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Research Article

Efficiency of Intranasal Fentanyl in Patients with Breakthrough Cancer Pain in Daily Practice – Results of the German Non-Interventional Study with Instanyl® (GENISIS)

Abstract

Objective: Breakthrough cancer pain (BTcP) affects 19-95% of cancer patients (dependent on the definition and methods used and the populations studied) and is associated with detrimental physical, psychological and social complications in affected individuals as well as with significant economic burden on society and the healthcare system. This study evaluated the analgesic efficacy and safety of intranasal fentanyl spray (INFS) for the treatment of BTcP in a clinical setting with a special focus on its impact on health care resource utilization.

Research design and methods: This was a prospective, open-label, non-interventional, multi-center study. Opioid-tolerant adult patients with BTcP received INFS in the course of routine clinical practice, and completed standardized questionnaires as well as BTcP diaries over a 28-day observation period.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT00994760

Main outcome measures: Efficacy was assessed using measures of BTcP intensities, the times to first and to the maximum effect of INFS, as well as changes in BTcP-related restrictions in quality-of-life (QoL), activities of daily life (ADL) and overall wellbeing. Further analyses based on INFS-related changes in health care resource utilization. Treatment emergent adverse events (TEAEs) were recorded throughout.

Results: Overall, 58 centers participated and enrolled 131 patients, of whom 116 (88.5%) completed the observation period and documented a total of 556BTcP episodes. The 100µg dose was judged as the most effective INFS dose in 64.0a% of patients, followed by 50 µg (28.0a%) and 200 µg (8.0 a%). The study recorded a substantial INFS-related improvement in maximum BTcP intensity, compared with baseline as well as prior use. Patients reported experiencing the first effects of the study drug within 5 minutes of administration in 81.9% of episodes, and a time to maximum effect within 10 minutes in 81.4% of episodes. QoL and BTcP-related restrictions in ADL showed considerable improvements during the observation period. INFS was well tolerated, with sixpatients (4.6%) experiencing ≥1 study drug-related adverse event. Study limitations include a modest size and duration, and the single-arm design.

Conclusion: Under the conditions of this non-interventional open-label study, INFS proved to be a rapid onset, highly effective and well tolerated alternative for the treatment of BTcP in opioid-tolerant cancer patients. INFS treatment was not only associated with substantial improvements in BTcP intensity as well as related restrictions in QoL and ADL, but also with a respectable decrease of health care resource demands – especially in the field of ambulatory palliative care nursing services.

Introduction

Breakthrough cancer pain (BTcP), first described by Portenoy and Hagen in 1990 [1], is currently defined as a transient exacerbation of pain in cancer patients that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain [2]. Due to epidemiological studies, BTcP is a common cancer complication with reported prevalence rates ranging between 19-95% (dependent on the definition and methods used, and the populations studied) [3-7], which is accompanied by detrimental restrictions in quality of life, daily functioning, social relationships and enjoyment of life in

individually affected patients [7,8], as well as a significant economic burden on society and the healthcare system [8-11].

Due to these unique characteristics, patients suffering from BTcP require – in addition to a slow release opioid regimen for their chronic background pain – an adequate supplemental short-acting medication characterized by a pharmacokinetic and -dynamic profile closely matching the temporal dynamics of the BTcP episodes (i.e. rapid onset of action and short duration of effect), as well as appropriate easy-to-use preparations [12].

Fentanyl, a synthetic highly potent pure μ-opioidreceptor agonist, characterized by a rapid onset of action and a short duration of effectafter iv administration, does not only closely matchthe temporal characteristics of BTcP [13,14], due to its high lipophilicity and its low potential for local irritation [15], it also opens new– transmucosal (buccal, sublingual, nasal, pulmonal) – administration pathways and has ledto the development of several alternative fentanyl preparations now commercially available for the treatment of BTcP, including the intranasal fentanylspray (INFS).

Due to clinical studies, INFS constitutes a promising new treatment approach for BTcP, having demonstrated not only clinically important analgesic efficacy within 10 minutes post-administration as well as a favorable safety/tolerability profile in two randomized, placebo-controlled trials [16,17], but even a superior analgesic efficacy in comparison to oral transmucosal fentanyl citrate (OTFC) during a randomized active controlled cross-over trial in cancer patients suffering from BTcP [18].

These findings provide robust evidence of the efficacy and safety of INFS within the restricted setting of clinical trials, however, cannot answer the question, if and to what extent the pharmacological advantages of INFS and the reported analgesic effects translate into improvements of outcomes relevant for individual patients with BTcP as well as for the associated social and economic burden. The current study 'GENISIS' (German Non-Interventional Study with InStanyl®) – a prospective open-label, non-interventional multicenter study – was designed to complement and expand upon the previous results by evaluating these parameters under less restricted treatment conditions, in the diverse population of patients encountered in daily practice. The primary research objective of the present 28-day, observational study with INFS was to expand the understanding of actual clinical outcomes related to the use of INFS for BTcP in opioid tolerant cancer patients, with a special focus on healthcare resource utilization.

Patients and Methods

Overall study design

This was a prospective, open-label, non-interventional study, conducted as post authorization observational study in accordance with German Drug Law (AMG) §67 at 58 treatment centers in Germany. INFS prescriptions were issued by healthcare professionals who are knowledgeable of and skilled in the use of strong opioids to treat cancer pain. The study was approved by the appropriate ethics committee at the State Authorisation Association for Medical Issues in Baden-Wuerttemberg (AZ: 2009-089-f), notified to the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) – the national German Authority, and reported to ClinicalTrials.gov – the international clinical trials registry at the National Institutes of Health (ClinicalTrials.gov Identifier: NCT00994760).

Patients provided written informed consent to the collection and release of anonymized data. Patients received INFS in the course of routine clinical practice, and completed questionnaires relating to their health and treatment over a 28-day observation period. Supplemental information was gathered through standardized questionnaires for physicians and palliative care nursing assistants (PCNA), which were filled in parallel to the course or at the end of the study. Patient selection was completely at the discretion of the responsible physician who was directed to observe the guidelines for the treatment of breakthrough pain contained in the technical information. The necessity for use of INFS was solely the decision of the responsible physician.

Study population

Male and female adult patients (age ≥ 18 years) suffering from cancer-related breakthrough pain despite a stable opioid regimen (with at least 60 mg of oral morphine daily, or 25 micrograms of transdermal fentanyl per hour, or 30 mg oxycodone or 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer) who were initiated to a supplemental analgesic treatment with INFS were eligible for enrollment into this study. In- and exclusion criteria were those given in the summary of product characteristics [19].

Study procedures

The 28-day observation period comprised 3 study visits and 2 additional documentation time-points (Figure 1). The study questionnaires and procedures were explained to patients in detail prior

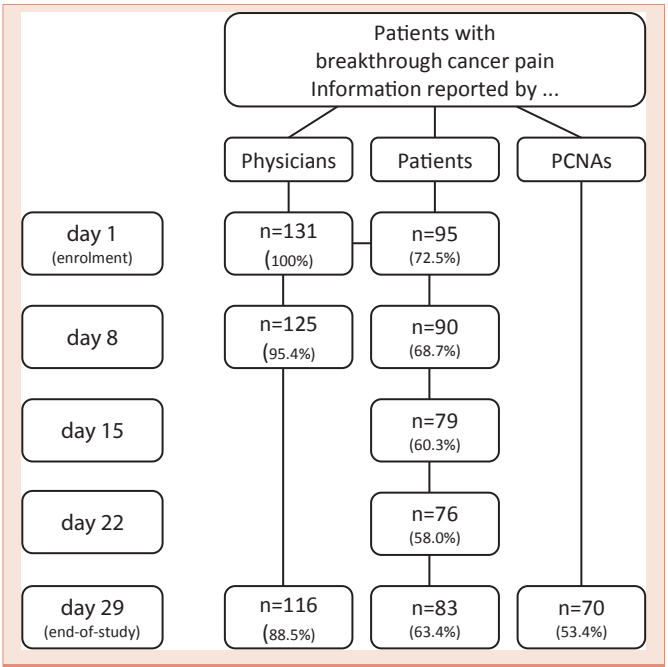

Figure 1: Design, flow of participants and patient assessment schedule/rates through the course of the trial.

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to commencement. Eligible patients provided data on their pre-study (baseline) health, treatment and pain by completing an enrollment questionnaire, during visit 1. At the end of each observation week subsequent questionnaires were completed by patients at home for the following 28 days and returned to the physician at the next study visit. Additionally, patients completed detailed BTcP questionnaires for the first (up to 12) BTcP episodes treated with INFS. Physicians completed corresponding questionnaires at baseline as well as after 8 and 29 days of treatment and participating PCNA documented their experience with INFS at the end of the observation period.

The questionnaires used in this study were developed by the Institute for Quality Assurance in Pain Therapy and Palliative Care (Institut für Qualitätssicherung in Schmerztherapie & Palliativmedizin, IQUISP) on behalf of the German Pain Society (Deutsche Gesellschaft für Schmerztherapie, DGS), based on standardized and validated questionnaires used for the routine evaluation of (cancer) pain [20] and palliative care patients [21,22], and were modified in accordance with the study schedule.

Treatment patterns and dose titration were solely at the discretion of the physician and the patient. INFS (available as multi dose nasal spray in three different dosage strengths containing 50, 100, and 200 µg fentanyl per dose) was prescribed after a thorough discussion of its appropriate use. Instructions and advice were provided according to the centers' clinical procedures, the summary of product characteristics and the patient information leaflet [19]. INFS initial dose was determined by the physicianon the basis of prior treatment, with consideration of the opioid dose for background pain and prior experience with alternative BTcP medications. INFS dose was then individually titrated as necessary, to find the dose that provided adequate analgesia without any or with tolerable adverse drug reactions. Titration was permitted and recorded throughout the whole study. Patients self-administered INFS, on an as-needed basis for BTcP episodes that occurred during the observation period. Adjunct therapies and rescue medication were administered in accordance with the treatment centers' standards of care and clinical procedures, and changes in treatment were permitted and recorded throughout the observation period.

Efficacy, quality of life and safety assessments

The efficacy of INFS was evaluated using measures of patients' experience of pain and pain relief. Pain intensity was measured using an 11-point numeric rating scale (NRS_{11}), from 0 ('no pain') to 10 ('strongest pain conceivable') [23-26]. Prior to initiation of treatment with INFS, patients were asked to describe their current pain intensity status ("as it was during the last week"). Patients recorded baseline scores for background (chronic) pain intensity in the enrollment questionnaire, as well as for the maximum pain intensity usually experienced during their BTcP episodes. During the observation period, patients used BTcP questionnaires to record the maximum BTcP intensities experienced before they administered INFS, as well as the pain intensities at the time-point of the maximum INFS effect.

Patients recorded their experience of pain relief following administration of the study drug in the BTcP questionnaire. Patients were asked to select from a list of time intervals under each of two phrases: 'time to first effect' and 'time to maximum effect'. Moreover, all patients were asked to rate INFS with respect to 'speed of action', 'strength of action', 'tolerability', 'ease of use', and 'global satisfaction' on a 6-point verbal rating scale, ranging from 'very good' to 'inefficient'. Patients who had previously used alternative supplementary pain relief medication for BTcP completed an additional section, in which they rated the effectiveness of INFS in comparison to their previous medicationon a 7-point verbal 'clinical global impression of difference scale' (CGIDS), ranging from 'very much better' to 'very much worse'.

BTcP-related functional and emotional restrictions in daily life were assessed in the enrollment and end-of-study questionnaires, using a modified version of the pain disability index (mPDI) [27], and the quality-of-life (QoL) impairment by pain inventory (QLIP) [28-30]. Using the mPDI, patients indicated their level of disability in each of seven dimensions ('household and family', 'leisure and recreation', 'social activities', 'work', 'independence in personal hygiene and daily life', 'sleep', and 'quality-of-life'), using an 11 point numeric rating scale ranging from 0 ('no disability') to 10 ('complete disability'). Quality-of-life was quantified on the basis of seven QLIP domains ('wellbeing', 'duration of sleep', 'temporal pattern of pain', BTcP-related influences of 'activities' and 'mood', 'patients ability to relieve pain' and the 'presence of BTcP- and/or treatment-emergent adverse experiences'), using appropriate verbal/numerical rating scales, and the calculation of a total score ranging from 0 ('worst QoL') to 40 ('best QoL').

Patient data was supplemented by additional information of the participating physicians as well as the responsible PCNA. Epidemiological data on cancer-type (tumor diagnosis, TNM-stage), and data on patientsphysical and performance status [according to the American Society of Anesthesiologists (ASA) physical status classification system) [31], performance [using the Karnofsky performance status scale (KPPS) [32,33], as well as the Eastern Cooperative Oncology Group (ECOG) performance status [34], co-morbidities, relevant sociodemographic factors, prior as well as current pain treatments, and current requirements with respect to nursing assistance/help (according to the German standards/ recommendations given by Radbruch et al. in 2009) [22], were recorded in special enrollment and end-of-study questionnaires. Information of PCNAs were gathered at the end of the study only and focused on INFS-induced changes with respect to BTcP-related global restrictions/disabilities and nursing assistance.

Patients were continuously monitored for treatment emergent adverse events (TEAEs) throughout the whole observation and events were evaluated for severity and relationship to study medication, as well as reported using the Medical Dictionary for Regulatory Activities (MedDRA) [35].

Primary outcome measures

The primary outcome measures were changes in pain intensity, as well as time to onset ('time to first effect') and time to maximum pain relief ('time to maximum effect') after INFS administration by patient self-report and proxy assessment. Further outcome measures focused on associated changes concerning BTcP-related functional and emotional restrictions in daily life activities, quality-of-life, and healthcare resource utilization demands.

Statistical analysis

No formal sample size calculation was performed. Data analyses were performed using IBM SPSS statistics (version 18.0). All analyses were exploratory; no confirmatory analyses were performed, or statements derived. Continuous variables were summarized using descriptive statistics (number of patients, mean, median, SD, range) and binary or categorical variables using absolute and relative (in case of missing data adjusted) frequencies (%/a%). Pre-/post treatment effects of categorical variables were compared using Cochran-Mantel-Haenszel test, while continuous variables were compared using the Wilcoxon test for paired samples.

Results

Patients

Overall, 58 centers participated and enrolled in total 131 patients into this study, of whom 116 (88.5%) could be followed-up for the whole 28-day observation period. In total, 95 patients (72.5%) supplemented the physician derived data at baseline and 83 at the end of the observation period by self-report. In addition, PCNAs added information for 70 patients after completion of the observation period (Figure 1).

Baseline demographic and clinical characteristics of study participants are presented in Table 1. Mean [SD] age was 62.1 [12.1] years (median, 64 years; range, 24–91 years), with an approximately equal gender balance (of 127 patients who provided gender data, 60 [47.2a%] were female); mean [SD] weight was 66.7 [14.4] kg, mean [SD] height was 169.3 [9.2] cm, and mean [SD] body mass index was 23.2 [4.4] kg/m^2. Patients' mean [SD] Karnofsky physical performance status was 58.6 [21.6] percent (median, 60%; range, 10–90%), ASA physical status was II in 17.5 a%, III in 31.7 a%, IV in 46.8 a% and V in 4.0a% of patients, and the ECOG performance status was "0"or "1" in 28.0 a%, "2" in 32.0 a%, "3" in 28.8 a% and "4" in 11.2 a%. The most frequently reported primary tumor sites were the GI-tract (27.0 a%), the breast (21.4 a%), the lung/respiratory system (16.7 a%) and the prostate (13.5 a%). Of 125 patients for whom this information was given, 71 (56.8 a%) suffered from a primary tumor stage of ≥T2, 90/124 (72.6 a%) presented with regional lymph node metastases, and 69/107 (64.5 a%) with distant metastases. Tumor or tumor treatment-related co-morbidities with relevance for BTcP treatments were reported for 99/131 patients (75.6%), with nausea (67.7 a%) most frequently observed, followed by vomiting and dysphagia (each 40.4 a%), mucositis (30.3 a%) and xerostomy (16.2 a%).Other than malignancies, cardiovascular and musculo-skeletal disorders were the most commonly reported concomitant illnesses (each 44.7 a%), followed by psychiatric (31.9 a%) and gastrointestinal disorders (29.8 a%). With 78.7 a% three of four patients for whom this information was given received outpatient care, and out of those 37.0 a% participated in specialist ambulatory palliative care programs.

On average [SD; median; range], patients experienced three [2.2; 3; 0.3-15] BTcP attacks per day, of which 57.6/29.3% usually lasted more than 30/60 minutes. Mean [SD] background pain intensity at enrollment was 5.6 [2.3] on the NRS_{11}, the tailored treatment target (TTT) was set at 4.0 [1.5], and maximum BTcP intensity was 8.3 [1.4].

Table 1: Baseline demographic and clinical characteristics of the study population (n=131).

Variable	n (%)	Mean (SD)	Range (Min-Max)
Age; years (N=130)		62.1 (12.1)	24-91
Gender; female (N=127)	60 (47.2)		
Weight; kg (N=126)		66.7 (14.4)	36-105
Height; cm (N=127)		169.3 (9.2)	146-192
Body mass index; kg/m^2 (N=126)		23.2 (4.4)	14-36
KPPS (N=125)		58.6 (21.6)	10-90
ASA-PS; ≥IV (N=126)	64 (50.8)		
ECOG; ≥3 (N=125)	50 (40.0)		
Primary tumor site (affecting at least 4 patients; N=126)			
GI-tract	34 (27.0)		
Breast	27 (21.4)		
Lung/respiratory system	21 (16.7)		
Prostate	17 (13.5)		
Lip, oral cavity and pharynx	8 (6.3)		
Urologic	7 (5.6)		
Female genital	4 (3.2)		
others	8 (6.3)		
Tumor size (N=125)			
Tx	10 (8.0)		
T0	4 (3.2)		
T1	40 (32.0)		
T2	22 (17.6)		
T3	20 (16.0)		
T4	29 (23.2)		
Lymph node involvement (N=124)			
Nx	12 (9.7)		
N0	22 (17.7)		
N1	52 (41.9)		
N2	38 (30.7)		
Metastasis (N=122)			
Mx	15 (12.3)		
M0	38 (31.2)		
M1	69 (56.6)		
Tumor-related BTcP-relevant comorbidities (N=99)			
Mucositis	30 (30.3)		
Xerostomy	16 (16.2)		
Nausea	67 (67.7)		
Vomiting	40 (40.4)		
Dysphagia	40 (40.4)		
others	18 (18.2)		

Analgesic medication at enrollment

The opioid medication most frequently used to treat background pain was fentanyl (62/130, 47.7 a%), followed by hydromorphone (22/130, 16.9 a%), oxycodone/naloxone (15/130, 11.5 a%) and morphine (12/130, 9.2 a%). The mean [SD] daily opioid dose equivalent to oral morphine (MEQ) was 176.8 [134.7] mg. With 70 (57.4 a%), the majority of those 122 patients for whom this information was given received low doses (equivalent to ≤180mg MEQ), while 45 (36.9 a%) and 7 (5.7 a%) received intermediate (>180-360mg MEQ/d) and high doses (>360mg MEQ/d).

Overall, 86 patients (65.6%) had no prior experience with BTcP medication. Among the 45 patients (34.4%) who recorded further information on their prior treatment experience, the most common BTcP medications used prior to study commencement were oral immediate-release morphine (27/45 [60.0%]), oral transmucosal fentanyl citrate (OTFC) and oral dipyrone (each 7/45 [15.6%]). Most frequently noted reasons for the switch to INFS were inadequateanalgesia and inefficient speed of onset (each 32/45 [71.1%]) of the pre-treatment.

Analgesic efficacy

In total, 556 BTcP episodes treated with INFS were documented by the patients throughout this study. With 41.2%, the majority of patients reported information on 10-12 BTcP attacks treated with IFNS, 27.9% on 6-9, 23.5% on 3-5, and only 7.4% on 1-2 BTcP attacks. Maximum pain intensities associated with BTcP attacks improved considerably with INFS treatment, compared to at time of enrollment (see Figure 2). Patients recorded a mean [SD] BTcP intensity of 3.4[2.1] at maximum effect for all episodes treated with INFS (median: 3; 95% CI: 3.31-3.50), compared with 8.3 [1.4] for those episodes experienced prior enrollment (median:9; 95% CI: 8.15-8.44; p<0.001) and 6.7 [2.2] (median: 7; 5% CI: 6.58-6.76; p<0.001) immediately before INFS-administration. Percentages of patients reporting BTcP-related pain intensities below NRS_{11} scores of 4 (i.e. better than defined by the reported TTT) increased from zero at enrollment to 56.0 a% for all BTcP attacks treated with INFS.

INFS-related pain relief was rated as "complete" or "very strong" in 38.8a% of attacks, as "strong" in further 31.0 a% and as "moderate" in 25.6 a%. Only in 2.9 / 1.6 a% of all BTcP attacks pain relief was classified as "mild" or "none".

Speed of onset

Patients reported that the time to first effect following INFS administration was ≤10 minutes in 94.3% of episodes (Figure 3). Indeed, first effect was reported within5 minutes in 81.9% of episodes, and within 2 minutes in 36.3% of episodes. Additionally, patients reported that the time to maximum effect following INFS administration was ≤10 minutes in 81.4%, ≤5 minutes in 45.1%, and ≤2 minutes in 16.1% of episodes.

BTcP-related restrictions in daily functioning, quality-of-lifeand overall well being mPDI scores indicated considerable improvements (decreases in score) in daily functioning during the observation period (Table 2). Overall improvement was seen in 92.3 a% of patients and average mPDI sub-scores dropped from 6.8-7.8 at enrollment to 3.6-4.4 at the end-of-study visit (p<0.001). In parallel, the percentages of patients reporting none or only mild BTcP-related restrictions (defined as scores ≤3) increased from 0.0-7.4 a% to 39.5-51.2 a% and those of patients experiencing severe or extreme restrictions (i.e.

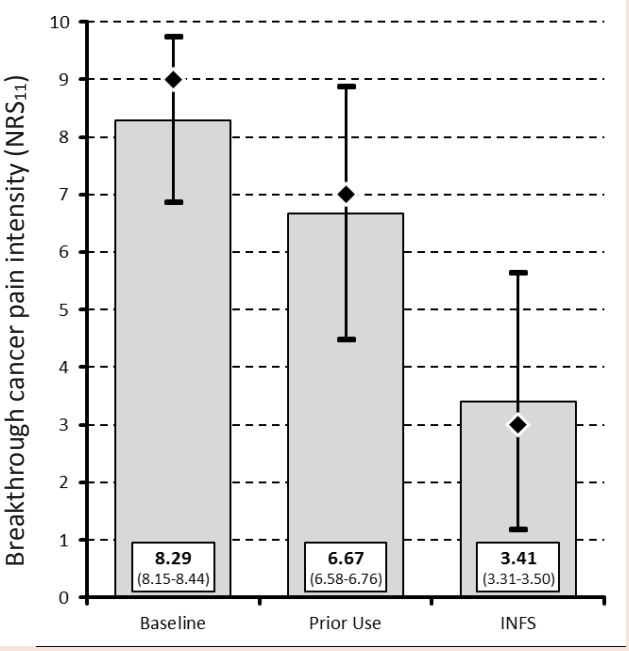

Figure 2: Scores for maximum intensity of breakthrough cancer pain (NRS11; 0=no pain, 10=worst pain conceivable) at the time of enrollment (baseline, left), prior use (middle), and at the maximum effect of intranasal fentanyl spray (right). Columns indicate mean scores; error bars represent standard deviation, trapezoids the corresponding medians. Parameters shown at the bottom of each column are the mean (95% confidence intervals) for each group of breakthrough cancer pain episodes.

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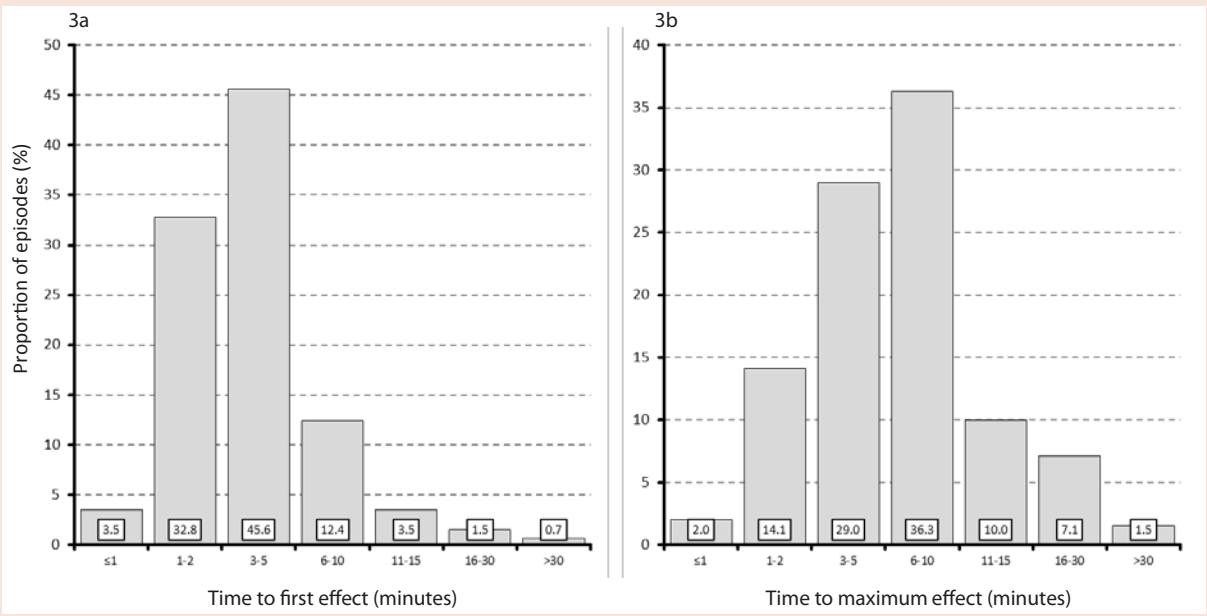

Figure 3: Time to first effect (left, 3a), and time to maximum effect (right, 3b) following administration of intranasal fentanyl spray for 556 episodes of breakthrough cancer pain treated and evaluated during the course of this trial.

Table 2: Mean ± standard deviation (95% confidence intervals) of breakthrough cancer pain-related restrictions in daily functioning assessed with the modified pain disability score (mPDI) at enrollment (baseline) vs. end-of-study.

mPDI dimension	Baseline	End-of-study	Significance
mPDI 1	7.2 ± 1.9	4.2 ± 2.4	p<0.001
household and family	(7.0-7.4)	(4.0-4.5)	
mPDI 2	7.6 ± 1.9	4.3 ± 2.5	p<0.001
leisure and recreation	(7.5-7.8)	(4.0-4.5)	
mPDI 3	7.7 ± 1.9	4.4 ± 2.5	p<0.001
social activities	(7.6-7.9)	(4.2-4.7)	
mPDI 4	7.8 ± 1.9	4.4 ± 2.6	p<0.001
work	(7.6-8.0)	(4.1-4.7)	
mPDI 5	6.8 ± 2.1	3.9 ± 2.3	p<0.001
independence in personal hygiene and daily life	(6.6-7.0)	(3.7-4.2)	
mPDI 6	6.9 ± 2.1	3.6 ± 2.3	p<0.001
sleep	(6.6-7.1)	(3.4-3.9)	
mPDI 7	7.7 ± 1.7	4.0 ± 2.5	p<0.001
quality-of-life	(7.5-7.9)	(3.7-4.2)	
mPDI 1-7	51.9 ± 11.4	29.1 ± 16.3	p<0.001
sum scor	(50.7-53.0)	(27.4-30.8)	

scores ≥8) dropped from 43.2-61.3 a% to 6.0-17.3a% (p<0.001 each). Highest improvement rates were found for BTcP-related restrictions in overall quality-of-life and sleep for which the percentages of patients reporting none or only mild BTcP-related restrictions (defined as scores ≤3) increased from 0.0/7.4a% to 48.2/51.2a% (p<0.001). Overall, the mean [SD; 95% CI] combined mPDI sum score improved from 51.9 [11.4; 50.7-53.0] at enrollment to 29.1 [16.3; 27.4-30.8] at the final study visit (p<0.001), corresponding to an average [SD; 95% CI] reduction of BTcP-related restrictions in daily life of 39.8% [36.7; 31.9-47.6%] and the percentage of patients experiencing high/severe/extreme levels of pain-related disabilities (defined as mPDI sum scores>40/50/60) dropped significantly from 83.7/58.7/27.2 a% at enrollment to 26.3/11.3/3.8 a% at the end-of-study (p<0.001 for each).

Scores on the QLIP inventory showed substantial quality-of-life improvements (increases in score) during the observation period

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(Figure 4). Mean [SD; 95% CI] QLIP sum scores increased from 12.3 [6.6; 11.6-13.0] at enrollment to 24.7 [7.3; 23.9-25.5; p<0.001] at the end of the observation period, and the proportion of patients experiencing significant BTcP-related quality-of-life restrictions (defined as QLIP sum scores <20) dropped from 86.0 a% at baseline to 25.6 a% at the end-of-study (p<0.001). As already shown for the mPDI, the sub-items with the greatest improvement rates were those addressing BTcP-related sleep disturbances: percentage of patients reporting inadequate sleep or sleep disturbances decreased from 85.3/64.6 a% at enrollment to 27.7/24.5 a% at end-of-study (p<0.001).

In parallel, patients reported a significant reduction in BTcP-related restrictions of their overall wellbeing with INFS, which improved from 7.6 [1.7] at enrollment (median: 8; 95% CI: 7.4 - 7.7) to 3.8 [2.3] at the end of the observation period (median: 3; 95% CI 3.5 - 4.0; p<0.001). The percentage of patients reporting none or mild BTcP-related restrictions (defined as NRS_{11} scores ≤3) increased from 1.1 a% at baseline to 54.2 a% at end-of-study (p<0.001).

Healthcare resource utilization

Changes with respect to the health care utilization demands of observed BTcP patients at enrollment were independently assessed both by physicians as well as palliative care nursing assistants at the end of the observation period. As shown in table 3, both ratings revealed major reductions in all dimensions evaluated in comparison to the situation at enrollment, however, differed with respect to the extent of INFS-related improvements. Improvement rates observed by the physicians varied from 17.1-81.8 a% with an average [SD] improvement of 42.2 a% [11.6] of patients per dimension, whereas those reported by PCNAs was 59.2 a% [13.0] with a variation from 44.1-97.0 a%. Highest improvement rates were concordantly reported by physicians/PCNAs for BTcP-related needs (81.8/97.0 a%), followed by those related to background pain medication (76.5 a%), anxiety (64.2 a%), stress (64.1 a%), nausea/daily routine (each 63.3 a%) and family (63.2 a%) from the PCNA point of view, respective nausea (53.6 a%), background pain medication (52.7 a%), anxiety (51.8 a%), and depression (49.1 a%) from the physicians point of view.

In addition, physicians/PCNAs reported INFS-related reductions with respect to healthcare demands for 72.7/60.8 a% of patients, independence for 86.8/84.0 a%, daily life for 89.9/85.4 a%, quality-of-life for 91.8/86.7 a% and medical resources for 64.6/69.5 a%.

Dose titration

All 131 enrolled patients received at least one dose of INFS. The INFS dose most frequently recommended for initial use was 50 µg (in 57.7 a% of patients), followed by 100 µg (38.5 a%) and 200 µg (3.8 a%), and differed slightly from those recorded "as used "in the patient records, where 100 µg was the most prevalent dose (52.2 a%), followed by 50 µg (44.8 a%) and 200 µg (3.0 a%). Subsequent titration data revealed only a moderate dose escalation for the observed BTcP attacks and the INFS dosages finally prescribed after completion of the observation period as being most effective (50 µg in 28.0 a%, 100 µg in 64.0 a%, and 200 µg in 8.0 a%) were close to those documented for the 6th BTcP attack (27.7/63.8/8.5 a%).

Titration effects

Figure 5 shows the BTcP intensity characteristics reported at enrollment as well as the pain intensity profiles reported by patients at the time point of the maximum INFS effect for the first 12 subsequently treated BTcP attacks. Percentages of patients temporarily reaching pain intensity scores ≤3 at the time point of maximum INFS effect increased from 42.6% for the 1st, over 49.2% for the 3rd, 57.4% for the 6th, and 62.2% for the 9th, up to 73.1% for the 12th BTcP attack.

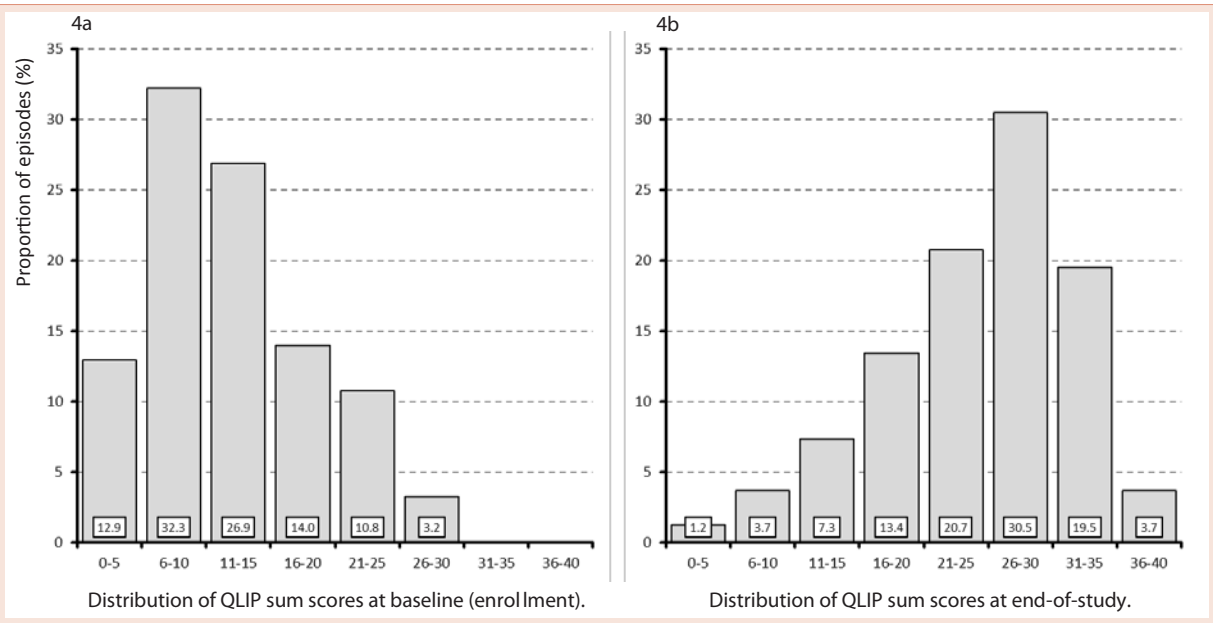

Figure 4: Sum scores of the Quality-of-Life Impairment by (breakthrough) Pain Inventory (QLIP) at enrollment (baseline, left/4a) and end-of-study (right/4b). Columns presented are percentages of patients with distinct QLIP scores, ranging from "0" (worst possible) to "40" (best possible), aggregated with respect to defined score ranges.

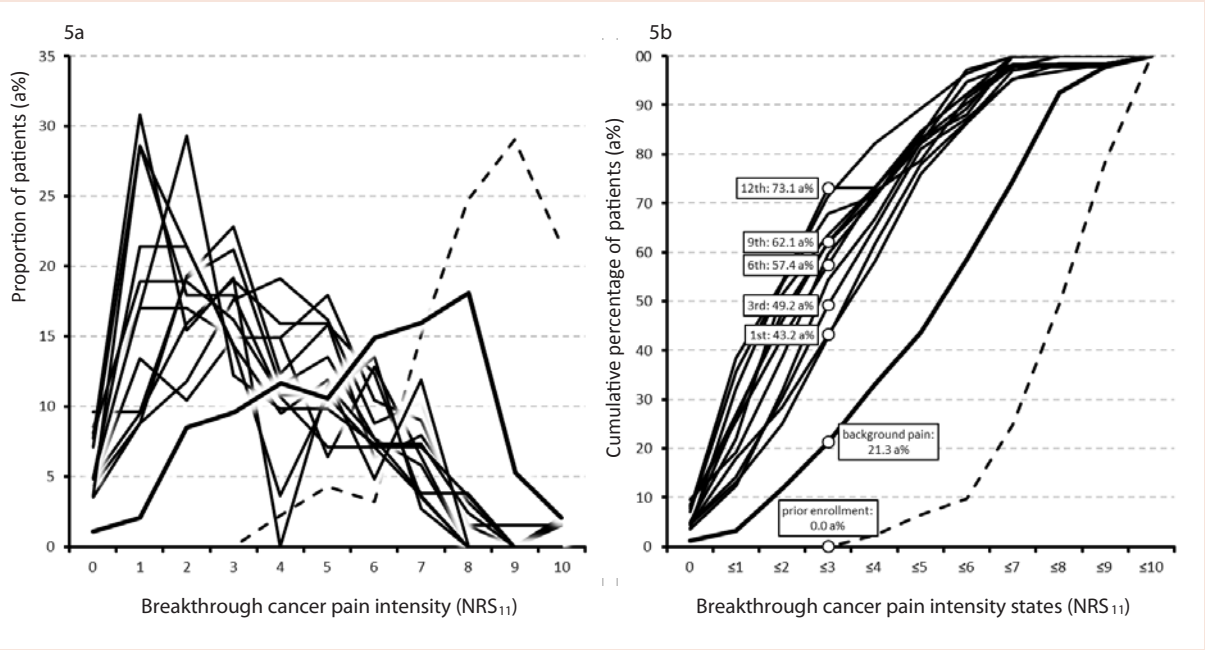

Figure 5: Average pain intensity profiles as reported by the patients during this study. Curvesbase on adjusted (left, 5a) and cumulative (right, 5b) percentages of patients reporting distinct pain intensity scores on the NRS11 for their background pain (thick line), breakthrough cancer pain episodes experienced prior to enrollment (dashed line), as well as the first 12 subsequentbreakthrough cancer pain attacks treated with INFS (thin lines). Note the continuous shift to the left with increasing number of breakthrough cancer pain episodes treated with INFS (see Figure 5b) and the increasing percentage of patients experiencing pain intensity scores of ≤3, especially in comparison to the corresponding curvesfor background pain and breakthrough pain attacks experienced prior enrollment.

In parallel, the percentage of patients classifying the pain relieving effects of INFS as "very strong" or "complete" increased from 26.5% (1st), over 33.3% (3rd), 43.5% (6th), and 45.9% (9th) to 48.0% (12th) for the corresponding BTcP episodes. In contrast, none or only minor effects were seen with respect to titration-related changes in speed of onset and/or time to maximum effect.

Table 3: Percentages of patients with a reduction in health resource utilization/ nursing demands between enrollment (baseline) and end-of-study as reported/ assessed by their physicians (left) and palliative care nursing assistants (PCNA, right).

Dimension	Physicians	PCNA
Background pain	52.7	76.5
Breakthrough pain	81.8	97.0
Nausea	53.6	63.3
Vomiting	44.6	52.4
Dyspnea	29.7	57.5
Constipation	35.1	44.1
Weakness	46.8	47.0
Loss of appetite	37.6	45.6
Fatigue	42.9	50.8
Wound treatment	21.4	48.6
Daily routine	40.5	63.3
Depression	49.1	62.6
Anxiety	51.8	64.2
Inner/mental tension	46.4	64.1
Confusion	17.1	52.2
Logistics	31.2	54.4
Family	34.8	63.2

Tolerability and safety

INFS tolerability was rated by patients/physicians/PCNAs as "very good" in 42.0/42.5/33.3a% or "good" in 43.1/47.8/53.6a% of cases, as "moderate" in 11.9/9.7/7.2a%, and only in 3.0/0.0/5.7a% as worse. The physician/PCNA recorded overall safety of INFS was scored as "very good" in 36.8/26.5, as "good" in 53.5/54.4 a% and worse in 9.6/19.1 a%. A total of six patients (4.6%) experienced eight treatment emergent adverse events during the observation period, the most common of which were vomiting and dizziness in two patients, followed by fatigue, rhinalgia, sneezing and euphoric mood (each in one patient). All TEAEs experienced by study participants were mild to moderate in nature and resolved completely without any counter measures. Overall, 20 deaths occurred during the study. All were attributed to progression of the underlying cancer disease and none was considered by the investigators as related to the intake study medication.

Comparison with prior/other BTcP medication

The 45 patients who had previously used a different BTcP medication rated INFS in comparison to their previous treatments. The majority of patients reported that, compared to previous medication, INFS was better in terms of speed of action (96.2 a%), strength of action (80.8 a%), tolerability (76.9 a%) and ease of handling (69.2 a%). In parallel, physicians/PCNAs scored INFS in comparison to their experience with alternative BTcP medications independently from the patients mentioned above and rated INFS as better in 97.2/95.6 a% for speed of onset, 86.4/78.2 a% for strength of action, 61.1/65.2 a% for tolerability, 54.0/65.2 a% for safety and

64.8/82.6 a% for ease of use. At the end of the study, 100/116 patients (86.2 a%) – including 43/45 patients (95.6 a%) who switched from alternative BTcP medications – chose to continue taking INFS.

Discussion

BTcP is a frequent complication of cancer especially in advanced stages of the disease, not only associated with severe detrimental effects on daily functioning, quality-of-life and social relationships[1,8], but also responsible for significant incremental direct as well as indirect costs [10,11,36,37].

Besides prevention, control is a key therapeutic challenge in BTcP management for affected patients, and an increasingly commonly used strategy is the administration of fast-acting (rapid onset) fentanyl preparations on demand basis, from which INFS seems to pharmacologically mirror the rapid onset and short duration of BTcP episodes better than older transmucosal therapies [18].

The major advantage of INFS is the bypass of the oral/enteral route, which makes it more acceptable to patients who experience oral mucositis, xerostomy, nausea, vomiting, and impaired gastrointestinal function. Fentanyl's high lipophilicity and short duration of action, characterizes the active pharmaceutical ingredient as the preferred one for BTcP treatment, and with a pH of 6.4, INFS has been formulated to closely match the physiological environment of the nasal cavity [38], hence lowering the potential for local irritation. In addition, this nasal spray formulation is of sufficient concentration to deliver an 'analgesic dose' in a volume that does not exceed nostril capacity (~150 µl)and that can be adequately absorbed by the mucosa [15], which is also demonstrated by the high absolute bioavailability of 89% [39].

This special formulation has been evaluated extensively in the restricted setting of placebo- [16,17] and even active-controlled clinical trials [18], having demonstrated not only a rapid onset of action (median 7 minutes) for the relief of dental post-operative pain [38], but for INFS at doses of 50-200 µg, a significantly faster (onsetofactivityat10 min) and more effective treatment when compared with placebo [16], as well as a significantly greater pain relief (from5minutes post dosing) and faster meaningful pain relief than OTFC [18].

Due to the results of these studies, INFS is now approved for the treatment of BTcP in opioid-tolerant adult patients, however, limited data are available on INFS-related treatment outcomes under daily practice conditions, where several key parameters (In particular factors such as patient demographics and concomitant drug use, etc.) are expected to differ from those in randomized controlled trials, which might be associated with differences in INFS-related pain relief and speed of action rates. Christrup et al. [38] demonstrated a rapid onset of pain relief with INFS, with a median time of 7 minutes in healthy individuals for the relief of dental post operative pain, and duration of effect of 56 minutes. According to the definitions given by Farrar et al. [40], INFS has previously been shown in patients with BTcP to produce clinically important/significant pain relief (i.e. ≥30% PI reduction/>2 PI difference in comparison to the situation prior use) as early as 5-10 minutes post-administration [16,18].

These results are now supported and strengthened by the data reported in the current study evaluating INFS in a palliative care population of cancer patients typical for ambulatory and outpatient scenarios, which proved an onset of action/time to maximum effect within 2/5/10 minutes after INFS administration in 36.3/81.9/94.3% of episodes, and for 59.7/62.4and 79.0/76.2% of episodes clinically important pain relief rates in comparison to the status prior use/enrollment. Differences reported with respect to the reference value (prior use vs. enrollment) raise an important question on the reasonability of one over the other. Efficacy analyses performed on pre/prior vs. post/after use measures provide real-time feedback on (in our case) INFS-related changes in BTcP intensities, but suffer the disadvantage that the pain intensity scores noted prior to use are rather dynamic (as patients start to use their rescue medication as soon they recognize the onset of their BTcP). Efficacy analyses based on comparisons of the after use measures (in our case the pain intensities experienced at the maximum effect of INFS) with those recorded at baseline (in our case the maximum BTcP intensities experienced prior to enrollment) have the advantage to use static pain intensity scores, however, have the disadvantage to rely on present and past BTcP intensity scores. As with so many things in the real life of pain therapy, neither method is right nor wrong nor the truth probably lies somewhere in between.

The fast onset and high response rates reported in this study confirm the results of previous controlled INFS trials. Gradual differences might in part be attributable to the open-label study design and differences of the patient populations evaluated. However, data reported from comparably designed non-interventional studies evaluating sublingual and buccal fentanyl preparations in assimilable BTcP populations supported our impression of superior time-to-effect rates for INFS, as the reported onset-of-action rates within 2/5/10 minutes in these reports were only 19.4/67.7/82.8vs.11.1/5 2.6/83.4% of episodes, and the corresponding time-to-maximum effect rates were only 4.3/10.7/29.1 vs. 1.7/10.4/39.6% of episodes, respectively [29,41].

Additional efficacy outcome measures were able to show clinically relevant improvements with respect to all dimensions evaluated between enrollment and end-of-study. The importance of this observation, as well as its medical and especially pharmaco economic relevance should not be underestimated, because BTcP is associated with a number of problematic physical, psychological/emotional and social complications which themselves are not only a relevant source of additional morbidity in these patients [36], but are also responsible for an increased use of social and healthcare services, outpatient visits, inpatient admissions and nursing assistance [10]. Factors that usually lead to higher levels of direct (e.g. prescription costs, costs for social services and nursing assistance), and indirect expenditures (e.g. transportation costs), for the health service, the patients and their care-givers [11,37]. The fact that the use of INFS for the treatment of BTcP in a highly impaired group of cancer patients translates almost immediately into clinically relevant improvements, underlines not only the potential of this new treatment option for daily practice, but also the detrimental effects of un- or insufficiently controlled BTcP.

Despite several advancements over the last century, the development of cost consciousness in healthcare is still ongoing and is matter of a complex transition. The battle between advancing medical practice through the implementation and utilization of new techniques, devices, or pharmacologic agents on one side, and containing associated medical costs on the other, evolves continuously. Complicating this charge is the fact that many new therapies (as e.g. INFS) are specific with respect to their actions, whereas related patients' conditions (here BTcP) are increasingly complex. Moreover, it becomes more and more difficult to assess the socio-economic ramifications of therapies for which traditional outcomes easily assessable from a fiscal point of view (e.g. length of hospitalization or mortality, etc.) may not be directly affected, but other more patient-relevant aspects such as daily functioning, quality-of-life, anxiety, and self-confidence are too complex to be used as economic parameters.

As reported in this study, the pain relieving potential of the INFS administration on demand basis, the re-establishment of some kind of self-confidence of affected cancer pain patients with respect to their individual handling concepts for threatening or current BTcP attacks, as well as related effects on daily functioning, quality-of-life, and overall wellbeing led to a surprising reduction in healthcare resource utilization and nursing assistance. Physicians as well as PCNA congruently reported average reductions with respect to HCR utilization/assistance requirements of 42.2/59.2 a% per patient and dimension evaluated, with a variation of 17.1-81.8/44.1-97.0 a%, which overall translate into a halving of nursing efforts and related direct costs.

The main factor driving all these aspects was neither the presence nor the absence of BTcP, but the availability of an effective rescue medication. From that point of view, it is important to focus on future pharmacoeconomic analyses not only on pure treatment-related costs, but to perform differential cost-benefit calculations, i.e. to weigh additional costs related to the use of new preparations (such as in our case INFS) against savings made through these treatment alternatives with respect to total cost of not undertaking the intervention (i.e. in comparison to the total cost of none or inadequate BTcP treatment).

The current study offers new insights into the acceptability of INFS from a patient perspective. More than one-third of patients had previously received alternative BTcP medication, the most common of which were oral immediate-release opioids (27/45 patients, 60.0 a%), and the majority of these patients reported that INFS provided improvements in each of the five effectiveness domains assessed, compared to their previous therapy. It is interesting to note that beside those 96.2/80.8 a% of patients that reported a faster/stronger pain relief and those 76.9 a% documenting a better tolerability in comparison to their previous BTcP medication, 69.5% reported that INFS provided improved ease of handling, lending support for the convenience of the intranasal route of administration in cancer patients with alterations of the oral/enteral pathway. Moreover, nine of ten patients who completed the study and for whom this information was given, chose to continue treatment with INFS (100/112 patients, 89.3 a%), confirming our practical experience with INFS as a well-accepted and convenient treatment option for BTcP patients.

Overall, INFS showed an acceptable safety profile in this patient population. The pattern of AEs and the number of patient deaths during the study are reflective of the underlying disease states of the patients. The AEs judged to be related to INFS included vomiting, dizziness, fatigue and euphoric mood, all of which are commonly observed with the use of rapid onset opioid analgesics in this indication [16,42,43], as well as rhinalgia and sneezing attributable to the intranasal mode of drug delivery. The lower frequency of AEs observed in the current study, compared with those reported in controlled studies [16-18], may in part reflect the shorter duration of this study, as well as differences in reporting procedures and study design.

The dose adjustments recorded during this study within the 4-week observation period indicate a relative dose increment of 16.6% (80.6→94.0 µg/dose) between the first BTcP episode treated with INFS and the finally prescribed/effective INFS dose (which is reached on average after/during the 6th BTcP episode treated). This upward trend reflects primarily ongoing titration efforts to optimize INFS dosage and is lower than those reported for sublingual fentanyl in a comparably designed non-interventional trial (38.3%) [29].

The continuous pain intensity shift to the left (associated with continuously decreasing average BTcP intensity scores) observed for the pain intensities reported at the maximum INFS effect for the 12 BTcP episodes documented during this study, might be taken as an indicator for a BTcP treatment optimization process, associated with dose escalation (especially for the first 6 attacks) and beyond (e.g. shortened delay between BTcP onset and INFS administration, increasing familiarity with the intranasal device and its un-/packaging, optimized application of INFS, etc.).

In contrast to previous clinical studies on INFS, inclusion in this study was not restricted to defined criteria. It is therefore interesting to note the demographic and baseline profile characteristics of the participants, as they directly reflect the patients usually encountered in clinical practice and outpatient care. With 62.1 vs.57.8/60.6 years, respectively, the patients in the current study were, on average, older than those in the controlled phase II/III studies with INFS reported by Kaasa et al. [17] and Kress et al. [16] and showed a broader age range (24-91 vs. 39-68/35-79 years). Patients in this study were also in a poorer state of health at the time of enrollment and reported a wider range of BTcP frequencies at enrollment (0.3-15 episodes per day), compared with those in the Phase III studies, where a maximum of 4 BTcP episodes per day were allowed. It is also notable that two thirds of patients in this study presented with background pain intensities equal to or greater than 5 on the NRS_{11} (an exclusion criteria for the controlled Phase II/III studies mentioned above), despite higher background pain opioid dosages. In combination with the high frequency of BTcP episodes recorded by some patients, these findings reflect the difficulty of balancing the need to control (background as well as breakthrough pain), with increasing side effects at higher opioid doses, in this patient group under real life conditions.

Overall, the findings of this study add valuable information to our knowledge of INFS. However, the study was only of a modest size and duration and therefore, the results should be augmented by following greater numbers of patients for a longer treatment period in

daily practice. In addition, this was an open-label observational study with a single-arm design conducted under daily clinical practice conditions, and therefore, several methodological limitations such as the lack of a direct comparison with other commonly used BTcP medications, the absence of monitoring or patients lost to follow-up were unavoidable and may lead to concerns with regard to data quality. Nevertheless, this non-interventional approach reflects the current treatment of patients with BTcP by pain and palliative care specialists in routine care and should therefore allow generalization of its results into real life. Complementary approaches, such as indirect comparisons with the results obtained from similarly designed non-interventional trials on further ROOs – such as sublingual and buccal fentanyl preparations – in matching patient populations, have given rise to a broad evaluation of the treatment outcomes for patients receiving INFS for treatment of BTcP. This methodology is supported by the IMMPACT recommendations on the core outcome measures in clinical trials of pain medications [26].

The evaluations conducted in this study may also be limited by the relatively subjective nature of the patient-assessed endpoints used. Nonetheless, patient reported outcome measures, such as the NRS_{11} for pain intensity used here, are widely employed in pain studies and are generally recognized as important and highly reliable measures of pain treatment outcome [26]. Similarly, assessments of temporal aspects, including time to onset of pain relief and its durability are recognized as important for evaluations of pain. At the same time, the measures of time to first and maximum effect used in the current study have not been formally validated, and further investigation would be required to evaluate the reliability of these measures, and how their findings relate to objective clinical outcomes. However, by comparing the results of this trial with those obtained from comparably designed studies – in which these instruments were used [29,41] – these methodological shortcomings become irrelevant.

Conclusion

INFS – a fast-acting intranasal formulation of the opioid fentanyl citrate with a pharmaco dynamic profile that fits very closely with the temporal characteristics of BTcP – offers unique advantages over other existing treatment options. Previously reported clinical studies have demonstrated that INFS is well-tolerated and provides analgesia superior to placebo/OTFC from as early as five to ten minutes after administration [16,18]. The current study evaluated the analgesic efficacy, ADL/QoL impact and safety of this formulation for treatment of BTcP in opioid-tolerant patients encountered in routine clinical practice. The findings demonstrated that INFS was associated with considerable reductions in BTcP intensity, compared to baseline/prior use. Time to first effect after INFS administration was ≤5 minutes in 81.9 a%, and the time to maximum effect was ≤10 minutes in 81.4 a% of BTcP episodes evaluated. Treatment with INFS was also associated with a substantial decrease in BTcP-related restrictions in daily functioning, quality-of-life and overall wellbeing, and the majority of patients with prior experience of alternative BTcP medications expressed preference for INFS. The study medication was well tolerated, and the observed pattern of AEs was consistent with that previously observed with this group of opioids or with the intranasal mode of administration. The population of the current study comprised patients who were prescribed INFS in the course of routine practice at 58 treatment centers in Germany. Therefore, it is anticipated that the benefits observed in this study will translate to patients in real-world settings.

Transparency

Declaration of funding

This study was funded by Nycomed GmbH. Nycomed GmbH was responsible for both the design and the conduct of the study. Nycomed GmbH funded the statistical analysis and medical writing/editing assistance for this manuscript. Relevant parties at Nycomed GmbH were allowed the opportunity to comment on the manuscript.

Declaration of Financial/Other Relationships

Michael A. Überall disclosed acting as consultant/advisor on Nycomed′s German Advisory Board and as speaker for Archimedes, Cephalon, Nycomed, and ProStrakan.

Bernd-Oliver Maier disclosed acting as advisor on Nycomed′s German Advisory Board and as speaker for Cephalon, Nycomed, and Mundipharma.

Thomas Nolte disclosed acting as a consultant/advisor on Nycomed's Advisory Board and as speaker for Mundipharma Germany.

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Authors' contributions

MAÜ, B-OM, and TN participated in the study design, the interpretation of results, and writing ofthe manuscript. All authors read and approved the final manuscript.

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