Clinical Trial Report Synopsis

Name of Company Nycomed	**Tabular format** Referring to Part of the Dossier:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient: Fentanyl citrate		

Short Title of Trial

Intranasal fentanyl for breakthrough pain in cancer: Randomised, double-blind, placebo-controlled, cross-over confirmatory trial

Long Title of Trial

Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 µg fentanyl and placebo in eight breakthrough pain episodes

Principal Investigators

A total of 31 investigators screened patients for the trial.

Trial Centre(s)

31 trial centres in seven European countries (Austria, Germany, Denmark, Finland, France, Italy, and Poland) screened patients; 27 trial centres randomised patients.

Publication (reference)

None

Studied period (years)	**Phase of development**
FPI: 16 May 2006 LPO: 13 May 2007	Phase III: Therapeutic Confirmatory

Objectives

To demonstrate efficacy of nasal fentanyl (NAF) in the treatment of breakthrough pain (BTP) in cancer patients, and to explore the relationship between the response to the NAF dose and the stable background pain opioid dose.

Methodology

Randomised, double-blind, placebo-controlled, cross-over, confirmatory trial.

0, 50, 100 and 200 µg fentanyl (Investigational Medicinal Product, IMP) was given twice in randomised order for treatment of 8 BTP episodes. The IMP was administered as one puff in one nostril. If insufficient pain relief, a second puff was taken after 10 min. Rescue analgesics was allowed after further 10 min.

To ensure safety of patients, a 200 µg test dose was given in-hospital prior to randomisation. If clinical significant intolerable reactions occurred, the patient was not randomised.

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Number of patients **(total and for each treatment)**

With a planned number of 175 completers and an expected drop-out rate of approximately 15%, 178 patients were randomised.

Diagnosis and main criteria for inclusion

Main inclusion criteria: adult in/out patient with cancer; use of stable, chronic opioid treatment for background pain. Minimum three BTP episodes per week and maximum four per day. Life expectancy of at least three months.

Test product, dose and mode of administration, batch number

Nasal fentanyl, supplied as a phosphate buffered solution of fentanyl citrate, available in 0.5 mg/ml, 1.0 mg/ml and 2.0 mg fentanyl/ml (equivalent to single doses of 50, 100 and 200 µg, respectively) in multiple-dose glass containers mounted with a standard spray device. Mode of administration: nasal spray. Batch Numbers: 10277300, 10277074, 10277075 for 50, 100 and 200 µg fentanyl, respectively.

Duration of treatment

Treatment of eight BTP episodes was expected to last up to three weeks.

Reference therapy, dose and mode of administration, batch number

Reference therapy: Placebo for nasal use was supplied as a phosphate buffered solution of sodium citrate in multiple-dose glass containers mounted with a standard spray device. Two of the eight treatments were placebo. Mode of administration: nasal spray. Batch Number: 10296658.

Criteria for evaluation

Efficacy (based on patient evaluation in diary):

Primary endpoint:

- Pain intensity (PI) difference at 10 minutes (PID_{10}) after administration of first IMP puff

Secondary endpoints:

- Sum of PI differences in the time interval 0 – 60 minutes ($SPID_{0-60}$)
- General impression (GI) with 5-point categorical verbal rating scale (VRS) at 60 min

PID and SPID were derived from PI scores using an 11-point numerical rating scale recorded at time points 0, 10, 20, 40, and 60 minutes

Safety

Adverse events (AEs)

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Statistical methods

The primary efficacy variable was PID10 after application of the first puff. The PID10 was calculated by subtracting the PI at 10 min from the PI recorded immediately before treatment. Reversal of the scale was applied so that high values indicated a positive result. The variation in PID10 between two episodes within a patient was calculated by dose and across all doses and expressed as the standard deviation (SD) and coefficient of variation (CV). Summary statistics (n, mean, median, SD, minimum, maximum) for PID10, SD, and CV were tabulated by dose. The PID10 for each patient for each dose was calculated as an average score for the two episodes. Individual as well as mean dose response curves were presented graphically. The PID10 was analysed by successive F-tests of the contrasts of 200 µg vs placebo, 100 µg vs placebo and 50 µg vs placebo. To ensure protection of the significance level, the tests were performed sequentially, only proceeding to the next test if the current test was statistically significant so it was not possible to conclude that 100 µg was effective if 200 µg was not. For each test, the hypothesis was that of no difference between mean response on active dose and mean response on placebo with the alternative that they differ. The trial followed a cross-over design with each of the four doses taken twice. The corresponding mixed linear model included the following fixed effects:

Treatment (0, 50, 100, 200 µg IMP) (categorical)

Centre (categorical)

Average baseline PI (over all episodes for a patient) (continuous)

Deviation of baseline PI for each episode from average baseline PI (continuous)

Patient was included in the model as a random effect.

It was assumed that very few patients would have their background pain treatment adjusted during the efficacy phase. If this happened for more than 5% of the patients, a stratified analysis was to be done using the model described above with an additional factor (categorical variable) describing the level of background medication associated with each treated BTP episode. However, only four patients (2.3%) had adjustments in their background pain treatment so this was not included as a factor in analysis of the primary efficacy endpoint.

The small centres were pooled for analysis purposes. The smallest pooled centre had at least 4 patients in the intent-to-treat (ITT) analysis set. As supportive evidence, a centre-by-dose interaction was added to the model for the primary efficacy endpoint, PID10, as a fixed effect. The analysis was run for the ITT and PP analysis sets. The interaction effect was statistically significant for both analyses and therefore, the dose response profiles were examined within each pooled centre. This examination revealed that the large

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centres had a consistent dose response, while some of the small centres, due to the variation between patients, did not have a clear dose-response. It was therefore concluded that the dose-by-centre interaction effect was merely a result of the variation between and within patients rather than an actual difference in effect between centres.

The primary efficacy model included a randomised dose, centre, baseline PI (mean and deviation from mean). The analysis was performed for the ITT and Per-Protocol (PP) datasets with main emphasis on the ITT analysis. The ITT analysis set was composed of all randomised patients that took at least one dose of double-blind trial drug for treatment of BTP. The PP analysis set was comprised of all patients who had at least one per-protocol episode for each dose of trial drug, did not violate the designated inclusion/exclusion criteria, and had all treated BTP episodes at least 8 hours apart. If more than 10% of the patients in the ITT analysis set were excluded from the PP analysis set, the analyses were also to be performed for the PP analysis set. This analysis was not done for the standard PP population because only 9.4% of ITT patients were excluded from the PP; however, an exploratory analysis of the PP analysis set that excluded an additional six patients was performed. These six patients had baseline background opioid daily doses that exceeded the protocol-specified limit of 500 mg (maximum dose used was 600 mg/d), identified after the blind was broken. Exclusion of these six subjects from the PP analysis set would have met the criterion for analysis of all of the secondary efficacy variables using the PP analysis set (If more than 10% of the patients in the ITT analysis set are excluded from the PP analysis set, the secondary variables will also be summarised for the PP analysis set). Therefore, a post hoc analysis of PID10 for this analysis and SPID0-60 and GI were analysed with these six patients excluded from the PP analysis set. The results were similar to those observed for the ITT analyses; therefore, inclusion of these subjects did not have any impact on the efficacy results.

The relationship between the IMP dose and the baseline dose of the background pain opioid (standardised to morphine equivalent doses) was evaluated for PID10 and for responders. A responder for a treated BTP episode was defined as having PID10>2 for that episode. The overall responder rate was equal to: (1) 100% if patient was a responder in both treated BTP episodes within a dose. (2) 50% if patient was a responder in one treated BTP episode and non-responder in the other treated BTP episode within a dose. (3) 0% if patient was a non-responder in both treated BTP episodes. Background opioids doses were devided into low (<180 mg/day), medium (>180-≤360 mg) and high (>360 mg).

The secondary efficacy variables were the sum of the PIDs over the time interval 0-60 min (SPID0-60) and the GI score. GI was calculated using a 5-point categorical VRS at 60 min after administration of the first IMP puff. The SPID0-60 denotes the average change in PI over the 60-min interval and was derived from the area under curve (AUC) for PID over

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the 0-60 min interval divided by the length of the interval (60 min).

Safety data for test dose withdrawals, patients randomised but not treated, and patients excluded from ITT analysis set were listed separately and included AEs and baseline data. All other safety presentations were based on the ITT analysis set. All AEs were tabulated by treatment, System Organ Class, preferred term, severity, and relationship to trial drug.

SUMMARY:

This trial was completed on 13 May 2007. It was conducted in accordance with Good Clinical Practice and with the World Medical Association Declaration of Helsinki and its most recent amendment. The trial was designed having considered the Committee for Proprietary Medicinal Products Efficacy Working Party Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain dated 21 November 2002. The trial was approved by competent authorities. The protocol, informed consent and patient information was approved by ethics committees. Written consent was obtained prior to any trial-related activities.

A total of 218 patients were screened, of which 184 were enrolled (i.e., received the NAF test dose). Of these 184 patients, six did not tolerate the test dose; therefore, 178 patients were randomised to treatment. Of the 178 patients who tolerated the test dose and were randomised, seven patients were excluded from the ITT analysis set and 16 patients were excluded from the PP analysis set. Fourteen ITT patients discontinued prematurely; 157 therefore completed the double-blind treatment phase. The reasons for discontinuation were: AEs (8 patients), protocol non-compliance (3 patients), and other reasons (3 patients).

The majority of patients were male (52.6%) and Caucasian (95.9%; data collected for 164 patients). Mean age was 61.8 years and ranged from 32 to 86 years. Mean BMI was 23.8 kg/m^2 for all patients. Mean weight and height were 68.6 kg and 172.1 cm , respectively, for the male patients and 65.2 kg and 163.0 cm, respectively, for the females.

Efficacy Results:

Mean PID_{10} scores were 1.44, 1.88, 2.34, and 2.80 for placebo, 50, 100 and 200 µg NAF, respectively. Scores for all NAF doses were significantly higher than for placebo ($P<0.001$). Responder rate was 23.5, 29.9, 45.5 and 53.9% for placebo, 50, 100 and 200 µg NAF, respectively. Similarly, all NAF dose groups had significantly higher mean GI scores compared with placebo ($p<0.001$) (0.96, 1.37, 1.63, 1.99 for placebo and the three NAF doses, respectively).

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A dose-response for NAF was also observed regarding $SPID_{60}$: 1.96, 2.62, 3.10 and 3.53 for placebo, 50, 100 and 200 µg, respectively, $p<0.001$. Based on this, it was concluded that:

- NAF was statistically superior to placebo for the primary efficacy endpoint of PID_{10} for all doses. Results were similar for the ITT and PP analysis sets.
- The reduction in PID_{10} showed a clear dose response. This was also reflected by the responder rate.
- For the secondary endpoints, all of the NAF dose groups had significantly higher mean GI scores compared with placebo with increasing effect with higher dose. The sums of the PI differences at the first 60 min postdose were significantly higher for the NAF doses compared with placebo, with the highest mean $SPID_{0-60}$ score observed for the 200 µg NAF dose.
- The background pain opioid (low, medium, or high) level did not have any effect on the efficacy of the NAF doses.

Safety Results:

Overall, 37 patients (21.6%) had AEs allocated to double-blind treatment. The percentage of patients who experienced at least one AE was similar for the treatments: 8.4% (14 patients) for 50 µg NAF, 6.5% (11 patients) for 100 µg NAF, and 6.6% (11 patients) for 200 µg NAF, and 7.3% (12 patients) for placebo. The most frequently occurring AE was progression of malignant neoplasms, reported following all treatments in this population of cancer patients: 4 patients (2.4%), 5 patients (3.0%) and 4 patients (2.4%) following the 50, 100 and 200 µg NAF doses, respectively, and 2 patients (1.2%) following placebo treatment. Nausea and vomiting were the most frequently reported AEs that were considered related to NAF treatment. Treatment-related nausea and vomiting were reported in 3 patients each: 2 patients (1.2%) following the 100 µg NAF dose and in 1 patient (0.6%) following the 200 µg NAF dose for both AEs. One AE of moderate, unrelated, nasopharyngitis, was the only AE of nasal symptomatology that was reported in this trial. No dose-response between NAF and frequency or severity of AEs was observed. A total of 14 SAEs were allocated to double-blind treatment, with 12 of these considered related to the patients' underlying disease, and one (dyspnoea) considered unrelated to the underlying disease and also unrelated to trial treatment (200 µg NAF). One SAE (severe respiratory depression) occurred following administration of two successive doses of 200 µg NAF and was considered to have a probable relationship to treatment; the patient was admitted to hospital and treated with naloxone. She recovered without sequelae. A total of 8 patients discontinued the double-blind phase of the trial due to AEs (i.e., the primary reason for discontinuation on the CRF was designated to be an AE):

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3 patients following treatment with 50 µg NAF, 1 patient following treatment with 100 µg NAF, 2 patients following treatment with 200 µg NAF, and 2 patients following treatment with placebo. The most common AE leading to withdrawal was disease progression (4 patients). Of the eight deaths allocated to the double-blind treatment phase, none were considered related to trial treatment; six were attributed to disease progression, one to unrelated dyspnoea, and one to unrelated cachexia.		
CONCLUSION: It can be concluded that NAF, at doses of 50, 100, and 200 µg, used in the treatment of cancer-related BTP, is superior to placebo; that the effect for all efficacy parameters increases with dose; and that all doses are safe, well tolerated, and clinically effective for patients regardless of their background level of opioid use.		
Date: 25 October 2007 Written by: Marianne Henriksen, MSc, PhD, Co-ordinating Trial Manager		

Amendment and Protocol for Review

Amendment1 and Updated Protocol for review

FT-017-IM

Document ID: C00009237

Version: 0.1

Substantial Protocol Amendment No. 1

Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 μg fentanyl and placebo in eight breakthrough pain episodes

Trial ID: FT-017-IM

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Trial phase: Therapeutic confirmatory

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Date protocol last modified: 24 October 2006
Date Amendment last modified: 24 October 2006

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For signatures see separate page

The present amendment to the protocol is depicted as follows: Deleted text is written with ~~strikethrough~~ letters.

Changes

1)

Section 7.4 Exclusion Criteria, Criterion 14:

Has the patient concomitant participation in any other trial with an investigational drug or device apart from ~~cancer treatment and~~ participation in NAF trial FT-016-IM within 30 days prior to inclusion in this trial?

I.e. new Exclusion Criterion 14 reads:

Has the patient concomitant participation in any other trial with an investigational drug or device apart from participation in NAF trial FT-016-IM within 30 days prior to inclusion in this trial?

2)

Section 10.1.1 Adverse Event (AE), Cancer:

~~**Cancer**~~

~~Progression of pre-existing cancer should not be recorded as an AE.~~

I.e. this section is to be deleted from the protocol.

Reason for Changes

1)

In order to evaluate safety data only in relation to this nasal fentanyl trial and not to unknown cancer treatment trials, participation in other trials are not allowed.

2)

Many, if not all, patients in this trial may experience progression of cancer. However, in order not to miss any information on AEs, also progression of cancer will be reported as AE. Patients who have already completed part of or all of the trial will have AE data on progression of cancer collected retrospectively.

CLINICAL TRIAL PROTOCOL

Short title: Intranasal fentanyl for breakthrough pain in cancer: Randomised, double-blind, placebo-controlled, cross-over confirmatory trial

Title: Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 µg fentanyl and placebo in eight break-through pain episodes

Trial ID: FT-017-IM

Sponsor: Nycomed
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Trial phase: Therapeutic confirmatory

Date protocol last modified: 24 October 2006

The protocol version includes Amendment Nos.:
Non-substantial Protocol Amendment No. 1
Substantial Protocol Amendment No. 1

This trial will be conducted in accordance with Good Clinical Practice.

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For signatures see separate page

Summary

Objectives

Primary objectives:

- To demonstrate efficacy of intranasal fentanyl (NAF) in the treatment of breakthrough pain (BTP) in cancer patients

Secondary objectives:

- To explore the relationship between the response to the NAF dose and the stable background pain opioid dose

Methodology

Randomised, double-blind, placebo-controlled, cross-over, confirmatory.

Number of patients

With a planned number of 150 completers and an expected drop-out rate of approximately 15%, 175 patients will be randomised for the trial. Planned 35 centres in 5-10 countries.

Diagnosis and main criteria for inclusion

Main inclusion criteria: adult in/out patient with cancer; use of stable, chronic opioid treatment for background pain. Minimum three BTP episodes per week and maximum four per day. Life expectancy of at least three months. Chemotherapy and palliative radiotherapy (except facial radiotherapy) allowed.

Investigational medicinal product (IMP), dose and mode of administration

Fentanyl sprays for intranasal application in the doses 0 (placebo), 50, 100 and 200 µg hereafter named Investigational medicinal product (IMP). Each dose will be given twice in randomised order for the treatment of a total of eight BTP episodes. The IMP is administered as one puff in one nostril. If the patient has insufficient pain relief, an extra puff is taken after 10 min, preferably in the other nostril. The maximum dose per BTP episode will therefore be 400 µg. Rescue analgesics are allowed as needed throughout the trial and can be taken 10 min after the second IMP puff.

Definition of BTP episodes to be treated with Investigational medicinal product

To qualify for treatment with IMP, a BTP episode must cause such strong pain that the patient judges it necessary to take additional analgesics (apart from the usual background pain medication). Only one BTP episode per day will be treated with IMP. This must be the first BTP in the day after 6 a.m. Other BTP episodes will be treated with the patient's usual analgesics.

Duration of treatment

Treatment of the eight BTP episodes will last for up to approximately 3 weeks. Maximum time allowed in the study is 8 weeks after which the patient will be withdrawn.

Follow-up study

Patients who participate in FT-017-IM are offered participation in a long-term follow-up study, FT-018-IM, in which they have the possibility to receive the trial drug until recovery, withdrawal or death.

Reference drug

Two of eight treatments will be placebo.

Criteria for evaluation

Efficacy (based on patient evaluation in diary):

Primary endpoint:

- Pain intensity difference at 10 minutes (PID_{10}) after administration

Secondary endpoints:

- Sum of pain intensity differences in the time interval 0 – 60 minutes, $SPID_{0-60}$
- General impression (GI) with 5-point categorical verbal rating scale (VRS) at 60 min

PID and SPID will be derived from pain intensity (PI) scores using an 11-point numerical rating scale recorded at time points 0, 10, 20, 40, and 60 minutes

Safety

- Adverse events

Statistical methods

The analysis of the primary endpoint, PID_{10}, will be based on a linear model with a step-down testing of the active doses versus placebo. The model will include randomised dose, centre, baseline PI (mean and deviation from mean). The analysis will be performed for the Intention-to-treat (ITT) and Per-Protocol (PP) datasets with main emphasis on the ITT analysis. $SPID_{0-60}$ and GI scores will be analysed similarly. Adverse events will be tabulated according to the Nycomed Full ICH Report Guideline.

Flow Chart

	Visit 1 Screening	Visit 2 Baseline (Day 8-10)	Treatment period 8 BTP episodes (~ 21 days)*	Visit 3 End-of-trial
Activities and assessments at visits/phone contacts:				
Informed consent	X			
Inclusion criteria 1-13 (includes a pregnancy test in urine) Exclusion criteria: All	X			
Inclusion criteria 14-16 based on diary recordings		X		
Demographic data	X			
Cancer related medical history	X			
Physical examination	X			X
Past and concomitant illnesses	X			
Concomitant medication	X	X	X	X
Adverse events		X	X	X
Patient diary (instruction/evaluation)	X	X	X	X
NAF 200 µg test dose		X		
Conclusion from test dose		X		
Randomisation		X		
Handing out trial drug		X		
Drug accountability		X		X
Check that dose of background pain opioid is adequate	(X)**	(X)**	X	
Adjustment of background pain opioid/re-titration and pausing patient	Any time when needed			
End-of-Trial				X
Patient activities at home:				
Treatment of 8 BTP with investigational medicinal product (max 1 BTP per day)			X	
Patient diary: Assessment of the 8 BTP episodes treated with investigational medicinal product			X	
Drug accountability		X	X	X

*Including daily contact (personal or by phone) until minimum three BTP episodes have been treated and subsequently every week until the treatment phase has been completed.

**Is part of the inclusion criteria

Table of Content

APPENDICES

List of Abbreviations and Definitions of Terms

AE:	Adverse Event
AR:	Adverse Reaction
BTP:	Breakthrough Pain
CA:	Competent Authority
CI:	Confidence Interval
CNS:	Central Nerve System
CPV:	Central Pharmacovigilance
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Coefficient of Variation
DCF:	Data Clarification Form
GCP:	Good Clinical Practice
GI:	General Impression
ICH:	International Conference of Harmonisation
EC:	Ethics Committee
ITT:	Intention-to-treat
IMP:	Investigational Medicinal Product
MAO:	Monoamine oxidase
MedDRA:	Medical dictionary for Drug Regulatory Affairs
NAF:	Intranasal Fentanyl
NRS:	Numerical Rating Scale
OEF:	Obvious Error Form
PI:	Pain Intensity
PID:	Pain Intensity Difference
PP:	Per-protocol
SD:	Standard Deviation
SAE:	Serious Adverse Event
SDV:	Source Data Verification
SOP:	Standard Operational Procedure
SPID:	Sum of Pain Intensity Difference
VRS:	Verbal Rating Scale

1 Ethical Rationale

Conventional treatment of cancer pain provides analgesia for both persistent pain and breakthrough pain (BTP). Historically, controlled-release oral morphine has been standard therapy for moderate to severe persistent pain, whereas immediate-release tablet or mixture of oral morphine is commonly used for BTP. BTP is typically rapid in onset, moderate to severe in intensity and relatively short in duration (1). The time-action characteristics of such immediate-release formulations of morphine include an onset of analgesic effect in 20-30 min and peak effect at 1-2 hours (2). This may not be optimal for many patients with BTP. Desirable characteristics of a BTP analgesic include more rapid onset of effect, duration of effect to cover the duration of the episode, no long-acting active metabolites and availability of a non-invasive formulation. Intranasal fentanyl (NAF) is expected to have these characteristics and thereby offer the patient an analgesic superior to oral and probably also to i.m. morphine. NAF will by-pass the oral route and therefore will be especially convenient for patients with nausea or vomiting, oral mucositis or impaired gastro-intestinal function, which are common symptoms and/or signs in cancer patients.

The selected NAF dose range (50 to 400 μg) is based on long-term experience of treating pain with fentanyl, on the published literature with special emphasis on the experience with transmucosal fentanyl (3-6) and on the experience from pilot studies with intranasal fentanyl (7-9).

The present trial will include cancer patients accustomed to taking opioid medication for their background pain. Patients receiving long-term opioid therapy usually develop tolerance to the respiratory-depressant effect of these drugs. Therefore, the risk of adding NAF to the analgesic regimen is reduced compared to treating opioid-naive patients.

In order to secure the safety of the patients, a 200 μg NAF test dose will be taken in-house where healthcare staff will carefully survey the patient for one hour after administration. This dose is the highest single dose that patients will receive during the trial. If intolerable reactions occur, the patient will not be included in the trial.

The risk of addiction in the present group of patients is considered overcome by excluding patients with a recent history of drug abuse.

Cancer patients with the need for BTP treatment have advanced disease, short life expectancy and severely impaired quality of life. The suicidal risk in this patient population is increased (10,11). Intranasal fentanyl can potentially be used for suicidal purpose. However, these patients have access to narcotic drugs for treatment of their background pain and BTP and thereby already have the possibility to use these drugs for suicide. Furthermore, there is a limit to how much the nasal mucosa can absorb, which means that much fentanyl will be swallowed if the patient continues to spray and the bioavailability of fentanyl through the gastrointestinal channel is very low due to first pass metabolism. With the very fast onset of effect of the intranasal fentanyl, patients are expected to have better BTP control. As the risk of suicide is correlated to poor pain control (10,11), the trial medication is likely to reduce the risk. In addition, the contribution in a clinical trial implies more attention from hospital staff, which may reduce the risk further.

Nevertheless, the potency of fentanyl gives reason for caution. In this trial, patients with impaired mental status, judged by the investigator to increase the risk of using intranasal fentanyl, are excluded.

After completion of this trial, FT-017-IM, all patients who are still eligible will be offered participation in a follow-up trial, FT-018-IM, which is expected to give them an improved treatment of BTP for an unlimited time. Patients who only received the NAF test dose in FT-017-IM may also continue to FT-018-IM at a lower dose, if this is well tolerated. This will be tested in the first phase of FT-018-IM by a titration starting with 50 µg/puff.

2 Legal Aspects

The trial will be conducted in accordance with the Declaration of Helsinki (12), local requirements, Good Clinical Practice (13,14) and any applicable regulations for protection of personal data (15). The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to.

2.1 Patient Information and Informed Consent

Prior to any trial-related activity, Investigator must give the patient oral and written information about the trial in a form that the patient can understand. The patient must be

given ample time according to local requirements to consider and to pose questions, before consenting.

Investigator must ensure that the patient is fully informed about the aims of the trial, procedures, potential risks, any discomforts and expected benefits. The patient must agree that sponsor personnel, their representatives or health authority personnel (National or other) may require direct access to the patient's data/personal records - including photocopying of source data in an anonymous form. The patient must also agree that his/her data will be processed and stored in an anonymous form for evaluation of this trial and any later overviews. Data may also be transferred in an anonymous form to third parties, e.g. other companies or authorities, which may be located in other countries with potentially different regulations for data. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, Nycomed/their representative and the investigator are bound to keep this information confidential. Data will follow the development of the product and be used for documentation of the product's efficacy and safety. Data will be transferred to involved parties only within the authority given by official agencies.

It must be emphasised that participation is voluntary and that the patient has the right to withdraw from the trial at any time without prejudice.

A physician who is a member of the trial team must obtain the patient's voluntary, personally signed and dated informed consent prior to any trial-related procedure. In the Informed Consent Form is stated that data collected will be kept even if consent is withdrawn.

2.2 Ethics Committees

The protocol, any amendments, the Patient Information/Informed Consent Form and any other relevant documents must be submitted to the Ethics Committee (EC). According to local requirements, documentation of either notification or approval must be obtained before initiation of the trial.

It is the responsibility of Sponsor to obtain approval from the ECs; Sponsor will provide Investigators with an accurate and complete record of all submissions and will also meet the ICH requirement for yearly updates of the status of the trial to the EC.

2.3 Authorities

Competent authorities must receive required documents according to national regulations. Nycomed will obtain approvals for the import of narcotic trial drug. Further, all necessary permits for the transport and storage of narcotics within countries will be obtained, if required.

3 Critical Documents

Before the trial is initiated at a site, the following documents from the site must be in the hands of Nycomed or their representative:

- Written agreement between Nycomed/their representative and Investigator(s)
- Current, signed and dated Curriculum Vitae for the Co-ordinating and Principal Investigator(s) and for other personnel listed in the Log of Staff
- Signed and dated protocol agreement with the original signature of the Principal Investigator
- Signed and dated substantial amendment agreement(s), if any
- Written EC approval/vote according to local requirements
- Patient Information and Informed Consent Form in local language (notification to/approval by EC)
- Competent Authority approval (according to local regulations)
- A copy of the Log of Staff document
- Signed Financial Disclosure Statement (16)

4 Introduction

Patients suffering from cancer often suffer from a more or less constant background pain. Furthermore, they often also suffer from pain that flares up and breaks through a background level of pain treatment. Such flares of pain are often referred to as episodes of breakthrough pain, hereafter called BTP. These can be invalidating since the intensity of pain may be high with a very rapid increase and with an unpredictable occurrence. The duration of BTP will often be limited to an hour or less. Conventional non-invasive therapy will often come short in treatment of BTP since it does not match the rapid increase in neither pain intensity nor the rather limited duration. Conventional therapy has a rather late onset of pain relief and most often overshoot the duration of the BTP episode with several hours.

In the present trial, we aim to demonstrate that intranasal fentanyl (NAF) is suitable for treatment of BTP due to a short time to onset of pain relief and an efficient reduction of pain. For further information on non-clinical studies and clinical trials with NAF, see the Investigator's Brochure (17).

It is known that opioids have different dose-response profiles in neuropathic, visceral and somatic pain states. However, in the present trial, there will be no attempt to differentiate between these kinds of pain, as this would be too complex in the present patient population. Instead, an inclusion criterion that the patient must have obtained relief of BTP with his/her usual opioid has been introduced.

5 Objectives

Primary:

- To demonstrate efficacy of NAF in the treatment of BTP in cancer patients

Secondary:

- To explore the relationship between the response to the NAF dose and the stable background pain opioid dose

6 Overall Design and Plan of the Trial

For an overall plan of the trial, see the Flow Chart, p. 6 and Section 8.1.

6.1 Rationale for trial design

According to the guideline for treatment of nociceptive pain (CPMP/EWP/612/00) (18), placebo-controlled designs with appropriate use of rescue medication are recommended for trials not aiming to show superiority to any active comparator. In the present trial, two of the eight trial episodes of BTP will be treated with placebo. In some patients, placebo or the lower fentanyl doses may not be sufficient to treat BTP. To ensure adequate pain treatment, patients are therefore allowed to take rescue analgesics as needed after 20 min. Any reservations to the use of placebo may be countered by the facts that the effect of placebo is known to be particularly high in pain (19, 20), that in this trial only two of eight trial treatments are placebo, and that rescue analgesics are allowed as needed.

The design of this trial is the cross-over design. Cross-over designs have frequently been used in studies of cancer pain due to the high inter-subject variability in these patients. We regard the risk of carry-over to be small given the high variability in pain intensity between pain episodes and the short duration of action of the trial drug. The cross-over design was previously used successfully during the development of transmucosal fentanyl for BTP (21) where 10 treatment units (seven active and three placebos) were given to patients in a randomised and blinded cross-over design.

6.2 Patients

Eligible patients are identified at the screening and baseline visits according to Section 7. Patients must tolerate a 200 µg NAF test dose given at baseline in order to be randomised and proceed into the trial. The planned number of patients to complete all eight BTP episodes is 150.

6.3 Trial Treatment

NAF is available in double-blind sprays with 0 (placebo), 50, 100 and 200 µg fentanyl/puff hereafter named Investigational Medicinal Product (IMP). Patients will receive eight IMP sprays for the treatment of eight BTP episodes. There will be two sprays of each strength in random order. For details, see Section 9.

6.4 BTP Episodes to be Treated with IMP and Procedure for Treatment

To qualify for treatment with IMP, a BTP episode must cause such strong pain that the patient judges it necessary to take additional analgesics (apart from background pain medication). Maximum one BTP episode per day will be treated with IMP. This must be the first BTP in the day after 6 a.m. Other BTP episodes will be treated with the patient's usual analgesics.

IMP is taken as one puff in one nostril. If pain relief after 10 min is insufficient, a second puff from the same spray is taken. A second puff is preferably administered in the other nostril, because the nostrils have a cycle in which one nostril is more open to air passage than the other nostril. This changes every 2-5 hours, which might interfere with uptake of intranasal medication (22). In order to limit the influence on absorption, both nostrils should be used. At 10 min after the second puff, the patient may take rescue analgesic.

6.5 Efficacy Endpoints

The primary efficacy endpoint is the Pain Intensity Difference at 10 min, PID_{10}. This is in agreement with the CPMP guideline on treatment of nociceptive pain (18) which recommends time specific pain intensity difference as the primary endpoint. Since early onset of pain relief is of primary interest in treating BTP episodes, the main emphasis is put on the PID at 10 minutes.

Secondary efficacy endpoints are sum of pain intensity differences over the 0-60 min time interval, $SPID_{0-60}$ and general impression (GI) score.

For details of assessment of efficacy and statistical analyses, see Sections 8.2.1 and 15.2.3.

Appropriateness of Numerical Rating Scale (NRS)

Assessment of pain intensity will be done with the Numerical Rating scale, NRS. It requires the patients to rate their pain from 0-10 (11-point scale) where 0 represents the absence of pain and 10 is “pain as bad as you can imagine”. The validity of NRS is well documented and it demonstrates positive and significant correlations with other measures of pain intensity (23-25). The NRS was chosen as it is extremely easy to use – also for elderly patients.

Appropriateness of a general impression scale

Efficacy in the treatment of BTP(s) will also be assessed 60 min after the first NAF puff using a categorical 5-point Verbal Rating Scale (VRS): 0=poor, 1=fair, 2=good, 3=very good; 4=excellent. Studies have shown that a single global question about the overall effectiveness of a pain intervention can provide estimates of analgesic efficacy equivalent to those obtained by multiple questioning about pain relief (26).

6.6 Adjustment of Background Pain Medication

Average background PI must in average be controlled to a mild level defined as ≤ 4 on an 11 point NRS, see Section 7.3, inclusion criterion 14. If the average background PI is too high or the patient experiences more than four BTP episodes per day, the patient must be paused from the trial, i.e. trial treatment is interrupted, and the dose of background opioid adjusted. This may also happen if investigator in any other way judges that adjustment is

needed. After adjustment, the patient continues the trial. The time required for adjustment is not regarded as part of the treatment period of the patient. Background opioids must not be taken during treatment of a BTP episode with IMP, including the 60 min when assessments are done, but can be taken after the 60 min.

6.7 Method Guidelines

The “Note for guidance on clinical investigation of medicinal products in the treatment of nociceptive pain” (CPMP/EWP/612/00) was followed in designing the present trial (18).

6.8 Trial Schedule

Planned first patient first visit:	Q1-Q2 2006
Planned recruitment period:	6 months
Planned last patient last visit:	Q4 2006 – Q1 2007
Planned completion of the Clinical Trial Report:	Q2-Q3 2007

7 Trial Population

7.1 Patients

Eligible patients are adult cancer patients in stable, chronic opioid treatment, which in general reduces the intensity of their background pain to a mild level. Eligible patients suffer from BTP episodes for at least three times per week but no more than four times per day. Patients are able to continue their normal routine. Concomitant chemotherapy and palliative radiotherapy (except facial radiotherapy) are allowed. Facial radiotherapy is excluded as this may cause damage to the epithelial cells of the nose and thereby change uptake of fentanyl. For in/exclusion criteria, see Sections 7.3-4.

Patients may be in- or out-patients and due to their severe illness, many will be hospitalised periodically during the trial. The environmental and psychosocial factors at home and in the hospital differ, which may influence the experience of pain. However, as the patients are acting as their own controls, it is unlikely that these factors will jeopardise the final result.

7.2 Number of Patients

With a planned number of completing patients of 150 and an expected drop-out rate of approximately 15%, 175 patients will be randomised for the trial; for details see Section 15.1.

The anticipated number of centres is 35 in 5-10 countries. Each centre should aim to randomise minimum 5 patients.

7.3 Inclusion Criteria

All inclusion criteria must be answered “yes” for a patient to participate in the trial.

Inclusion criteria at screening

1. Has the patient given informed consent according to local requirements before any trial-related activities? Trial-related activities are any procedure that would not have been performed during the routine management of the patient
2. Is the patient a cancer patient with breakthrough pain?
3. Is the patient aged ≥ 18 years?
4. Has the patient received for at least the past month either oral morphine, oxycodone, hydromorphone or transdermal fentanyl for treatment of background pain?
5. Is the current dose of the scheduled background pain opioid of the patient equivalent to 60-500 mg oral morphine/day or to transdermal fentanyl 25-200 µg/hour? For conversion table, see Appendix 1.
6. Is the background pain generally stable and on average controlled to a mild level (defined as ≤ 4 on an 11 point NRS) by the background pain opioid?*
7. Is the BTP(s) in general of so severe pain intensity that the patient judges he/she needs additional analgesics (apart from background pain medication) and does it normally last for more than 15 minutes?
8. Does the patient in general while using a stable, fixed-schedule, opioid regimen have at least three BTP episodes per week but no more than four BTP episodes per day?*
9. Has the patient obtained at least partial relief of BTP(s) with his/her usual immediate-release strong opioid, i.e. oral morphine, oxycodone, hydromorphone or transmucosal fentanyl?
10. Is the life expectancy of the patient at least 3 months?
11. Is the patient able to use intranasal drugs?

* If background pain and/or number of BTP episodes are too high, please continue screening after adjustment of background pain medication.

For female patients of childbearing potential (Childbearing potential is considered until menopause has lasted more than 12 months. Surgically hysterectomised and surgically successfully sterilised females may be included on the same conditions as male patients).

12. Does the patient use adequate contraceptive precaution (contraceptive pill, implant or injection or intrauterine device) in the trial period?
13. Does the patient have a negative pregnancy test?

Additional inclusion criteria evaluated before the 200 µg NAF test dose at baseline-visit:
The inclusion criteria 14-16 must apply based on the diary recordings performed by the patient during seven days between screening and baseline visit. Adjustment of background pain opioid followed by diary recording must continue until inclusion criteria 14-16 apply.

14. Was the background pain during minimum five of the seven days controlled to a mild level (defined as ≤ 4 on an 11-point NRS) by the background pain opioid?
15. Did the patient have at least three BTP episodes during the seven days but no more than four BTP episodes per day?
16. Was the BTP(s) of such severe pain intensity that the patient took additional analgesics (apart from the usual background pain opioid)?

7.4 Exclusion Criteria

All exclusion criteria must be answered “no” for a patient to participate in the trial.
Exclusion criteria at screening

1. Does the patient have a recent history of substance abuse?
2. Is the patient pregnant or nursing during the trial period?
3. Has the patient neurological or psychiatric impairment that may compromise data collection?
4. Has the patient severe hepatic impairment? (Investigator’s judgement according to local practice)
5. Has the patient had any recent therapy, which could potentially alter pain or response to analgesics to a degree, where the need for background pain opioid will be

a) less than 60 mg morphine or morphine equivalents/day or
b) less than 25 µg/hour transdermal fentanyl

or the number of BTP episodes will be less than three per week during the trial period?

6. Has the patient had facial radiotherapy?
7. Has the patient been treated with MAO inhibitor within the last 14 days?
8. Does the patient use Methadone or Buprenorphine?
9. Does the patient have an impaired respiratory function to an extent, which may severely increase the risk of clinically relevant respiratory depression by BTP fentanyl treatment?
10. Does the patient use drugs for intranasal administration?
11. Does the patient have nasopharyngeal probe?
12. Is the patient known to be hypersensitive to fentanyl or to other opioids or any of their excipients?
13. Has the patient any head injury, primary brain tumour or other pathological conditions, which could significantly increase the risk of increased intracranial pressure or impaired consciousness?
14. Has the patient concomitant participation in any other trial with an investigational drug or device apart from participation in NAF trial FT-016-IM within 30 days prior to inclusion in this trial?
15. Does the patient have pathological conditions of the nasal cavity as contraindication to intranasal fentanyl?

7.5 NAF test dose

Eligible patients fulfilling in/exclusion criteria will at the baseline visit receive a 200 µg NAF test dose, which is the highest single dose given in the trial. In order to continue for randomisation, the patient must not develop clinically significant respiratory depression or other clinically significant intolerable reactions such as intolerable sedation, vertigo or nausea.

7.6 Withdrawal of Patients

For patients that do not tolerate the 200 µg NAF test dose at baseline

A patient who does not tolerate the 200 µg test dose will not continue in the trial. Only the screening CRF for such patients will be filled in. These patients may participate in the long-term efficacy-safety follow-up trial, FT-018-IM, on a lower dose if this is well tolerated. This will be tested in the first phase of FT-018-IM by a titration starting with 50 µg/puff.

AEs in connection with the test dose must be recorded as such.

For patients that receive at least one of eight IMP doses

A patient, who discontinues trial treatment prematurely, i.e. does not treat the protocol planned eight BTP episodes, must, if possible, be called in for an End-of-Trial visit. Even if the patient cannot attend, the End-of-Trial Form must be completed and the Drug Accountability Form filled in. All trial medication must be collected from the patient. Patients that discontinue prematurely may participate in the follow-up trial, FT-018-IM, if they comply with entry criteria.

7.7 Deviations from the Protocol

Deviations from the protocol should not be made. If a deviation occurs, the reason, date and any implications must be recorded. Investigator and Monitor must discuss if the deviation has any consequence for the continued participation of the patient in the trial. This must be documented in the Investigator File and in the Trial Master File.

8 Methods and Assessments/Measurements

8.1 Visit Procedures and Patient Activities

For an overall view of activities and assessments, see the Flow Chart, p 6. For details, see below. Activities and assessments will be described for the visit/period when they are first mentioned and are only listed later.

Treatment of the eight BTP episodes will last for up to approximately 3 weeks. Maximum time allowed in the study is 8 weeks after which the patient will be withdrawn.

Visit 1 – Screening

- **Informed consent.** Before any trial-related activities, the patient must sign and date the Informed Consent Form. See Section 2.1
- **Pregnancy test**. A positive urine pregnancy test is an exclusion criterion
- **Inclusion criteria 1-13 and all exclusion criteria**. See Sections 7.3-4. Regarding inclusion criteria 6-8: Dose of background pain opioid must be adjusted if investigator judges that it is needed in order to fulfil these criteria (see also Section 6.6).

- **Demographic data** include age/date of birth, sex, race, height, weight
- **Cancer related medical history**
- **Physical examination**
- **Past and concomitant illnesses**. For details see Section 8.3
- **Concomitant medication**. For details see Section 8.3
- **Patient diary.** In order to evaluate inclusion criteria 14-16 at the next visit (base-line visit), patients are instructed to fill in a screening diary for 7 days during the period from screening (Visit 1) to baseline (Visit 2) 8-10 days later. The patient will record daily information of the background pain intensity (11-point NRS) as well as the time of all BTP episodes and time for use of analgesics apart from background pain opioid (see Section 8.2.3). The patient must assess scores and in general fill in the diary him/herself. However, the patient may receive help from relatives or staff personnel for recording in the diary.

Visit 2 – Baseline

- **Inclusion criteria 14-16.** Investigator will judge these criteria based on patient diary from screening to baseline, see Section 7.3.
- **Concomitant medication**
- **Adverse events** since the patient signed the Informed Consent Form. For details see Section 10
- **Patient diary.** Screening diary to be evaluated and instruction for use of trial diary
- **NAF 200 µg test dose.** Before the test dose, the patient will learn how to use the spray by application of placebo puff(s). Subsequently, the patient applies the 200 µg NAF test dose to ensure that the highest single trial dose will be tolerable in terms of adverse reactions. The patient must be followed carefully for min one hour. The test dose does not need to be applied in connection with a BTP-episode. For details, see Section 9.1.1
- **Conclusion from test dose assessment**
- **Randomisation.** The eligible patient will be randomised to a double-blind eight spray sequence of 0 (placebo) 50, 100 and 200 µg NAF with two sprays per strength. For details, see Section 9
- **Handing out trial drug.** The patient will receive a box containing eight sprays. The sprays are numbered 1-8 and must be taken in this order. For details, see Section 9.1.3

- **Drug accountability.** Investigator will place a tear-off label from the test kit in the CRF. Furthermore, if the patient is randomised, investigator will place 1 tear-off label from the trial kit in the CRF (see Section 9.1.2)

Treatment period (eight BTP episodes)

Patient activities at home:

- **Treatment of BTP episodes**. Eight episodes of BTP are treated with IMP in the order the sprays are numbered. Only one BTP per day will be treated with IMP, the earliest administration is the day after the baseline visit. A trial episode must be the first severe episode in the day after 6 a.m. In case of insufficient pain relief of the first IMP puff, a second puff is taken 10 min after the first puff, preferably in the other nostril. At 10 min after the second puff, the patient may take rescue analgesic, for details see Sections 6.4 and 9.2.
- **Assessment of BTP episodes** treated with IMP. Recordings will start when the episode begins and will include date and time for IMP dose(s), assessments of PI and General Impression (GI), see Section 8.2.3. Time for any rescue analgesics if applicable according to Sections 8.2.2 and 9.2 is recorded. BTP episodes not treated with IMP is treated as described in Section 9.2
- **Drug accountability**. The patient must place the tear-off label from each spray in the diary by the time it is used. Further, the patient must record the date and time of administration of trial drug as well as number of puffs (one puff at time 0 min and a possible second puff at 10 min) for details, see Section 9.1.2.

Phone contacts/personal contact

During the treatment period, patients will be contacted daily either personally (in-patients) or by phone until a minimum of three BTP episodes have been treated with IMP in order to ensure compliance. During these contacts, the following items are checked and recorded in the CRF:

- **Concomitant medication**
- **Adverse events**
- **Patient diary.** Further instruction for the patient if needed
- **Check that dose of background pain opioid is adequate.** Investigator must tick yes or no, and if no, then dose of background pain opioid must be adjusted (see below).

- **Adjustment of background pain opioid and pausing patients**, if needed, see Section 6.6.

End-of-Trial Visit

This visit is to be performed after last dose of IMP was taken.

- **Physical examination**
- **Concomitant medication**
- **Adverse events**
- **Patient diary.** The patient returns the diary, which will be checked for correctness/completeness by the trial staff, e.g. that the assessments are entered as intended by the patient, correct understanding of the scales, all fields entered etc.
- **Drug accountability.** The patient returns the IMP sprays (used and un-used). The trial staff will record this in the CRF. Investigator will judge patient compliance and appropriate use of the IMP, see Section 9.1.2.
- **End-of-Trial** entry fields in the CRF must be filled in.

8.2 Methods of Assessment

8.2.1 Efficacy Variables

- **Pain intensity (PI)** will be assessed using an 11-point Numerical Rating Scale (NRS) (0=no pain to 10=pain as bad as you can imagine). The derived variables, PID and SPID, will be based on PI as described in Section 15.2.3
- **General Impression (GI)** of efficacy in the treatment of BTP(s) will be assessed 60 min after the first NAF puff using a categorical 5-point Verbal Rating Scale (VRS): 0=poor, 1=fair, 2=good, 3=very good; 4=excellent

8.2.2 Use of IMP and rescue analgesics

Administration of first and second puff. If pain relief is insufficient at 10 min after the first puff, a second puff is taken from the same spray, preferably in the other nostril. The time of administration is recorded.

Use of rescue analgesics. If relief of BTP with trial drug is insufficient, rescue analgesics may be used. Rescue analgesics should not be taken until 10 min after administration of the second NAF puff. The time of administration of rescue analgesic is recorded.

8.2.3 Assessment of BTP episodes

Before randomisation

Patients will record the time of BTP episodes and use of analgesics (yes/no and time for administration) in the screening diary during 7 days in the 8-10 day period from screening to baseline visit. The BTP episodes to be recorded must have a severity that requires additional analgesic treatment (apart from background pain analgesics) as judged by the patient (for definition see Section 6.4).

After randomisation

The flow of the 60 min following each of the eight BTP episodes will be as shown in the Flow chart below. The variables will be recorded in the diary and CRF according to Section 8.2.

Flow chart for individual IMP treated BTP episodes

Time (min)	**0**	**10**	**20**	**40**	**60**
Administration of medication:					
First IMP puff	X				
One additional IMP puff, if needed		(X)			
Rescue analgesic, if needed			(X)…….. (X)		
Assessments:					
Pain intensity (PI)*	X	X	X	X	X
General impression (GI)					X

X = mandatory activity or assessment; (X) = activity if applicable

*Assessments must be recorded before administration of IMP and rescue analgesics

8.3 Past and concomitant Illnesses and Concomitant Medication

Definitions:

Past illness relevant illnesses that the patient has had in the past

Concomitant illness any illness that is present at the start of the trial

Concomitant medication any medication other than the trial product that is taken during the trial - including the screening period

A worsening in severity or frequency of a concomitant illness recorded at screening as well as any new illness diagnosed during the trial must be regarded as an AE whether or not considered to be related to the trial product and must be reported as such (see Section 10). Any change in concomitant medication or treatment procedures must be recorded at each visit or telephone contact.

During the trial, patients will receive their stable background pain opioid(s) and are allowed to take their usual analgesic for any type of pain, i.e. also as rescue analgesic for BTP in case of IMP failure; such administration must be recorded in the diary.

Concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform (e.g. erythromycin, ketoconazole, and certain protease inhibitors), and alcoholic beverages may produce increased depressant effects. The concomitant use should therefore be carefully administered.

Chemotherapy and palliative radiotherapy (except facial radiotherapy) are allowed during the trial.

8.4 Extension Use

Patients that receive at least the NAF test dose may participate in the long-term follow-up efficacy and safety trial FT-018-IM, if they comply with the entry criteria.

9 Trial Treatment

9.1 Intranasal Fentanyl and Placebo

Fentanyl for intranasal use, NAF, is supplied as sprays containing a phosphate buffered solution of fentanyl citrate. NAF is available in three strengths: 0.5 mg/ml, 1 mg/ml and 2 mg/ml in multiple-dose sprays. The corresponding doses are 50, 100 and 200 μg/puff. NAF is applied as one puff in one nostril. One puff defines and equals one dose. Thus, a 100 μg dose is one puff in one nostril from a spray delivering 100 μg/puff. If pain relief after 10 min is insufficient, a second NAF puff from the same spray is taken, preferably in the other

nostril. 1-2 puffs are considered trial treatment, i.e. there is no need to take a second puff if one puff is sufficient to treat the BTP.

Placebo for intranasal use is supplied as sprays containing a phosphate buffered solution of sodium citrate.

Volume/doses in the sprays: All sprays (NAF and placebo) contain 6 ml. The volume per puff is 100 µl. It is possible to obtain at least 40 puffs per spray.

Standard emergency procedures
In case of severe opioid-related adverse events, naloxone i.v. up to 0.4 mg per injection will be given at hospital during test dose.

9.1.1 Packaging and Labelling

NAF test kit
The test kit contains one NAF spray with 200 µg fentanyl/puff and one placebo spray. These will be packed together in an outer box with a tear-off label for the investigator to insert in the screening CRF. Each patient will be instructed in the procedure for using the spray at the baseline visit and will be able to practise this. For this purpose, the placebo will be used. Subsequently, the test dose of 200 µg will be given to the patient.

NAF trial kit
Each patient will receive a NAF trial kit containing eight sprays with 0 (placebo), 50, 100 and 200 µg fentanyl/puff 2 sprays of each strength. These will be packed together in an outer box with a tear-off label for investigator to insert in the CRF upon handout of the IMP. Each strength will be available in random order. The eight sprays will be numbered 1 to 8 and must be taken in this order. Each spray contains a tear-off label for the patient to insert in the diary upon use.

All supply will be labelled with white labels, containing trial specific information according to Annex 13, European guideline (27). Translation of the label text will be done as needed and according to local requirements.

The supply will have a trial reference code, which will make an immediate investigator/site identification of each package possible.

9.1.2 Storage and Drug Accountability

Nycomed is responsible for the packaging and delivery of IMP as well as for ensuring central storage, transportation and distribution of IMP to investigators. Investigator is responsible for storing, administering and keeping account of all IMP received, dispensed and returned (including from each patient). Investigator must only dispense IMP to patients enrolled in the trial. After the trial all IMP sprays must be returned to the respective warehouses, which are responsible for destruction after written approval from Nycomed. Fentanyl must be stored under secured conditions approved for narcotic drugs. The storage must have access control. Only trial staff is allowed to dispense fentanyl. Storage temperature is 5-25 degrees C.

Fentanyl is delivered in a multiple dose nasal spray as intended for marketing. The patients will receive a set of 8 nasal sprays each containing approx. 40 doses out of which the patients will use one or two doses per nasal spray. Accountability of IMP sprays will be made by the use of unique identified sprays. The dispense and return of IMP sprays for each patient will be documented in the CRF by the investigator.

Various methods (e.g. weighing and visual inspection) to determine whether or not the sprays have been used by the patients in accordance with the protocol have been discussed, but for technical reasons these methods are not feasible. For example, documenting the amount of drug used by weighing is not feasible because priming of the nasal spray typically varies between one and five strokes while the dosages taken by the patient are maximum two doses per spray. Consequently, it is not possible to distinguish between a primed nasal spray and a primed and used nasal spray given other variations in weight of sprays such as a) the actual weight of each spray, b) the number of puffs used for priming (one – five puffs) and c) the number of tear-off labels present on the spray. In addition, it is not possible to verify whether the spray is used or unused by visual inspection. The change in level of liquid resulting from taking one dose is 0.25 mm and this change can not be identified by the eye using e.g. marks on the spray.

Consequently, drug accountability of IMP sprays will be handled by documenting the dispense and return of unique identified sprays. In addition, returned sprays will be visually inspected for whether the spray is empty or not. If the nasal spray is empty, this information will be correlated with patient data. This does not serve to document the actual amount of IMP used, but potential misuse due to the IMP being a narcotic can be identified. The patient will be informed of this.

9.1.3 Randomisation and Blinding

Randomisation

Patients will be randomised to a sequence of administrations where each of the four doses (including placebo) is received twice. The randomisation will be restricted such that the first four episodes are treated with four different doses and similarly for the last four episodes. The randomisation can be described as a block randomisation within each patient where the first four episodes (block one) are randomised to the four doses (including placebo) and the last four episodes (block two) are randomised to the four doses. The order of the last four doses is not restricted to the same order as the first four doses. The patient will receive the set of eight sprays with the lowest number available at the site.

Patient assignment

At randomisation, the set of eight IMP sprays with the lowest number available at the site must be assigned to the patient. Investigator must keep a Patient Identification Code List, which connects patients and randomisation numbers.

Blinding and code break

Nycomed provides randomisation and sealed code envelopes. The randomisation lists will be stored at Clinical Trial Supply, Nycomed until the database has been released. Three sets of sealed code envelopes are prepared and kept at the centre, the monitoring CRO and Nycomed Central Pharmacovigilance (CPV), respectively, during the entire trial period.

Investigator may break the code for a patient in a medical emergency if knowledge of the treatment (NAF dose/placebo) will influence the further treatment of the patient. The Investigator who breaks the code must sign it and record the reason, date and time. Before a code is broken, Nycomed must be contacted, if possible. In all cases, Monitor must be notified within 24 hours after the code was broken.

In addition, Nycomed CPV may break the code for a patient if an SAE is judged reportable on an expedited basis and for reporting of safety data according to Directive 2001/20/EC (14). Blinding will be maintained for all persons responsible for analysis and interpretation of trial results.

9.2 Rescue Analgesics

An effective NAF dose will generally lead to an onset of pain relief within 10 min. This was demonstrated in a previous trial comparing onset of pain relief after i.v. and intranasal administration of fentanyl (see Figure 1) (7). If sufficient pain relief is not obtained at 10 min, a second NAF puff from the same spray may be taken and a further 10 min should elapse to obtain pain relief. If pain relief is still not sufficient at 10 min after the second puff, the patient may take his/her usual immediate-release opioid or any other rescue analgesic.

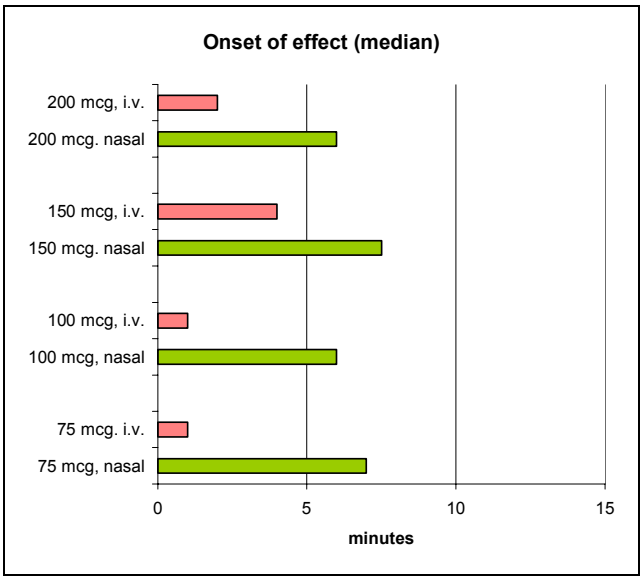

Figure 1: Onset of pain relief with i.v. and intranasal fentanyl (7).

An additional, second puff of NAF at 10 min will be regarded as trial treatment, whereas intake of other analgesics in the period until 60 min will be regarded as rescue analgesic. Analgesics other than NAF taken outside the time interval 0-60 min – apart from the background pain opioid(s) - are regarded as concomitant medication.

9.3 Background Pain Opioids

Patients receive their usual stable background sustained-release opioid treatment during the trial period. The dose may be adjusted, if needed, see Section 6.6.

10 Safety

10.1 Definitions

10.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following should not be recorded as an AE, if recorded at screening:

- A pre-planned procedure, unless the condition for which the procedure was planned has worsened since baseline.
- A pre-existing condition found as a result of screening procedures.

Complications to pre-planned procedures should be reported as AEs.

Clinical laboratory adverse event

A clinical laboratory adverse event is any clinical laboratory abnormality, which suggests a disease and/or organ toxicity, and which is of a severity that requires active management, i.e. change of dose, medical treatment, discontinuation of drug, more frequent follow-up or diagnostic investigation.

10.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is a medical important adverse event that is not immediately life threatening or does not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

* Life-threatening in this definition refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it had been more severe.
** Only inpatient hospitalisation including an over-night admission will be regarded as a seriousness criterion.

10.1.3 Non-Serious Adverse Event

Any AE that does not meet the criteria for an SAE.

10.1.4 Adverse Reaction (AR)

All untoward and unintended response to an IMP related to any dose administered.

10.2 Classification

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the patient's daily activities
- Moderate: Marked symptoms, moderate interference with the patient's daily activities
- Severe: Considerable interference with the patient's daily activities.

Causality

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an aetiology other than the trial product
- Not related: Good reasons and sufficient documentation to assume a causal relationship can be excluded.

Outcome Categories

- Recovered: Fully recovered or the condition has returned to the level observed at baseline
- Recovered with sequelae: As a result of the AE, the patient suffered persistent and significant disability/incapacity, e.g. became blind, deaf or paralysed
- Not recovered
- Fatal
- Unknown.

10.3 Adverse Event Recording

All events that meet the definition of an AE and occur in the period from the patient signed the Informed Consent Form and until 35 hours after last dose of IMP must be reported.

At each contact between the centre and the patient (visit or phone), the patient must be asked if he/she has experienced any health problems since the last contact. All AEs, either observed by the Investigator or reported by the patient, must be recorded by Investigator and evaluated according to Section 10.1.

Investigator must record all AEs on the standard AE Form. Investigator must record only one adverse event per AE form. For serious adverse events, the Serious Adverse Event Form must also be completed.

Investigator should record the diagnosis, if available. If no diagnosis is available, Investigator should record each sign and symptom as individual AEs.

Investigator should make an evaluation of the seriousness and the causality between the trial drug and the AE.

10.4 Adverse Event Reporting

Investigator must report all SAEs to Monitor immediately (within 24 hours) after obtaining knowledge of the event. The initial report must be promptly followed by detailed, written reports.

Monitor must report all fatal or life-threatening SAEs to Nycomed CPV within 24 hours. All other SAEs must be forwarded to CPV within 48 hours.

Nycomed will comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse reactions to the regulatory authorities and the ECs. Nycomed will be responsible for this reporting.

10.5 Follow-Up of Adverse Events

During and after participation of a patient in a clinical trial, the Investigator/Institution must ensure that adequate medical care is provided to the patient for any AEs, including clinically significant laboratory values, related to the trial. The Investigator/Institution must inform the patient when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

All AEs classified as serious or severe and possibly/probably related to the IMP must be followed by the Investigator until the patient has recovered, recovered with sequelae or died, and until all queries related to these AEs have been resolved.

All other AEs must be followed by Investigator until the patient has recovered or until 5 terminal half-lives of fentanyl has past, meaning 35 hours after last dose of IMP, whichever comes first, and until all AE-related queries for the patient have been resolved.

Investigator must forward follow-up information on SAEs to Monitor within 24 hours of obtaining knowledge hereof. Follow-up information should be supplied on the Adverse Event Extra Form and/or the Serious Adverse Event Extra Form, both marked follow-up.

10.6 Pregnancy

Female patients must be advised to notify Investigator immediately if they become pregnant. Investigator must report any pregnancy in trial patients to Monitor within 14 days of obtaining information of the patient being pregnant. Investigator must follow the pregnancy to termination or delivery. The infant must be followed at least until age one month. Miscarriage, stillbirth and any malformation/disease must be reported as SAEs.

Investigator must report information on pregnancy outcome other than miscarriage, stillbirth and any malformation/disease and follow-up of the infant within 14 calendar days of obtaining the information using the Pregnancy Form and the Pregnancy Follow-Up Form, respectively.

Consent of a parent must be obtained before registration of infant data.

10.7 Precautions/Overdose

Please see the current version of Investigator's Brochure (17).

Standard emergency procedure

In case of severe opioid-related adverse events, naloxone i.v. up to 0.4 mg per injection will be given at the investigational site.

10.8 Coding of Adverse Events

All AEs will be coded by Nycomed CPV using the MedDRA terminology, current version.

10.9 Sponsor's Assessment of Expectedness

Nycomed CPV will evaluate all AEs with respect to seriousness, causality and expectedness in accordance with the Directive 2001/20/EC. The expectedness of an AE will be determined according to Investigator's Brochure (17), current version.

11 Case Report Form

The Case Report Forms/patient diary (CRFs) for patients participating in the trial will be provided by Nycomed via a CRO. CRFs will consist of a screening section for assessment of eligibility and a treatment section for the data relating to treatment of BTP episodes with IMP. Patients will receive a screening number for eligibility testing and a patient number when they are randomised. The completed original CRFs are the sole property of Nycomed and must not be made available in any form to third parties, except for authorised representatives of Nycomed or appropriate regulatory authorities, without written permission from Nycomed.

11.1 Rules for Completing Case Report Forms

Investigator must write legibly with a dark ballpoint pen (blue or black) and ensure that all relevant questions are answered and that no empty data blocks exist.

If a test/assessment is not done and will not be available, indicate this by writing "ND" (Not done) in the respective answer field in the CRF. If the question is irrelevant, (e.g. not applicable), indicate this by writing "NA" (Not applicable) in the respective answer field.

Investigator or Investigator's authorised staff must ensure that all information has been accurately transcribed and that correct dates and initials or signatures are present. All entries to the CRFs must be made as described in the Case Report Form Completion Guideline at study initiation.

The responsible Investigator at the centre signs the overall Affirmation Statement for each patient verifying the data in the CRF for the patient.

11.2 Corrections to Case Report Forms

Investigator must correct errors in the CRFs by drawing a straight line through the incorrect entry and writing the correct value next to the crossed-out entry. All corrections must be initialised and dated.

Corrections necessary after the CRF has been collected from the site must be documented on a Data Clarification Form (DCF). Queries issued on a DCF must be answered by Investigator.

After the overall Affirmation statement for a patient has been signed, the Principal Investigator must approve later corrections in writing.

11.3 Flow of Case Report Forms

After completion, the NCR paper CRFs (original and first copy) will either be collected by Monitor or dispatched by courier. The original is sent for data handling to a CRO (see Section 17). The second copy will remain with Investigator.

12 Verification

12.1 Monitoring Procedure

The following data must be entered in official hospital records, laboratory records or similar documents:

1. Demographic data for the patient
2. Detailed cancer history and other concomitant and relevant past illnesses
3. Date of inclusion in the trial, patient No in the trial, Trial ID and sponsor name
4. Visit dates
5. Serious Adverse Events
6. Concomitant medication

For the following data, the CRF/patient diary is considered the source document: All recordings of PI, GI and time for intake of IMP and rescue analgesics. In addition, number of BTP episodes and background pain intensity in the screening diary is considered source data.

If source data are electronic, these must be printed, signed and dated by Investigator and stored in the Investigator File. Monitor will perform 100% source data verification (SDV) and ensure that completed CRFs are collected.

During the course of the trial, the Monitor will visit the centre before trial initiation and at approximately 7 weeks intervals or more often depending on recruitment and be available for discussions by phone. Monitoring visits may be performed more often depending on recruitment and Monitor will be available for discussions by phone. The purpose of the monitoring visits is to check the completeness of the patient records, the accuracy of entries on the CFRs the adherence to the protocol and to GCP (please see Section 2), the progress of enrolment, and also to ensure that study drug is being stored, dispensed and accounted for according to specifications.

Key study personnel must be available to assist Monitor during these visits. Investigator must give Monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study centre. The presence of informed consent, adherence to the

inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables will be fully verified. The original, signed Informed Consent Forms must be kept in the Investigator File. Essential documents must be filed in the Investigator File on an ongoing basis.

Before study initiation, at a site initiation visit or at an investigator's meeting, Nycomed or their representative will review the protocol and CRFs with the investigators and their staff.

12.2 Audit from Quality Assurance Unit

The International Clinical Quality Assurance Unit at Nycomed may audit the trial to ensure that trial procedures and data comply with the principles of GCP, protocol and standard operating procedures, and that data are correct and complete. Audits will be performed according to current SOPs.

12.3 Inspection by Competent Authorities

Investigator must be aware that representatives from CAs may inspect the data and associated patient records. Investigator must notify Nycomed or their representatives of the inspection and must make the records available.

13 Data Management

A CRO will perform the data management. Patients will be identified in the database only by patient identification number, centre and Trial ID.

The following measures will be taken to ensure the accuracy, consistency, and reliability of the data collected from this clinical study:
Data from the CRF will be entered twice into the database and verified with computerised cross-checking routines. Any changes to the CRF will be sent to the principal investigator who will indicate approval of the change(s) by signing a DCF; a copy of the signed DCF (and/or Obvious Errors Form [OEF] where appropriate) will be retained with the CRF.
Major protocol violators will be identified and SAEs in the clinical database will be reconciled with the SAE database and CRFs before clinical database lock.

The random code will be broken after all patients have completed the study and the database is frozen. The statistical analysis will be carried-out and a clinical study report issued with the relevant study results.

14 Evaluability of Patients for Analysis

The Intention to Treat (ITT) dataset includes all randomised patients who take at least one dose for treatment of BTP. Excluding patients who do not take any doses will not bias estimates of dose effects since the trial is double-blind.

Patients will be excluded from the Per Protocol (PP) dataset for the following reasons:

- the first four of the eight BTP episodes not completed
- violation of inclusion criteria 2, 4, 5, 6, 7, 8, 9, 14, 15 or 16
- violation of exclusion criteria 5, 6, 7 or 8
- any other major violation obscuring the PI scoring

The decision to exclude patients from the PP dataset will be taken and documented in collaboration between the coordinating trial manager, the medical adviser and the trial statistician before the code is broken. The documentation must be stored together with the remaining trial documentation.

The safety dataset includes all randomised patients exposed to NAF and is identical to the ITT dataset. Any adverse events reported for patients, who are exposed only to the NAF test dose, i.e. who withdraw before randomisation (referred to as test dose withdrawals), will be reported separately.

15 Statistical Considerations

A CRO will perform the statistical analyses and the statistical reporting of the trial, see Section 17.

15.1 Sample Size Calculation

The sample size calculation is based on Farrar et al, 1998 (21), who investigated transmucosal treatment of BTP in cancer patients. In Fig. 1 of Farrar et al (21), 95% confidence intervals are indicated for pain intensity difference (PID) are shown at time points

15, 30, 45, and 60 min. Using the result at 15 minutes the width of the confidence interval is approximately 0.5 indicating a standard error (SE) of about 1/8. Since this is based on a contrast between 7 active and 3 placebo treated episodes for 89 patients the intra-subject SD can be estimated as

$$SD = 1/8 \cdot \sqrt{89 \cdot (1/7 + 1/3)^{-1}} \approx 1.71$$

This is also the SD for contrasts of each dose versus placebo since they are differences between the averages of two episodes.

Considering the results of Farrar et al (21) an effect size of about 0.5 for PID seems relevant. With each dose assessed in two episodes, with a hypothesis of no difference between the doses, assuming a linear model for the analysis, with a significance level of 5%, and a power of 90%, the following sample sizes may be derived:

#Patients	Within-patient SD		
Mean PID_{10} difference	1.6	1.7	1.8
0.4	171	192	215
0.5	110	124	139
0.6	77	87	97

On this basis, a sample size of 150 completing patients has been decided. Although about 20% of the patients may be anticipated not to complete treatment of all the scheduled episodes they will be included in the ITT analyses with available episodes. Assuming therefore an *effective* drop-out rate of about 15%, 175 patients will be randomised.

15.2 Statistical Methods

15.2.1 Disposition of Patients

All patients included in the trial will be accounted for. Number of patients enrolled, randomised, and who completed each phase of the trial will be tabulated. Post-randomisation discontinuations will be tabulated by reason. Pre-randomisation discontinuations will be listed including reason.

Protocol deviations leading to exclusion from the PP dataset will be listed, see Section 14.

15.2.2 Demographics and Other Baseline Characteristics

Demographics and disease history of patients will be summarised by descriptive statistics.

15.2.3 Efficacy Analyses

Two-sided tests at a significance level of α = 5% will be used throughout. No correction of test level will be performed for secondary endpoints, as these are supportive. All analyses will be performed for the ITT dataset. As supportive evidence, the analysis of the primary endpoint will be performed for the PP dataset as well. If more than 10% of the patients in the ITT dataset are excluded from the PP dataset, the analyses of the secondary endpoints will also be done for the PP dataset.

15.2.3.1 Derivation of Efficacy Endpoints from PI scores

Pain Intensity (PI) is recorded on an 11-point NRS at 0, 10, 20, 40 and 60 min for each episode. For patients, who take rescue analgesic before 60 min, the last value prior to dropping out/taking rescue analgesic will be carried forward (LOCF) and imputed for all time points after intake of rescue analgesic. Rescue analgesics include any analgesic taken between time=0 min and time=60 min as a supplement to the investigational product. A possible second puff of NAF is allowed and it is not considered rescue medication. Missing values are imputed within each episode.

Pain Intensity Difference (PID) is calculated as the PI before the first puff subtracted at all following time points, and with reversal of the scale to have high values indicating a positive development, i.e. $PID_t = PI_0 – PI_0$, where PI_t is the PI at time t.

Sum of Pain Intensity Difference (SPID) is calculated for each episode as the area under curve (AUC) for PID over the 0 – 60 min interval divided by the length of this time interval, 60 min. This is denoted $SPID_{0\text{-}60}$. $SPID_{0\text{-}60}$ may be interpreted as the average improvement in PI over the 60 min.

In cases not covered by the above descriptions, missing data points will be imputed with the last available non-missing value. A missing value in General Impression (GI) will not be imputed.

15.2.3.2 Primary Efficacy Endpoint

The primary endpoint is PID_{10}, the PID at 10 min after application of the first NAF puff. PID_{10} will be analysed by successive F-tests of the contrasts of 200 µg vs placebo, 100 µg vs placebo and 50 µg vs placebo. To ensure protection of the significance level, the tests will be performed sequentially, only proceeding to the next test if the current test is significant. Thus, it is not possible to conclude that 100 µg is effective if 200 µg is not. For each test, the hypothesis is that of no difference between mean response on active dose and mean response on placebo with the alternative that they differ. The trial follows a cross-over design with each of the four doses taken twice. The corresponding mixed linear model will include the following fixed effects:

- Treatment (0, 50, 100, 200 µg NAF) (categorical)
- Centre (categorical)
- Average baseline PI (over all episodes for a patient) (continuous)
- Deviation of baseline PI for each episode from average baseline PI (continuous)

Patient will be included as a random effect.

The split of the covariate effect of baseline PI into two variables corresponds to the separate regressions in the between-patient and within-patient strata, respectively.

It is assumed that very few patients have their background pain treatment adjusted during the efficacy phase. If this happens for more than 5% of the patients a stratified analysis will be done including a factor describing the level of background medication (before/after dose adjustment).

Each patient will participate in the analysis with the available episodes and with the randomised dose. There will be no imputation for missing episodes.

As supportive evidence to the primary analysis a centre-by-dose group interaction will be added to the model as a fixed effect. This analysis will explore possible heterogeneity in dose-response between centres and provide an estimate of average dose-response in the case of heterogeneity. The primary endpoint will be analysed for the ITT and PP datasets with main emphasis on the ITT analysis. All results will be presented with estimated means

for each dose (including placebo), estimated differences for each active dose versus placebo with 95% confidence intervals and p-values.

The variation in PID_{10} between two episodes within patient will be calculated by dose and across all doses and expressed as SD and CV. The summary statistics (n, mean, median, SD, min, max) will be tabulated by dose. Individual as well as mean dose response curves will be presented graphically.

In addition to the analysis of PID_{10} scores, average responder rates will be computed by dose. A positive response to treatment of a BTP episode is defined as $PID_{10} > 2$ (28). The average response rates will be calculated by computing the average response rate by dose within each patient and then averaging those averages across all patients for each dose

15.2.3.3 Secondary Efficacy Variables

Sum of Pain Intensity Differences 0-60 min ($SPID_{0-60}$)

The $SPID_{0-60}$ will be analysed using the same model and presentation as described for the primary endpoint.

PI scores will be summarised by dose and time point and presented graphically as mean PI versus time by dose. In addition, PID will be tabulated for all time points, 10, 20, 40 and 60 min. PID will be presented graphically by dose as mean PID versus time.

General Impression (GI)

GI will be analysed as described for the primary endpoint. Although GI is recorded on a 5-point VRS, from poor (0) to excellent (4) the averaging over repeated doses justifies the use of this approach. Average GI scores by dose will be summarised by descriptive statistics.

Supplementary exploratory analyses may be performed for the efficacy endpoints.

15.2.4 Safety Analyses

Safety data for test dose withdrawals (see Section 14) will be listed separately; these listings will include adverse events and baseline data. All other safety presentations will be based on the ITT dataset.

Adverse events will be tabulated by treatment, System Organ Class, preferred term, severity and relation. Tabulation will follow the Nycomed Full ICH Report Guideline.

15.2.5 Other Analyses

The relationship between the NAF dose and the dose of the stable background pain opioid will be evaluated for the endpoints PID_{10}, responders ($PID_{10} > 2$) and GI. For this purpose the background pain opioid dose will be standardised to morphine equivalent doses using the guidelines by Breitbart et al. 2000 (29), see also Appendix 1. Based on the distribution of patients on those doses, cut points will be defined to define low, medium, and high dose of background pain opioid. Summary statistics for each endpoint by dose will be presented by category of background dose (low, medium, high).

The patients may discontinue due to adverse events, lack of efficacy or for other reasons. The number of completed episodes will be tabulated by dose as another indication of satisfaction with the treatment.

The number of times that repeat NAF at 10 min was used will be tabulated by dose. Additionally, the proportion of all episodes where any type of rescue analgesic was taken, will be tabulated by dose and time point.

15.3 Interim Analyses

No interim analysis is planned.

16 Trial Termination

16.1 Planned End of Trial

The End-of-Trial is defined as the time when the last patient has completed the last visit, and the 35-hour safety follow-up period (see Section 10.3 and 10.5).

Nycomed or their representative will ensure that End-of-Trial notification is submitted to the CA and EC for each site and for the complete trial.

16.2 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the Investigator/Institution should promptly inform the trial patients and assure appropriate therapy and follow-up of the patients.

If Investigator terminates or suspends a trial without prior agreement of the Sponsor, Investigator should inform the Institution where applicable. The Investigator/ Institution should promptly inform Sponsor and should provide the Sponsor with a detailed written explanation of the termination or suspension.

If Sponsor terminates or suspends a trial, Investigator should promptly inform the Institution where applicable.

In both cases, Nycomed or their representative will promptly inform the CA and EC and provide them with a detailed written explanation of the termination or suspension.

If the CA or EC terminates or suspends its approval/favourable opinion of a trial, Sponsor should inform Investigators and Institutions and provide them with a detailed written explanation of the termination or suspension.

17 Responsibilities

A CRO will be responsible for the overall project management including the following tasks:

- Preparation and submission of clinical trial applications/notifications to relevant national authorities
- Obtaining approval of protocols and amendments by Health Authorities
- Obtaining approval of protocols, amendments and informed consent by local and central Ethics Committees
- Identification of and contracts with investigational sites
- Securing safe storage of documents and medication at investigational sites
- Conduct and reporting of pre-trial visits, monitoring visits and close-out visits
- Ensuring site training
- Securing patient inclusion
- Securing that the Investigator's Files are complete

- Handling safety data according to agreement with Nycomed
- Data management including resolution of data clarification forms
- Performing statistical analyses according to procedure described in protocol
- Write Clinical Trial Report

A CRO with warehouses in the relevant countries will be responsible for IMP with regards to:

- Central storage
- Transportation and distribution of IMP to investigators

18 Reports and Publications

Clinical Trial Report

Nycomed or their representative will prepare a full Clinical Trial Report based on the results obtained and complying with the ICH guidelines. The co-ordinating investigator will sign the Clinical Trial report on behalf of all investigators.

Publication

Nycomed reserves the right to write and publish a manuscript based on the results described in the Clinical Trial Report. In any such publication, the first seven sites to include a minimum of ten evaluable patients will qualify as contributors. The senior author of a publication will be the co-ordinating investigator. Each qualified centre may provide one co-author; co-authors will be listed in descending order according to the number of evaluated patients from their centre. Nycomed may provide one co-author who will be listed second last. All other participating investigators will be acknowledged in the publication. Investigators invited to act as co-author for the publication will only be mentioned in the manuscript if he/she gives permission to do so.

The manuscript will be submitted for review and comments to all co-authors, who must respond within eight weeks. Investigators have the right to have their interpretation of the data properly represented in the publication. In the event of any disagreement, the opinion of both investigators and Nycomed will be fairly and sufficiently presented in the publication.

After publication of the results or 24 months after the Clinical Trial Report has been finalised, whichever comes first, Nycomed acknowledge the Investigator's rights to publish

results from this trial. Any such scientific paper, presentation, communication, or other information concerning the investigation described in this protocol, must be submitted to Nycomed for review prior to submission for publication/presentation. Review comments will be given within a month from receipt of the manuscript.

Nycomed reserves the right to use the results for registration purpose and internal presentation and promotion.

Investigators are not allowed to disclose or publish any information concerning patent applications, manufacturing processes, or formulation information about the investigational product to others without permission from Nycomed.

19 Retention of Clinical Trial Documentation

Investigator must arrange archiving of the Investigator File, CRF copies and source data and must keep these documents in a secure place protected from fire and theft.

These documents must be archived:

- until at least 2 years after the last approval of a marketing application in an ICH region
- until there are no pending or contemplated marketing applications in an ICH region or
- until at least 2 years have elapsed since the formal discontinuation of the clinical development of the trial product

The documents should, however, be archived for a longer period if required by the applicable regulatory authorities or if agreed with Sponsor.

It is the responsibility of Sponsor to inform the Investigator/Institution when these documents no longer need to be archived.

Nycomed will maintain the documentation pertaining to the trial as long as the trial product is on the market and the Clinical Trial Report 5 years hereafter.

20 Indemnity Statement

To the extent, Nycomed is legally liable; Nycomed accepts liability for any harmful effects suffered by a patient arising from administration of Investigational Medicinal Products or trial procedures in said trial.

Nycomed does not undertake liability in the event of negligence, cross-negligence or wilful misconduct by the clinics/hospitals or doctors conducting clinical trials or by persons for whom the said clinic/hospital or doctors are responsible.

21 References

1. Patt RB, Ellison NM. Breakthrough pain in cancer patients: characteristics, prevalence, and treatment. Oncology (Huntingt) 1998; 12(7):1035-1046.
2. Fass Läkemedel i Sverige. Hedstrand A-G, editor. 1-1-2001. LINFO Läkemedelsinformation AB.
3. Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E et al. Dose-titration, multicenter trial of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol 1998; 16(10):3238-3245.
4. Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 1999; 79(2-3):303-312.
5. Streisand JB, Varvel JR, Stanski DR, Le Maire L, Ashburn MA, Hague BI et al. Absorption and bioavailability of oral transmucosal fentanyl citrate. Anesthesiology 1991; 75 (2):223-229.
6. Streisand JB, Busch MA, Egan TD, Smith BG, Gay M, Pace NL. Dose proportionality and pharmacokinetics of oral transmucosal fentanyl citrate. Anesthesiology 1998; 88(2):305-309.
7. Nycomed, Denmark. A pilot cross-over study to evaluate the tolerability, pharmacokinetic profile, as well as onset duration and extent of pain relief of two different formulations of IMAFT in patients with post operative pain after oral surgery. Clinical Trial Report, Trial ID FT-001-IN, 1-87, 13-12-2001.
8. Nycomed, Denmark. A randomised double-blind study of the dose schedule finding of the successful doses of 50, 100, 200, 400 and 800 µg intranasal fentanyl in break-through pain followed by a randomised controlled, two-way cross-over, double-blind

study of the successful doses versus the dose level below in 12 breakthrough pain episodes. Clinical Trial Report, Trial ID FT-003-IN, in preparation.

9. Nycomed, Denmark. An open safety follow-up study of intranasal fentanyl in the treatment of breakthrough pain in patients completing either the intranasal pharmacokinetic or the dose schedule finding study and receiving chronic opioid or WHO cancer pain ladder, step 1 analgesic for their background pain. Clinical Trial Report, Trial ID FT-011-IN, in preparation.
10. Breitbart W. Suicide in cancer patients. Oncology 1987; 1:49-53.
11. Breitbart W. Cancer pain and suicide. In: Foley KM, editor. Advances in pain research and therapy. New York: Raven, 1990: 399-412.
12. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Patients. Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, South Africa 1996 and Edinburgh 2000.
13. ICH Harmonised Tripartite Guideline for Good Clinical Practice, E6.
14. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities L/21/34 1.5.2001.
15. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data.
16. Financial Disclosure by Clinical Investigators. Federal Register: 31 December 1998 (Volume 63, Number 251), 21CFR Part 54.
17. Nycomed, Denmark. Investigator's Brochure on Nasal Fentanyl.
18. Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain. Note for Guidance. CPMP/EWP/612/00. 21-11-2002. EMEA, Committee for Proprietary Medicinal Products.
19. Sauro MD, Greenberg RP. Endogenous opiates and the placebo effect: a meta-analytic review. J Psychosom Res 2005; 58(2):115-20
20. Haour F. Mechanisms of the placebo effect and of conditioning. Neuroimmunomodulation. 2005;12(4):195-200. Review.

21. Farrer JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomised, double-blinded, placebo-coltrolled trial for treatment of breakthrough pain in cancer patients. J of the National Cancer Inst 1998; 90(8):611-616.
22. Anatomy, physiology and function of the nasal cavaties in health and disease. Mygind N. Dahl R. Advanced drug delivery reviews 29 (1998) 3-12
23. Downie W, Leatham P, Rhind V, Wright V, Branco J, Anderson J. Studies with pain rating scales. Ann. Rheum. Dis 1978; 37, 378-381.
24. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27, 117-126.
25. Kremer E, Atkinson J, Ignelzi R. Measurements of pain: patient preferences does not confound pain measurement. Pain 1981;10, 241-248.
26. Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for megatrials: is a simple global assesment good enough? Pain 2001; 91, 189-194.
27. Annex 13/2003/94/EC, Volume 4.Good manufacturing practices Annex 13. Manufacture of investigational medicinal products, July 2003
28. Farrer JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000; 88, 287-294,.
29. Breitbart W, Chandler S, Eagel B, Ellison N, Enck RE, Lefkowitz M, Payne R. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Expert consensus. Oncology 2000, 695-701.

Substantial Protocol Amendment No. 1

Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 μg fentanyl and placebo in eight breakthrough pain episodes

Trial ID: FT-017-IM

Sponsor: Nycomed
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Phone: + 45 46 77 11 11
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Trial phase: Therapeutic confirmatory

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Date protocol last modified: 24 October 2006
Date Amendment last modified: 24 October 2006

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For signatures see separate page

The present amendment to the protocol is depicted as follows: Deleted text is written with ~~strikethrough~~ letters.

Changes

1)

Section 7.4 Exclusion Criteria, Criterion 14:

Has the patient concomitant participation in any other trial with an investigational drug or device apart from ~~cancer treatment and~~ participation in NAF trial FT-016-IM within 30 days prior to inclusion in this trial?

I.e. new Exclusion Criterion 14 reads:

Has the patient concomitant participation in any other trial with an investigational drug or device apart from participation in NAF trial FT-016-IM within 30 days prior to inclusion in this trial?

2)

Section 10.1.1 Adverse Event (AE), Cancer:

~~**Cancer**~~

~~Progression of pre-existing cancer should not be recorded as an AE.~~

I.e. this section is to be deleted from the protocol.

Reason for Changes

1)

In order to evaluate safety data only in relation to this nasal fentanyl trial and not to unknown cancer treatment trials, participation in other trials are not allowed.

2)

Many, if not all, patients in this trial may experience progression of cancer. However, in order not to miss any information on AEs, also progression of cancer will be reported as AE. Patients who have already completed part of or all of the trial will have AE data on progression of cancer collected retrospectively.

Country specific Substantial Protocol Amendment No. 02: France

Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 μg fentanyl and placebo in eight breakthrough pain episodes

Trial ID: FT-017-IM

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