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

Efficacy and safety of intranasal fentanyl in the treatment of breakthrough pain

Long Title of Trial

A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 µg with an open long-term safety follow-up in cancer patients with breakthrough pain

Principal Investigators

A total of 23 investigators participated in the trial.

Trial Centre(s)

35 centres were initiated; 23 centres screened and enrolled patients (Austria, Germany, Denmark, France and Poland).

Publication (reference): None

Studied period (years)	**Phase of development**
13 June 2006 to 13 Sept 2007	Phase III: Therapeutic Confirmatory

Objectives

To confirm the efficacy of nasal fentanyl (NAF) titrated to doses of 50, 100 and 200 µg for treatment of breakthrough pain (BTP) in cancer patients, and establish the long-term safety of treatment with NAF, and to explore the relationship between the dose of background pain opioid treatment and the titrated NAF dose.

Methodology

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

Trial drug 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 furter 10 min.

Titration, Phase I: Patients were titrated to a 'successful' dose starting at 50 µg fentanyl up to a maximum of 200 µg. A successful dose was reached when three of four BTP episodes had been treated successfully (one or two NAF puffs) defined as: 1) No need of rescue analgesic within the first 60 min; 2) A score of ≥2 on the General Impression scale (5-point categorical verbal rating scale (VRS) scale assessed by the patient at 60 min after the first NAF puff); 3) No severe undesirable effects such as pronounced hypoventilation, unacceptable sedation or drowsiness. If after up to four titration steps (all three doses and possibly one down-titration) a successful dose was not identified, the patient was withdrawn.

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Double-blind efficacy, Phase II: Patients received the successful NAF dose reached in the titration phase and placebo for treatment of eight BTP episodes (six NAF and two placebo)

Safety follow-up, Phase III: Patients continued with open-label treatment with the successful NAF dose.

Number of patients (total and for each treatment)

With a planned number of a minimum of 100 randomised patients, 135 patients were randomised.

Diagnosis and main criteria for inclusion

Main inclusion criteria: adult opioid tolerant in/out patient with cancer (use of stable, chronic opioid treatment for background pain). Minimum of three BTP episodes per week and maximum four per day. Life expectancy of at least three months. Patients were recruited from participants in previous trials using NAF.

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/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. Bulk batch numbers: 10277256, 10277068 and 10277070 for 50, 100 and 200 µg NAF, respectively.

Duration of treatment

Titration and efficacy phases were expected to last up to 3 weeks each, followed by a safety follow-up for 4 months after the last patient was included.

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 supplied to patients in the double-blind efficacy phase were placebo. Mode of administration: nasal spray. Bulk batch number: 10296657.

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 puff of IMP (Investigational Medicinal Product, i.e. NAF or placebo) on an 11-point numerical rating scale at 0, 10, 20, 40 and 60 minutes for each episode (0 reflects no pain, and 10 reflects the worst possible pain).

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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 were derived from the PI scores

Safety

Adverse events (AEs)

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 treated BTP episodes within patient was calculated by treatment (NAF or placebo) 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 NAF dose and the combined NAF doses.

The null hypothesis tested was that the average response to active treatment was the same as the response to placebo versus the alternative that they differed. This was tested using an F-test of the active versus placebo contrast for the treatment effect in the described model. The corresponding mixed linear model included the following fixed effects:

- Treatment (active, placebo) (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.

Each patient participated in the analysis with the available episodes. There was no imputation for missing episodes. If rescue medication was taken within the first 10 min, the PI scores were set to missing for all consecutive time points; i.e. the PID_{10} was missing as well. For patients who took rescue analgesic after 10 min and before 60 minutes, the last value prior to dropping out/taking rescue analgesic was carried forward (LOCF) and imputed for all time points after intake of rescue analgesic.

As supportive evidence to the primary analysis, treatment-by-centre interaction was added to the model as a fixed effect.

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The primary endpoint was analysed for the ITT and Per-protocol (PP) datasets with main emphasis on the ITT analysis. Estimated means by treatment (NAF and placebo) were presented with estimated difference between NAF and placebo with 95% confidence intervals and p-values. PID10 for each patient for each treatment (NAF or placebo) was calculated as an average score for the treated BTP episodes.

In addition to the analysis of PID10 scores, overall responder rates were computed by treatment. A positive response to treatment of a BTP episode was defined as PID10 > 2. The average response rates were calculated by computing the average response rate by treatment (NAF or placebo) within each patient and then averaging those averages across patients for placebo and NAF treatment, respectively.

The relationship between the NAF dose reached in titration phase and the dose of background pain opioid was evaluated. For this purpose, the background pain opioid dose at the end of the titration phase was standardised to morphine equivalent doses.

Safety data for test dose withdrawals, patients titrated but not treated with double-blind trial drug, and patients excluded from the 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 trial phase, System Organ Class, preferred term, and severity, and relationship to trial drug.

SUMMARY

Cut-off for the safety follow-up phase of this study was 13 Sept 2007. Safety will be monitored for an additional six months and the trial will be concluded. The complete safety data will be summarised in an amendment to this report. This trial 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 for all patients.

All 135 enrolled patients were included in the Safety Analysis set; 128 patients were randomised to double-blind treatment and 126 patients were treated in the efficacy phase and therefore included in the ITT analysis set. Twelve patients were excluded from the ITT analysis set leading to 114 patients in the PP analysis set. Of the 125 patients who completed the efficacy phase, 123 continued into the safety follow-up phase. At the safety cut-off date (4-months after last patient in), 31 patients were still ongoing; 104 patients discontinued from the trial:, 51 discontinued due to AEs (44 of these took place in the safety follow-up phase) These discontinuations included 44 patients who died.

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The ratio of male to females patients was one (63 of each). All patients for whom race data was recorded were Caucasian (96.8%; data collected for 122 patients). Mean age was 60.9 years and ranged from 33 to 83 years. Mean BMI was 24.1 kg/m^2 for all patients. Mean weight and height were 71.7 kg and 173.7 cm, respectively, for the male patients and 65.8 kg and 163.7 cm, respectively, for the females.

Titration Results:

127 patients completed titration and of those, 124 patients (93%) obtained a successful dose according to trial definitions. Eighteen patients were titrated to 50 µg, 58 patients to 100 µg and 51 to 200 µg. Since down-titration was not needed in any patients, the successful dose was achieved in relatively few titration steps. Furthermore, 123 patients continued into the safety follow-up phase indicating a high degree of satisfaction with the obtained dose. There seemed to be some correlation between the background pain opioid dose and the titrated dose. Patients with low level background pain opiod dose tended to achieve effective pain relief with a correspondingly lower NAF dose compared to the patients taking the higher levels of background pain opioids.

Efficacy Results:

The primary efficacy variable was PID_{10} after the first IMP puff. All NAF doses provided higher mean PID_{10} scores (ranging from 2.04 to 2.84), and therefore better pain relief, compared with placebo (1.20). For the comparison of all NAF doses combined, the LS Mean PID_{10} score was statistically significantly higher (1.46; Confidence Interval (CI): 1.25, 1.66) compared to placebo ($p<0.001$).

The mean responder rate at 10 min was 33.3%, 64.6%, and 54.5% for the 50, 100 and 200 µg NAF doses, respectively, and 55.7% for all NAF doses combined. The mean responder rate at 10 min was lowest for placebo (19.2%).

The mean GI scores at 60 min were higher with increasing doses: 1.73, 1.91, and 2.10 for the 50, 100, and 200 µg NAF doses, respectively (LS Mean score of 1.11 for all NAF doses combined and 0.87 for placebo; CI: 0.96, 1.25). The total NAF LS Mean GI score was significantly higher compared with placebo ($p<0.001$).

$SPID_{0-60}$ scores were significantly higher for all the NAF doses compared with placebo ($p<0.001$ for total NAF compared to placebo). Mean $SPID_{0-60}$ scores were 3.01, 3.74, 3.59 and 3.57 for the 50, 100, and 200 µg NAF doses and total NAF, respectively (LS Mean scores of 1.80 and 1.72 for total NAF and placebo, respectively; CI: 1.58, 2.02), indicating a better response for the higher NAF doses.

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Based on the efficacy results it was concluded that:

- Primary endpoint: The pooled NAF doses was statistically superior to placebo for PID_{10}; this effect was more pronounced for the 100 and 200 µg doses. This was also reflected by the responder rate. Results were similar for the ITT and PP analysis sets
- Secondary endpoints: The pooled NAF doses was significantly superior ro placebo for GI score compared with placebo. GI scores increased with the NAF dose. $SPID_{0-60}$ was significantly higher for the pooled NAF doses compared with placebo
- There seemed to be some correlation between the background pain opioid dose and the titrated successful NAF dose. The clearest correlation was observed for the patients ending on 50 µg in the titration phase.

Safety Results:

Overall, 84 patients (62.2%) had AEs during the trial: 24 patients (17.9%) had AEs allocated to the titration phase, 18 patients (14.3%) to the efficacy phase, and 70 patients (56.9%) to the safety follow-up phase. The most frequently occurring AE overall was progression of malignant neoplasm, reported in 54 patients (40.0%) across the three phases of the trial in this population of cancer patients. Malignant neoplasm progression and nausea were the only AEs reported by > 1% of patients in all three phases of the study: 5 patients (3.7%) in the titration phase, 2 patients (1.6%) in the efficacy phase, and 49 patients (39.8%) in the safety follow-up phase for malignant neoplasm; 3 patients (2.2%) in the titration phase, 4 patients (3.2%) in the efficacy phase, and 5 patients (4.1%) in the safety follow-up phase, for nausea. As expected, the majority of AEs reported in > 1% of patients occurred during the longest part of the study, the safety phase (151 of a total of 219 AEs). The largest proportion of patients experienced disease progression during this phase (39.8%) as well as other AEs associated with cancer and cancer treatment, such as constipation (4 patients, 3.3%), decubitus ulcer (4 patients, 3.3%), vomiting (2 patients, 1.6%), anaemia (2 patients, 1.6%), anxiety (2 patients, 1.6%) and depression (2 patients, 1.6%).

Approximately half of all patients experienced AEs that were mild (40 patients, 29.6% total) or moderate (27 patients, 20.0% total) in severity. Severe AEs were reported in all phases of the trial (57 patients, 42.2% total): 6 patients (4.5%) in the titration phase, 3 patients (2.4%) in the efficacy phase, and 51 patients (41.5%) in the safety follow-up phase. The most frequently reported severe AE was progression of malignant neoplasm: 3 patients (2.2%), 1 patient (0.8%) and 41 patients (33.3%) in the titration, efficacy and safety follow-up phases, respectively. Severe AEs reported during the safety follow-up phase only were generally related to advanced metastatic disease and were reported for one patient (0.8%) each.

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Overall, 14 patients (10.4%) experienced a total of 35 AEs that were considered related to treatment. The most frequently reported treatment-related AEs were vertigo (5 patients, 3.7% - all of the reported events) and nausea (related in 4 of 10 patients, 3.0%; that reported nausea). In the titration phase, vertigo in 4 patients (3.0%), and sedation, accidental overdose, and hot flush (each reported for one patient, 0.7%) were considered related to treatment. In the efficacy phase, nausea (3 patients, 2.4%), vertigo (2 patients, 1.6%), and dysguesia and dizziness (one patient each, 0.8%) were considered related to treatment. In the safety follow-up phase, nausea, constipation, vomiting, dysguesia, malignant neoplasm progression (in a patient for whom disease progression later in the trial was considered to be unrelated), and epistaxis were considered related to treatment in one patient each (0.8%). Dysguesia was the only severe AE that was considered possibly related to treatment (in one patient in the efficacy and safety phases).

A total of 57 patients (42.2%) reported 74 SAEs during this trial: 5 patients (3.7%) in the titration phase, 2 patients (1.6%) in the efficacy phase and 52 patients (42.3%) in the safety follow-up phase. The most frequently reported SAE was malignant neoplasm progression in 45 patients (33.3%). A total of 46 patients (34.1%) died during this trial: 3 patients (2.2%) in the titration phase, 1 patient (0.8%) in the efficacy phase and 42 patients (34.1%) in the safety follow-up phase. A total of 51 patients (37.8%) discontinued due to AEs (i.e. the primary reason for discontinuation on the CRF was designated to be an AE): six patients (4.5%) in the titration phase, one (0.8%) in the efficacy phase and 44 patients (35.2%) in the safety follow-up phase. This included 44 of the patients that died. Three patients discontinued due to AEs that were considered to be probably related to treatment: accidental overdose in one patient in the titration phase, vertigo in one patient in the titration phase, and dysgeusia in one patient in the safety phase.

CONCLUSION:

It can be concluded that NAF, at doses of 50, 100, and 200 µg, used in the treatment of BTP in cancer patients is superior to placebo. Almost all patients achieved a successful dose in the titration phase. There seemed to be some correlation between the background pain opioid dose and the titrated successful NAF dose. All doses were shown to be safe, well tolerated, and clinically relevant.

Date: 7 November 2007

Written by: Marianne Henriksen, MSc, PhD, Co-ordinating Trial Manager

1 Title Page

Title: A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 µg with an open long-term safety follow-up in cancer patients with breakthrough pain

Trial ID: FT-018-IM

Sponsor: Nycomed
Langebjerg 1, DK-4000 Roskilde
Denmark

Trial phase: Therapeutic confirmatory (Phase III)

EudraCT No.: 2005-002348-24

Name of Test Drug / Investigational Drug: Instanyl® (intranasal fentanyl spray; INFS)

Indication studied: Breakthrough pain in cancer patients

Date of Report: 10 November 2010
Version no.: 1.2

Date of trial initiation: 13 June 2006 (first subject, first visit)
Date of trial completion: 20 March 2008 (last subject, last visit)

This trial was conducted in accordance with Good Clinical Practice (GCP).

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For signatures see separate page

2 Synopsis

Title of the trial: A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 µg with an open long-term safety follow-up in cancer patients with breakthrough pain

Investigators and Investigational Sites: 35 centres were initiated; a total of 23 investigators enrolleded patients in the trial (Austria, Germany, Denmark, France and Poland). Subjects enrolled at one site in Germany (Site 51) are excluded from all analyses due to trial misconduct.

Coordinating investigator: Thomas Nolte, MD; Wiesbaden, Germany

Publication (reference): Kress et al, 2009

Studied period: 13 June 2006 to 20 March 2008

Clinical phase: Therapeutic confirmatory (Phase III)

Objectives: To confirm the efficacy of intranasal fentanyl spray (INFS) titrated to doses of 50, 100 and 200 µg for treatment of breakthrough pain (BTP) in cancer patients, and establish the long-term safety of treatment with INFS, and to explore the relationship between the dose of background pain opioid treatment and the titrated INFS dose.

Methodology: Randomised, double-blind, placebo-controlled, cross-over multi-centre confirmatory trial.

The trial consisted of 3 phases. In Phase 1, patients were titrated to an effective dose via open-label step-wise titration. Initial dose was 50 µg, and if needed according to efficacy and adverse reactions, the patient could step-wise continue to titrate upwards to 100 µg and 200 µg. An effective dose was reached when three of four BTP episodes had been treated successfully with one or two puffs of INFS. Patients who completed a successful titration then entered a double-blind efficacy phase (Phase 2) in which they received the effective INFS dose reached in Phase 1 and placebo for treatment of eight BTP episodes (six INFS and two placebo in randomised order). Patients continued in a safety follow-up phase

(Phase 3).

Subsequently patients were offered INFS on a named patient treatment. In countries where named patient use was not acceptable, INFS was offered in an extension phase.

No. of patients (total and for each phase) planned and analyzed: With a planned number of a minimum of 100 randomised patients, 120 patients were enrolled. All 120 enrolled patients were included in the safety analysis set; 113 patients were randomised to double-blind treatment and 111 patients were treated in the efficacy phase and therefore included in the intent-to-treat (ITT) analysis set.

Diagnosis and main criteria for inclusion: adult opioid tolerant in/out patient with cancer (use of stable, chronic opioid treatment for background pain). Minimum of three BTP episodes per week and maximum four per day. Life expectancy of at least three months. Patients were recruited from participants in previous trials using INFS.

Test product, dose, mode of administration, batch no.: 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/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. Bulk batch numbers: 10277256, 10277068 and 10277070 for 50, 100 and 200 µg INFS, respectively.

Reference product, dose, mode of administration, batch no.: 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 supplied to patients in the double-blind efficacy phase were placebo. Mode of administration: nasal spray. Bulk batch number: 10296657.

Duration of treatment: Titration and efficacy phases were expected to last up to 3 weeks each, followed by a safety follow-up for 10 months after the last patient was included.

Criteria for evaluation: The primary efficacy endpoint was pain intensity (PI) difference at 10 minutes (PID_{10}) after administration of first puff of IMP (Investigational Medicinal Product,

i.e. INFS or placebo). For each episode the pain intensity was assessed on an 11-point numerical rating scale at 0, 10, 20, 40 and 60 minutes after first puff of IMP (0 reflects no pain, and 10 reflects the worst possible pain). This assessment was based on the patient's evaluation as recorded in their diary. Secondary efficacy endpoints were the sum of PID in the time interval 0 – 60 minutes ($SPID_{0-60}$) and the general impression (GI) score, using a 5-point categorical verbal rating scale (VRS) at 60 minutes postdose. Safety was analyzed via the monitoring of adverse events (AEs).

Statistical methods: PID_{10} was calculated by subtracting the PI at 10 minutes from the PI recorded immediately before treatment. Reversal of the scale was applied so that high values indicated a positive result. The variation in PID_{10} between treated BTP episodes within patient was calculated by treatment (INFS or placebo) 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 PID_{10}, SD and CV were tabulated by INFS dose and the combined INFS doses. The null hypothesis tested was that the average response to active treatment was the same as the response to placebo versus the alternative that they differed. This was tested using an F-test of the active versus placebo contrast for the treatment effect in the described model.

The primary endpoint was analysed for the ITT and Per-protocol (PP) datasets with main emphasis on the ITT analysis. Estimated means by treatment (INFS and placebo) were presented with estimated difference between INFS and placebo with 95% confidence intervals (CIs) and p-values. PID_{10} for each patient for each treatment (INFS or placebo) was calculated as an average score for the treated BTP episodes.

Overall responder rates were computed by treatment. A positive response to treatment of a BTP episode was defined as $PID_{10} > 2$. The average response rates were calculated by computing the average response rate by treatment (INFS or placebo) within each patient and then averaging those averages across patients for placebo and INFS treatment, respectively.

The relationship between the INFS dose reached in titration phase and the dose of background pain opioid was evaluated. For this purpose, the background pain opioid dose at the end of the titration phase was standardised to morphine equivalent doses.

SUMMARY – CONCLUSIONS

Demography and baseline characteristics: In the ITT analysis set, there were 56 males and 55 females. Mean age was 60.6 years and ranged from 35 to 79 years. Mean body mass index (BMI) was 24.0 kg/m^2 (range 15.4-50.2). Mean weight was 70.3 kg for the male patients (range 48.0-106.0), and 65.3 kg (range 40.0-130.0) for the females. Mean height was 172.7 cm for the male patients (range 158-192), and 163.2 cm (range 150-178) for the females. All patients for whom race was reported were Caucasian (data collected for 107 patients, 96.4%).

Titration Results: 112 patients completed titration and of those, 108 patients (96%) obtained an effective dose according to trial definitions. Seventeen patients were titrated to 50 µg, 51 patients to 100 µg and 44 patients to 200 µg. Since down-titration was not needed in any patients, the effective dose was achieved in relatively few titration steps. Furthermore, all 108 patients continued into the safety follow-up phase indicating a high degree of satisfaction with the obtained dose.

Efficacy Results: The pooled INFS doses were statistically superior to placebo for PID_{10}; this effect was more pronounced for the 100 and 200 µg doses. This was also reflected by the responder rate. Results were similar for the ITT and PP analysis sets. The pooled INFS doses were significantly superior to placebo for GI score compared with placebo. GI scores increased with the INFS dose. $SPID_{0-60}$ was significantly higher for the pooled INFS doses compared with placebo. Data may suggest some correlation between the background pain opioid dose and the titrated effective INFS dose. Patients with low level background opioid pain treatment achieved effective pain relief with a correspondingly lower INFS dose compared with the patients taking the higher levels of background pain opioids. The clearest correlation was observed for the patients ending on 50 µg in the titration phase.

Safety Results: Overall, 99 patients (82.5%) had AEs during the trial: 38 patients (31.9%) had AEs allocated to the titration phase, 22 patients (19.8%) to the efficacy phase, and 83 patients (76.9%) to the safety follow-up phase. The majority of patients experienced AEs that were not considered related to treatment. A total of 47 patients (39.2%) died during this trial: 2 patients (1.7%) in the titration phase, 1 patient (0.9%) in the efficacy phase and 44 patients (40.7%) in the safety follow-up phase. None of the reported deaths were considered related

to treatment. A total of 57 patients (47.5%) discontinued due to AEs (i.e. the primary reason for discontinuation on the CRF was designated to be an AE). Three patients discontinued due to AEs that were considered to be probably related to treatment: accidental overdose in one patient in the titration phase, vertigo in one patient in the titration phase, and dysgeusia in one patient in the safety phase. The most frequently occurring AE overall was progression of malignant neoplasm, reported in 62 patients (51.7%) across the three phases of the trial in this population of cancer patients. A few patients reported more than one progression of malignant neoplasm in different phases: 9 patients (7.6%) in the titration phase, 4 patients (3.6%) in the efficacy phase, and 55 patients (50.9%) in the safety follow-up phase.

Conclusions: It can be concluded that INFS used in the treatment of BTP in cancer patients at doses of 50, 100, and 200 µg, is superior to placebo. Almost all patients achieved an effective dose in the titration phase. Data may indicate some correlation between the background pain opioid dose and the titrated effective INFS dose. All doses were shown to be safe, well tolerated, and clinically effective.

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4 List of Abbreviations and Definitions of Terms

AE:	Adverse Event
AUC:	Area Under Curve
BTP:	Breakthrough Pain
CA:	Competent Authority
CI:	Confidence Interval
CHMP:	Committee for Medicinal Products for Human Use (formerly CPMP (Committee for Proprietary Medicinal Products)
CRF:	Case Report Form
CRO:	Clinical Research Organisation
CV:	Coefficient of Variation
DCF:	Data Clarification Form
EMA	European Medicines Agency (formerly EMEA, European Medicines Evaluation Agency)
EOT	End of Trial
EWP:	Efficacy Working Party
GCP:	Good Clinical Practice
GI:	General Impression
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety (formerly CPV, Centrakl Pharmacovigilance)
IEC:	Independent Ethics Committee
IMP:	Investigational Medical Product
INFS	Intranasal fentanyl spray (also Instanyl®; “NAF” in tables and listings)
ITT:	Intent-To-Treat (analysis set)
i.v.:	Intravenous
LOCF:	Last Observation Carried Forward
MAOI:	Monoamine Oxidase Inhibitor
MedDRA:	Medical Dictionary for Regulatory Activities
NRS:	Numerical Rating Scale
OTFC:	Oral transmucosal fentanyl citrate
PI:	Pain Intensity
PID:	Pain Intensity Difference

PID_{10}:	Pain Intensity Difference at 10 min
PP:	Per-Protocol (analysis set)
PT:	Preferred Term
QA:	Quality Assurance
SAE:	Serious Adverse Event
SD:	Standard Deviation
SE:	Standard Error
SOC:	System Organ Class
SOP:	Standard Operational Procedure
SPID:	Sum of the Pain Intensity Difference
$SPID_{0-60}$:	Sum of the Pain Intensity Differences over the time interval 0-60 min
VRS:	Verbal Rating Scale

5 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The trial was reviewed by relevant Independent Ethics Committees (IECs). A list of the IECs that reviewed and approved the clinical trial protocol and amendments is provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Trial

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and its most recent amendment (World Medical Association, 2000). The trial was designed having considered the Committee for Medicinal Products for Human Use (CHMP; previously the Committee for Proprietary Medicinal Products Efficacy Working Party; (CPMP/EWP/612/00, 2002). Conduct of the trial was in accordance with the International Conference on Harmonisation (ICH) Technical Requirements for the Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guidelines for Good Clinical Practice (GCP) and any applicable regulations for protection of personal data.

5.3 Subject Information and Consent

The patients were informed by the Investigator of the risks and benefits of the trial and were advised that they could withdraw at any time for any reason. Written consent was obtained from the patient prior to any trial-related activities and archived by the Investigator.

The Master Patient Information Sheet and the Master Informed Consent Form used in the trial is presented in Appendix 16.1.3.

6 Investigators and Trial Administrative Structure

Function	Name	Affiliation
Sponsor		Nycomed P.O. Box 88, Langebjerg 1, DK-4000 Roskilde
Medical Responsible (at time of current reporting)	Lars Popper	Nycomed Medical Scientific Strategy Dept., Nycomed.
Medical Responsible (during conduct of the trial)	Lars Popper	Nycomed Medical Scientific Strategy Dept., Nycomed
Co-ordinating Trial Manager (at time of current reporting)	Lene Hartmann	Clinical Trial Operations Dept., Nycomed.
Co-ordinating Trial Manager (during conduct of the trial)	Troels Ravn Bæhrentsen	Clinical Trial Operations Dept., Nycomed.
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7 Introduction

Patients with cancer often suffer from more or less constant background pain. Furthermore, they often also suffer from pain that flares up and breaks through their background level of pain treatment. Such flares of pain are often referred to as episodes of BTP. These can be incapacitating since the intensity of pain may be high with a very rapid increase and an unpredictable occurrence. BTP is generally rapid in onset (pain peak within minutes), moderate to severe in intensity and relatively short in duration (Patt et al, 1998; Mercadante et al, 2002.; Portenoy and Hagen, 1990). Conventional non-invasive opioid therapy will often fall short in the treatment of BTP since it does not match the rapid onset and increase in pain intensity (PI) or the limited duration. Conventional therapy, such as oral morphines, has a later onset of pain relief and most often overshoots the duration of the BTP episode by several hours (Collins et al, 1998). Currently, controlled-release oral morphine is the standard therapy for moderate to severe persistent pain, whereas immediate-release oral morphine, oxycodone or hydromorphone are most commonly used for BTP. Oral transmucosal fentanyl citrate (OTFC); Actiq), was the only approved therapies indicated for BTP in Europe at the time of this trial. The onset of action of immediate-release formulations of morphine is typically 30-40 minutes and peak effect typically occurs at 1-2 hours (Collins et al, 1998; Thompson, 1990). Considering the short time to peak, intensity and duration of a typical BTP episode as described above, these characteristics may not be optimal for many patients with BTP.

The nasal route of administration of fentanyl gives a fast onset of action and a relatively short duration of effect, which may be ascribed to its lipophilic properties and the fact that it passes the blood-brain barrier very quickly. Furthermore, intranasal fentanyl spray (INFS) by-passes the oral/gastrointestinal route and is therefore especially convenient for patients with nausea or vomiting, oral mucositis, dry mouth syndrome or impaired gastro-intestinal function, which are common symptoms and/or signs in cancer patients.

Two previous Nycomed trials (FT-001-IN and FT-016-IM) have shown the pharmacokinetics in dental pain patients (Christrup et al, 2008; Foster, 2008) and in cancer patients (Kaasa, 2010) and resulting dynamic effects (pain relief) of fentanyl given by the nasal route to be optimal for the treatment of acute pain compared to currently available alternatives. These effects were confirmed in a randomised non-titrated cross-over trial in which INFS doses of

50, 100, and 200 μg were shown to be superior to placebo for the treatment of BTP and the effect for all efficacy parameters increased with dose (Nycomed FT-017-IM; 2007).

In the present trial, the aim was to confirm the efficacy of INFS titrated to doses of 50, 100 or 200 μg for treatment of BTP in cancer patients tolerant to opioids, to establish the long-term safety of treatment with INFS and to explore the relationship between the dose of background pain opioid treatment and the titrated INFS dose. Safety data (until 4 months after randomisation of the last patient) and efficacy data were evaluated and summarised in a previous report. The trial continued for a further 6 months as a safety follow-up period (see also Section 9.1). The current report summarises the safety and efficacy data after completion of the entire 10 months following randomisation of the last patient.

This trial was conducted from 13 June May 2006 to 20 March 2008 and was included in the marketing authorization application for INFS (Instanyl®). Due to a suspicion of misconduct during a later trial (FT-019-IM), a for-cause audit was conducted at Site 51 in Germany, a site that also participated in the FT-018-IM trial. The European Medicines Agency (EMA) was notified regarding the suspected misconduct. The EMA initiated GCP inspections of the FT-018-IM trial in Germany and Poland (May through July 2008). Subsequently, Nycomed had all of the trial sites re-monitored by a third party (PPD) from 11 September 2008 to 9 October 2008. This resulted in a separate re-monitoring report, submitted as part of the marketing authorisation application. Details of the re-monitoring plan are provided in Appendix 16.1.1 and Section 9.6.4.

This current version includes updated tables, listings and graphs as well as adhering to an updated Nycomed Clinical Trial Report template. See more details in Section 9.6.5.

8 Trial Objectives

Primary objectives

- To confirm the efficacy of INFS titrated to doses 50, 100 or 200 μg for treatment of BTP in cancer patients
- To establish the long-term safety of treatment with INFS

Secondary objective

- To explore the relationship between the dose of background pain opioid treatment and the titrated INFS dose.

9 Investigational Plan

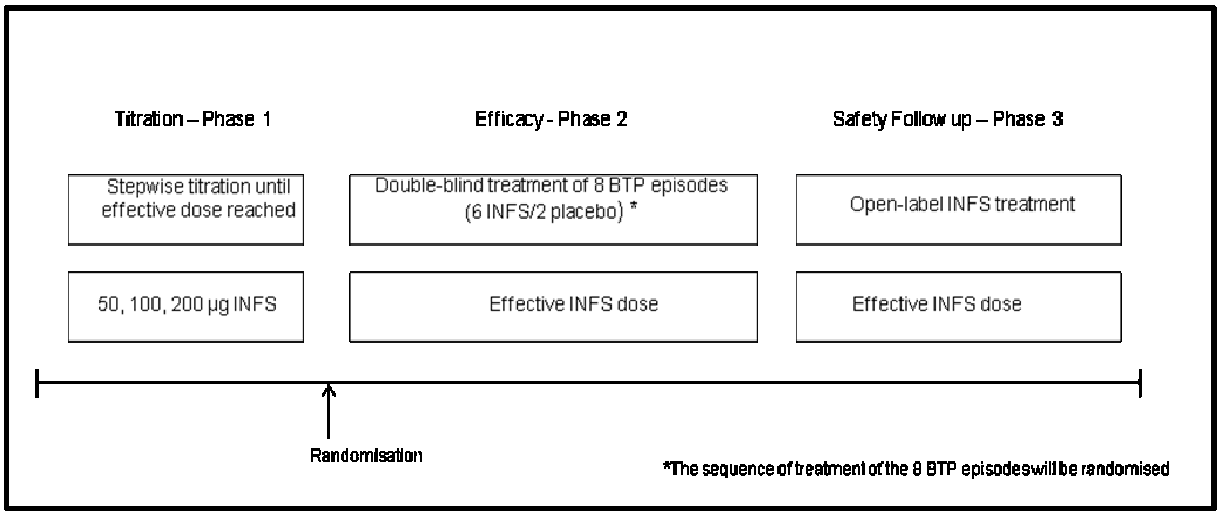
9.1 Overall Trial Design and Plan Description

This was a randomised, double-blind, placebo-controlled, cross-over multi-centre trial to demonstrate the efficacy and safety of titrated doses of INFS in the treatment of BTP in cancer patients with an open follow-up safety period. The trial was performed in pain centres, anaesthesiology wards, palliative care units and oncology clinics in patients that had received at least one dose in one of the earlier trials FT-016-IM or FT-017-IM.

The trial was conducted in accordance with the guideline for treatment of nociceptive pain (CPMP/EWP/612/00, 2002), which recommends the use of placebo-controlled designs with appropriate use of rescue medication for trials not aiming to show superiority to any active comparator.

Trial design is presented in Figure 1. The first phase of the trial was a dose-finding titration phase (Phase 1), in which the effective INFS dose for each patient's BTP was to be established per a defined dose-adjustment algorithm (see Section 9.4.4). Once this dose was established, the patient entered the efficacy phase of the trial (Phase 2), in which the INFS dose identified in Phase 1 was used to treat 6 BTP episodes and placebo was used to treat 2 episodes in a double-blind randomised sequence. Pain Intensity (PI) and General Impression (GI) scores were assessed for each BTP episode. Following assessment of the double-blind treatment of the 8 BTP episodes, patients continued participation in the trial in a safety follow-up phase (Phase 3) during which they received open-label INFS treatment for BTP episodes. The trial was planned to last until 10 month after the last patient was included.

Figure 1 Trial design



Investigational Medical Product (IMP); i.e. INFS and placebo was to be administered as one puff in one nostril. If the first puff brought insufficient pain relief, a second puff was allowed 10 minutes after the first puff. To ensure adequate pain treatment in those patients where placebo or the given INFS dose was not sufficient to treat their BTPs, patients were allowed to take rescue analgesics if needed after 20 min. after intake of first puff of IMP. Any analgesics (with the exception of INFS) taken within 60 minutes of the first puff of IMP were classified as rescue medication; analgesics taken outside this window were to be classified as concomitant medication. The maximal dose was 2 x 200 µg INFS taken 10 minutes apart.

All BTP episodes, up to four per day, for which the patient had such strong pain that he/she judged it necessary to take analgesics, were to be treated with IMP throughout this trial.

After the safety follow-up phase (Phase 3), patients were offered INFS on a named patient treatment. In countries where named patient use was not acceptable, INFS was offered in a safety extension phase. Safety data from the extension phase is reported separately.

Background opioid treatment could be adjusted during any of the three phases of the trial. Mean background PI had to be controlled to a mild level defined as ≤ 4 on an 11-point numerical rating scale (NRS), see Section 9.3.1, inclusion criterion 6. Thus, If a patient experienced less than 3 BTP episodes per week or more than 4 per day (or if the

investigator for any other reason found it necessary), the background opioid treatment were to be adjusted and meanwhile the patient should pause the intake of IMP. If adjustment was required in Phase 1, the titration to the effective INFS dose was repeated. If adjustment of background pain opioid treatment was required in Phase 2, participation in this phase was stopped and the patient entered the open-label safety phase after repeating the dose titration.

9.2 Discussion of Trial Design, Including the Choice of Control Group

This was a double-blind, cross-over, randomised, placebo-controlled trial with an open safety follow-up period. The planned number of randomised patients was a minimum of 100 and a maximum of 200 (a sample size of 100 to 150 patients for the efficacy phase was considered sufficient to detect treatment effects.

The inclusion of placebo was considered acceptable from an ethical perspective in this trial as the positive effect of placebo is known to be particularly high in the treatment of pain (Sauro and Greenberg, 2005; Haour, 2005) and as rescue medication was allowed. In addition, only treatment of only two of the many episodes treated in the trial were with placebo.

A cross-over design was in this trial chosen for the patient to be their own control, and hereby minimize the impact of the high inter-patient variability,expected to be seen in the patients subjective description of their cancer breakthrough pain treatment. The trial population is terminally ill with a short life expectancy and is known to have a disease progression. The risk of spontaneous change in the disease is considered relatively limited as the study duration is expected to be two weeks or less.

9.3 Selection of Trial Population

Eligible patients were adult in- or out-patients with cancer, aged 18 years or more, who received at least one INFS dose in a previous Nycomed trial FT-016-IM or FT-017-IM. Patients had stable, chronic opioid treatment equivalent to 60-500 mg oral morphine/day or to transdermal fentanyl 25-200 μg/hour, which in general reduced the intensity of their background pain to a mild level (≤ 4 on an 11-point numerical rating scale (NRS)). Eligible patients also suffered episodes of BTP at least three times per week but no more than four

times per day – for the purpose of covering the majority of BTP patients, and still being able to recruit patients in an acceptable rate.

During the trial patients were able to continue their normal daily routine and activities.Concomitant chemotherapy and palliative radiotherapy were allowed, with the exception of facial radiotherapy, as this may cause damage to the epithelial cells of the nose and/or oral mucosa and thereby change uptake of fentanyl.

Although the risk of addiction in this population is minor, patients with a recent history of drug abuse as well as patients with impaired mental status, as judged by the investigator, were excluded.

Cancer patients with the need for BTP treatment have advanced disease, short life expectancy and severely impaired quality of life. As a result, the risk of suicide in this patient population is likely to be increased (Breitbart, 1987 and 1990). As INFS can potentially be used for suicide it was necessary to consider this risk. However, this population of patients already has access to narcotic drugs for treatment of their background pain and BTP and routinely handle drugs with potential for suicide. Furthermore, the maximum volume to avoid run-off into the pharynx by a single administration in one nostril in humans is 150 µl, which puts a limit to how large a volume of fentanyl can be retained and subsequently absorbed by the nasal mucosa (Dale et al, 2002). Thus, any excess of nasally administered fentanyl will be swallowed and/or leaked out of the nose if the patient continues to spray. Since the bioavailability of INFS through the gastrointestinal tract is low due to first pass hepatic metabolism, the risk of overdose is considered low

The selection of in-/exclusion criteria are justified by encircling the planned indication for anticipated regulatory approval of INFS, being BTP in cancer patients in stable chronic opioid treatment for background pain.

9.3.1 Inclusion Criteria

In order for a patient to participate in this trial,the following inclusion criteria had to be fulfilled (answers to all had to be YES).

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?
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 opioid? Note 1
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? Note 1
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 patient able to use intranasal drugs?

Note 1: 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.

11. Does the patient use adequate contraceptive precaution (contraceptive pill, implant or injection or intrauterine device) in the trial period?
12. Did the patient have a negative pregnancy test at the inclusion evaluation in studies FT-016-IM or FT-017-IM?

9.3.2 Exclusion Criteria

In order for the patient to participate in this trial, none of the following exclusion criteria were to have been fulfilled (the answers to all had be NO).

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 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 a 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 had any head injury, primary brain tumour, or other pathological condition which could significantly increase the risk of increased intracranial pressure or impaired consciousness?

14. Has the patient participated in any other trial with an investigational drug or device apart from participation in INFS trials FT-016-IM/FT-017-IM within 30 days prior to inclusion in this trial? (Original final protocol)

14.1 Has the patient concomitant participation in any other trial with an investigational drug or device apart from participation in INFS trials FT-016-IM/FT-017-IM within 30 days prior to inclusion in this trial? (Substantial protocol amendment 1)

15. Does the patient have pathological conditions of the nasal cavity as contraindication to intranasal fentanyl?

9.3.3 Removal of Patients from Therapy or Assessment

If any of the below criteria applied to the patient, the patient were to have been discontinued:

- If after up to four titration steps (all three doses and possibly one down-titration), Phase II was not reached, the patient was to have been discontinued from the trial. Furthermore if Phase 1 and 2 in total lasted more than 14 weeks the patient was also to be discontinued
- If a patient received facial radiotherapy (palliative radiotherapy was allowed)
- If despite adjustment of their background pain opioid medication, could not have the background pain stabilised

A patient who discontinued the trial prematurely was to have been called in for a last visit. Even if the patient was not able to attend, the End Of Trial (EOT) Form had to be completed and the Drug Accountability Form filled in. As a minimum, a 35-hour follow-up contact to collect AEs was to have been done. At the EOT visit, all IMPs and the patient diary must have been collected from the patient.

9.4 Treatments

9.4.1 Treatment Administered

The IMP (placebo, or INFS 50, 100 or 200 µg) had to be administered as one puff in one nostril, where one dose equals one puff of 100 µl. Treatment of a BTP episode with IMP could either be one or two doses with a minimum of 10 minutes apart, that is, if the patient had insufficient pain relief, an extra puff could be taken after 10 minutes, preferably in the other nostril.

If pain relief was still not sufficient at 20 minutes, the patient could take either their usual immediate-release opioid or any other rescue analgesic (if not administered nasally). Figure 2 provides an overview of treatment of a BTP episode in terms of IMP and rescue analgesics intake.

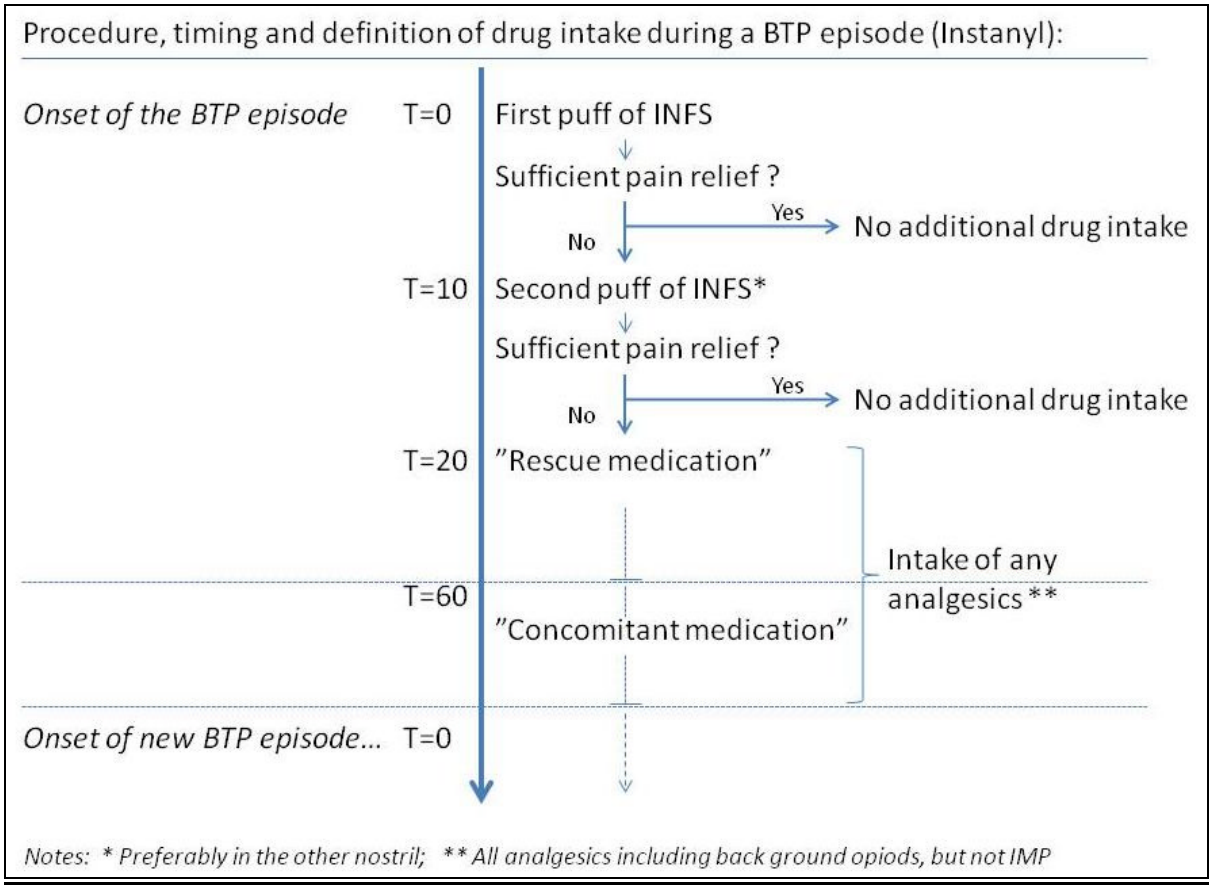


Figure 2 Overview of administration of IMP

Source: Adapted from the clinical trial protocol, see Appendix 16.1.1.

Patients were instructed to treat all BTP episodes (up to a maximum of four per day) with IMP. If the patient had more than four BTP episodes per day, background pain medication was to be adjusted (see Section 9.1).

9.4.2 Identity of Investigational Medicinal Product

All supplies were labelled with white labels, containing trial specific information, according to Annex 13, European guideline (XXXX). An example is presented in Appendix 16.1.6.

translation of the label text was performed as needed according to local requirements. The supply also had atrial reference code, which made an immediate identification of each package possible.

INFS was supplied in a brown glass bottle with a standard nasal spray pump and actuator, containing 6 ml corresponding to 40 doses. INFS was available as a phosphate buffered solution of fentanyl citrate in three concentrations: 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml fentanyl in multiple-dose spray bottles. The corresponding doses were 50, 100 and 200 μg fentanyl/puff.

Placebo for nasal use was supplied in glass bottles that were identical to INFS bottles, containing sodium citrate in a phosphate buffered solution.

At the first titration phase visit in Phase 1, the patient was allocated a titration kit, which included a total of 3 bottles containing either 50, 100 or 200 μg INFS per puff. The patient took home one bottle from each visit in the titration phase and exchanged this one with a new bottle at the following visit until an optimal dose was reached. For further description of the titration schedule see Section 9.4.5.

In the efficacy phase (Phase 2), each patient received a INFS efficacy kit, that contained eight sprays (numbered 1–8); six sprays contained the dose strength identified in Phase 1 and two contained placebo. The sequence was randomised, ensuring that of the two placebo treatments, one occurred in episodes 1-4 and one in episodes 5-8. The eight BTP episodes were to be treated with IMP in the order the spray bottles were numbered (1 to 8). Each spray bottle was packed in a box. For France, patients received only two bottles at a time (Section 9.8.1).

In Phase 3 the patient received INFS bottles with the required strength for approximately 1 month of use.

For each kit all sprays were packed together in an outer box with a tear-off label for the investigator to insert in the CRF upon dispensing of the IMP. Each individual spray contained a tear-off label for the patient to insert in the diary upon use (Phase 1 and 2).

All IMP had to be stored at 5-25°C, under secure, access controlled conditions approved for narcotic drugs; only trial staff were allowed to dispense IMP.

For batch numbers, expiry dates and release certificates, see Appendix 16.1.8.

9.4.3 Methods of Assigning Subjects to Treatment Groups

The IMP was to be administered only to patients included in the trial following the procedures set out in the clinical trial protocol, Appendix 16.1.1.

In Phase 1 and Phase 3 the patients were to be treated with INFS in open-label manner, whereas in Phase 2 the patients were assigned a double-blind randomised sequence of six INFS treatments and two placebo treatments.

At randomisation, the efficacy kit, (with INFS treatment of the appropriate dose strength), with the lowest randomisation number available at the centre was assigned to the patient. The investigator kept a Patient Identification Code List which connected patients and randomisation numbers.

Nycomed provided the randomisation list, that was stored at Clinical Trial Supply during the conduct of the trial and until release of the database. Nycomed provided also sealed code envelopes that could be used for unblinding in special situations (see Section 9.4.6) Randomisation list displaying randomisation number and treatment sequence are included in Appendix 16.1.7.

9.4.4 Selection of Doses in the Trial

The selected INFS dose range in this clinical trial was based on long-term experience of treatment of pain with fentanyl, on published literature with emphasis on the experience with OTFC (Christie et al, 1998; Portenoy et al, 1999; Streisand et al, 1991 and 1998) and on experience from a Nycomed pilot study and a Nycomed clinical trial with INFS (Nycomed FT-001-IN, 2001, FT-003-IN/FT-011-IN, 2007). The appropriate dose is one that relieves a patient's pain throughout its dosing interval without causing unmanageable adverse drug reactions. The dose range is expected to cover the clinical needs of most cancer patients. INFS 50 µg, 100 µg and 200 µg is considered equivalent to Actiq 200 µg, 400 µg and 800

µg, respectively. Published guidelines for the use of other short-acting supplemental opioids for BTP (Derby et al, 1998) have been derived from clinical experience but have never been formally studied. In an earlier standard relative potency trial in postoperative patients, the OTFC:intravenous morphine equivalence was determined to be approximately 1:10 (Lichtor et al, 1999). Based on this estimate, 800 µg OTFC would be equivalent to 8 mg intravenous morphine, which is equivalent to 24 mg oral morphine.

9.4.5 Selection and Timing of Dose for Each Subject

In Phase 1 the patients were titrated to an effective dose by a step-wise predefined algorithm. The algorithm is summarised in Figure 3Figure 3Algorithm for Dose Adjustment during Titration.

For each BTP episode treated with IMP, the patients had to assess a GI score for rating the efficacy of the treatment at 60 minutes after the first dose.

Figure 3 Algorithm for Dose Adjustment during Titration

Pain Relief	**Yes**		**No**	
Undesirable effects	**No**	**Yes**	**No**	**Yes**
Decision	Go to Efficacy Phase	One dose strength down. For 50 µg INFS/200 µg Actiq: discontinue	One dose strength up. For 200 µg INFS/1600 µg Actiq: discontinue	Discontinue

Pain Relief
Yes: Three of four BTP episodes with GI ≥ 2, no use of rescue analgesic
No: At least two episodes with GI < 2 and/or use of rescue analgesic

Undesirable effects
Yes: One or more undesirable effects
No: No severe undesirable effects

Source: Adapted from clinical trial protocol, Appendix 16.1.1

A successfully treated BTP episode was defined as:

- No need for rescue analgesics within 60 minutes after first intake of BTP.
- The patient had a score of ≥2 on the GI scale 60 minutes after first intake of IMP, equivalent to “good”, “very good” or “excellent”.
- No occurrence of severe intolerable effect such as pronounced hypoventilation, unacceptable sedation or drowsiness.

The initial dose of IMP in the titration phase (phase 1) was always 50 ug INFS. In order to establish the effective IMP during Phase 1, the patient was to have evaluated 3 out of 4 BTP episodes as being successfully treated with the specific IMP dose. If 2 episodes had been evaluated as unsuccesful, the patient had to proceed to the next dose. If in 3 of 4 episodes pain relief was obtained only after a second puff, the investigator was to consider increasing the dose, based on a balance between efficacy and safety.

In Phase 2 the patients were to have been treated with the effective INFS dose obtained in Phase 1, and in Phase 3 the same dose were to have been used, unless it was judged by the investigator that a different dose was required in accordance with the treatment recommendations given for titration.

Patients who needed to have their background medication adjusted in the trial period were paused until a new stable dose was established (please see Section 9.1).

Intranasal fentanyl was available on named-patient basis according to local requirements after Phase 3. In countries where named-patient use or compassionate use was not acceptable, INFS was provided in an extension phase (in which only safety information was collected).

9.4.6 Blinding

In the efficacy phase, Phase 2, the treatment sequence was double-blind and randomised ensuring that one placebo treatment occurred in episodes 1-4 and one in episodes 5-8. See Appendix 16.1.7 for sequences of INFS and placebo. Investigators, , patients and clinical research organisation (CRO) personnel responsible for monitoring, and analysis and interpretation of trial results thus remained unaware of the assigned treatments during conduct of the trial.

Three sets of sealed code envelopes were prepared by Nycomed. One set was to have been kept at the investigator site, one set at the monitoring CRO and one set at Nycomed International Drug Safety (IDS) during the entire trial period.

The investigator could break the code for a the patient in a medical emergency if knowledge of the treatment (INFS dose/placebo) could have influenced the further treatment of the patient. If the code was broken, the investigator was requested to document the reason, date and time and Nycomed were to have been contacted if possible prior to the code break. In all cases the monitor was to have been notified within 24 hours after the code was broken.

Nycomed IDS could perform unblinding if a SAE was required to be expedited or required for surveillance purposes.

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9.4.7 Prior and Concomitant Therapy

During the trial, patients received their stable fixed-schedule background pain opioid(s) and were allowed to take their usual analgesic for any type of pain. The relevant concomitant medication including background pain opioids and any other rescue analgesics, were recorded in the CRF. Administration of rescue analgesic for BTP in case of IMP treatment failure was recorded in the diary (see Section 9.4.1 for definition of “rescue” medications). Analgesics other than IMP taken outside the time interval of 0-60 minutes after first IMP administration for a BTP episode were regarded as concomitant medication.

Any change in concomitant medication or treatment procedures were to have been recorded at each visit or telephone contact.

Concomitant use of other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazine, tranquillisers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform (e.g. erythromycin, ketoconazole, and certain protease inhibitors) and alcoholic beverages could produce increased depressant effects. The concomitant use of such was therefore to be observed by investigator.

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

9.4.8 Treatment Compliance

Accountability of IMP was made by uniquely numbered tear-off labels on each bottle which the patient was to attach to the diary upon use in Phases 1 and 2 and which the investigator was to attach to the patient's CRF in Phase 3. In Phase 3 patients were instructed to use the entire content of the bottle. Dispensing and return of all of the IMP bottles for each patient were documented in the CRF by the investigator. The dose and number of bottles were recorded in the CRF. Returned bottles were inspected visually to see if a bottle was empty or not. If empty, this was correlated with patient data. Although this did not serve to document the actual amount of IMP used, any potential misuse of fentanyl could be identified. Patients were informed about this.

At the warehouses, there was a control to confirm that the correct number of IMP bottles were returned from the investigator sites. Overall accountability was performed at each warehouse after drug return from the investigators. Any discrepancies were documented as a deviation and followed up.

According to Substantial Protocol Amendment 1 (see Section 9.8.1) for the centres in France, the used bottles were to be disposed in a locked disposal box. In France therefore, the patient returned the locked disposal box with the eight used bottles from Phase 2. In Phase 3 the patient received one bottle at a time only (the used bottle was exchanged with a new bottle).

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

An overview of procedures and assessments is provided in the flow chart in Table 1.

Table 1 Flow Chart

	Phase 1 Dose titration		Phase 2 Efficacy	Phase 3 Safety follow-up		End of Trial
Activities and assessments	**Visit 1 Eligibility check**	**Dose titration visits**	**Visits**	**Visits (monthly)**	**Phone contacts (weekly)**	**End of Trial visit**
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demographic data	X					
Cancer related medical history	X					
Physical examination	X					
Past and concomitant illness	X					
Concomitant medication	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Check that dose of background opioid is adequate	(X)*	X	X	X	X	
Adjustment of background opioid/ re-titration and pausing patient	Any time when needed					
Estimated number of INFS-treated BTP episodes per day				X	X	X
Patient diary (instruction/evaluation)	X	X	X			
INFS hand-out/ drug accountability	X	X	X	X		X
End of Trial						X
Patient activities at home:						
INFS treatment	X	X	X	X	X	
Assessment of INFS treated BTP episodes in diary	X	X	X			

BTP = breakthrough pain; INFS = intranasal fentanyl spray
*As defined in the inclusion criteria
Source: Appendix 16.1.1

9.5.1.1 Measurements per trial phase and visits

9.5.1.1.1 Titration phase - Phase 1

Visit 1 – Eligibility check

During this visit the informed consent was obtained (before any other trial-related activities were performed) and the following were assessed/recorded: inclusion/exclusion criteria, demographic data, cancer-related medical history, physical examination, past and concomitant illnesses.

A patient diary was issued. The patient*s* were instructed to assess the scores on their own, but were allowed to receive help from relatives or staff personnel for recording in the diary.

A bottle of INFS (dose strength 50 ug/puff) was handed out to the patient to begin titration at home from the following day. For patients drug withdrawn from trials FT-016-IM or FT-017-IM due to undesirable effects of a INFS dose, this visit took place a minimum of 1 day after this dose. The first dose of the titration phase was in this case taken at the research facility and the patient was monitored by health-care staff for 1 hour.

Dose titration visits

During these visits AEs and changes in concomitant medications and concomitant procedures were recorded. Dose of back pain opioid was checked and adjusted as necessary. Patient diary was evaluated and drug accountability performed. After titration to the effective dose, patients entered Phase 2.

During Phase 1 the patients were to treat BTP episodes at home as well as assess the episodes (GI 60 min after first INFS puff for each episode in the diary).

9.5.1.1.2 Efficacy phase - Phase 2

Patients were to treat six BTP episodes with the effective dose reached in Phase 1 and treat two BTP episodes with placebo in a double-blind, randomised order. The episodes were to be assessed (PI and GI) using the diary..

Visit 1

During this visits AEs and changes in concomitant medications and concomitant procedures were recorded. Dose of back pain opioid was checked and adjusted as necessary. Patient diary from Phase 1 was evaluated and drug accountability performed. If dose of background pain opioid was adjusted the titration had to be repeated starting with the lowest dose without recording in the diary and in that case the titration bottles handed out in Phase 1 were to be re-used. Subsequently the patient could continue in the efficacy phase.

Last visit (also the first visit of Phase 3)

During this visit AEs and changes in concomitant medicationss and concomitant procedures were recorded. Dose of background pain opioid was checked and adjusted as necessary. Patient diary was evaluated and drug accountability performed. If dose of background pain opioid was adjusted the titration had to be repeated starting with the lowest dose without recording in the diary and in that case the titration bottles handed out in Phase 1 were to be re-used. In these cases the patient were to proceed to Phase 3 (Safety follow-up) after succesful titration.

9.5.1.1.3 Safety follow up phase - Phase 3

Visits were scheduled approximately every month or more frequently if needed. This would be the case if the dose of background pain opioid or INFS needed adjustment or if the investigator considered that AEs required follow-up. During the visits AEs and changes in concomitant medications and concomitant procedures were recorded, dose of background pain medication was adjusted if necessary (if so, re-titration was needed) and drug accountability performed. In addition, weekly phone contacts were performed, during which AEs and changes in concomitant medication and concomitant procedures were recorded and the dose of background pain opioid evaluated. During all visits/contacts the number of INFS treated episodes was assessed and recorded in the case report form (CRF). There was no diary in this phase. The EOT visit took place at the end of the trial or when a patient for any reason discontinued participation in the trial and the EOT page had to be filled in.The investigator was to ensure that INFS bottles were returned to the clinic in case of a patient's death (according to agreement with the monitor).

9.5.1.2 Efficacy Measurements

The following efficacy variables were assessed by the patient and recorded in the patient diary:

- The GI of efficacy in the treatment of BTP(s) was assessed 60 minutes after the first the INFS puff using a categorical 5-point VRS: 0=poor, 1=fair, 2=good, 3=very good; 4=excellent (Collins et al, 2001).
- PI was assessed using an 11-point NRS (0=no pain to 10=pain as bad as you can imagine). The derived variables, pain intensity difference (PID) and the sum of the pain intensity difference (SPID), were based on PI.

After randomisation for each IMP treated episode during Phase 2, the patients had to assess and record their PI before IMP treatment (t=0) and after 10, 20, 40 and 60 minutes after IMP administration. They also were to assess GI after 60 minutes of the first IMP puff (see also Figure 4).

Figure 4 Dose Administration and Assessment of BTP Episodes in Phase 2

Time (min)	0	10	20	40	60
Administration of IMP					
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

IMP = investigational medicinal product; X = mandatory activity or assessment; (X) = activity if applicable
*Assessments had to be recorded before administration of IMP and any rescue analgesics.
Source: Appendix 16.1.1

9.5.1.3 Safety Measurements

The objectives of the safety analyses were to assess the safety and tolerability of INFS when used for the treatment of BTP. The safety assessments were the incidence and nature of AEs occurring during the trial and any events that required follow-up.

9.5.1.3.1 Adverse Events

9.5.1.3.1.1 Adverse Event Definition, Classification and Categorisation

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which did not necessarily have a causal relationship with the treatment.

All AEs and serious AEs (SAEs) were defined according to GCP standards (as defined in the clinical trial protocol, Appendix 16.1.1).

Classification of the severity of AEs was assessed as follows:
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.

The causality of AEs was assessed as follows:

- 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.

The outcomes of the reported AEs were assessed as follows:

- 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

Adverse events were collected throughout the trial and categorised into different groups during statistical reporting (refer also to Figure 5):

- Treatment emergent AEs (TEAE): Adverse events with onset after first dose of IMP *in the titration phase* and until 2 days after last IMP dose.
- AEs with onset more than 2 days after last dose of IMP

Adverse events with onset after first dose of IMP in the titration phase and until 2 days after last dose of IMP was defined as treatment emergent in this trial.

If the patient completed the trial (EOT visit) and afterwards experienced an AE; the AE was considered treatment emergent if it occurred within 2 days after last dose of IMP; if it occurred more than 2 days after the last IMP dose, it was described as an AE with onset after the last dose of IMP

Figure 5 Adverse Event Categorisation

Insert figure

9.5.1.3.1.2 Adverse Event Recording and Follow up Procedures

At each contact between the site and the patient (visit or phone) the patient was to have been asked about AEs since the last contact. This was to have been done by open questions to the patient, e.g. “Have you experienced any medical problems since the last contact?” All AEs, either observed by the Investigator or reported by the patient, were to have been recorded by the Investigator on the applicable SAE/AE forms in the CRF.

During and after participation of a patient in the trial the investigator/institution were to have ensured that adequate medical care were provided to the patient for any AEs including clinically significant laboratory values related to the trial. The investigator/institution were to have informed the patient when medical care was needed for intercurrent illness(es) of which the investigator became aware.

All AE classified as serious or severe and possible/probable related to IMP were to have been followed by the investigator until the patients had recovered, recovered with sequelae or died and until all queries related to these AEs were resolved. All other AEs were to have been followed by the Investigator until the patient has recovered or until 35 hours after last

dose of trial drug, whichever occurred first, and until all AE related queries for the patient had been resolved.

9.5.1.3.2 Clinical Laboratory Variables

No clinical laboratory evaluations were performed as safety analyses during trial participation. However, if a subject was required to have a clinical laboratory analysis as part of the standard clinical management, any abnormal result was to have been evaluated to determine if it was an AE. Any clinical laboratory abnormality that suggested a disease and/or organ toxicity and was of a severity that required active management; i.e.change of dose, medical treatment, discontinuation of drug, more frequent follow-up or diagnostic investigation, was to have been considered, and been reported as an AE.

9.5.1.3.3 Other Safety Variables

No other safety variables were measured.

9.5.2 Appropriateness of Measurements

PI was assessed on an 11-point NRS. The validity of the NRS is well documented and it has been demonstrated to show positive and significant correlations with other measures of PI (Jensen et al, 1986; Downie et al, 1978; Kremer et al, 1981). The NRS was also selected because it is easy to use and suitable for elderly patients.

The GI of efficacy in the treatment of BTP was assessed 60 minutes after the first INFS puff. Previous studies have shown that when using this VRS, a single global question about the patient's overall impression of the effectiveness of a pain intervention can provide a reliable estimate of analgesic efficacy that is equivalent to results obtained by multiple questioning about pain relief (Collins et al, 2001).

9.5.3 Primary Efficacy Variable

The primary efficacy variable was the PI difference at 10 min (PID_{10}) after application of the first puff. The PID_{10} 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.

Responder rate was computed from the number of patients with a $PID_{10} > 2$ (see Section .

9.5.4 Drug Concentration Measurements

No measurements of drug concentration was performed in this trial.

9.6 Data Quality Assurance

The quality of data collected during the trial was maintained by means of monitoring, auditing and data quality control/quality assurance (QA) procedures.

9.6.1 Monitoring

The trial was monitored regularly by Nycomed/CRO staff by means of on-site visits, telephone calls and regular inspection of the CRFs in order to ensure that all aspects of the protocol, GCP as well as local regulations, were followed and to verify the following: patient enrolment; compliance with the protocol; the completeness and accuracy of data entered in the CRFs by verification against original source documents; compliance in use of IMP, drug accountability and recording of AEs.

9.6.2 Audits

The trial was audited on 5-6 July and 2-3 October 2006 by Nycomed International Clinical QA with regard to Project Management. In addition, a separate audit of six sites was performed by Nycomed International Clinical QA: Austria (site 02, audit performed on 6-8 September 2006), Denmark (site 21, audit performed on 26-27 February 2007), France (site 41, audit performed on 18-19 December 2006), Germany (site 51, audit performed on 22-24 November 2006), Norway (site 90, audit performed 25-26 June 2007), and Poland (site 72, audit performed on 30-31 October 2006). An internal audit was conducted in 2009. Audit certificates can be found in Appendix 16.1.8.

Due to suspicion of misconduct in a later trial (FT-019-IM), a for-cause audit was performed at the German site 51. As the site, apart from the FT-019-IM also had participated in this trial FT-018-IM, the EMA was notified about the suspicion of misconduct. This notification prompted EMA to conduct a GCP inspection of Site 51 and furthermore of a site (72) in Poland in relation to the FT-018-IM trial as part of the assessment of the Marketing Authorisation Application in EU in 2008.

Following the for-cause audit at Site 51, an internal decision in Nycomed was made to exclude this site from all analyses, summaries, and listings.

9.6.3 Data Handling

Data from the CRF were entered twice into the database and verified with computerised cross-checking routines. Any changes to the CRF after its collection from the site were sent to the principal investigator who indicated approval of the change(s) by signing the data clarification form (DCF). A copy of the signed DCF (and/or obvious error form, where appropriate) was archived with the CRF. Before clinical database lock, protocol deviations were identified and SAEs in the clinical database were reconciled with the SAE database.

9.6.4 Re-monitoring

As a consequence of findings during the GCP inspections, a decision was made by Nycomed to re-visit all sites to confirm that all AEs had been collected. Re-monitoring was conducted from 11 September 2008 to 9 October 2008 at all sites by a third party. Details of the re-monitoring procedures are provided in Appendix 16.1.1.

9.6.5 Re-opening of the Hardlocked Database and Re-reporting

During the remonitoring of the trial, several AEs that occurred 2 days after the last IMP dose were reported, but as the protocol required only the capture of AEs occurring up to 35 hours after the last IMP, the database locked after re-monitoring (locked 4 November 2008) only contained events with onset dates within 2 days of the last IMP.

In 2010 it was decided by Nycomed to re-open the database in order to include the AEs that had occurred beyond the original 35-hour window as some inconsistencies related to deletion of the AEs had been identified. In addition to the inclusion of the AEs with onset more than 2 days after the last IMP dose, a few other inconsistencies identified during an additional thoroughly review of the AEs and the SAE reconciliation of the complete dataset have been corrected. These corrections were all related to data recorded on AE forms or coding of AEs. The database was re-opened on dd MM 2010 and relocked on 29 July 2010. In total, 6 AEs for XX patients were re-entered into the clinical database.

This version of the clinical trial report is based on tables, listings and graphs of the updated clinical trial database. Compared to the previous version of the clinical trial report some text sections have been clarified and the format has been adapted to a new Nycomed template

The analysis of the updated data set has not resulted in any new conclusions that would impact the earlier reported safety or efficacy profile of INFS.

For further descriptions of the amendment to the statistical analysis plan (SAP), see Section 9.8.3 and Appendix 16.1.9. Further details on the re-opening of the database are also included in Appendix 16.1.9.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

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

Pain Intensity (PI) was recorded on an 11-point NRS at 0, 10, 20, 40 and 60 min for each episode. For patients, who took rescue analgesic before 60 min, the last value prior to dropping out/taking rescue analgesic was to be carried forward (LOCF) and imputed for all time points after intake of rescue analgesic. Rescue analgesics included any analgesic taken between time=0 min and time=60 min as a supplement to the investigational product. A possible 2nd puff of INFS was allowed and was not considered rescue medication. Missing values were to be imputed within each episode.

Pain Intensity Difference (PID) was to be 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. $PID_t = PI_0 – PI_t$, where PI_t is the PI at time t.
Sum of Pain Intensity Difference (SPID) was to be 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 was denoted $SPID_{0-60}$. $SPID_{0-60}$ may be interpreted as the average improvement in PI over the 60 min.

In cases not covered by the above descriptions, missing data points were to be imputed with the last available non-missing value.
The efficacy analysis should focus on the results of the efficacy phase of the trial. Data from the titration phase was to be summarised by descriptive statistics including the distribution of patients on doses after titration.
The primary endpoint was defined as PID_{10}, the PID at 10 min after application of the first INFS puff. PID_{10} was to be analysed using a mixed linear model including the following fixed effects:

- •Treatment (active, placebo) (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 to 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.
The null hypothesis to be tested was that the average response to active treatment is the same as the response to placebo versus the alternative that they differ. This was to be tested using an F-test of the active versus placebo contrast for the treatment effect in the described model.

Each patient should participate in the analysis with the available episodes. No imputation for missing episodes was to be done.

As supportive evidence to the primary analysis treatment-by-centre interaction was to be added to the model as a fixed effect. This analysis would explore possible heterogeneity in treatment effect between centres and provide an estimate of average treatment effect in the case of heterogeneity. The primary endpoint was to be analysed for the ITT and PP datasets with main emphasis on the ITT analysis. Estimated means by treatment (active and placebo)

was to be presented with estimated difference between active and placebo with 95% confidence intervals and p-values.

The variation in PID_{10} between two episodes within patient was to be calculated by treatment expressed as SD and CV. The summary statistics (n, mean, median, SD, min, max) was to be tabulated by treatment.
In addition to the analysis of PID_{10} scores, average responder rates was to be computed by treatment. A positive response to treatment of a BTP episode was defined as $PID_{10} > 2$.
The average response rates was to be calculated by computing the average response rate by treatment (active or placebo) within each patient and then averaging those averages across all patients for placebo and active treatment respectively.

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

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

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

General Impression (GI)

GI was to be analysed as described for the primary endpoint but without covariate adjustment for baseline since no baseline value is available for GI. 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 treatment were to be summarised by descriptive statistics.

Supplementary exploratory analyses were considered for the efficacy endpoints.

The planned statistical analyses were expanded in the Statistical Analysis Plan dated 5 October 2007 (Appendix 16.1.9). Final database lock for the 4-month data took place on 15 October 2007; database lock for ‘all data’ took place on 8 May 2008 (with exclusion of patients from Site 51, see Section XX); database lock for after re-monitoring of safety data,

including AEs, concomitant medication, concomitant illness and concomitant procedures took place on 4 November 2008 (see Section 9.6.4).

In 2010, the database was opened to include a number of AEs that occurred more than two days after the last dose of IMP. The database was relocked on 29 July 2010 and the Statistical Analysis Plan Amendment 1 of 21 July 2010 was created to describe the handling of missing values and additional safety tables, listings and graphs, there was no amendments to efficacy analyses.

9.7.2 Determination of Sample Size

The sample size calculation is based on Farrar et al, 1998, who investigated transmucosal treatment of BTP in cancer patients. In Fig. 1 of Farrar et al, 1998, 95% confidence intervals are indicated for PID and are shown at time points 15, 30, 45 and 60 min. Using the result at 15 min, 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 seven active and three placebo treated episodes for 89 patients, the intra-subject standard deviation (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.

In this trial, the treatment contrast is between six active and two placebo treated episodes resulting in an SD of $1.71 \cdot \sqrt{1/6 + 1/2} = 1.40$.

Patients in this trial were recruited among patients who completed the FT-016-IM or FT-017-IM trial so the expected sample size was 100 to 150 patients. With six episodes treated with active doses and two treated with placebo and a hypothesis of no treatment effect, assuming a linear model for the analysis with a significance level of 5%, the following tables of power may be derived for mean PID_{10} differences around 0.5:

Table 2 Table of Estimated Power Based on Sample Size

Power		SD for treatment contrast		
Sample size	Mean PID_{10} difference	1.3	1.4	1.5
N=100	0.4	86%	80%	75%
	0.5	96%	94%	91%
	0.6	99%	98%	97%
N=150	0.4	96%	93%	90%
	0.5	99%	99%	98%
	0.6	99%	99%	99%

PID_{10} = pain intensity difference at 10 min; SD = standard deviation
Source: Appendix 16.1.1

As seen from these considerations, a sample size of 100 to 150 patients for the efficacy phase was considered sufficient to detect treatment effects of size 0.4 to 0.6. Excluding Site 51 leaves 111 patients in the ITT and 101 patients in PP, i.e. still within the planned number of patients. The observed intrasubject SD (around 1.4) was somewhat lower than assumed and therefore leaves the power above 90%.

9.8 Changes in the Conduct of the Trial or Planned Analyses

9.8.1 Amendments to the Protocol

A total of four substantial amendments and two non-substantial amendments were made to the protocol.

Substantial Amendments

Amendment 1 (for France only) dated 27 July 2006 introduced the following changes:

- For patients in France, each spray bottle (Phases 2 and 3) was to be packed in a child-resistant outer package. The used bottles were to be disposed in a locked disposal box
- After completion of Phase 2, the patient returned the locked disposal box containing the eight used bottles. In Phase 3, patients received one bottle at a time (the used bottle was exchanged for a new bottle)
- Allowed for additional patient contacts to be made by trial personnel in order to facilitate delivery of the bottles to patients as needed.

Amendment 1 (for all countries except France) dated 20 November 2006 introduced the following changes:

- Participation in cancer treatment trials was removed from exclusion criterion 14; i.e., participation in cancer treatment trials was not allowed. This was to allow evaluation of safety data related only to this INFS trial and not to unknown cancer treatment trials; please see exclusion criteria 14 (previous wording) and 14.1 (wording after new version).
- Progression of cancer was to be recorded as an AE. This change allowed data on cancer-related AEs to be recorded in order not to miss any information on AEs possibly related to the product. Patients who had already completed part of or all of the trial had AE data on progression of cancer collected retrospectively.

Amendment 2 (for France only) dated 20 November 2006 incorporated the same changes as substantial Amendment 1 for all countries.

Amendment 2 dated 26 February 2008 introduced the following changes:

- In countries where named patient use was not acceptable, INFS was to have been offered in an extension phase. In the extension phase, only safety information would be collected and reported. The reason for this amendment was that Nycomed had been approached by several investigators, who have declared that it was considered unethical not to provide treatment with INFS after completion of the trial. The changes had no impact on the trial, since the clinical trial report were to be prepared and provided to regulatory authorities as planned in the protocol.

Non-substantial Amendments

Amendment 1 (for all countries) dated 27 July 2006 announced a new Co-ordinating Trial Manager.

Amendment 2 (for all countries) dated 15 October 2007 announced a new Co-ordinating Trial Manager.

9.8.2 Remonitoring

All sites were re-monitored in 2008 (please see more details in Section 9.6.4 and re-monitoring plan in Appendix 16.1.1.

9.8.3 Amendments to the Statistical Analysis Plan

In 2010, the database was opened to include a number of adverse events that occurred 2 days or more after use of the last dose of IMP (see section 9.6.5). The planned statistical analyses of the data in the updated database were described in Amendment 1 to the Statistical Analysis Plan approved 21 July 2010. Only the safety results were affected, i.e. there were no changes in the efficacy data or the pre-specified statistical analyses of efficacy. More specifically the amendment contained descriptions of:

- The rerun of tables, listings and graphs
- The definition of a treatment emergent adverse event
- The handling and presentation of medical history reported on the AE form
- The handling and presentation of AEs leading to discontinuation from the trial and AEs leading to withdrawal of IMP
- Data handling rules

The Statistical Analysis Plan Amendment 1 is included in Appendix 16.1.9.

x

10 Trial Subjects

10.1 Disposition of Subjects

The trial was conducted in male and female cancer patients ≥ 18 years of age who experienced BTP episodes despite taking background opioid pain medication.

Patients and data from site 51 are excluded in all tables, listings and graphs, though presented specifically in Listings XXX and YYYY.

Summaries of the patient analysis sets and patient disposition are provided in Table 3, Table 4 and Figure 6. A total of 120 patients were included in the Safety Analysis set; 113 patients were randomised to the double-blind efficacy phase; 111 patients who entered the double-blind efficacy phase were treated with double-blind IMP and consequently included in the ITT analysis set and 101 patients were included in the PP analysis set.

Table 3 Patient Analysis Sets

Number of Patients	
Enrolled	120
Safety Analysis Set	120 (100.0%)
Randomised	113 (94.2%)
Intent-to-treat analysis set (ITT)	111 (92.5%)
Per-protocol analysis set (PP)	101 (84.2%)

Source: Table 14.1.02.1

The number of patients by centre is presented in Table 14.1.01.

One patient (no. 0202) entered the titration phase but was not titrated; this patient was assigned to the 200 μg dose for Phases 2 and 3. Therefore, 119 patients were in the titration phase. Of these, 112 patients completed the titration phase: seven patients discontinued (five due to AEs and two due to withdrawal of consent). Of the 112 patients who completed the titration phase plus patient 0202, 111 were treated with double-blind IMP in the double-blind efficacy phase; two patients discontinued without taking double-blind IMP(one due to drug withdrawn consent (no. 0152) and one due to AE (no. 4101)) (Section 12.3.1.3 and Listing 16.2.05.2). Of these 111 patients, 110 completed the efficacy phase; one patient (7219) discontinued due to AEs. Of the 110 patients who completed efficacy, 108 continued into the safety follow-up phase; two patients completed the efficacy phase but were discontinued from the trial due to drug withdrawn consent (no. 7003) and other reason (no. 5401), (see Listing 16.2.05.1). A total of 15 patients completed all three phases, the titration phase, the efficacy phase and 10 months of safety follow-up. A total of 105 patients discontinued: 57 due to AEs (see Section 12.3.1.3), 5 were drug withdrawn due to non-compliance, 38 withdrew consent and 5 withdrew for other reasons (Table 4).

Figure 6 Schematic of Patient Disposition

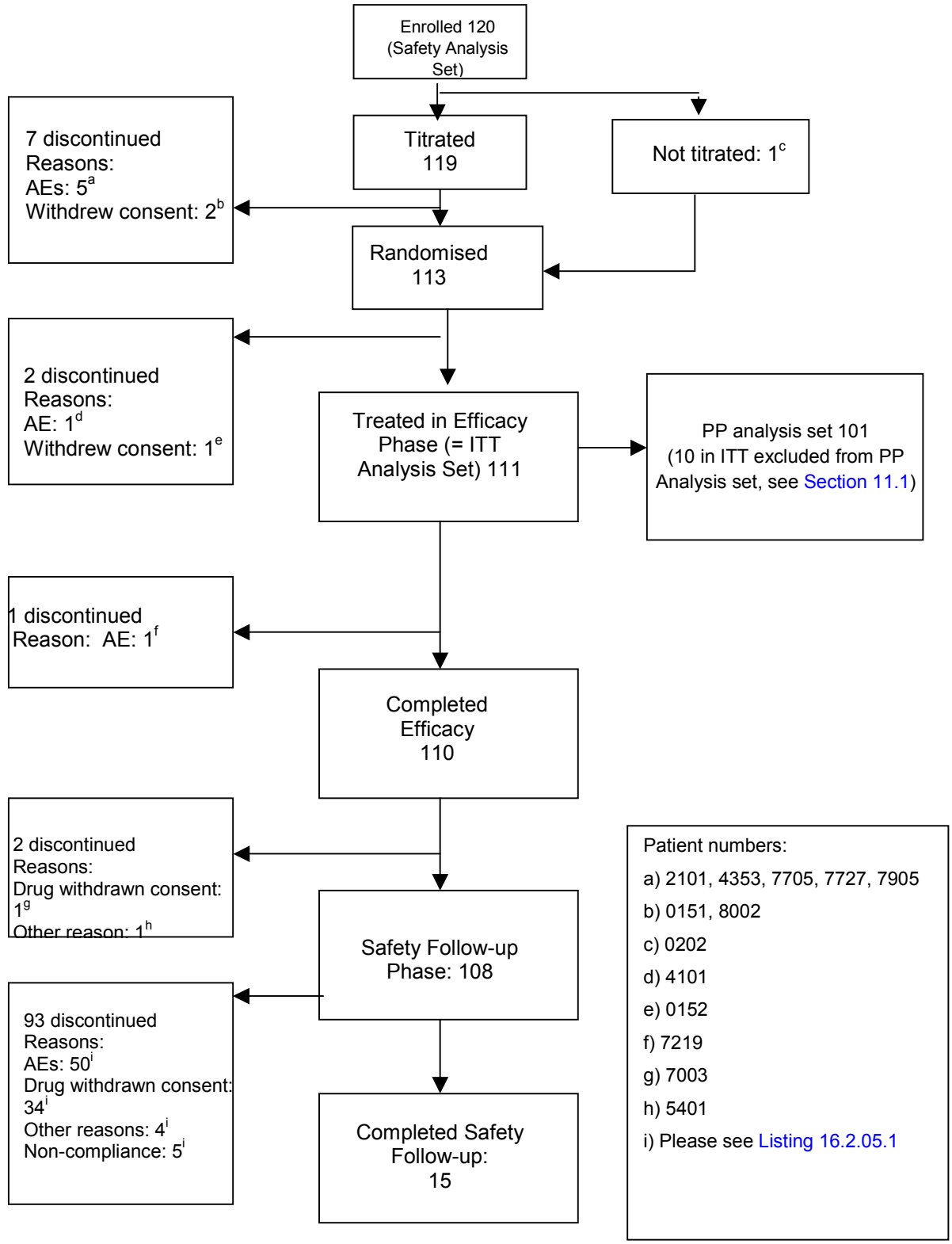


Table 4 Patient Disposition by Phase

	Titration Phase	Randomised Not Treated	Efficacy Phase	Efficacy Not Safety	Safety Follow-Up Phase	Total
Total	119 (100.0%)	2 (100.0%)	111 (100.0%)	2 (100.0%)	108 (100.0%)	120 (100.0%)
Completed	112 (94.1%)	0	110 (99.1%)	0	15 (13.9%)	15 (12.5%)
Discontinued from trial:	7 (5.9%)	2 (100.0%)	1 (0.9%)	2 (100.0%)	93 (86.1%)	105 (87.5%)
Adverse Events	5 (4.2%)	1 (50.0%)	1 (0.9%)	0	50 (46.3%)	57 (47.5%)
Non-compliance with protocol	0	0	0	0	5 (4.6%)	5 (4.2%)
Drug withdrawn consent	2 (1.7%)	1 (50.0%)	0	1 (50.0%)	34 (31.5%)	38 (31.7%)
Other	0	0	0	1 (50.0%)	4 (3.7%)	5 (4.2%)

Randomised Not Treated = Patients randomised but not treated with double-blind trial drug.
Efficacy Not Safety = Patients treated eight BTP episodes in efficacy phase, but safety follow-up kit was not dispensed.
Patient 0202 was not titrated; this patient received 200 µg INFS for phases 2 and 3 and was analysed accordingly.
Source: Table 14.1.02.2

10.2 Protocol Deviations

The following protocol violations occurred which led to the exclusion of 10 patients from the PP analysis set (Listing 16.2.06 and also see Section 11.1).

- Three patients had a violation of an inclusion criterion 5 (i.e. scheduled background pain opioid was >500 mg oral morphine/day)
- Four patients received double-blind INFS treatment that was not justified as having been an effective dose, per the protocol, in the titration phase
- One patient did not have at least one per-protocol BTP episode for each trial treatment (INFS and placebo)
- One patient treated all types of pain, not just BTPs
- One patient was given an incorrect INFS dose in the efficacy phase by mistake

Other protocol deviations that did not result in exclusion of patients from the PP analysis included missed visits/phone calls, using the bottles in the wrong order (these episodes were excluded from the PP analysis, see Section 11.1) or treating too many BTP episodes per day, background opioid doses not changed when > 4 BTP episodes were reported per day, minor variations in conduct of dose titration by the investigator, and minor errors made by patients in the BTP diaries. All protocol deviations are documented in Listings 16.2.07.1 and 16.2.07.2.

One patient (5503) exceeded the maximum 14 weeks for treatment in phases 1 and 2 but continued to phase 3.

Patient 4101 inadvertently received the FT-018-IM study drug kit while he was in Study FT-017-IM. In Study FT-018-IM, this patient was discontinued after randomization but before receiving double-blind drug.

Patient 5001 took 35 puffs/day?!!!

11 Efficacy Evaluation

Trial medication details are presented in Tables 14.1.07.1, 14.1.07.2, 14.1.07.3, 14.1.08.1, 14.1.08.2, 14.1.09.1, and 14.1.09.2. All efficacy results are presented in Tables 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.2.1, 14.2.2.2, 14.2.2.3 and 14.2.3.

11.1 Data Sets Analysed

Safety analysis set

The safety analysis set is defined as all patients that took at least 1 dose of IMP. A total of 120 patients are in the safety analysis set.

ITT analysis set (111 patients)

ITT analysis set defined as: All randomised patients that took at least one dose of double-blind IMP for treatment of BTP (efficacy phase).

ITT analysis set: As described in Section 10.1, the ITT analysis set included 111 of the 120 enrolled patients: seven patients discontinued from the titration phase and two patients were randomised but not treated with double-blind trial drug (Listing 16.2.05.2).

PP analysis set (101 patients)

PP analysis set defined as: All patients in the ITT analysis set excluding patients who met any of the following criteria:

- Patients who did not have at least one per-protocol episode for each treatment (INFS or placebo).
- violation of inclusion criteria 2, 4, 5, 6, 6, 8, or 9;
- violation of exclusion criteria 5, 6, 7, or 8;

- any other major violation obscuring the PI scoring in the efficacy phase. Either the patient or one or more episodes may have been excluded.

PP analysis set: Only the primary analyses were performed for the PP population since <10% of ITT patients (10 of 111 patients; 9.0%) were excluded from the PP population (see Section XX). Ten patients were excluded from the PP analysis set for the following reasons (Listing 16.2.06):

- Three patients (0101, 7212, and 7607) had a violation of a inclusion criterion 5 (i.e. scheduled background pain opioid was >500 mg oral morphine/day)
- Four patients (0202, 4352, 7002 (see also Section XX), and 7606) received double-blind INFS treatment that had not been justified as the protocol-defined effective dose in the titration phase
- One patient (5401) treated all types of pain, not just BTP episodes
- One patient (7219) did not have at least one per-protocol episode for each trial treatment (INFS and placebo)
- One patient (7402) was given the wrong INFS dose in the efficacy phase (investigator error)

Additionally, 10 BTP episodes in six patients were excluded from the PP analysis. Six of these 10 episodes were excluded in five patients because the patients did not use the double-blind sprays in the correct order (Listing 16.2.19): 7115 (one episode), 7201 (one episode), 7209 (one episode), 7211 (two episodes), and 7310 (one episode). The remaining four episodes were excluded in one patient (7720); background opioid pain medication was adjusted; however, double-blind treatment was not interrupted as required by the protocol. Therefore, these four episodes following opioid medication adjustment were excluded from the PP analysis set.

11.2 Demographic and other Baseline Characteristics

Demographic and baseline characteristics were recorded at screening. Data for individual patients for demography by centre can be found in Listing 16.2.08.1 (ITT) and 16.2.08.2 (for titration phase withdrawals and patients randomised but not treated with double-blind trial drug).

11.2.1 Demographic Data

In the ITT analysis set the numbers of male and female patients were approximately equal (56 males, 55 females) (Table 14.1.03). Mean age was 60.6 years and ranged from 35 to 79 years. Mean body mass index (BMI) was 24.0 kg/m^2 (range 15.4-50.2). Mean weight was 70.3 kg for the male patients (range 48.0-106.0), and 65.3 kg (range 40.0-130.0) for the females. Mean height was 172.7 cm for the male patients (range 158-192), and 163.2 cm (range 150-178) for the females. All patients for whom race was reported were Caucasian (data collected for 107 patients, 96.4%). Race for 5? patients were not reported.

The findings in physical examination results performed at baseline were consistent with a population of patients with ongoing cancer (Table 14.1.06). The majority of patients had abnormal findings (100 patients; 90.1%), with the most frequently reported abnormalities in the musculoskeletal system (reported for 53 patients, 47.7%, in the ITT analysis set). Results for all physical examinations are provided in Listing 16.2.12.1.

11.2.2 Medical History and Concomitant Diseases

The majority of patients (95 patients, 85.6%) reported a past or concomitant illness, including previous neoplasms (Table 14.1.05). The most frequently reported were vascular disorders in 54 patients (48.6%). The mean number of concomitant illnesses was 3.5 (median = 3). The maximum number of concomitant illnesses per patient was 16 (for one patient) and the minimum was one (19 patients).

Cancer related medical history by site of primary tumour for the ITT analysis set is summarised in Table 14.1.04. The most frequently reported primary tumour sites were breast (18 patients, 16.2%), lung respiratory system (17 patients, 15.3%), colon/rectal (14 patients, 12.6%); and female genital (12 patients, 10.8%) (Listing 16.2.09.1).

Due to reporting procedure during re-monitoring some medical histories were reported on adverse event forms (refer to 9.8). A listing of AEs with onset date prior to the date of the informed consent (Listing 16.2.29.1) describes pre-enrolment medical conditions that should be considered part of medical history.

For the patient XX, one AE reported as “related” was reported during patients participation in FT-017. This AE was transcribed to FT-018, and due to the fact that it started in FT-017 and has onset prior to the date of informed consent this event is included in Listing 16.2.29.1

11.2.3 Drug Therapy History and Concomitant Medications

A minority of patients (35 patients, 31.5%) had concomitant procedures during the trial (Table 14.1.11). Most frequently reported were surgical and medical procedures (33 patients, 29.7%), the most common being radiotherapy (6 patients, 5.4%), bladder catheterisation (4 patients, 3.6%), and enema, hospitalisation and massage (3 patients each, 2.7%).

The most frequently reported concomitant medications were ketoprofen (41 patients, 36.9%), omeprazole (36 patients, 32.4%), megestrol acetate (32 patients, 28.8%), lactulose (27 patients, 24.3%), dexamethasone (25 patients, 22.5%), and furosemide (29 patients, 26.1%) (Table 14.1.10). The majority of concomitant medications taken during this trial were related to treatment of the patient’s primary diagnosis as well as palliative treatments for sequelae of radiation or chemotherapy.

11.2.4 Background Pain Opioid Medication

A table of background pain opioid medications taken any time during the trial for the ITT analysis set is presented by medication class in Table 14.1.07.1. The most frequently reported were fentanyl (60 patients, 54.1%) and morphine (51 patients, 45.9%).

The mean standardised morphine equivalent dose of background opioid pain medication at the end of titration was 190.0 mg/d (Table 14.1.07.2). The majority of patients (75 patients, 67.6%) were in the ‘low’ dose category (≤ 180 mg/d); 20.7% were in the ‘medium’ dose category (> 180 - ≤ 360 mg/d), and 11.7% were in the ‘high’ dose category (> 360 mg/d). For a description of the relationship between the effective INFS dose reached in the titration phase and the patient’s background opioid medication see Section **Error! Reference source not found.**.

11.2.5 Rescue Medication

Rescue medications used during the titration and efficacy phases by medication class and PT are summarised in Table 14.1.08.2. The most frequently used rescue medication was

morphine (101 patients; 91.0%). Rescue medications during the safety follow-up phase are summarised under concomitant medications and discussed in Section 11.2.3.

A summary of treatment of eight BTP episodes with trial or rescue medication is presented in Table 14.1.09.2. The results show that generally rescue medication was taken after two puffs only. Following placebo, fewer episodes treated with two puffs did not require rescue medications (39.3%) compared to those that did require rescue medication (44.71%). For the combined INFS doses, the proportion of episodes treated with two puffs and no rescue medication (54.5%) was approximately four times the proportion of episodes treated with two puffs and rescue medication (14.2%).

The proportion of treated BTP episodes that required rescue medication in the efficacy phase is presented in Table 14.1.08.1 and Table 14.1.09.2. This proportion was lower after administration of any dose of INFS (15.7%, 14.5%, and 13.3% for the 50, 100, and 200 μg INFS dose groups, respectively; 14.2% for all INFS groups combined) compared with placebo (45.2%). The time interval at which rescue medication was most frequently used was ≥20,<40 min after administration of the first IMP puff. Two patients (7225 and 7226) required rescue medication following placebo treatment within the first 10 min after the first IMP puff (Table 14.1.08.1 and Listing 16.2.17.2.1). Within the time interval ≥10, <20 minutes, rescue medication was required in 38 episodes (17.4%) following placebo compared with 0.9% to 1.8% of episodes following treatment with the three INFS doses.

11.3 Measurements of Treatment Compliance

No measurements of body fluids in order to investigate treatment compliance were performed in this trial.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

Efficacy results are given for the ITT analysis set. Analyses of the PP population were conducted for the primary endpoint and those results were considered to be ‘qualitatively’ different from the ITT results. Consequently, only ITT results are shown in this section.

11.4.1.1 Primary Endpoint

11.4.1.1.1 Pain Intensity Difference at Ten Minutes

The primary efficacy variable was PID_{10} after the first IMP puff. All INFS doses provided higher raw mean PID_{10} scores (ranging from 2.00 to 2.74), and therefore better pain relief, compared with placebo (1.28). For the comparison of all INFS doses combined, the least squares mean (LS Mean) PID_{10} score was statistically significantly higher (1.26; $p<0.001$; Confidence Interval (CI): 1.03, 1.48) compared to placebo as summarised in Table 5.

Table 5 Summary of PID_{10} Results by INFS Dose – Efficacy Phase, ITT Analysis Set

Overall Pain Intensity Difference at 10 Minutes (PID_{10}), ITT Analysis Set	Placebo	Fentanyl 50 µg INFS	Fentanyl 100 µg INFS	Fentanyl 200 µg INFS	Total Fentanyl INFS
N	110	18	48	45	111
Mean	1.28	2.00	2.74	2.60	2.56
Standard Deviation	1.447	1.083	1.379	1.447	1.378
Median	1.0	1.5	3.0	2.7	2.8
Minimum	-1.0	0.5	-0.5	0.4	-0.5
Maximum	6.0	4.3	4.5	5.3	5.3
LS Mean	1.10				2.36
95% CI	(0.84, 1.36)				(2.16, 2.56)
P-value	<0.001				<0.001
LS Mean (vs placebo)					1.26
95% CI (vs placebo)					(1.03, 1.48)
P-value [1] (vs placebo)					<0.001

[1] The pairwise p-value is based on least squares means from mixed linear model with fixed effects for treatment, centre, average baseline pain intensity (PI) (over all treated break through pain (BTP) episodes for a patient), deviation of baseline PI for each treated BTP episode from average baseline PI, and random effect for patient.
$PID_{10} = PI_0 - PI_{10}$ for each episode; higher scores indicate better pain relief. Overall PID_{10} is calculated as the average score from the treated BTP episodes for each treatment (NF or placebo) within a patient.
ITT = intent-to-treat; INFS = intranasal fentanyl spray; LS Mean = least squares mean; CI = confidence interval; vs = versus
Source: Table 14.2.1.1

Similar results were seen for the PP analysis set (Table 14.2.1.2).

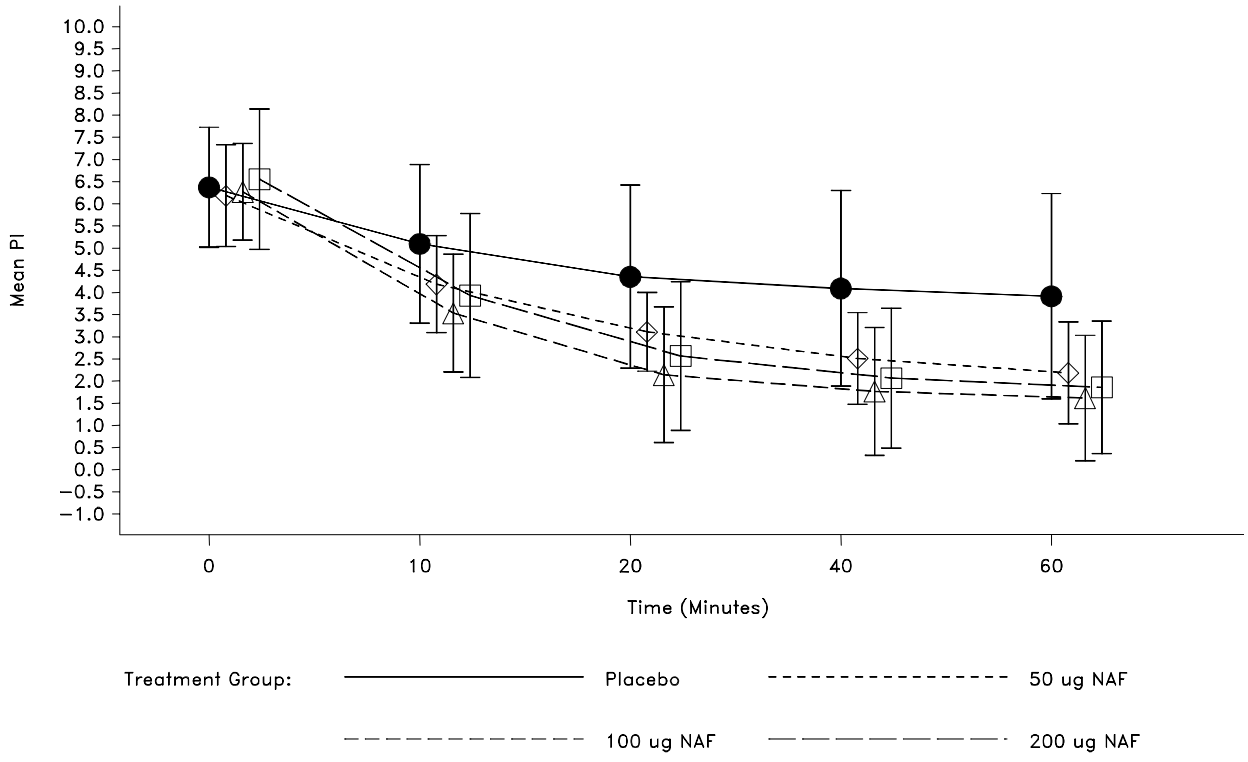
As an exploratory analysis, a centre-by-dose interaction was added to the model for the primary efficacy endpoint, PID_{10}, as a fixed effect. The analyses were run for the ITT and PP analysis sets. The interaction effect was statistically significant for both analyses and therefore, the dose response profiles were examined by centre (individual or pooled).

This examination revealed that all centres, except one, had a positive effect of active versus placebo. This single centre was a pool of four small centres, adding up to a total of 13

patients in the ITT analysis. 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 (Appendix 1.9).

A graphic representation of mean PI values at each time point by treatment dose is provided in Figure 7 which illustrates the higher decreases in PI scores with time for the INFS doses compared to placebo.

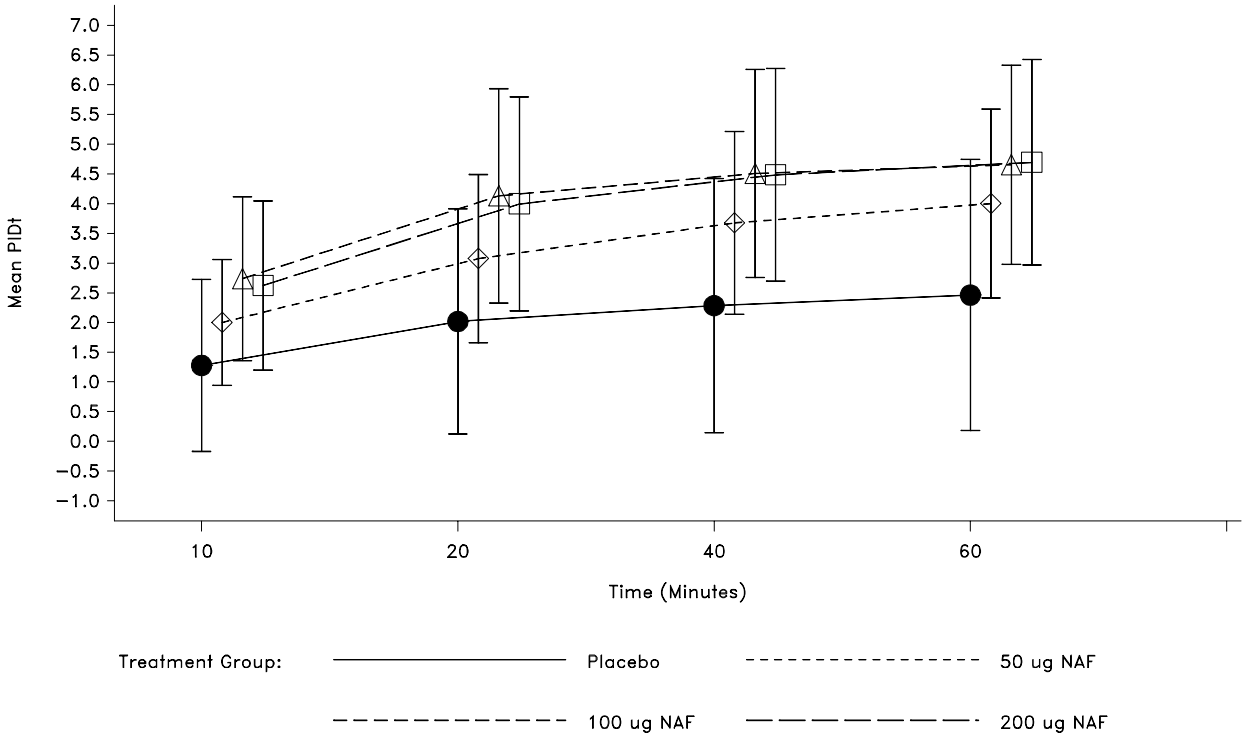
Figure 7 Mean Overall Pain Intensity by Treatment Dose and Time Point - Efficacy Phase, ITT Analysis Set



Source: Figure 14.2.2

A graphic representation of the mean PID over time by treatment dose is provided in Figure 8. The figure illustrates the larger mean PID values from 10 to 60 min postdose for the INFS doses compared with placebo.

Figure 8 Mean Overall Pain Intensity Difference by Treatment Dose and Time Point - Efficacy Phase, ITT Analysis Set



Bars indicate +/- one standard deviation

Source: Figure 14.2.3

A summary of INFS puffs for the treatment of eight BTP episodes is presented in Table 14.1.09.1. The results show that the majority of all episodes were treated with two puffs of IMP. The proportion of BTP episodes treated with two puffs was highest for placebo (84.0%) compared to all INFS doses (68.7% for all INFS doses combined).

The overall PI by time point and the PID by time point (0, 10, 20, 40 and 60 min from first IMP puff) are presented in Tables 14.2.2.2 and 14.2.2.3, respectively. The overall PID by timepoint is represented in Figure 8. The results show that all INFS doses achieved higher levels of PID at all timepoints compared with placebo.

11.4.1.2 Secondary Efficacy Endpoints

The secondary efficacy variables were the GI of efficacy in the treatment of BTP and the $SPID_{0-60}$ calculated for each episode as the AUC for PID over the 0 – 60 min interval divided by the length of this time interval, 60 min.

11.4.1.2.1 General Impression Score

The overall GI score at 60 min is presented in Table 14.2.3. The mean GI scores at 60 min were higher with increasing doses: 1.71, 1.80, and 2.00 for the 50, 100, and 200 μg INFS doses, respectively. Mean overall GI score for placebo was 0.94. For the comparison of all INFS doses combined, the LS Mean GI score was statistically significantly higher (0.93; CI: 0.77, 1.08; $p<0.001$) compared to placebo.

11.4.1.2.2 Overall Sum of the Pain Intensity Difference From 0 to 60 Minutes

The overall $SPID_{0-60}$ is presented in Table 14.2.2.1. The results show higher mean $SPID_{0-60}$ scores for all INFS doses compared with placebo. Mean $SPID_{0-60}$ scores were 3.05, 3.81, 3.66 and 3.63 for the 50, 100, and 200 μg INFS doses and total INFS, respectively , and 1.89 for placebo. For the comparison of all INFS doses combined , the LS Mean $SPID_{0-60}$ score was statistically significantly higher (1.7; CI:1.45, 1.94; $p<0.001$), compared with placebo.

11.4.1.2.3 Additional analyses

Additional statistical analysis was carried out on the PID_{10} scores to determine the response rate among patients. A responder was defined as having a $PID_{10} > 2$ for a given BTP episode. The average response rate was calculated by computing the average response rate by treatment (INFS or placebo) within each patient and the averaging those averages across all patients for placebo and active treatment, respectively. The responder rate for the ITT analysis set is presented in Table 6.

Table 6 Responder Rate at 10 Minutes – ITT Analysis Set

Responder Rate at 10 Minutes, ITT Analysis Set	Placebo	Fentanyl 50 µg INFS	Fentanyl 100 µg INFS	Fentanyl 200 µg INFS	Total Fentanyl INFS
N	110	18	48	45	111
Mean	20.91	31.48	60.42	48.95	51.08
Standard Deviation	34.122	31.772	38.535	37.383	38.108
Median	0.0	16.7	66.7	66.7	66.7
Minimum	0.0	0.0	0.0	0.0	0.0
Maximum	100.0	83.3	100.0	100.0	100.0

A responder for a treated break through pain (BTP) episode has pain intensity difference at 10 min (PID_{10}) >2 for that episode. Overall responder rate is defined as the percentage of BTP episodes with a positive response to treatment (INFS or placebo) within a patient. ITT= intent-to-treat; INFS = intranasal fentanyl spray
Source: Table 14.2.1.4

The responder rate was highest for 100 µg compared to the 200 µg and 50 µg INFS doses. The mean responder rate at 10 min was 31.5%, 60.4%, and 49.0% for the 50, 100 and 200 µg INFS doses, respectively, and 51.1% for total INFS. The mean responder rate at 10 min was lowest for placebo (20.9%).

11.4.2 Statistical and Analytical Issues

11.4.2.1 Adjustment for Covariates

As this was a crossover study, each patient received all treatments. Patient was a factor in the model, and comparisons of treatments were carried out within the patient. In addition, the analysis of the key efficacy parameters based on PI used the baseline pain intensity as a covariate, as well as adjusting for centre effects. The third efficacy parameter, GI score, adjusted only for the centre effects

Patient was included in the model 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.

As supportive evidence to the primary analysis, treatment-by-centre interaction was added to the model as a fixed effect. This analysis explored possible heterogeneity in treatment effect between centres and provided an estimate of average treatment effect in the case of heterogeneity.

The $SPID_{0-60}$ was analysed using the same model and method of presentation as described for the primary endpoint, i.e. including treatment, centre, average baseline PI and deviation of baseline PI for each episode from average baseline PI.

GI was analysed as described for the primary endpoint but without covariate adjustment for baseline PI in any way. Although GI was 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 and for the total INFS treatment were summarised by descriptive statistics.

11.4.2.2 Handling of Dropouts or Missing Data

Missing data were represented on patient listings as either a hyphen ("-") with a corresponding footnote ("- = missing") or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate. Missing descriptive statistics or p-values due to non-estimability were reported as "-". The following sections describe the handling of missing data for the individual efficacy variables.

Handling of missing data for patients that received at least one of eight IMP doses

Patients were included in the efficacy analyses with their available episodes. There was no imputation for missing episodes.

Handling of missing data for patients that took rescue medication

Patients that took rescue analgesic before 60 min and after 10 min had the last value of PI before taking rescue analgesic carried forward and imputed for all time points after administration of rescue analgesic. Rescue analgesics included any analgesic taken between time=0 min and time=60 min as a supplement to the IMP puff(s). Patients who took rescue analgesic before 10 min after having taken the first puff had their PI values from 10 min and onwards set to missing in order not to carry forward baseline values. Patients may have listed any and/or all pain medications in their diary as a 'rescue' medication even if it was taken beyond time=60 minutes; these would be included in the listing of rescue medications derived from the diaries, but only those reported within the 60-minute window were used for calculations of rescue medication use within BTP episode.

11.4.2.3 Interim Analyses and Data Monitoring

The protocol described that an interim analysis will be performed four months after the last patient had been included. All efficacy data as well as safety data collected up to four months after randomisation were included in this analysis. Efficacy data were only analysed once, and consequently the type I error rate was not affected by this. The trial continued for a further 6 months as a safety follow-up period. After completion of the entire 10 months following randomisation of the last patient the remaining safety data were analysed. The safety data were analysed by trial phase, i.e. not by treatment group or dose of fentanyl, and therefore the results of the analyses of the remaining safety data were not affected by the unblinding of the trial four months after the last patient had been included.

No data monitoring committee was established for this trial.

11.4.2.4 Multicentre Trials

The small centres were pooled for analysis purposes. The smallest pooled centre had at least 11 patients in the intent-to-treat (ITT) analysis set. Centres were pooled by country, if possible. The size of a pooled centre was not larger than the largest freestanding centre (Table 14.1.01). The pooling strategy was documented prior to unblinding of the treatment codes. The result of the pooling is summarised in Table 7.

Table 7 Summary of Pooled Centres

Pooled Centre No.	Country	Centre No.	Investigator	Number of ITT Patients	Number of Patients in the Pooled Centre
90	Austria	01	Hans Georg Kress	10	11
	Austria	02	Wilfried Ilias	1	
91	Germany	50	Thomas Flöter	2	12
	Germany	53	Thomas Nolte	3	
	Germany	54	Stefan Grond	1	
	Germany	55	Dorothea von der Laage	1	
	Germany	56	Andreas Meier-Hellmann	1	
	France	43	Danièle Lefebvre	3	
	France	46	Marie Cécile Douard	1	
92	Poland	70	Ewa Ebel	2	15
	Poland	71	Maciej Sopata	8	
	Poland	73	Andrzej Stachowiak	5	
93	Poland	74	Ewa Solska	2	13
	Poland	75	Wiesùawa Juraszek	4	
	Poland	76	Iwona Furman	5	
	Poland	78	Zbigniew Popow	2	

ITT = intent to treat
Source: Listing 16.2.03 and Table 14.1.1

Multiple Comparison/Multiplicity

There was only one primary endpoint. Only one comparison was performed, between INFS and placebo. No adjustments for multiple comparisons were necessary as the analysis in the PP analysis set was only supportive.

No correction of the test level was performed for secondary endpoints, as these were considered supportive.

11.4.2.5 Use of an "Efficacy Subset" of Subjects

The ITT analysis set was defined as all randomised patients that took at least one dose of double-blind IMP for treatment of BTP (efficacy phase); this included 111 of the 120 enrolled patients. The PP dataset was a subset of the ITT (see Section 11.1). Only the primary analyses were performed for the PP population since <10% of ITT patients (10 of 111 patients; 9.0%) were excluded from the PP population (see Section **Error! Reference source not found.**).

11.4.2.6 Active-Control Trials Intended to Show Equivalence

There was no active control used in this trial.

11.4.2.7 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response Data

Individual response data are provided in Appendix 16.2.

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

A total of 112 patients completed titration. The majority of patients were titrated to the 100 μg (51 patients, 45.5%) or 200 μg doses (44 patients, 39.3%). The remaining 17 patients were titrated to the 50 μg dose, as summarised in Table 14.3.2.

Six patients had maximum INFS doses that differed from the INFS dose reached in the titration phase: 7003 was titrated to 200 μg, then had a change in background pain opioid and was re-titrated to 50 μg (effective dose); 0101 was titrated to 200 μg by mistake, 100 μg was the effective dose; 5004 was titrated to 100 μg (effective dose) and completed Phase II at 100 μg, but this patient always needed two puffs, so the investigator decided to dispense 200 μg INFS in Phase 3; 7002 was titrated to 100 μg, then continued in titration and administered 200 μg dose without consulting the investigator; 7401 was titrated to 200 μg, then had a change in background pain opioid and was re-titrated to 100 μg (effective dose); 5001 was titrated to 200 μg (effective dose), but there is only a 100 μg titration diary for this patient. No patients were down-titrated during the titration phase.

A summary of the relationship between the effective INFS dose reached in the titration phase and the patient's background opioid medication is presented in Table 14.1.07.3. Among the 75 patients with low background pain opioid medication (≤180 mg/d) at baseline, 15 (20.0%) were titrated to 50 μg, 37 (49.3%) were titrated to 100 μg, and 23 (30.7%) were titrated to 200 μg INFS. Among the 23 patients with medium background pain opioid medication (> 180 mg/d - ≤ 360 mg/d), 2 (8.7%) were titrated to 50 μg, 7 (30.4%) were titrated to 100 μg, and 14 (60.9%) were titrated to 200 μg INFS. Among the 13 patients with high background pain opioid medication (> 360 mg/d), 5 (38.5%) were titrated to 100 μg and

7 (53.8%) were titrated to 200 µg INFS (one patient was not titrated). These results may suggest that patients with low level background opioid pain treatment achieve effective pain relief with a correspondingly lower INFS dose compared with the patients taking the higher levels of background pain opioids.

The relationships for response of INFS 50, 100, and 200 µg as 1 or 2 doses taken after BTP episodes were evaluated in this study (see Section 11.4.1).

The trial design required patients to be titrated to their effective dose. Therefore, this trial was not designed to evaluate dose response.

No study drug concentrations were measured in this study.

11.4.5 Drug-drug and Drug-disease Interactions

The relationship between the response to IMP and concomitant medication use, such as background pain opioids, is considered to be of insignificant clinical relevance, since the effective dose of both INFS and Actiq was found by titration with each respective IMP.

The potential impact of past and concurrent illness on the response to the IMP was considered avoided by excluding patients with history of abuse, oral/nasal surgery, facial radiotherapy and any pathological condition of the nasal and/or oral cavity.

11.4.6 By-Subject Displays

By-patient information is provided in Appendix 16.2. US archival listings or patient profiles have not been generated.

11.4.7 Efficacy Conclusions

- Primary endpoint: The pooled INFS doses were statistically superior to placebo for PID_{10}; this effect was more pronounced for the 100 and 200 µg doses. This was also reflected by the responder rate. Results were similar for the ITT and PP analysis sets
- Secondary endpoints: The pooled INFS doses were significantly superior to placebo for GI score compared with placebo. GI scores increased with the INFS dose. $SPID_{0-60}$ was significantly higher for the pooled INFS doses compared with placebo.

- Data may suggest some correlation between the background pain opioid dose and the titrated effective INFS dose. The clearest correlation was observed for the patients ending on 50 µg in the titration phase. The implication of these results is discussed in Section 13.

12 Safety Evaluation

All safety analyses were performed using the Safety dataset (all 120 patients enrolled), which includes all randomised patients exposed to INFS.

12.1 Extent of Exposure

12.1.1. Distribution of patients by titration dose during titration phase

The distribution of patients by titration dose during the titration phase is presented in Table 14.3.2. Most patients readily found a dose that was suitable for them and, for the most part, remained in that dose group. Only 6 patients changed their maximum titrated dose: 1 patient from 50 µg to 200 µg; 4 patients from 100 µg to 200 µg; and 1 patient from 200 µg to 100 µg.

12.1.2. Exposure by number of BTP episodes

12.1.2.1. Efficacy phase

The extent of exposure by the number of treated BTP episodes during the efficacy phase (0, 1, 2, 3, 4, 5, 6, or 7) for each dose and statistical analysis set (ITT and PP) is presented in Table 14.3.3. The results show that for the ITT analysis set, the majority of patients (98.2%), following all INFS doses, treated 6 BTP episodes, whereas 99.1% of patients treated 2 episodes with placebo.

12.1.2.2. Safety phase

Following the efficacy phase, patients continued participation in the study in a 10-month safety follow-up phase during which they received open-label INFS treatment for BTP episodes. A summary of the number of treated BTP episodes per day in the safety follow-up phase is presented in Table 14.3.4. Mean number of INFS treated BTP episodes per day were 1.9, 2.4, and 3.6 for the 50, 100, and 200 µg INFS doses, respectively (mean score of 2.8 for total INFS). The mean number of treated

episodes per day ranged from 0.8 to 24.7. The high value of 24.7 for mean number of daily treated episodes is attributed to 1 patient, no. 5001 (a 54-year-old man with lung cancer that had metastasized to the musculoskeletal system and liver). This patient used considerably more doses of 200 µg INFS during the safety follow-up phase than was stipulated in the protocol. In the first month, he started using 6 doses per day and escalated to as many as 35 per day by the third month. This patient was in the terminal phase of his illness, and the Investigator agreed, per the patient's request, to allow the use of INFS on an as-needed basis for relief of pain. This patient died of progression of his disease after 5 months of safety follow-up; no other adverse events were reported for him.

12.1.3. Exposure by number of INFS puffs

A summary of INFS puffs for the treatment of eight BTP episodes in the efficacy phase is presented in Table 14.1.09.1. The results show that the majority of all episodes were treated with two puffs of IMP. The proportion of BTP episodes treated with two puffs was highest for placebo (84.0%) compared to all INFS doses (68.7%).

12.1.4. Duration of exposure

A summary of the number of days of exposure to study drug by phase is presented in Table 14.3.1. The mean number of days of exposure was 8.3 for the titration phase (median 5, range: 2 to 70 days), 7.1 for the efficacy phase (median 5, range: 1 to 54 days), and 135 for the safety phase (median 93, range: 1 to 533 days).

12.2 Adverse Events

All AEs were coded using the MedDRA (version 10.1) AE dictionary. AEs were allocated to INFS doses and trial phase according to AE onset: if AE onset was in a particular phase, then the AE was allocated to that phase. Similarly, if AE onset was on or after a particular dose of INFS, then the AE was allocated to that INFS dose. The AEs were tabulated by phase, SOC, PT, severity and relationship to IMP. AEs that occurred >2 days postdose were not considered to be treatment emergent.

12.2.1 Brief Summary of Adverse Events

Overall, 99 patients (82.5%) had treatment emergent AEs during the trial: 38 patients (31.9%) had AEs allocated to the titration phase, 22 patients (19.8%) to the efficacy phase, and 83 patients (76.9%) to the safety follow-up phase. The majority of patients experienced treatment emergent AEs that were not considered related to treatment. Treatment emergent SAEs were reported for a total of 60 patients (50.0%): 4 patients (3.4%) had SAEs allocated to the titration phase, 2 patients (1.8%) to the efficacy phase, and 56 patients (51.9%) to the safety follow-up phase. A total of 47 patients (39.2%) died: 2 patients (1.7%) during the titration phase, 1 patient (0.9%) during the efficacy phase, and 44 patients (40.7%) during the safety follow-up phase. Severe treatment emergent AEs were reported for a total of 58 patients (48.3%) : 6 patients (5.0%) in the titration phase, 3 patients (2.7%) in the efficacy phase, and 53 patients (49.1%) in the safety follow-up phase (Table 8).

Table 9 Overall Summary of Treatment Emergent Adverse Events by Phase

	Titration Phase (N=119)			Efficacy Phase (N=111)			Safety Follow-Up Phase (N=108)			Total (N=120)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Patients with at least one AE	38	(31.9)	65	22	(19.8)	40	83	(76.9)	358	99	(82.5)	463
Patients with at least one severe AE	6	(5.0)	6	3	(2.7)	4	53	(49.1)	69	58	(48.3)	79
Patients with at least one related (probably or possibly) AE	7	(5.9)	14	6	(5.4)	17	5	(4.6)	9	16	(13.3)	40
Patients with at least one serious AE	4	(3.4)	5	2	(1.8)	2	56	(51.9)	77	60	(50.0)	84
Patients who died	2	(1.7)	2	1	(0.9)	1	44	(40.7)	46	47	(39.2)	49
Patients with AEs leading to withdrawal of IMP	3	(2.5)	3		0		19	(17.6)	21	22	(18.3)	24

N = Number of exposed, n = Number with event, % = Number with event as % of exposed, AE = adverse event; E = Number of events.
Note: AEs with missing seriousness are counted as serious. AEs with missing severity are counted as severe.
Source: Table 14.3.5.1

In this trial, there were, two categories of recorded withdrawals due to AEs: Those patients for whom the primary reason for discontinuation from the trial on the EOT Form in the CRF

was due to an AE, and those who had IMP withdrawn due to an AE as listed on the AE page of the CRF (these patients did not necessarily discontinue their participation in the trial). These are the numbers used in Table 4 (see Section 10.1), and those who had IMP drug withdrawn due to an AE as listed on the AE page of the CRF. These are the numbers used in the last row of Table 8; these patients were not necessarily discontinued from the whole trial.

12.2.2 Display of Adverse Events

Adverse event information for this trial is presented in Tables 14.3.5.1, 14.3.5.2.1, 14.3.5.2.2, 14.3.5.2.3, 14.3.5.2.4, 14.3.5.2.5, 14.3.5.3.1, 14.3.5.3.2, 14.3.5.4.1, 14.3.5.4.2, 14.3.5.4.3, 14.3.5.4.4, 14.3.5.4.5, 14.3.5.4.6, 14.3.5.5, 14.3.5.6.1, 14.3.5.6.2, 14.3.5.7, 14.3.5.8 and 14.3.5.9. Note that patients could have experienced several AEs allocated to different phases of the trial. Therefore, the number of patients in the total column in the summary tables is not necessarily equal to the sum of the number of patients having AEs allocated to the different phases.

Treatment emergent AEs with a rate of >1% (i.e. two or more patients with an AE in a phase of the trial) are shown by PT in descending order of occurrence in Table 8.

Table 8 Adverse Events Occurring in >1% of Patients by Phase of the Trial

Preferred Term	Titration Phase (N=119)			Efficacy Phase (N=111)			Safety Follow-Up Phase (N=108)			Total (N=120)		
	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)	E
Malignant neoplasm progression	9	(7.6)	10	4	(3.6)	4	55	(50.9)	139	62	(51.7)	153
Nausea	3	(2.5)	3	5	(4.5)	8	10	(9.3)	14	16	(13.3)	25
Constipation	3	(2.5)	3	0			9	(8.3)	9	12	(10.0)	12
Asthenia	2	(1.7)	2	1	(0.9)	1	8	(7.4)	12	11	(9.2)	15
Vertigo	6	(5.0)	9	2	(1.8)	7	2	(1.9)	2	9	(7.5)	18
Vomiting	3	(2.5)	3	0			5	(4.6)	7	8	(6.7)	10
Anaemia	3	(2.5)	3	0			3	(2.8)	3	6	(5.0)	6
Decubitus ulcer	1	(0.8)	1	0			5	(4.6)	6	6	(5.0)	7
Oedema peripheral	1	(0.8)	1	1	(0.9)	1	4	(3.7)	4	6	(5.0)	6
Anxiety	1	(0.8)	1	0			4	(3.7)	4	5	(4.2)	5
Hypertension	1	(0.8)	1	0			4	(3.7)	4	5	(4.2)	5
Anorexia	0			0			4	(3.7)	4	4	(3.3)	4
Catheter related complication	0			0			4	(3.7)	7	4	(3.3)	7
Dysuria	1	(0.8)	1	0			3	(2.8)	3	4	(3.3)	4
Decreased appetite	1	(0.8)	1	0			2	(1.9)	2	3	(2.5)	3
Depressed mood	3	(2.5)	3	0			0			3	(2.5)	3
Depression	0			1	(0.9)	1	3	(2.8)	3	3	(2.5)	4
Insomnia	0			0			3	(2.8)	3	3	(2.5)	3
Nasopharyngitis	0			0			3	(2.8)	3	3	(2.5)	3
Pruritus	0			0			3	(2.8)	3	3	(2.5)	3
Upper respiratory tract infection	0			1	(0.9)	1	2	(1.9)	2	3	(2.5)	3
Urinary tract infection	0			1	(0.9)	1	2	(1.9)	2	3	(2.5)	3
Abdominal pain	0			0			2	(1.9)	2	2	(1.7)	2
Bronchitis	2	(1.7)	2	0			0			2	(1.7)	2
Crepitations	0			0			2	(1.9)	2	2	(1.7)	2
Diarrhoea	0			0			2	(1.9)	2	2	(1.7)	2
Disease progression	0			0			2	(1.9)	6	2	(1.7)	6
Dry mouth	0			0			2	(1.9)	2	2	(1.7)	2
Dry skin	0			0			2	(1.9)	2	2	(1.7)	2
Headache	0			0			2	(1.9)	2	2	(1.7)	2
Hiccups	0			0			2	(1.9)	2	2	(1.7)	2
Hot flush	2	(1.7)	3	0			0			2	(1.7)	3
Hyperhidrosis	0			0			2	(1.9)	2	2	(1.7)	2
Infection	0			0			2	(1.9)	2	2	(1.7)	2
Osteoarthritis	0			0			2	(1.9)	2	2	(1.7)	2
Rash	0			0			2	(1.9)	2	2	(1.7)	2
Sciatica	0			0			2	(1.9)	2	2	(1.7)	2

N = number of patients exposed to treatment; n = number of patients with event;
% = number of patients with event per patients exposed; E = number of events; INFS = intranasal fentanyl spray
Source: Table 14.3.5.2.2

During the data review in connection with the reopening of the trial database (see Section 9.6.5) it was identified that for 6 patients (nos. 5605, 7221, 7228, 7229, 7718 and 7730) 8 concomitant medications were prescribed after signing the informed consent, where no corresponding AE was reported. These potential AEs are not counted and tabulated, but have been medically reviewed and evaluated to not be altering the safety profile. The concerned concomitant medications are included in Table 14.1.10. The reported indications (potential AEs) were: anxiety (no. 5605), diarrhoea (no. 7221), nausea (no. 7228), constipation (no. 7229), anorexia (no. 7718) and lumbar tenderness (no. 7730). The potential AEs for all these patients could be treatment emergent. CRFs for the 6 patients are presented in Appendix 16.3.2.

12.2.3 Analysis of Adverse Events

The most frequently occurring treatment emergent AE overall was progression of malignant neoplasm, reported in 62 patients (51.7%) across the three phases of the trial in this population of cancer patients: 9 patients (7.6%) in the titration phase, 4 patients (3.6%) in the efficacy phase, and 55 patients (50.9%) in the safety follow-up phase (Table 9). Nausea and vertigo were the only other treatment emergent AEs reported by > 1% of patients in all three phases of the trial; for nausea 3 patients (2.5%) in the titration phase, 5 patients (4.5%) in the efficacy phase, and 10 patients (9.3%) in the safety follow-up phase, and for vertigo 6 patients (5.0%) in the titration phase, 2 patients (1.8%) in the efficacy phase, and 2 patients (1.9%) in the safety follow-up phase. Depressed mood was the only treatment emergent AE reported by > 2% of patients in the titration phase only (3 patients, 2.5%). Anorexia and catheter-related complications were reported for >3% of patients in the safety follow-up phase only (4 patients, 3.7%, for each). As expected, the majority of treatment emergent AEs reported in > 1% of patients occurred during the longest part of the trial, i.e. the safety follow-up phase. The largest proportion of patients experienced disease progression during this phase (50.9%) as well as treatment emergent AEs (other than the previously described nausea and anorexia) associated with cancer and cancer treatment, such as constipation (9 patients, 8.3%), asthenia (8 patients, 7.4%), vomiting (5 patients, 4.6%), decubitus ulcer (5 patients, 4.6%), depression (3 patients, 2.8%), and insomnia (3 patients, 2.8%). All treatment emergent AEs by phase, SOC and PT are presented in Table 14.3.5.2.1.

The number of treatment emergent AEs by SOC, PT and severity for the safety analysis set by phase are presented in Tables 14.3.5.2.3, 14.3.5.2.4, and 14.3.5.2.5. A total of 74 patients (61.7%) experienced 281 treatment emergent AEs that were mild and 49 patients

(40.8%) experienced 103 treatment emergent AEs that were moderate in severity. Severe treatment emergent AEs were reported in all phases of the trial (78 AEs in 58 patients, 48.3% total): 5 patients (4.2%) in the titration phase, 3 patients (2.7%) in the efficacy phase, and 53 patients (49.1%) in the safety follow-up phase. The most frequently reported severe treatment emergent AE was progression of malignant neoplasm: 2 patients (1.7%), 1 patient (0.9%) and 43 patients (39.8%) in the titration, efficacy, and safety follow-up phases, respectively. Severe pneumonia, ileus, and decreased platelet count were reported for one patient each in the titration phase only. Severe peripheral oedema was reported for one patient in the efficacy phase only. Severe dysguesia was reported for one patient in the efficacy and safety follow-up phases. Severe treatment emergent AEs reported during the safety follow-up phase only were generally related to advanced metastatic disease and were reported for one patient (0.9%) each: metastases to the central nervous system, metastatic pain, general physical health deterioration, abscess, erysipelas, dysgeusia, serotonin syndrome, cardiopulmonary failure, coronary artery disease, gastrointestinal necrosis, intestinal perforation, cardiovascular insufficiency, venous stasis, femoral neck fracture, anxiety, and ureteric obstruction.

Overall, 16 patients (13.3%) experienced a total of 40 treatment emergent AEs that were considered probably or possibly related to treatment (Table 14.3.5.3.1). The most frequently reported treatment-related AEs were vertigo (6 patients, 5.0%) and nausea (4 patients, 3.3%). In the titration phase, vertigo in 5 patients (4.2%), and sedation, somnolence, and accidental overdose (each reported for one patient, 0.8%) and hot flush (2 patients, 1.7%) were considered related to treatment. In the efficacy phase, nausea (3 patients, 2.7%), vertigo (2 patients, 1.8%), and dysguesia, dizziness, and myoclonus (one patient each, 0.9%) were considered related to treatment. In the safety follow-up phase, nausea, constipation, vomiting, dysguesia, malignant neoplasm progression and epistaxis were considered related to treatment in one patient each (0.9%). In patient 7101, a 60-year-old female with cancer of the head and neck that had metastasised to the musculoskeletal system; approximately 2 weeks later, the investigator reported mild malignant neoplasm progression for this patient to be considered not related to trial drug; also see Section 12.3.3. Dysguesia was the only severe treatment emergent AE that was considered possibly related to treatment (in one patient in the efficacy and safety phases).

A total of 60 patients (50.0%) reported 84 treatment emergent SAEs during this trial: 4 patients (3.4%) in the titration phase, 2 patients (1.8%) in the efficacy phase and 56 patients (51.9%) in the safety follow-up phase (Table 14.3.5.4.1). The most frequently reported treatment emergent SAE was malignant neoplasm progression in 49 patients (40.8%). Treatment emergent SAEs are summarised by severity in Tables 14.3.5.4.2, 14.3.5.4.3 and 14.3.5.4.4. None of the treatment emergent SAEs were considered related to treatment (Tables 14.3.5.4.5 and 14.3.5.4.6). For further discussion of SAEs, see Section 12.3.1.2.

A total of 11 patients experienced AEs more than two days after the last dose of IMP (Table 14.3.5.9). The events reported more than two days after the last IMP dose were malignant neoplasm progression/metastases to central nervous system (10 patients, 8.3%) and somnolence (1 patient, 0.8%).

A total of 47 patients (39.2%) died during this trial: 2 patients (1.7%) in the titration phase, 1 patient (0.9%) in the efficacy phase and 44 patients (40.7%) in the safety follow-up phase (Table 14.3.5.5). None of the reported deaths were considered related to treatment. For further discussion of deaths, see Section 12.3.1.1.

A total of 57 patients (47.5%) discontinued from the trial due to AEs (the primary reason for discontinuation on the EOT page of the CRF was “AE”): 5 patients (4.2%) in the titration phase, 1 patient was randomised and then discontinued prior to taking any IMP in the efficacy phase, 1 patient (0.9%) in the efficacy phase and 50 patients (46.3%) in the safety follow-up phase (Table 14.1.02.2).

As described this report summarises the safety results based on the revised database derived from the re-monitoring of FT-018-IM in addition to the reopening of the database to include events with onset of more than 2 days after last dose of IMP and correction of some inconsistencies (see Section 9.6.5). This resulted in further events to be included into the study database. However, the events identified during re-monitoring were almost entirely AEs associated with the underlying diseases of the patient population of adults with cancer, and did not reveal any new severe, serious or other important events considered related to the study drug. The AEs added during re-opening of the database were 6 AEs in total. In conclusion neither the AEs identified during the re-monitoring of the FT-018-IM trial nor the

AEs newly added and inconsistencies corrected during reopening of the hard locked database did alter the safety profile previously reported for INFS.

12.2.4 Listing of Adverse Events by Patients

All AEs for individual patients in the safety analysis set are provided in Listing 16.2.22.1; 16.2.22.2; 16.2.22.3; all SAEs for individual patients in the safety analysis set are provided in Listing 16.2.22.4; deaths for individual patients in the safety analysis set are listed in 16.2.22.5; AEs reported for individual patients in the safety analysis set who discontinued from the study for any reason are listed in 16.2.22.6.1; AEs for all patients in the safety analysis set resulting in withdrawal of trial medication are listed in 16.2.22.6.2; all AEs for patients in the safety analysis set who discontinued from the trial due to an AE are listed in 16.2.22.6.3; and all AEs for patients who withdrew during titration, or who were randomised but not treated with double-blind medication are listed in 16.2.22.7.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listings of Deaths, Other Serious Adverse Events and other Significant Adverse Events

12.3.1.1 Deaths

A total of 47 patients (39.2%) died during the study within 48 hours after the last dose of study drug as summarised in Table 9. None of the deaths were considered by the investigator to be related to trial treatment. The majority of deaths were attributed to the underlying disease ie progression of malignant neoplasm (43 patients) and one patient experienced metastases to central nervous system. Of these, two occurred during the titration phase, one occurred during the efficacy phase, and 41 occurred during the safety follow-up phase. Three patients died of unrelated events other than progression of malignant neoplasm/metastases (all in the safety follow-up phase). One patient died of cardiopulmonary failure, intestinal perforation and gastrointestinal necrosis; one patient of general physical health deterioration; and one patient of cardiovascular insufficiency.

Additionally, 8 patients died due to malignant neoplasm progression more than 48 hours after the last dose (Listing 16.2.22.5).

Table 9 Summary of Patients Who Died During the Trial

Patient ID	AE Resulting in Death	Phase of Trial	INFS Dose[a]
0158	Malignant neoplasm progression	Safety	100 µg
4301	Malignant neoplasm progression	Safety	100 µg
4302	Malignant neoplasm progression	Safety	200 µg
5004	Malignant neoplasm progression	Safety	200 µg
5302	Malignant neoplasm progression	Safety	200 µg
5503	Malignant neoplasm progression	Safety	200 µg
5605	Metastases to central nervous system	Safety	100 µg
7110	Malignant neoplasm progression	Safety	200 µg
7114	Malignant neoplasm progression	Safety	50 µg
7115	Malignant neoplasm progression	Safety	100 µg
7201	Malignant neoplasm progression	Safety	200 µg
7204	Malignant neoplasm progression	Safety	100 µg
7205	Malignant neoplasm progression	Safety	200 µg
7207	Malignant neoplasm progression	Safety	200 µg
7211	Malignant neoplasm progression	Safety	100 µg
7212	Malignant neoplasm progression	Safety	200 µg
7215	Malignant neoplasm progression	Safety	200 µg
7219	Malignant neoplasm progression	Efficacy	100 µg
7220	Malignant neoplasm progression	Safety	100 µg
7221	Malignant neoplasm progression	Safety	200 µg
7222	Malignant neoplasm progression	Safety	100 µg
7223	Malignant neoplasm progression	Safety	100 µg
7226	Malignant neoplasm progression	Safety	200 µg
7227	Malignant neoplasm progression	Safety	100 µg
7228	Malignant neoplasm progression	Safety	100 µg
7229	Malignant neoplasm progression	Safety	200 µg
7233	Malignant neoplasm progression	Safety	100 µg
7236	Malignant neoplasm progression	Safety	200 µg
7237	Malignant neoplasm progression	Safety	100 µg
7303	Cardiovascular insufficiency	Safety	200 µg
7307	Malignant neoplasm progression	Safety	200 µg
7401	General physical health deterioration	Safety	100 µg
7601	Malignant neoplasm progression	Safety	100 µg
7606	Cardiopulmonary failure Intestinal perforation Gastrointestinal necrosis	Safety	200 µg
7608	Malignant neoplasm progression	Safety	100 µg
7701	Malignant neoplasm progression	Safety	100 µg
7702	Malignant neoplasm progression	Safety	100 µg
7709	Malignant neoplasm progression	Safety	200 µg
7712	Malignant neoplasm progression	Safety	100 µg
7713	Malignant neoplasm progression	Safety	200 µg
7718	Malignant neoplasm progression	Safety	200 µg
7719	Malignant neoplasm progression	Safety	200 µg
7721	Malignant neoplasm progression	Safety	200 µg
7724	Malignant neoplasm progression	Safety	200 µg
7727	Malignant neoplasm progression	Titration	50 µg
7730	Malignant neoplasm progression	Safety	200 µg
7905	Malignant neoplasm progression	Titration	100 µg

[a]Treatment at time of death; no deaths were considered related to trial treatment.
Source: Listing 16.2.22.5

Narratives for the 47 patients in the safety analysis set who died are provided in Section 14.3.3.

12.3.1.2 Other Serious Adverse Events

A total of 84 treatment emergent SAEs were observed in 60 patients (50%): 4 patients (3.4%) experienced treatment emergent 5 SAEs in the titration phase; 2 patients (1.8%) experienced 1 treatment emergent SAE each in the efficacy phase; and 56 patients (51.9%) experienced 77 treatment emergent SAEs in the safety-follow-up phase (Table 14.3.5.1 and 14.3.5.4.1). None of the reported SAEs were considered related to trial drug (Table 14.3.5.4.5). The most frequently reported treatment emergent SAE was malignant neoplasm progression in 49 patients (40.8%). Anaemia was reported for two patients (both during the safety follow-up phase); all other treatment emergent SAEs were reported for one patient each. The majority of the treatment emergent SAEs (in 56 of 60 patients) were reported during the safety follow-up phase. A summary of the patients with all SAEs, including those that were not treatment emergent, is provided in Table 10.

Table 10 Summary of all Serious Adverse Events

Pat. ID	Serious Adverse Event	Phase of Trial	Action Taken	Outcome	INFS Dose[a]
0158	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
0161	Erysipelas	Safety	Dose unchanged	Recovered	200 µg
0202	Leukopenia	Safety	Dose unchanged	Recovered	200 µg
4101	Malignant neoplasm progression	Post[d]	Drug withdrawn	Fatal	Not applicable
4301[b]	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
4302	Bone pain Malignant neoplasm progression	Pre-titration Safety	Dose unchanged Drug withdrawn	Recovered Fatal	N/A 200 µg
4352	Hyperplasia	Safety	Dose unchanged	Recovered with sequelae	100 µg
4601	Anaemia Malignant neoplasm progression	Safety Safety	Dose unchanged Drug withdrawn	Recovered Not recovered	200 µg 200 µg
5001	Malignant neoplasm progression	Post[d]	Not applicable	Fatal	Not applicable
5004	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
5302	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	200 µg
5503	Malignant neoplasm progression Anaemia	Safety Safety	Not applicable Dose unchanged	Fatal Recovered	200 µg 200 µg
5605	Oedema peripheral Metastases to central nervous system	Efficacy Safety	Dose unchanged Drug withdrawn	Recovered Fatal	100 µg 100 µg
7108	Ureteric obstruction Malignant neoplasm progression	Safety Post[d]	Dose unchanged Not applicable	Recovered Fatal	200 µg Not applicable
7110	Pneumonia Femoral neck fracture Metastatic pain Malignant neoplasm progression	Safety Safety Safety Safety	Dose unchanged Dose unchanged Dose increased Dose unchanged	Recovered Recovered Recovered Fatal	100 µg 200 µg 100 µg 200 µg
7113	Malignant neoplasm progression	Post[d]	Not applicable	Fatal	Not applicable
7114	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	50 µg
7115	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7201	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7202	Coronary artery disease	Safety	Drug withdrawn	Recovered	200 µg
7204	Catheter related complication Malignant neoplasm progression	Safety Safety	Dose unchanged Not applicable	Recovered Fatal	100 µg 100 µg
7205	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7207	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	200 µg
7211	Jaundice Malignant neoplasm progression	Safety Safety	Dose unchanged Drug withdrawn	Not recovered Fatal	100 µg 100 µg
7212	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	200 µg
7215	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	200 µg
7219	Malignant neoplasm progression	Efficacy	Not applicable	Fatal	100 µg
7220	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7221	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg

7222	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	100 µg
7223	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	100 µg
7224	Malignant neoplasm progression	Post[d]	Not applicable	Fatal	Not applicable
7226	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	200 µg
7227	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7228	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	100 µg
7229	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	200 µg
7230	Malignant neoplasm progression	Post[d]	Not applicable	Fatal	Not applicable
7232	Malignant neoplasm progression Venous stasis	Safety Safety	Dose unchanged Dose unchanged	Recovered Recovered	100 µg 100 µg
7233	Gastrostomy failure Malignant neoplasm progression	Safety Safety	Dose unchanged Drug withdrawn	Not recovered Fatal	100 µg 100 µg
7235	Malignant neoplasm progression	Safety	Drug withdrawn	Recovered with sequelae	100 µg
7236	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	200 µg

Table 14 Continued

Pat. ID	Serious Adverse Event	Phase of Trial	Action Taken	Outcome	INFS Dose
7237	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7239	Malignant neoplasm progression	Safety	Drug withdrawn	Not recovered	100 µg
7303	Cardiovascular insufficiency	Safety	Dose unchanged	Fatal	200 µg
7307	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7310[b]	Malignant neoplasm progression	Safety	Dose unchanged	Recovered	200 µg
7401	General physical health deterioration	Safety	Drug withdrawn	Fatal	100 µg
7601	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7606	Cardiopulmonary failure Intestinal perforation Gastrointestinal necrosis	Safety Safety Safety	Drug withdrawn Drug withdrawn Drug withdrawn	Fatal Fatal Fatal	200 µg 200 µg 200 µg
7608	Malignant neoplasm progression Anxiety	Safety Safety	Not applicable Dose unchanged	Fatal Recovered	100 µg 100 µg
7701	Malignant neoplasm progression	Safety	Not applicable	Fatal	100 µg
7702	Paresis cranial nerve Malignant neoplasm progression	Safety Safety	Dose unchanged Drug withdrawn	Recovered with sequelae Fatal	100 µg 100 µg
7705	Ileus	Titration	Drug withdrawn	Recovered with sequelae	50 µg
7708	Abscess	Safety	Dose unchanged	Unknown	50 µg
7709	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7712	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	100 µg
7713	Malignant neoplasm progression	Safety	Drug withdrawn	Fatal	200 µg
7717	Malignant neoplasm progression	Post[d]	Not applicable	Fatal	Not applicable

7718	Malignant neoplasm progression	Safety	Dose unchanged	Fatal	200 µg
7719	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7721	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7724	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7727	Malignant neoplasm progression	Titration	Not applicable	Fatal	50 µg
7730	Malignant neoplasm progression	Safety	Not applicable	Fatal	200 µg
7804	Malignant neoplasm progression Depression	Safety Safety	Dose unchanged Dose unchanged	Recovered Recovered	200 µg 200 µg
7905	Malignant neoplasm progression Paraparesis	Titration Titration	Not applicable Dose unchanged	Fatal Recovered with sequelae	100 µg 100 µg

[a]Treatment at time of SAE; no SAEs were considered related to trial treatment.
When the same event was reported more than once for a patient, only the last occurrence is included.
[b]Patient 4301 also experienced this SAE in the titration phase.
[c]Patient 7310 also experienced this SAE more than two days after last dose of IMP.
[d] AE onset is after last dose of study drug plus 2 days.

Source: Listing 16.2.22.4

12.3.1.3 Other Significant Adverse Events

In this trial, there were, two categories of recorded withdrawals due to AEs: Those patients for whom the primary reason for discontinuation from the trial on the EOT Form in the CRF was due to an AE, and those who had IMP withdrawn due to an AE as listed on the AE page of the CRF (these patients did not necessarily discontinue their participation in the trial).

During the trial 57 patients discontinued due to an AE (Table 14.1.02.2) primarily reported as malignant neoplasm progression. All adverse events in patients who discontinued the trial are shown in Listing 16.2.22.6.3.

A total of 22 patients had treatment emergent AEs leading to withdrawal of study drug. i.e. action taken on the AE page was “Drug withdrawn” (Table 14.3.5.1). All adverse events in patients who had treatment emergent AEs leading to withdrawal of study drug are shown in Listing 16.2.22.6.2.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Narrative summaries for the patients who died, for patients with SAEs, and for patients who discontinued due to AEs are provided in Section 14.3.3. In addition it was decided to

describe AEs with follow-up information separately. These descriptions are also included in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

The overall incidence of deaths reported as treatment emergent was 39.2%, not an unexpected incidence in this population of patients with cancer in an advanced stage who were monitored for up to 10 months following completion of the efficacy phase of the trial. No death was considered related to treatment. Similarly, SAEs were not related to trial medication but were associated with the patients' underlying disease. Discontinuations from treatment were generally also associated with progression of disease, although three AEs resulting in discontinuation were considered to have a probable relationship to trial medication: moderate vertigo in one patient, moderate accidental overdose in one patient, and severe dysgeusia in one patient. Patient 4353 (a 44-year-old female with breast cancer) experienced mild vertigo and hot flush in the titration phase that the investigator considered probably related to trial drug; the events resolved on the day of onset. Two days later, she experienced moderate vertigo that was considered probably related to trial drug and was discontinued from the trial; the vertigo resolved within 3 days of onset. Patient 2101 (a 61-year-old female with breast cancer) took one puff of the 100 μg INFS titration spray and was described by the investigator as being "cerebrally affected". The event was reported as probably related, moderate accidental overdose. Trial drug was discontinued and no other events were reported for this patient. Patient 7224 (a 75-year-old female with breast cancer that had metastasised to the musculoskeletal and lymphatic systems), experienced severe dysgeusia in the efficacy phase the continued into the safety follow-up phase, at which time study drug was discontinued. After a total duration of 5 days, the dysgeusia was considered resolved.

As INFS concerns intranasal application, AEs of the nasal cavity were of particular interest. The incidence of localised events was low. Two patients reported one AE each of pharyngitis; the events were non-serious, mild in severity, and were considered unlikely to be related to trial drug by the investigator. One patient (7224) experienced dysgeusia (as discussed above) that was non-serious, severe, resulted in discontinuation of trial drug, and was considered probably related by the investigator. One patient (7108) reported a moderate non-serious AE of mucosal dryness. The event was considered unlikely to be related by the

investigator, who considered increased furosemide dose as an alternative aetiology. Also, an AE of non-serious mild mucosal inflammation was reported (4302). It was considered not related by the investigator who considered chemotherapy treatment as an alternative aetiology. Finally, one patient (5605) reported a moderate non-serious AE of epistaxis, which was considered possibly related by the investigator. This patient had a medical history of lung and respiratory cancer and was concomitantly treated with acetylsalicylic acid which may increase the risk of bleeding. The patient recovered without changes to trial drug. No other AEs of nasal symptomatology were reported (see Table 14.3.5.2.1 and Listings 16.2.22.1-16.2.22.3).

12.4 Clinical Laboratory Evaluation

Not applicable.

12.5 Vital Signs, Physical Examination Findings and Other Observations Related to Safety

Changes in physical examination findings were reported as AEs and were not unexpected in a population of patients with cancer.

No pregnancies were recorded during the trial.

12.6 Safety Conclusions

As expected in this population of patients with cancer, the majority of the treatment emergent AEs were reported in the safety follow-up phase, were predominantly related to the patients' underlying disease and not considered related to trial medication. Treatment emergent AEs that were considered related to trial treatment were infrequent (13.3% of all patients) and they were all non-serious. Three treatment emergent AEs that were considered related to trial drug by the investigator occurred in more than one patient: nausea (four patients), vertigo (six patients), and hot flush (two patients). The remaining related treatment emergent AEs were reported in only one patient each: constipation, vomiting, dysgeusia, dizziness, myoclonus, sedation, somnolence, accidental overdose, malignant neoplasm progression (see discussion of patient 7101 in Section 12.2.3), and epistaxis. The AE of moderate epistaxis, which resolved without sequelae, was the only AE of nasal symptomatology that was considered to have a possible relationship to treatment in this trial; this was reported for a patient who had been taking acetylsalicylic acid which may have increased the risk of

bleeding. The majority of the SAEs reported in this trial were related to progression of disease, occurred during the safety-follow-up phase and none were considered related to treatment. A total of 57 patients discontinued the trial due to AEs, primarily due to malignant neoplasm progression. Three patients had AEs leading to discontinuation that were considered probably related to trial drug (moderate vertigo in one patient, moderate accidental overdose in one patient, and severe dysgeusia in one patient). Of the 47 deaths that occurred during this trial, the majority were during the safety follow-up phase, all were attributed to progression of disease or were disease-related and none were considered related to trial treatment.

13 Discussion and Overall Conclusions

1.1 Discussion

Titration. A total of 112 patients completed titration and of those, 108 patients (96%) obtained an effective dose according to trial definitions. Seventeen patients were titrated to 50 µg, 51 patients to 100 µg and 44 patients to 200 µg. No patients were down-titrated in either the titration or efficacy phases indicating that in general the effective dose was achieved without any undesirable effects. Since down-titration was not needed, the effective dose was achieved in relatively few titration steps. Furthermore, 108 patients continued into the safety follow-up phase which may indicate a high degree of satisfaction with the obtained dose.

Efficacy. The primary endpoint in this trial was the PID at 10 min postdose. Since the pain intensity related to a BTP episode increases rapidly, this is a clinically relevant parameter of measuring PI. Moreover, the patients kept daily records of their BTP episodes and assessed the PI also at 20, 40, and 60 min after the first puff of the IMP. This allowed assessment not only of $PID_{10,}$ but also of the persistence of pain relief beyond the first 10 min. At 60 min postdose, patients also recorded their GI of pain relief and use of INFS.

Analysis of PID at the 10, 20, 40 and 60 min timepoints indicated that higher mean scores (indicating higher PID) were observed for all of the INFS doses compared with placebo.

The average overall responder rate (the average response rate by treatment (INFS or placebo) within each patient) at 10 min was highest for the 100 μg dose. The lowest responder rate was observed for placebo.

Also, for $SPID_{60}$ and GI the pooled INFS doses were statistically significantly superior to placebo.

Looking at the combined efficacy results, a clinical benefit in terms of better pain relief for all INFS doses was shown.

Of interest in this trial was also the assessment of any possible correlation between a patient's level of background opioid treatment (low, medium, or high) and response to INFS for BTP treatment as determined by the effective dose achieved in the titration phase. The effective dose achieved in titration was analysed with regard to the baseline background opioid treatment doses. All of the patients with 50 μg INFS as the effective dose achieved in the titration phase were treated with low (≤ 180 mg/d) or medium level (> 180 mg/d - ≤ 360 mg/d) background opioid pain medication, i.e. no patients with high background pain opioid doses (> 360 mg/d) used 50 μg INFS as the 'effective' INFS dose. Therefore, the data may suggest that patients treated with low background opioid doses achieve effective pain relief with a correspondingly lower INFS dose compared with the patients treated with high doses of background pain opioids. However,this trial was not appropriately designed to explore this fundamental issue of need for titration in debth. For future investigation into this area a randomised controlled study, comparing titrated doses with background opioid treatment correlated doses, would be needed.

Number of Treated Episodes and Rescue Medication. The majority of patients (98.2%) treated six BTP episodes with INFS, whereas 99.1% of patients treated two episodes with placebo. The proportion of BTP episodes requiring rescue medications was almost three times higher for placebo (45.2%) than for any dose of INFS (ranging from 13.3% to 15.7% for the individual dose groups and 14.2% for all INFS groups combined). Within the first 20 minutes, the contrast was most evident, with rescue medication taken in 40 episodes (18.3%) following placebo compared with 0.9% to 1.8% of episodes following treatment with the three INFS doses, a difference of approximately 13-fold. Consistent with the observed GI

results and the overall trend for the higher INFS doses to have the most beneficial effect, the lowest proportion of patients requiring rescue medication was in the 200 μg INFS dose group.

Safety and Tolerability. Adverse events were the main criterion for the safety evaluation. Throughout this trial the reported AEs were predominantly mild or moderate in severity during the titration and efficacy phases of the trial and not related to trial drug. The most commonly reported AE was progression of the underlying disease in this population of patients with cancer; this was particularly evident in the safety follow-up phase in which many patients were in the terminal phase of their illness and 48.3% of patients had severe AEs.

Underlying disease was also the main reason cited for the reported SAEs and deaths during all phases of the trial. No SAEs or deaths were considered related to treatment. Three patients discontinued treatment due to AEs that were considered by the investigator to have a probable relationship to trial drug: moderate vertigo in one patient, moderate accidental overdose in one patient (during the titration phase), and severe dysgeusia in one patient.

One patient (no. 5001) used considerably more doses of 200 μg INFS during the safety follow-up phase than was allowed according to the protocol. This patient's number of BTPs gradually increased due to progression of disease; the background pain medication was not adjusted and the BTP episodes were treated with INFS as needed per the patient's request and the investigator's decision. This patient died of progression of disease after 5 months of safety follow-up; no other adverse effects were reported for him.

Though nausea and vertigo were among the AEs most commonly considered related to INFS treatment in this trial, they occurred at a relatively low frequency (5.0% or less of patients in all INFS dose groups). One patient with cancer of the head and neck that had metastasised to the musculoskeletal system, had mild malignant neoplasm reported as an AE with a 'possible' relationship to trial drug during the safety phase. It was, however, upon further evaluation, considered to be unlikely that the progression of this patient's advanced state of cancer was influenced by treatment with the trial drug.

The safety profile of INFS was similar after 10 months as had been observed at the 4 month evaluation (Nycomed FT-018-IM, 2007). The incidence of localized adverse reactions associated with the nasal cavity was low, as was the incidence of trial drug-related AEs. The primary cause of discontinuation, SAEs and death was the patients' underlying disease. Over the duration of the trial, 38 patients withdrew consent; only 11 of these patients had experienced any AEs (predominantly mild to moderate in severity and generally unrelated to INFS).

13.1 Overall Conclusion

It can be concluded that INFS, titrated to effective doses of 50, 100, and 200 µg, used in the treatment of BTP in cancer patients is superior to placebo. Almost all patients achieved an effective dose in the titration phase. Data may indicate some correlation between the background pain opioid dose and the titrated effective INFS dose. All doses were shown to be safe, well tolerated, and clinically efficacious. INFS was generally well tolerated during the 10-month extended treatment period

14 Tables, Figures and Graphs referred to but not included in the Text

14.1 Demographic Data

Table 14.1.01 Patient Enrolment by Centre, All Patients Enrolled

Table 14.1.02.1 Patient Analysis Sets, All Patients Enrolled

Table 14.1.02.2 Patient Disposition by Phase (After Re-monitoring), Safety Analysis Set

Table 14.1.03 Demographic Characteristics, ITT Analysis Set

Table 14.1.04 Cancer Related Medical History by Site of Primary Tumour, ITT Analysis Set

Table 14.1.05 Past and Concomitant Illness by System Organ Class and Preferred Term, ITT Analysis Set

Table 14.1.06 Abnormal Physical Examination Findings, ITT Analysis Set

Table 14.1.07.1 Background Pain Opioid Medication by Medication Class and Preferred Term, ITT Analysis Set

Table 14.1.10 Concomitant Medications by Medication Class and Preferred Term (After Re-monitoring), ITT Analysis Set

Table 14.1.11 Concomitant Procedures by Procedure Class and Preferred Term (After Re-monitoring), ITT Analysis Set

14.2 Efficacy Data

Table 14.1.07.2 Distribution of Standardised Dose of Background Pain Opioid Medication at the End of Titration Phase, ITT Analysis Set

Table 14.1.07.3 Summary of the Relationship of NF Dose Reached at Titration Phase and Dose of Background Pain Opioid Medication, ITT Analysis Set

Table 14.1.08.1 Proportion of Treated Episodes Where Any Rescue Medications Were Taken: Efficacy Phase, ITT Analysis Set

Table 14.1.08.2 Rescue Medications by Medication Class and Preferred Term, ITT Analysis Set

Table 14.1.09.1 Summary of NF Sprays for Treatment of Eight BTP Episodes: Efficacy Phase, ITT Analysis Set

Table 14.1.09.2 Treatment of BTP Episode with Trial Medication and/or Rescue Medication: Efficacy Phase, ITT Analysis Set

Table 14.2.1.1 Overall Pain Intensity Difference at 10 Minutes (PID_{10}): Efficacy Phase, ITT Analysis Set

14.3 Safety Data

14.3.1 Display of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

16.2.22.6 Adverse Events of Withdrawals for Any Reason by System Organ Class and Preferred Term (After Re-monitoring), Safety Analysis Set (67 pages)

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Section 14.3.3

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16 List of Appendices

The following lists all Appendices available for the Clinical Trial Report. Appendices, which are not included in the regulatory submission, are available upon request.

16 Appendices

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 IRB roster, IRB approval letter(s), and sample subject consent form

16.1.3.1 IRB roster

16.1.3.2 IRB approval letters

16.1.3.3 Sample subject consent form

16.1.4 List of investigators and other important participants in the study and their curricula vitae

16.1.4.1 List of investigators and other important participants in the study

16.1.4.2 Curricula vitae of investigator and other important participants in the study

16.1.5 Signatures of principal or coordinating investigator(s) and sponsor's responsible medical officer

16.1.6 Study drug information

16.1.6.1 Listing of patients receiving trial product(s)/investigational product(s)

16.1.6.2 Analytical certificates and release certificates

16.1.6.3 Description of packaging and labeling

16.1.7 Randomization scheme and codes

16.1.8 Audit certificates (if available)

16.1.8.1 Audit certificates

16.1.8.2 Description on Co-operation with PharmaNet AG and PPD

16.1.8.3 Remonitoring plan

16.1.9 Documentation of statistical methods

16.1.9.1 Statistical analysis plan

16.1.9.2 SAS output

16.1.9.3 Data handling plan

16.1.10 Certificates of laboratory accreditation, documentation for analytical methods used, and quality assurance procedures

16.1.10.1 Certificates of laboratory accreditation

16.1.10.2 Bioanalytical sample analysis report

16.1.11 Publications based on the study

16.1.12 Publications referenced in the report

16.2 Patient data listings

16.2.1 Discontinued patients

16.2.2 Protocol deviations

16.2.3 Patients excluded from the efficacy analyses

16.2.4 Demographic and baseline data

16.2.5 Compliance and/or drug concentration data

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each patient)

16.2.8 Listing of abnormal individual laboratory measurements by patient

16.3 Case report forms (CRFs)

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for adverse events

16.3.2 Other CRFs submitted

16.4 Individual patient data listings

Amendment and Protocol for Review

Amendment 1 and Updated Protocol for review

FT-018-IM

Document ID: C00009233

Version: 0.1

Substantial Protocol Amendment No. 1

A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 μg with an open long-term safety follow-up in cancer patients with breakthrough pain

Trial ID: FT-018-IM

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

Co-ordinating Trial Manager: Rikke Bischoff, MSc. Pharm.
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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 7.3 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 trials FT-016-IM/ FT-017-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 trials FT-016-IM/ FT-017-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 this 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: Efficacy and safety of intranasal fentanyl in the treatment of breakthrough pain

Title: A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 µg with an open long-term safety follow-up in cancer patients with breakthrough pain

Trial ID: FT-018-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 confirm the efficacy of intranasal fentanyl (NAF) titrated to doses 50, 100 or 200 µg for treatment of breakthrough pain (BTP) in cancer patients
- To establish long-term safety of treatment with NAF

Secondary objectives:

- To explore the relationship between dose of background opioid treatment and titrated NAF dose

Methodology

Follow-up trial in three phases of three NAF doses, 50, 100 and 200 µg:

Titration phase (Phase 1). Open dose-finding phase, in which the patient by titration establishes a successful NAF dose for treatment of BTP.

Efficacy phase (Phase 2). Double-blind phase, in which the patient receive the NAF dose identified in Phase 1 for treatment of six BTP and placebo for treatment of two BTP episodes in randomised order. Pain Intensity (PI) and General Impression (GI) is assessed in each of the eight BTP episodes.

Safety follow-up (Phase 3). Open safety follow-up phase, in which patients receive NAF for BTP. Dose of background opioids and NAF are adjusted as needed.

If background opioid is adjusted:

1. During titration phase: Titration is repeated and the patient continues to Efficacy phase
2. During Efficacy phase: The patient will stop this phase and enter Safety follow-up phase after having repeated titration (without patient assessments in a diary).

Number of patients

The number of patients aimed for is minimum 100 and maximum 200. Planned 35 centres in 5-10 countries.

Diagnosis and main criteria for inclusion

Adult in/out patient with cancer and breakthrough pain; use of stable, chronic opioid treatment for background pain. Eligible patients are those, who received at least one NAF dose in FT-016-IM (NAF pharmacokinetic trial) or FT-017-IM (NAF confirmatory efficacy trial). Entry criteria must apply. Chemotherapy and palliative radiotherapy (except facial radiotherapy) are 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/puff, hereafter named Investigational medicinal product (IMP). 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 maximal dose will be 400 µg. The initial NAF dose in Phase 1 will be 50 µg per puff. Two BTP episodes will be treated with placebo in Phase 2. Rescue analgesics are allowed as needed throughout the trial and can be taken 10 min after the second IMP puff.

BTP episodes to be treated with IMP

The BTP episodes for which the patient has such strong pain that he/she judges it necessary to take analgesics. All such BTP episodes up to four episodes per day will be treated with IMP throughout this trial.

Reference drug

In Phase 2, two of eight treatments are placebo.

Duration of treatment

Phase 1 and 2 are expected to last between one and eight weeks. Maximum allowed time in Phase 1+2 is 14 weeks after which the patient will be withdrawn. Four months after inclusion of the last patient in the trial, an interim analysis will be performed. Safety data will be collected for further six months and the trial will then be terminated. Subsequently, patients are offered the NAF medication on a named patient treatment until recovery, withdrawal or death.

Criteria for evaluation

Efficacy (based on patient evaluation in diary):

Primary endpoint:

- Pain intensity difference at 10 min (PID_{10}) derived from PI scores

Secondary endpoint:

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

Safety

- Adverse events

Statistical methods

The analysis of the primary endpoint, PID_{10}, will be based on a linear model including treatment (active, placebo), centre, and baseline PI (mean and deviation from mean) as effects. The null hypothesis of no treatment effect will be tested in this model. 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

	Phase 1 Dose titration		Phase 2 Efficacy	Phase 3 Safety follow-up		End-of-Trial
Activities and assessments at visits/phone contacts	**Visit 1 Eligibility check**	**Dose titration visits**	**Visits**	**Visits (monthly)**	**Phone contacts (weekly)**	**End-of-Trial visit**
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demographic data	X					
Cancer related medical history	X					
Physical examination	X					
Past and concomitant illnesses	X					
Concomitant medication	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Check that dose of background opioid is adequate	(X)*	X	X	X	X	
Adjustment of background opioid/re-titration and pausing patient	Any time when needed					
Estimated number of IMP treated BTP episodes per day				X	X	X
Patient diary (instruction/evaluation)	X	X	X			
NAF handing-out/ drug accountability	X	X	X	X		X
End-of-Trial						X
Patient activities at home:						
NAF treatment	X	X	X	X	X	
Assessment of NAF treated BTP episodes in diary	X	X	X			

*Is part of the inclusion criteria
Duration of Phase 1 and 2: Expected 1-8 weeks, maximum 14 weeks.
Duration of Phase 3: Interim analysis when 4 months has elapsed after the last patient was included in the trial. This is followed by an additional 6 month-period, during which safety data are collected.

Afterwards, patients are offered to receive NAF on a named treatment basis.

Table of Content

APPENDICES

List of Abbreviations and Definitions of Terms

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

Patients who did not tolerate the test dose of 200 µg fentanyl in trial FT-017-IM or any of the doses received in trial FT-016-IM and who wish to proceed to FT-018-IM, will receive the first dose of titration (50 µg fentanyl) in-house. Here, healthcare staff will carefully survey the patient for one hour after administration. Enrolment in FT-018-IM will take place minimum one day after withdrawal from FT-016-IM or FT-017-IM.

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 associated with the use of intranasal fentanyl, are excluded.

Patients will receive a convenient and fast acting drug for their pain and are offered NAF for an unlimited time. Nycomed will collect data for 10 months after the last patient has been included. After this, patients will be offered the medication on a named patient basis.

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 Form

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 left with 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 (this includes 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 will be 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 Competent Authorities

Competent authorities must receive required documents according to national regulations. Nycomed will obtain approvals for the import of narcotic trial medication. Further, all necessary permits for the storage and transport 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.

The objectives of this trial are to demonstrate that a suitable dose of intranasal fentanyl (NAF) can be identified for treatment of BTP (Phase 1) and that long-term use of NAF is effective (Phase 2) and safe (Phase 3).

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

- To confirm the efficacy of intranasal fentanyl titrated to doses 50, 100 or 200 µg for treatment of BTP in cancer patients
- To establish long-term safety of treatment with intranasal fentanyl
- To explore the relationship between dose of background opioid treatment and titrated NAF dose

6 Overall Design and Plan of the Trial

This trial is a double-blind, placebo-controlled confirmation of efficacy of titrated doses of NAF for treatment of BTP with an open safety follow-up.

Rationale for trial design The patients will be individually titrated to an optimal dose. Subsequently, the efficacy of this dose is confirmed by treatment of eight BTP episodes of which two treatments are placebo. For the placebo treatment as well as any treatment of BTP throughout the trial, patients are allowed to take rescue analgesic, when/if pain relief after trial drug is insufficient. According to the guideline for treatment of nociceptive pain (CPMP/EWP/612/00) (17), placebo-controlled designs with appropriate use of rescue medication are recommended for trials not aiming to show superiority to any active comparator. 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 (18,19). In addition, only two of eight trial treatments are placebo and 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 (20) where 10 treatment units (seven active and three placebos) were given to patients in a randomised and blinded cross-over design. In addition, the cross-over design provides within-subject dose-response data, which can support the titration regimen.

Patients. Adult in/out patients with cancer and breakthrough pain, who receive stable, chronic opioid for background pain. Eligible patients are those who received at least one IMP dose in FT-016-IM (NAF pharmacokinetic trial) or FT-017-IM (NAF confirmatory efficacy trial) and who comply with entry criteria, see Sections 7.2 and 7.3.

Trial treatment. Available NAF strengths are 0 (placebo), 50, 100 and 200 µg fentanyl/puff, hereafter named Investigational Medicinal Product (IMP), see Section 9.1. One puff is administered in one nostril. If the patient has insufficient pain relief after 10 min, a second puff 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 (21). 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.

Use of rescue analgesics. If relief of BTP with IMP is insufficient, rescue analgesics may be used. This applies throughout the trial. Rescue analgesics should not be taken until 10 min after administration of a second NAF puff, see also Section 9.2.

BTP episodes to be treated with IMP. All BTP episodes up to four per day, for which the patient has such strong pain that he/she judges it necessary to take analgesics, will be treated with IMP throughout this trial.

Adjustment of background medication. Average background pain intensity must be controlled to a mild level (≤ 4 on an 11-point NRS), see Section 7.2. 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. Background opioids must not be taken during treatment of a BTP episode with IMP, i.e. including the 60 min when assessments are done, but can be taken after the 60 min.

Please note:

Adjustment of background opioid during the titration or efficacy phase is only expected for a few patients. However, if this occurs, the procedure is as follows.

1. During titration phase (Phase 1): Titration is repeated and the patient continues to Efficacy phase
2. During Efficacy phase (Phase 2): The patient will stop this phase and enter Safety follow-up phase (Phase 3) after having repeated titration (without patient assessments in a diary).

Phase 1 - Dose titration (open): The initial NAF dose will be 50 µg/puff with the option to increase the dose according to efficacy and adverse reactions. A successful dose is reached when three of four treated BTP episodes have been rated as successful according to definitions, see Section 8.2.1

Phase 2 - Efficacy assessment (double-blinded, randomised): The patient will treat six BTP episodes with the dose reached in Phase 1, and two BTP episodes with placebo in randomised order. Efficacy will be assessed as PI in all eight BTP episodes. See Section 8.2.2.

Phase 3 - Safety follow-up (open): Four months after inclusion of the last patient, an interim analysis will be performed. Safety data will be collected for additionally six months and the trial terminated. Subsequently, patients are offered NAF on a named patient treatment until death, recovery or withdrawal. The dose of background opioids and NAF may be adjusted as needed. There will be no patient assessments in this phase. For details, see the Flow chart, p 6 and Section 8.1.3, Visit procedures.

6.1 Efficacy Endpoints and General Impression Scale

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 (17) 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 endpoint is sum of pain intensity differences over the 0-60 min time interval, $SPID_{0-60}$.

For details of assessment of efficacy and statistical analyses, see Sections 8.2 and 15.2.3.

Appropriateness of Numerical Rating Scale (NRS)

Assessment of PI 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 (22-24). The NRS was chosen, as it is extremely easy to use – also for elderly patients.

Appropriateness of a general impression scale

For definition of successful treatment of BTP(s) during the titration phase, patients will assess their “General Impression” at 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 (25).

6.2 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 (17).

6.3 Trial Schedule

Planned first patient first visit:	Q2-Q3 2006
Planned recruitment period:	6 months
Planned last patient last visit:	10 months after the last patient was included
Interim analysis	4 months after the last patient was included
Planned completion of Clinical Trial Report:	Q2-Q3 2007

7 Trial Population

See Section 6. 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. 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, it is not possible to keep the patients hospitalised for the entire trial period. In the efficacy phase, the patients are acting as their own controls, and it is unlikely that these factors will jeopardise the final result.

7.1 Number of Patients

The number of patients will depend on the number of eligible patients from FT-016-IM and FT-017-IM, and will reach a maximum of approximately 200. The minimum number aimed for is 100 patients. Anticipated number of centres are 35 in 5-10 countries. Each centre should aim to include a minimum of five patients.

7.2 Inclusion Criteria

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

Inclusion Criteria

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 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 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 analgsics) 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 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).

11. Does the patient use adequate contraceptive precaution (contraceptive pill, implant or injection or intrauterine device) in the trial period?
12. Did the patient have a negative pregnancy test at the inclusion in studies FT-016-IM or FT-017-IM?

7.3 Exclusion Criteria

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

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 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 trials FT-016-IM/ FT-017-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?

7.4 Withdrawal of Patients

A patient who wishes to discontinue trial treatment must, if possible, be called in for End-of-Trial visit. Even if the patient is not able to attend, the End-of-Trial Form must be completed and the Drug Accountability Form filled in. All trial medication and patient diary must be collected from the patient.

7.5 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. The Investigator and the Monitor must discuss if the deviation has any consequences for the continued participation of the patient in the trial. This must be documented in the Investigator File and the Trial Master File.

8 Methods and Assessments

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 performed and are only listed later.

8.1.1 Dose Titration - Phase 1

In this phase, a successful NAF dose will be established for the individual patients. Patients will assess up to four BTP episodes per NAF strength starting with the lowest dose, 50 µg/puff according to Section 8.2.1. Assessments will be done for each strength until a successful NAF strength (one or two puffs) is identified.

Duration: Anticipated to last up to 6 weeks. Maximum allowed time in Phase 1+2 is 14 weeks after which the patient will be withdrawn.

Visit 1 – Eligibility check

For patients who were withdrawn from trials FT-016-IM or FT-017-IM due to undesirable effects of a NAF dose, this visit will take place minimum 1 day after this dose. Furthermore, the first dose of titration will be taken in-house and the patient monitored by health-care staff for one hour.

- **Informed consent**. Before any trial-related activities, the patient must sign and date the Informed Consent Form. See Section 2.1.
- **Inclusion/Exclusion criteria.** For details, see Sections 7.2-3. Regarding inclusion criteria 6 and 8: Dose of background medication must be adjusted if investigator judges that it is needed (see also Section 6).

- **Demographic data.** Age/date of birth, sex, race, height, weight (data are available from FT-016-IM/FT-017-IM)
- **Cancer-related medical history.** Data may be transferred from FT-016-IM/FT-017-IM
- **Physical examination.** Data may be transferred from last visit of FT-017-IM
- **Past and concomitant illnesses.** For details see Section 8.3
- **Concomitant medication.** For details see Section 8.3
- **Patient diary.** Handing out and instructing patient in use of the diary. 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.
- **NAF handing-out/accountability.** The patient will receive the spray containing 50 µg fentanyl/puff to begin titration at home from the following day. See also Section 9.1.
- **NAF open dose titration – procedure:** Step-wise titration will continue until a successful NAF dose is identified. A successful NAF dose is reached when three of four BTP episodes have been treated successfully with one or two NAF puffs, i.e. with sufficient pain relief and without intolerable adverse drug reactions, see Section 8.2.1. Please bear in mind that if two BTP episodes have been rated unsuccessful on a specific dose, the three successful episodes can no longer be reached on this dose and the patient should proceed to a new dose.

After each step of up to four BTP episodes, it is decided whether:

1. the patient should proceed to Phase 2 with the successful NAF dose identified,
2. the NAF dose should be increased (from 50 to 100 or from 100 to 200 µg fentanyl/puff),
3. the NAF dose should be decreased (from 200 to 100 or from 100 to 50 µg fentanyl/puff) or
4. the patient should be withdrawn, which must occur if a successful NAF dose is not established after four steps

All BTP episodes (up to four per day) for which the patient judges it necessary to take analgesics should be treated with NAF.

Patient activities at home

- **NAF treatment.** According to the procedure described above.

- **Assessment of NAF treated episodes in patient diary.** This will be done with the General Impression 5-point verbal rating scale (VRS) 60 min after the first NAF puff, for details see Section 8.2.

Following visits (dose titration visits)

- **Concomitant medication**
- **Adverse events**
- **Check, that dose of background opioid is adequate.** Investigator must tick yes or no, and if no, background opioid must be adjusted (see below).
- **Adjustment of background pain opioid and pausing patients**, if needed, see Section 6. Please note that after adjustment, titration must be repeated starting with the lowest dose and recordings in the diary. Subsequently, the patient continues to the Efficacy phase.
- **Patient diary.** Evaluation of patient's assessments.
- **NAF handing-out/drug accountability.** At each visit during dose titration, the patient will return the NAF spray (used or un-used). Dose and number of sprays will be recorded in the CRF. The patient will receive a new spray with the next dose to be tested if the previous dose was unsuccessful. The dose and number of sprays handed out are recorded in the CRF. Investigator will judge patient compliance and appropriate use of the IMP, see Section 9.1.2. The titration kit must be kept by investigator in case re-titration is required in Phase 2 and/or 3.

Patient activities at home

- **NAF treatment**
- **Assessment of NAF treated BTP episodes in diary**

8.1.2 Efficacy – Phase 2

This is an efficacy phase, in which the patient will treat six BTP episodes with the successful dose reached in Phase 1, and two BTP episodes with placebo in randomised order. Efficacy will be assessed as PI and GI in all eight BTP episodes.

Duration: Anticipated to last up to 3 weeks. Maximum allowed time in Phase 1+2 is 14 weeks after which the patient will be withdrawn.

First visit

- **Concomitant medication**
- **Adverse events**
- **Check that dose of background pain opioid is adequate**
- **Adjustment of background pain opioid and pausing patients,** if needed, see Section 6. Please note that after adjustment, titration must be repeated starting with the lowest dose without recordings in the diary. The titration kit sprays handed out in Phase 1 are re-used. Subsequently, the patient starts the Efficacy phase.
- **Patient diary.** Evaluation of patient's assessments in Phase 1 and instruction for Phase 2.
- **NAF handing out/drug accountability.** The patient will return the IMP spray (used/un-used) from the titration phase (Phase 1). The trial staff will record the dose of the returned spray in the CRF. The patient will receive the set of eight sprays. The sprays are numbered 1-8 and must be taken in this order. Investigator will judge patient compliance and appropriate use of the IMP, see Section 9.1.2.

Patient activities at home

- **NAF treatment.** The patient will treat eight BTP episodes with IMP.
- **Assessment of IMP-treated BTP episodes.** All eight BTP episodes will be assessed for PI and GI according to Section 8.2.2.

Last visit (is also first visit of Phase 3)

- **Concomitant medication**
- **Adverse events**
- **Check that dose of background pain opioid is adequate**
- **Adjustment of background pain opioid and pausing patients,** if needed**.** Please note that after adjustment, titration must be repeated starting with the lowest dose without recordings in the diary. The titration kit sprays handed out in Phase 1 are re-used. Subsequently, the patient enters the Safety follow-up phase.
- **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.

- **NAF handing-out/drug accountability**. The patient will return the IMP sprays (used and unused) from Phase 2 and the trial staff will record this in the CRF. The patient will receive NAF sprays in the appropriate dose for approximately one-month use for Phase 3. The strength and number will be recorded in the CRF. See also Section 9.1.1. Investigator will judge patient compliance and appropriate use of the IMP, see Section 9.1.2.

Patient activities at home until next visit

- **NAF treatment –** no assessments, no patient diary.

8.1.3 Phase 3 – Safety Follow-Up

In this phase, patients are offered the possibility of NAF treatment of BTP episodes for an unlimited time. An interim analysis 4 months after the last patient has been included in the trial will be performed. Safety data will be collected for additionally six months. Thereafter, patients are offered NAF on a named patient treatment until recovery, withdrawal or death. For the four+six months period, visits will be scheduled for approximately every month or more frequently when needed. This would for example be the case if the dose of background pain opioid or dose of NAF needs adjustment or in case of adverse events judged by investigator to require follow-up. In addition, weekly phone contacts will be performed and during these, adverse events and concomitant medication will be recorded and the dose of background pain opioid evaluated. The patient's estimated number of IMP treated BTP episodes per day will be recorded in the CRF. There will be no diary in this phase. The End-of-Trial visit will take place at the end of trial or in case of patient's withdrawal, recovery or early termination of the trial. Investigator is responsible for ensuring that trial drug and patient diary are returned to the clinic in case of patient's death (according to agreement with Monitor).

Visits (first visit = last visit of Phase 2)

- **Concomitant medication**
- **Adverse events**
- **Check that dose of background pain opioid is adequate**
- **Adjustment of background pain opioid and pausing patients,** if needed followed by dose titration without assessments in patient diary, see Section 6.

- **Estimated number of IMP treated BTP episodes per day** as estimated by the patient will be recorded in the CRF.
- **NAF handing-out/drug accountability.** The dose of the NAF sprays is the same as in Phase 2, unless Investigator judges that the patient requires a different dose according to treatment recommendations given for titration (three out of four BTP treatments successful), see Sections 8.1.1 and 8.2.1. The patient will receive NAF sprays in the appropriate dose for approximately one-month use for Phase 3. The strength and number will be recorded in the CRF. The patient returns used and unused sprays, which will be recorded in the CFR. Investigator will judge patient compliance and appropriate use of the IMP, see Section 9.1.2.
- **End-of-trial form** to be filled in at last visit/last contact/death.

Weekly phone contacts

During these contacts, the following items are checked and recorded in the CRF:

- **Concomitant medication**
- **Adverse events**
- **Check that dose of background pain opioid is adequate**
- **Adjustment of background pain opioid and pausing patients** if needed followed by dose titration without assessments in patient diary, see Section 6.
- **Estimated number of IMP treated BTP episodes per day** as estimated by the patient will be recorded in the CRF.

Patient activities at home

- **NAF treatment –** no assessments, no patient diary.

8.2 Methods of Assessment

8.2.1 Phase 1 – Dose Titration

In Phase 1, efficacy is assessed by General Impression (GI) at 60 min.

Flow chart

Activities and assessments of BTP episodes in Phase 1				
Time (min)	**0**	**10**	**20**	**60**
Administration of medication:				
First IMP puff	X			
One additional IMP puff, if needed		(X)		
Rescue analgesic, if needed			(X)……(X)	
Assessments:				
General Impression (GI)				X

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

The following will be recorded in the diary:

- **Date, time and dose** of the first NAF puff and, if applicable, the time of the second puff
- **Rescue analgesic.** Any use of and time to rescue analgesic within 20-60 min
- **General impression** of efficacy at 60 min using a categorical 5-point VRS, 0=poor, 1=fair, 2=good, 3=very good; 4=excellent

The definition of successful NAF treatment (one or two puffs) is:

- No need of rescue analgesic within the first 60 min
- A score of ≥ 2 on the GI scale by the patient at 60 min after the first NAF puff
- No severe undesirable effects such as pronounced hypoventilation, unacceptable sedation or drowsiness

For a NAF dose (50, 100 or 200 µg/puff) to be successful, treatment of at least three of four BTP episodes must be considered successful by the patient according to the above definition. If two treatments with a given dose are unsuccessful, the patient should proceed to the next dose (one step up or down) since three out of four can no longer be reached. If in three of four episodes, pain relief is obtained only after a second NAF puff, Investigator may consider increasing the dose. This consideration should be based on the balance between efficacy and adverse events.

Algorithm for dose adjustment

BTP treatment	**Successful**		**Unsuccessful**	
Undesirable effects	**No**	**Yes**	**No**	**Yes**
Decision	Go to Phase 2	One strength down For 50 µg: withdrawal	One strength up For 200 µg: withdrawal	Withdrawal

Pain relief	Yes:	Three or four BTP episodes with GI ≥ 2, no use of rescue analgesic
	No:	At least two episodes with GI < 2 and/or use of rescue analgesic
Undesirable effects	Yes:	One or more undesirable effects
	No:	No severe undesirable effects

If after up to four titration steps (all three doses and possibly one down-titration), Phase 2 is not reached, the patient must be withdrawn.

8.2.2 Efficacy - Phase 2

All eight BTP episodes will be assessed for pain intensity and general impression.

Flow chart

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

8.2.3 Phase 3 – Safety Follow-Up

The trial staff will record Adverse Events and concomitant medication in the CRF during visits and at all phone consultations.

8.3 Past and Concomitant Illness 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

A worsening in severity or frequency of a baseline concomitant illness as well as any new illness diagnosed during the trial must be regarded as adverse events whether or not they are 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 and 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 treatment failure.

The 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.

9 Trial Treatment

9.1 Intranasal Fentanyl and Placebo (IMP)

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.

Application of a second NAF puff

An effective NAF dose will generally lead to an onset of pain relief within 10 min. If sufficient pain relief is not obtained at 10 min, an extra 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 20 min, the subject may take either his/her usual immediate-release opioid or any other rescue analgesic. For use of rescue analgesic after 20 min, see Section 9.2. The reason for asking patients to wait for 10 min, is that onset of pain relief generally occurs during this period as seen in a previous trial (see Figure 1) (7).

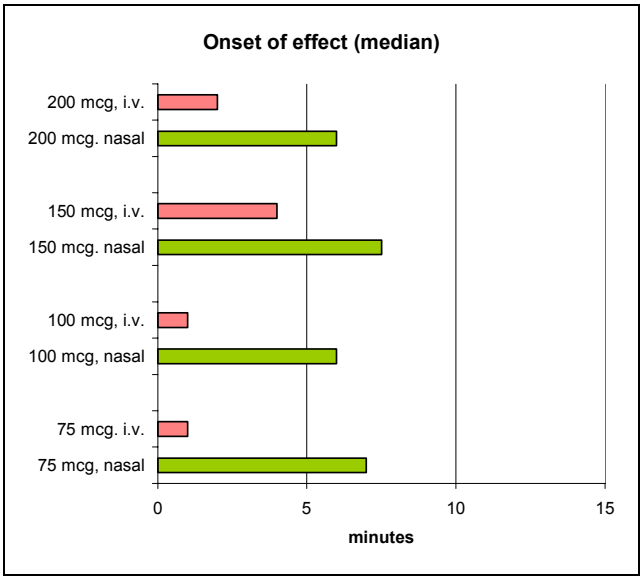

Figure 1: Onset of pain relief with i.v. and intranasal fentanyl

9.1.1 Packaging and Labelling

Phase 1: Titration kit

The titration kit includes a total of three sprays containing 50, 100 and 200 µg/puff, respectively. These will be packed together in an outer box. Each patient will receive a titration kit. The patient will bring home one spray from each visit in the titration phase and exchange this one with a new dose at the following visit until an optimal dose has been reached. Each spray has two tear-off labels. Investigator must insert one tear-off label in the diary when a spray is handed out. The second tear-off label is available if down-titration is required. Investigator must keep the titration kit for re-use if titration needs to be repeated later in the trial.

Phase 2: Efficacy kit

Each patient will receive a kit containing eight sprays: Six sprays with the successful dose identified in the titration phase and two placebo sprays. 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. 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.

Phase 3: Safety follow-up

The patient will receive sprays with the required strength for approximately one-month use. Each spray is packed in an outer box with a tear-off label for the investigator to insert in the CRF upon handout of the IMP.

All supply will be labelled with white labels, containing trial specific information according to Annex 13, European guideline (26). 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 containing approx. 40 doses as intended for marketing 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 in Phase 1 and 2 are only few 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 sprays from Phase 1 and 2 are 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.

In Phase 3, patients are instructed to use the entire content of the spray and this will be verified by visual inspection of whether the spray is empty or not.

9.1.3 Randomisation and Blinding (Phase 2)

Randomisation

Eligible patients will be randomised to a double-blind; eight spray sequence. Eight BTP episodes will be treated in total: Six BTP episodes with the NAF dose identified at dose titration and two episodes with placebo. The patient will receive the set of eight sprays with the lowest number available at the site. The sequence of administration of the six NAF and the two placebo treatments is randomised. Of the two placebo treatments, one occurs in episodes 1-4 and one in episodes 5-8.

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 Central Pharmacovigilance (CPV) Nycomed, 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 Central Pharmacovigilance (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

If pain relief is still insufficient 10 min after the second IMP puff, the patient may take rescue analgesic, either his/her usual immediate-release opioid or any other rescue analgesic. Any other analgesic than IMP taken during the 60 min after the first IMP puff will be regarded as rescue analgesic. Analgesics 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. Dose of background pain opioid must be adjusted according to investigator's judgement (background pain exceeds 4 on the 11 point NRS or > four BTP episodes per day). Adjustment of background pain opioid must be individual and according to the actual development of the cancer. Background opioids must not be taken during treatment of a BTP episode with IMP, including the 60 min when assessments are done. See also Section 6, Adjustment of background medication.

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 AE 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

- 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 trial drug 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 trial product 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 trial drug, 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 (27).

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 using the MedDRA terminology, current version.

10.9 Sponsor's Assessment of Expectedness

Nycomed Central Pharmacovigilance will evaluate all AEs with respect to seriousness, causality and expectedness in accordance with the Directive 2001/20/EC (14). The expectedness of an AE will be determined according to Investigators Brochure (27), current version.

11 Case Report Forms

The Case Report Forms (CRFs)/diary for patients participating in the trial will be provided by Nycomed via a CRO. The completed original CRFs are the sole property of Nycomed and

should 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 on 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. Queries issued on a Data Clarification Form 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 will be 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, number of IMP puffs taken and time for intake of IMP and rescue analgesics.

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 7-8 weeks intervals until 4-month data (4 months after last patient has been included) and subsequently every 3 months during the 6 months follow-up period. 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. Audit will be performed according to current SOPs.

12.3 Inspection from Competent Authorities

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

13 Data Management

A CRO will perform the data management. The patient 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 Data Clarification Form (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 patients who enter the efficacy phase of the trial and treats at least one BTP episode with investigational product.

The per-protocol (PP) dataset includes the subset of the ITT dataset with the following criteria for exclusion:

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

The safety dataset includes all patients that received a dose of investigational product.

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 (20), who investigated transmucosal treatment of BTP in cancer patients. In Fig. 1 of Farrar et al (20), 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.

In this trial the treatment contrast is between 6 active and 2 placebo treated episodes resulting in an SD of $1.71 \cdot \sqrt{1/6 + 1/2} = 1.40$.

Patients for this trial will be recruited among patients completing the FT-016-IM and FT-017-IM trial so the expected sample size is 100-150. With six episodes treated with active doses and two treated with placebo, with a hypothesis of no treatment effect, assuming a linear model for the analysis, with a significance level of 5%, the following tables of power may be derived for mean PID_{10} differences around 0.5:

Power		SD for treatment contrast		
Sample size	Mean PID_{10} difference	1.3	1.4	1.5
N=100	0.4	86%	80%	75%
	0.5	96%	94%	91%
	0.6	99%	98%	97%
N=150	0.4	96%	93%	90%
	0.5	99%	99%	98%
	0.6	99%	99%	99%

As seen from these considerations, a sample size of 100-150 patients for the efficacy phase is sufficient to detect treatment effects of size 0.4 – 0.6.

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. Discontinuations will be tabulated by 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 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 2nd 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 $SPID_{0-60}$. $SPID_{0-60}$ 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.

15.2.4 Efficacy Analyses

The efficacy analysis will focus on the results of the efficacy phase of the trial. Data from the titration phase will be summarised by descriptive statistics including the distribution of patients on doses after titration.

The primary endpoint is PID_{10}, the PID at 10 min after application of the first NAF puff. PID_{10} will be analysed using a mixed linear model including the following fixed effects:

- Treatment (active, placebo) (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.

The null hypothesis to be tested is that the average response to active treatment is the same as the response to placebo versus the alternative that they differ. This will be tested using an F-test of the active versus placebo contrast for the treatment effect in the described model.

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

As supportive evidence to the primary analysis treatment-by-centre interaction will be added to the model as a fixed effect. This analysis will explore possible heterogeneity in treatment effect between centres and provide an estimate of average treatment effect in the case of heterogeneity. The primary endpoint will be analysed for the ITT and PP datasets with main emphasis on the ITT analysis. Estimated means by treatment (active and placebo) will be presented with estimated difference between active and placebo with 95% confidence intervals and p-values.

The variation in PID_{10} between two episodes within patient will be calculated by treatment expressed as SD and CV. The summary statistics (n, mean, median, SD, min, max) will be tabulated by treatment.

In addition to the analysis of PID_{10} scores, average responder rates will be computed by treatment. 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 treatment (active or placebo) within each patient and then averaging those averages across all patients for placebo and active treatment respectively.

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

General Impression (GI)

GI will be analysed as described for the primary endpoint but without covariate adjustment for baseline since no baseline value is available for GI. 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 treatment will be summarised by descriptive statistics.

Supplementary exploratory analyses may be performed for the efficacy endpoints.

15.2.5 Safety Analyses

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

15.2.6 Other Analyses

The relationship between NAF dose and the dose of the stable background pain opioid will be explored by summarising the distribution of patients on NAF doses after titration by doses of background pain opioids grouped in low, medium and high dose. In this analysis, background pain opioid doses will be standardised to morphine equivalent doses using guidelines by Breitbart et al. 2000 (29), see also Appendix 1. For grouping of background pain opioid doses, the same cut points as defined in FT-017-IM for low, medium, and high dose will be used.

The number of times that repeat NAF at 10 min was used will be tabulated by treatment (active, placebo). In addition, the proportion of all episodes where any type of rescue medication was taken will be tabulated by treatment and time point.

15.3 Interim Analyses

An interim analysis will be performed four months after the last patient has been included. The Clinical Trial Report will be based on these data. For the remaining six months, only safety data will be collected. An amendment for the Clinical Trial Report will contain these safety data.

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 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 subjects and assure appropriate therapy and follow-up of the subjects.

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 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 including:

- 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 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 8 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

The Investigator must arrange archiving of the Investigator File, CRF copies and source data. The Investigator 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 the Sponsor.

It is the responsibility of the 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 subject 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/hospital or doctors conducting clinical trials or by persons for whom the said clinic/hospital or doctors are responsible.

21 References

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Country specific Substantial Protocol Amendment No. 02: France

A double-blind, randomised, placebo-controlled trial confirming the efficacy of intranasal fentanyl titrated to 50, 100 or 200 μg with an open long-term safety follow-up in cancer patients with breakthrough pain

Trial ID: FT-018-IM

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Trial phase: Therapeutic confirmatory

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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 7.3 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 trials FT-016-IM/ FT-017-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 trials FT-016-IM/ FT-017-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 this 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.

FT-018-IM

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