Pre-dose nicotine level not below 0,5ng/ml at both visits
px2	X2	LN	Discontinuation during visit 1
px3	X3	LO	Pre-dose nicotine level not below 0,5ng/ml at both visits
px4	X4	RF	Pre-dose nicotine level not below 0,5ng/ml at both visits
px8	X8	FL	Pre-dose nicotine level not below 0,5ng/ml at both visits

16.2.4 Demographic data and other baseline characteristics

Patient ID	Number	Initials	Gender	Age	Weight	Height	Systolic	Diastolic	Heart Rate	ECG	#Cig/day	Fagerström Score
p#1	A46	YS	Female	51	76	168	120	65	75	Without remarks	10	3
p#10	A13	CL	Female	46	82	177	100	70	65	Without remarks	20	3
p#11	B41	RS	Male	25	80	183	120	70	60	Without remarks	10	2
p#12	B33	AE	Female	24	56	167	110	60	60	Without remarks	14	3
p#13	A23	TG	Female	25	57	168	100	70	60	Not clinically significant	10	2
p#14	B32	MS	Female	32	55	160	90	60	65	Without remarks	13	2
p#15	A14	TO	Female	37	50	161	110	80	60	Without remarks	18	4
p#16	B31	AO	Female	25	74	176	135	80	75	Without remarks	12	4
p#17	A21	AV	Male	25	65	170	120	70	60	Without remarks	10	2
p#18	B43	JB	Female	24	65	177	120	75	65	Without remarks	8	0
p#19	B22	DL	Male	21	69	179	100	50	70	Without remarks	20	3
p#2	A44	NC	Female	25	71	187	110	60	55	Not clinically significant	9	2
p#20	A22	OZ	Male	25	67	180	105	70	60	Not clinically significant	20	2
p#21	A31	RH	Female	55	66	170	120	80	75	Not clinically significant	10	1
p#22	B12	FG	Female	37	77	166	100	70	70	Without remarks	7	2
p#23	B21	SM	Male	45	72	169	130	75	70	Without remarks	17	3
p#24	B11	MR	Female	43	60	168	90	50	70	Without remarks	20	4
p#3	A42	SK	Male	24	77	183	120	70	70	Without remarks	18	3
p#4	B45	MJ	Female	41	53	166	100	60	60	Without remarks	12	3
p#5	A32	JA	Female	42	70	172	120	70	70	Without remarks	15	2
p#6	B23	JL	Female	25	64	170	100	60	60	Without remarks	7	1
p#7	A12	JR	Male	55	83	184	120	75	60	Without remarks	10	0
p#8	A24	IM	Female	23	54	164	95	65	55	Without remarks	10	2

Patient ID	Number	Initials	Gender	Age	Weight	Height	Systolic	Diastolic	Heart Rate	ECG	#Cig/day	Fagerström Score
p#9	B13	PI	Female	39	70	168	120	60	70	Without remarks	20	4
px1	X1	RR	Male	43	82	187	100	70	60	Without remarks	15	3
px10	X10	MB	Female	39	69	172	110	70	60	Without remarks	7	0
px11	X11	MV	Female	45	69	165	130	75	70	Without remarks	15	2
px12	X12	ACP	Female	50	62	162	100	70	65	Without remarks	12	3
px13	X13	JH	Male	35	81	175	130	85	60	Without remarks	7	0
px14	X14	HF	Male	21	76	182	100	70	60	Without remarks	10	0
px15	X15	LN	Male	18	75	190	130	80	72	Not clinically significant	7	0
px16	X16	MO	Female	31	53	167	90	55	60	Without remarks	15	3
px2	X2	LN	Female	18	80	168	100	70	60	Not clinically significant	18	1
px3	X3	LO	Male	53	77	190	100	60	50	Not clinically significant	20	3
px4	X4	RF	Male	49	79	177	120	80	55	Without remarks	7	0
px5	X5	EB	Female	21	64	174	130	75	60	Without remarks	15	3
px6	X6	DB	Female	21	75	172	110	70	75	Without remarks	10	2
px7	X7	VO	Female	25	65	174	120	70	65	Without remarks	18	1
px8	X8	FL	Female	28	69	168	95	60	60	Without remarks	10	0
px9	X9	JC	Male	44	80	188	120	70	65	Without remarks	8	0

16.2.6 Individual efficacy response data

Patient_ID	Number	Initials	Group	Drug	T0	T2	T5	T10	T20	T30	T45	T60	T120	T180	T240	T360
p#12	B33	AE	K, S	ODF	0.5000	0.5000	0.8860	1.4410	2.5320	2.0850	2.5460	2.9320	2.2940	1.2880	0.9090	0.5000
p#12	B33	AE	K, S	Spray	0.5000	0.5000	0.8860	1.4410	2.5320	2.0850	2.5460	2.9320	2.2940	1.2880	0.9090	0.5000
p#18	B43	JB	K, S	ODF	0.5000	0.5000	1.2100	2.2740	2.4770	2.7650	2.9470	3.0520	2.2230	1.7890	1.1590	0.6120
p#18	B43	JB	K, S	Spray	0.5000	0.5000	1.2100	2.2740	2.4770	2.7650	2.9470	3.0520	2.2230	1.7890	1.1590	0.6120
p#21	A31	RH	K, S	ODF	0.5000	0.5000	1.7480	4.4030	4.8180	5.1500	5.1240	4.7440	4.1050	2.9350	2.0390	1.0670
p#21	A31	RH	K, S	Spray	0.5000	0.5000	1.7480	4.4030	4.8180	5.1500	5.1240	4.7440	4.1050	2.9350	2.0390	1.0670
p#22	B12	FG	K, S	ODF	0.5000	0.6080	2.2220	2.6120	3.3880	5.5970	3.1300	3.0640	3.3840	2.2970	1.4990	0.7780
p#22	B12	FG	K, S	Spray	0.5000	0.6080	2.2220	2.6120	3.3880	5.5970	3.1300	3.0640	3.3840	2.2970	1.4990	0.7780
p#6	B23	JL	K, S	ODF	0.5000	1.8160	2.8130	2.7920	3.4550	3.7200	4.3040	4.0580	2.9550	1.7070	1.2170	0.5870
p#6	B23	JL	K, S	Spray	0.5000	1.8160	2.8130	2.7920	3.4550	3.7200	4.3040	4.0580	2.9550	1.7070	1.2170	0.5870
p#7	A12	JR	K, S	ODF	0.5000	0.5000	4.8800	5.2030	6.0470	NULL	4.8260	3.8740	2.3310	1.7940	1.2290	0.5000
p#7	A12	JR	K, S	Spray	0.5000	0.5000	4.8800	5.2030	6.0470	NULL	4.8260	3.8740	2.3310	1.7940	1.2290	0.5000
px10	X10	MB	K, S	ODF	0.5000	1.7470	5.3070	5.6170	3.9850	3.4530	3.0960	2.9240	3.0290	1.9130	1.2330	0.6140
px10	X10	MB	K, S	Spray	0.5000	1.7470	5.3070	5.6170	3.9850	3.4530	3.0960	2.9240	3.0290	1.9130	1.2330	0.6140
px13	X13	JH	K, S	ODF	0.5000	0.5910	4.1830	8.3550	4.0940	4.0420	3.4560	3.1130	2.2780	1.4490	1.0050	0.8600
px13	X13	JH	K, S	Spray	0.5000	0.5910	4.1830	8.3550	4.0940	4.0420	3.4560	3.1130	2.2780	1.4490	1.0050	0.8600
px15	X15	LN	K, S	ODF	0.5000	0.5000	2.5390	3.7820	4.8270	4.7770	3.8550	4.7690	3.7950	3.3180	2.3670	1.3090
px15	X15	LN	K, S	Spray	0.5000	0.5000	2.5390	3.7820	4.8270	4.7770	3.8550	4.7690	3.7950	3.3180	2.3670	1.3090
px5	X5	EB	K, S	ODF	0.5000	0.7340	4.0390	4.7010	4.5380	4.1620	4.4450	4.2850	3.7260	2.4640	1.6250	0.8060
px5	X5	EB	K, S	Spray	0.5000	0.7340	4.0390	4.7010	4.5380	4.1620	4.4450	4.2850	3.7260	2.4640	1.6250	0.8060
px6	X6	DB	K, S	ODF	0.5000	0.5000	1.1810	1.7420	1.6820	2.0880	2.1120	2.1740	2.1630	1.4140	1.1530	0.5010
px6	X6	DB	K, S	Spray	0.5000	0.5000	1.1810	1.7420	1.6820	2.0880	2.1120	2.1740	2.1630	1.4140	1.1530	0.5010
px7	X7	VO	K, S	ODF	0.5000	0.5000	1.3500	2.4970	3.3830	4.0450	3.3990	3.0510	2.3110	1.7300	1.1500	0.8390
px7	X7	VO	K, S	Spray	0.5000	0.5000	1.3500	2.4970	3.3830	4.0450	3.3990	3.0510	2.3110	1.7300	1.1500	0.8390

Patient_ID	Number	Initials	Group	Drug	T0	T2	T5	T10	T20	T30	T45	T60	T120	T180	T240	T360
px9	X9	JC	K, S	ODF	0.5000	0.5000	2.2820	2.0780	2.2200	2.0760	1.8380	1.9250	2.9950	2.1130	1.4660	0.8770
px9	X9	JC	K, S	Spray	0.5000	0.5000	2.2820	2.0780	2.2200	2.0760	1.8380	1.9250	2.9950	2.1130	1.4660	0.8770
p#1	A46	YS	S	ODF	0.7100	0.9180	5.1550	8.7740	7.4260	6.2490	5.4940	4.6620	3.2030	1.9780	1.5040	0.9660
p#1	A46	YS	S	Spray	0.7100	0.9180	5.1550	8.7740	7.4260	6.2490	5.4940	4.6620	3.2030	1.9780	1.5040	0.9660
p#10	A13	CL	S	ODF	0.7110	0.5560	0.8340	1.9280	3.4640	3.7240	3.0590	3.2620	2.2870	2.0500	1.5090	0.8180
p#10	A13	CL	S	Spray	0.7110	0.5560	0.8340	1.9280	3.4640	3.7240	3.0590	3.2620	2.2870	2.0500	1.5090	0.8180
p#11	B41	RS	S	ODF	4.2230	3.9660	8.9450	7.8320	6.6760	7.3550	7.9250	8.8270	5.3430	3.5000	2.9150	2.0550
p#11	B41	RS	S	Spray	4.2230	3.9660	8.9450	7.8320	6.6760	7.3550	7.9250	8.8270	5.3430	3.5000	2.9150	2.0550
p#13	A23	TG	S	ODF	0.5950	0.6120	1.5860	2.7400	3.4740	3.2730	3.6950	3.8610	2.8060	1.9770	1.3270	0.7760
p#13	A23	TG	S	Spray	0.5950	0.6120	1.5860	2.7400	3.4740	3.2730	3.6950	3.8610	2.8060	1.9770	1.3270	0.7760
p#14	B32	MS	S	ODF	1.5580	1.7290	2.3440	2.8190	3.9780	4.4870	4.9720	4.7490	4.0750	2.2590	1.6710	0.9780
p#14	B32	MS	S	Spray	1.5580	1.7290	2.3440	2.8190	3.9780	4.4870	4.9720	4.7490	4.0750	2.2590	1.6710	0.9780
p#15	A14	TO	S	ODF	1.2130	1.0400	3.4540	4.3310	3.9280	4.0040	4.5500	4.2540	3.0290	2.5050	2.0630	1.0370
p#15	A14	TO	S	Spray	1.2130	1.0400	3.4540	4.3310	3.9280	4.0040	4.5500	4.2540	3.0290	2.5050	2.0630	1.0370
p#16	B31	AO	S	ODF	0.5000	0.8030	2.4550	2.6770	3.2430	3.4400	3.3760	3.0080	2.1290	1.3130	0.9850	0.6150
p#16	B31	AO	S	Spray	0.5000	0.8030	2.4550	2.6770	3.2430	3.4400	3.3760	3.0080	2.1290	1.3130	0.9850	0.6150
p#17	A21	AV	S	ODF	0.9800	0.9250	2.8280	4.0800	4.2280	4.4230	4.8050	4.3910	2.7530	1.8630	1.4410	0.9010
p#17	A21	AV	S	Spray	0.9800	0.9250	2.8280	4.0800	4.2280	4.4230	4.8050	4.3910	2.7530	1.8630	1.4410	0.9010
p#19	B22	DL	S	Spray	1.5270	1.4660	3.4840	4.9560	5.3840	5.3380	5.6110	4.4130	2.4200	1.5690	1.1600	0.8300
p#2	A44	NC	S	ODF	0.6380	0.6840	1.7010	2.5030	2.9020	2.7580	3.0160	2.8470	2.7800	1.9050	1.2270	0.8290
p#2	A44	NC	S	Spray	0.6380	0.6840	1.7010	2.5030	2.9020	2.7580	3.0160	2.8470	2.7800	1.9050	1.2270	0.8290
p#20	A22	OZ	S	ODF	1.6910	2.5320	9.5160	13.6170	10.5710	9.2810	7.8350	7.0340	5.3130	3.8810	2.6580	1.6700
p#20	A22	OZ	S	Spray	1.6910	2.5320	9.5160	13.6170	10.5710	9.2810	7.8350	7.0340	5.3130	3.8810	2.6580	1.6700
p#23	B21	SM	S	ODF	0.5000	0.9440	3.4600	3.6800	4.2410	3.9010	3.7540	3.3870	2.3710	1.8900	1.2970	0.6650
p#23	B21	SM	S	Spray	0.5000	0.9440	3.4600	3.6800	4.2410	3.9010	3.7540	3.3870	2.3710	1.8900	1.2970	0.6650
p#24	B11	MR	S	ODF	1.9490	2.1890	3.5960	5.3980	6.2550	5.8690	6.5530	8.1970	5.1990	4.3480	3.4850	2.3970
p#24	B11	MR	S	Spray	1.9490	2.1890	3.5960	5.3980	6.2550	5.8690	6.5530	8.1970	5.1990	4.3480	3.4850	2.3970

Patient_ID	Number	Initials	Group	Drug	T0	T2	T5	T10	T20	T30	T45	T60	T120	T180	T240	T360
p#3	A42	SK	S	ODF	5.4310	4.9460	6.8190	11.7830	10.7600	10.7520	10.8900	10.7950	9.3660	7.0950	5.8840	4.1700
p#3	A42	SK	S	Spray	5.4310	4.9460	6.8190	11.7830	10.7600	10.7520	10.8900	10.7950	9.3660	7.0950	5.8840	4.1700
p#4	B45	MJ	S	ODF	1.8690	1.9930	3.8370	5.3600	6.6750	7.3290	8.7760	7.7140	5.5030	4.4200	3.4730	1.8640
p#4	B45	MJ	S	Spray	1.8690	1.9930	3.8370	5.3600	6.6750	7.3290	8.7760	7.7140	5.5030	4.4200	3.4730	1.8640
p#5	A32	JA	S	ODF	25.5510	23.8440	27.2030	26.7310	24.8610	24.6310	24.2780	20.6700	17.3120	12.5670	7.3120	4.0640
p#5	A32	JA	S	Spray	25.5510	23.8440	27.2030	26.7310	24.8610	24.6310	24.2780	20.6700	17.3120	12.5670	7.3120	4.0640
p#8	A24	IM	S	ODF	0.5000	0.5000	1.4090	2.5990	3.2450	2.6940	2.6610	2.7610	2.4160	1.5070	1.5000	0.8320
p#8	A24	IM	S	Spray	0.5000	0.5000	1.4090	2.5990	3.2450	2.6940	2.6610	2.7610	2.4160	1.5070	1.5000	0.8320
p#9	B13	PI	S	ODF	14.0300	12.4280	13.7130	14.0430	16.0490	12.0440	9.6570	16.7340	13.8040	11.7250	10.7030	6.8750
p#9	B13	PI	S	Spray	14.0300	12.4280	13.7130	14.0430	16.0490	12.0440	9.6570	16.7340	13.8040	11.7250	10.7030	6.8750
px1	X1	RR	S	ODF	1.2730	1.5780	6.6440	8.8240	8.0070	6.6300	5.9620	4.8120	2.4820	1.9690	1.6360	0.7860
px1	X1	RR	S	Spray	1.2730	1.5780	6.6440	8.8240	8.0070	6.6300	5.9620	4.8120	2.4820	1.9690	1.6360	0.7860
px11	X11	MV	S	ODF	0.5000	0.5000	1.3350	3.1100	3.6190	3.8220	3.7770	2.4000	2.8060	1.7260	1.1650	0.7230
px11	X11	MV	S	Spray	0.5000	0.5000	1.3350	3.1100	3.6190	3.8220	3.7770	2.4000	2.8060	1.7260	1.1650	0.7230
px12	X12	ACP	S	ODF	0.6720	0.9150	5.7120	5.8580	7.7680	7.1200	6.8320	5.9150	3.7360	2.8690	1.8210	1.0620
px12	X12	ACP	S	Spray	0.6720	0.9150	5.7120	5.8580	7.7680	7.1200	6.8320	5.9150	3.7360	2.8690	1.8210	1.0620
px14	X14	HF	S	Spray	0.5000	1.1250	5.6530	3.5860	3.4760	2.9010	4.4690	4.8900	3.8130	3.1910	2.0280	1.3340
px16	X16	MO	S	ODF	0.5000	1.2150	2.9510	3.3100	4.0390	3.7490	3.5630	3.8840	3.5770	2.4660	1.7930	1.0990
px16	X16	MO	S	Spray	0.5000	1.2150	2.9510	3.3100	4.0390	3.7490	3.5630	3.8840	3.5770	2.4660	1.7930	1.0990
px2	X2	LN	S	Spray	0.5000	0.9480	1.8110	2.2470	2.0140	2.3640	2.5310	2.0020	2.4830	NULL	NULL	NULL
px3	X3	LO	S	ODF	0.6410	0.5770	2.5650	5.0960	4.7130	5.4730	4.0450	3.6280	2.7740	1.7580	1.2720	0.8510
px3	X3	LO	S	Spray	0.6410	0.5770	2.5650	5.0960	4.7130	5.4730	4.0450	3.6280	2.7740	1.7580	1.2720	0.8510
px4	X4	RF	S	ODF	0.5710	2.1540	8.6600	10.2130	8.8620	6.9900	5.9110	5.3550	3.6510	2.6760	1.9370	1.1390
px4	X4	RF	S	Spray	0.5710	2.1540	8.6600	10.2130	8.8620	6.9900	5.9110	5.3550	3.6510	2.6760	1.9370	1.1390
px8	X8	FL	S	ODF	2.1460	2.0910	3.2970	3.6970	4.2340	4.5110	4.7540	4.8510	3.3680	2.6870	2.1810	1.4240
px8	X8	FL	S	Spray	2.1460	2.0910	3.2970	3.6970	4.2340	4.5110	4.7540	4.8510	3.3680	2.6870	2.1810	1.4240

*)"NULL" means; No data. **) Group S means Safety, K means Kinetic.

16.2.7 Adverse event listings (each subject)

Patient ID	Number	Initials	Age	Gender	AdvEvtText	MedDRA	StartDate	EndDate	Duration	Severity	Serious	Action	Outcome	Causality	Drug	DrugDate
p#7	A12	JR	55	Male	Vasovagal reaction	10047166	2012-05-26	2012-05-26	0	Moderate	No	No action taken	Complete recovery	Certain	ODF	2012-05-26
p#10	A13	CL	46	Female	Globus	10051180	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-26
p#10	A13	CL	46	Female	Hiccups	10020039	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-02
p#15	A14	TO	37	Female	Nausea	10028813	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-26
p#15	A14	TO	37	Female	Globus	10051180	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-26
p#15	A14	TO	37	Female	Globus	10051180	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-02
p#15	A14	TO	37	Female	Nausea	10028813	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-02
p#17	A21	AV	25	Male	Coughing	10011232	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Probable	ODF	2012-05-27
p#13	A23	TG	25	Female	Globus	10051180	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-27
p#13	A23	TG	25	Female	Globus	10051180	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-09
p#8	A24	IM	23	Female	Globus	10051180	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-27
p#8	A24	IM	23	Female	Headache	10019218	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-05-27
p#8	A24	IM	23	Female	Globus	10051180	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-09
p#5	A32	JA	42	Female	Globus	10051180	2012-06-03	2012-06-03	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-03
p#3	A42	SK	24	Male	Hiccups	10020039	2012-06-17	2012-06-17	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-17
p#3	A42	SK	24	Male	Globus	10051180	2012-06-17	2012-06-17	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-17
p#2	A44	NC	25	Female	Globus	10051180	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-09
p#2	A44	NC	25	Female	Nausea	10028813	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-09
p#2	A44	NC	25	Female	Globus	10051180	2012-06-17	2012-06-17	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-17
p#24	B11	MR	43	Female	Hiccups	10020039	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-26
p#24	B11	MR	43	Female	Nausea	10028813	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-26
p#24	B11	MR	43	Female	Nausea	10028813	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-02

Patient ID	Number	Initials	Age	Gender	AdvEvtText	MedDRA	StartDate	EndDate	Duration	Severity	Serious	Action	Outcome	Causality	Drug	DrugDate
p#24	B11	MR	43	Female	Palpitation	10033556	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-02
p#24	B11	MR	43	Female	Globus	10051180	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-02
p#24	B11	MR	43	Female	Headache	10019218	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Possible	ODF	2012-06-02
p#22	B12	FG	37	Female	Globus	10051180	2012-06-02	2012-06-02	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-02
p#9	B13	PI	39	Female	Globus	10051180	2012-05-26	2012-05-26	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-26
p#23	B21	SM	45	Male	Globus	10051180	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-27
p#6	B23	JL	25	Female	Globus	10051180	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-27
p#6	B23	JL	25	Female	Nausea	10028813	2012-05-27	2012-05-27	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-05-27
p#16	B31	AO	25	Female	Globus	10051180	2012-06-03	2012-06-03	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-03
p#16	B31	AO	25	Female	Pain throat	10033494	2012-06-10	2012-06-10	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-10
p#14	B32	MS	32	Female	Nausea	10028813	2012-06-03	2012-06-03	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-03
p#14	B32	MS	32	Female	Nausea	10028813	2012-06-10	2012-06-10	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-10
p#11	B41	RS	25	Male	Globus	10051180	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-06-09
p#18	B43	JB	24	Female	Nausea	10028813	2012-06-10	2012-06-10	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-06-10
p#4	B45	MJ	41	Female	Dizziness	10013573	2012-06-09	2012-06-09	0	Mild	No	No action taken	Complete recovery	Possible	Spray	2012-06-09
px1	X1	RR	43	Male	Globus	10051180	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-08
px1	X1	RR	43	Male	Nausea	10028813	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-16
px10	X10	MB	39	Female	Globus	10051180	2012-09-09	2012-09-09	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-09
px10	X10	MB	39	Female	Globus	10051180	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-16
px11	X11	MV	45	Female	Globus	10051180	2012-09-09	2012-09-09	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-09
px11	X11	MV	45	Female	Globus	10051180	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-16
px11	X11	MV	45	Female	Nausea	10028813	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-16

Patient ID	Number	Initials	Age	Gender	AdvEvtText	MedDRA	StartDate	EndDate	Duration	Severity	Serious	Action	Outcome	Causality	Drug	DrugDate
px3	X3	LO	53	Male	Hiccups	10020039	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-16
px3	X3	LO	53	Male	Cough (drug-induced)	10058276	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-16
px5	X5	EB	21	Female	Nausea	10028813	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-15
px5	X5	EB	21	Female	Chest pain	10008479	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-15
px6	X6	DB	21	Female	Nausea	10028813	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-08
px6	X6	DB	21	Female	Nausea	10028813	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-15
px6	X6	DB	21	Female	Cough (drug-induced)	10058276	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-15
px7	X7	VO	25	Female	Vertigo	10047340	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-08
px7	X7	VO	25	Female	Globus	10051180	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-08
px7	X7	VO	25	Female	Hiccups	10020039	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-15
px7	X7	VO	25	Female	Globus	10051180	2012-09-15	2012-09-15	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-15
px8	X8	FL	28	Female	Nausea	10028813	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-08
px8	X8	FL	28	Female	Dizziness	10013573	2012-09-08	2012-09-08	0	Mild	No	No action taken	Complete recovery	Certain	Spray	2012-09-08
px8	X8	FL	28	Female	Nausea	10028813	2012-09-16	2012-09-16	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-16
px9	X9	JC	44	Male	Nausea	10028813	2012-09-09	2012-09-09	0	Mild	No	No action taken	Complete recovery	Certain	ODF	2012-09-09