LONG-TERM SAFETY AND TOLERABILITY OF FENTANYL CITRATE NASAL SPRAY IN THE TREATMENT OF BREAK THROUGH CANCER PAIN (BTCP) IN SUBJECTS TAKING REGULAR OPIOID THERAPY

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ABSTRACT
An ideal patient-controlled analgesic (PCA) opioid would have rapid onset and longer duration of action when compared to the currently existing opioids including morphine. The purpose of this study was to verify the efficacy and safety in cancer patients experiencing breakthrough cancer pain. Selected patients with Break through Cancer Pain (BTCP) episodes received the fentanyl citrate nasal spray. Pain relief score, pain intensity score and BTCP episodes per day were assessed directly by questionnaires, recorded data and analyzed statistically. Demographic and medical data were showed that only 18.5% of patients suffered from headache, 25.9% of patients suffered from dizziness, 25.9% of patients suffered from nausea and 33.3% of patients suffered from constipation. Fentanyl citrate nasal spray showed quick onset of action within 5 minutes. Fentanyl citrate nasal spray and morphine sulphate tablets were comparable in controlling BTCP episodes. However, fentanyl nasal spray was rated better than morphine sulphate tablets for its quick onset of action and ease of care by patients and nurses.

KEY WORD: Break through Cancer Pain (BTCP), fentanyl nasal spray, patient-controlled analgesic (PCA).

INTRODUCTION
Breakthrough pain, defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain, is typically treated with oral opioids, such as morphine. The effective treatment of breakthrough pain in cancer subjects is not a fully met medical need, as oral dose forms can take a longer time to relieve pain and injections are not acceptable to many subjects. Fentanyl is an established drug with many years of clinical use in the treatment of pain including cancer pain. Fentanyl citrate nasal spray is being developed to fulfill these needs, having a speed of onset of action of pain relief of about 5 minutes and being delivered as a simple to use low volume nasal spray. The Fentanyl-pectin formulation was selected following an initial phase I clinical study, in healthy volunteers, as it exhibited good bioavailability, but absorption was not accompanied by high peak plasma concentrations of the drug (Cmax) (which might lead to more pronounced side-effect) compared with the other nasal formulations tested. The study also indicated that the pectin formulation was the best locally-tolerated nasal formulation.

Aims and objectives
Primary objective
The primary objective of the study is to demonstrate the superior efficacy of Fentanyl citrate nasal spray over immediate release morphine sulphate in the treatment of BTCP in opioid tolerant subjects who are receiving regular opioid therapy.

Secondary objective
The secondary objective of the study is to investigate the long-term safety, tolerability, and acceptability of Fentanyl citrate nasal spray in the treatment of BTCP.

MATERIALS AND METHODOLOGY

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Archimedes Development Ltd.</th>
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<tbody>
<tr>
<td>Product</td>
<td>Fentanyl citrate Nasal spray.</td>
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<td>Materials</td>
<td>Nebulizer (Nasal spray container).</td>
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</table>

Study title
An open-label study investigating long-term safety and tolerability of fentanyl citrate nasal spray in the treatment of breakthrough cancer pain (btcp) in subjects taking regular opioid therapy.

Clinical Phase
III

Objective
To investigate the long-term safety, tolerability, and acceptability of Fentanyl citrate nasal spray in the treatment of BTCP.

Design
This was an open-label study conducted at multiple centers world wide. Subjects newly enrolled into the study or subjects entered into this study after completing Fentanyl citrate nasal spray studies. For the newly enrolled subjects, the main study consisted of 4 phases:
- Screening phase (up to 10 days).
- Open, Dose-Titration Phase (up to 14 days).
- Open-Label Treatment phase (up to 16 weeks).
- End-of-Treatment Phase (1 to 14 days after last dose).

All the subjects came to the study centre for up to 8 visits. The total duration of individual subject participation was up to approximately 5 months.

Following completion of the Main Study, the subjects were entitled to continue treatment with study drug in an Extension Period, for as long as necessary until Fentanyl citrate nasal spray becomes available commercially.

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Male and female subjects, aged 18 years and older, with a malignancy who were taking regular, 24-hours medication (at least 60 mg of oral morphine or equivalent Opioid) for his or her underlying persistent cancer pain and who typically had 1 to 4 episodes of BTCP per day are eligible for participation.

Subjects with uncontrolled or rapidly escalating pain or whose condition was unstable or rapidly deteriorating should not be enrolled. Additionally, subjects with a medical condition (i.e., respiratory, cardiac, hepatic, renal, neurological, and psychiatric) that would make them unsuitable for the study were not enrolled. Subjects with a history of alcohol or substance abuse were not eligible.

A sufficient number of subjects enrolled to ensure that 500 subjects have been exposed to Fentanyl citrate nasal spray and that 150 of these had been dosed for 3 or more months.

The maximum Main study duration for the individual subjects was 5 months. Thereafter, continuation in the Extension Period was at the decision of the subject and his/her clinician, according to clinical need.

The maximum Main study duration for the individual subjects was 5 months. Thereafter, continuation in the Extension Period was at the decision of the subject and his/her clinician, according to clinical need.

Adverse events.
Objective nasal examination.
Subjective nasal assessment.
Withdrawal due to AEs.
Physical examination, including vital signs.
Laboratory assessments.
Subject acceptability assessments.

It was anticipated that the maximum amount of blood taken was exceeded 30 ml for all the samples taken during the subject’s study participation. All blood samples were analyzed at the central laboratory.

<table>
<thead>
<tr>
<th>HEMATOLOGY</th>
<th>SERUM CHEMISTRY</th>
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<tr>
<td>Hemoglobin</td>
<td>Total cholesterol</td>
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<td>Hematocrit</td>
<td>Random blood sugar (RBS)</td>
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<tr>
<td>Total leukocyte count</td>
<td>Creatinine</td>
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<td>Differential leukocyte</td>
<td>Sodium</td>
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<td>count</td>
<td>Potassium</td>
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<td>Red blood cell count</td>
<td>Urea</td>
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<td>Platelet count</td>
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<td>Erythrocyte sedimentation rate (ESR)</td>
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<tr>
<th>LIVER FUNCTION TESTS</th>
<th>SEROLOGY</th>
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<tr>
<td>Total bilirubin</td>
<td>Human immunodeficiency virus (HIV) 1 and 2</td>
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<tr>
<td>Total protein</td>
<td>Hepatitis B</td>
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<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Hepatitis C</td>
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<td>Aspartate aminotransferase (AST)</td>
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<td>Alkaline phosphatase</td>
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<td>(ALP)</td>
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<tr>
<th>URINE ANALYSIS</th>
<th>TESTS FOR DRUGS OF ABUSE</th>
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</thead>
<tbody>
<tr>
<td>Color</td>
<td>Alcohol</td>
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<tr>
<td>Transparency</td>
<td>Tetrahydrocannabinol</td>
</tr>
<tr>
<td>PH and specific gravity</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Protein</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Glucose</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Ketones and nitrates</td>
<td></td>
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<tr>
<td>Bilirubin and urobilinogen</td>
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<tr>
<td>Blood</td>
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<tr>
<td>Pregnancy test</td>
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<td>Chest X-Ray (PA view)</td>
<td>12-Lead</td>
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<td></td>
<td>Electrocardiogram(ECG)</td>
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</tbody>
</table>

CLINICAL / DIAGNOSTIC LABORATORY TESTS
It was anticipated that the maximum amount of blood taken was exceeded 30 ml for all the samples taken during the subject’s study participation. All blood samples were analyzed at the central laboratory.

If female, and of childbearing potential (not surgically sterile or ≤1 year after the onset of amenorrhea due to menopause)-
(a) Had a negative serum pregnancy test,
(b) Was not be lactating, and
(c) Agreed to practice a reliable form of contraception or abstinence during the study.

4. Subjects who had a historically documented diagnosis of a malignant solid tumor or a hematological malignancy causing cancer-related pain.

5. Subjects who were taking at least 60 mg oral morphine or equivalent for at least 1 week for cancer-related pain as regular, 24-hour medication for their underlying persistent cancer pain.

6. Subjects who were experiencing, on average, but not necessarily every day, 1 to 4 episodes of BTCP per day that are adequately controlled with a stable dose of standard rescue medication, typically a fast-acting opioid, of which the subject should gave an adequate supply throughout the study. Breakthrough pain is defined as a transitory flare of moderate to severe pain (on a 4-point scale from 1 to 3 [none, mild, moderate, severe]) that occurs on a background of persistent pain controlled to moderate intensity or less by the opioid regimen. If the subject has more than 1 type of breakthrough pain, or has breakthrough pain in more than 1 location, only 1 of the pains will be identified as a “target” breakthrough pain.

7. Subjects who, in the opinion of the investigator, were willing and able (personally or with the help of a care taker) to
- Evaluated and recorded pain intensity and pain relief.
- Assessed the medication performance at specific times after dosing.
- Recorded Adverse Events.
- Recorded each instance of the use of study drug and standard rescue medication in a subject diary for the duration of the main study.

Selection of subjects
Inclusion Criteria
Subjects were included in the study if they met all of the following criteria:
1. Subjects who were able and willing to provide written informed consent.
2. Male and female subjects, 18 years of age and older.

For the purposes of this study, the following tests were analyzed:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Laboratory Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
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<td>Barbiturates</td>
</tr>
<tr>
<td>Blood</td>
<td>12-Lead Electrocardiogram(ECG)</td>
</tr>
</tbody>
</table>
8. Subjects with an Eastern Cooperative Oncology Group (ECOG) Score of ≤ and a life expectancy which, in the opinion of the investigator, allowed them to participate for the duration of the main study.

**Exclusion Criteria**

Subjects were excluded form participating in the study if they met any of the following criteria:

1) Subjects with an opioid or Fentanyl intolerance.
2) Subjects with uncontrolled or rapidly escalating pain.
3) Subjects using intrathecal or epidural opioids.
4) Subjects whose condition was unstable or rapidly deteriorating, such that they were (in the opinion of the investigator) unlikely to be able to make an effective contribution to the study.
5) Subjects with sleep apnea or active brain metastases with increased intracranial pressures.
6) Subjects with any respiratory or cardiac condition that, in the opinion of the investigator, may be worsened by opioids.
7) Subjects with any other medical condition that, in the judgment of the investigator, confounded the objectives of the study.
8) Subjects with a recent history of alcohol or substance abuse that compromise data collection.
9) Subjects with a history of or current neurological or psychiatric impairment, or cognitive dysfunction that, in the opinion of the investigator, would compromise data collection.
10) Subjects with clinically significant renal and hepatic dysfunction test results at screening outside the following limits:
    a) Serum creatinine must be ≤2.0mg/dl, or creatinine clearance calculated by Cockcroft-Gault formula must be ≥50ml/min.
    b) Serum total bilirubin must be ≤2.0mg/dl.
    c) Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be ≤3 times the upper limit of normal (≤5 times the upper limit of normal if due to liver metastases).
11) Subjects taking any medication likely to affect the physiology of the nasal mucosa.
12) Any abnormal nasal physiology and/or pathology which, in the opinion of the investigator, would not allow the objective of the study to be accomplished.
13) Subjects with known intolerance to nasal sprays and/or pharmaceutical materials found in the investigational products.
14) Subjects taking monoamine oxidase inhibitors (MAOIs) within 14 days of the screening visit or with an anticipated need for MAOIs during the study.
15) Subjects with uncontrolled infection.
16) Subjects whose primary source of breakthrough pain is not cancer related.

**Withdrawal and termination criteria**

In accordance with the Declaration of Helsinki, each subject was free to withdraw from the study at any time without prejudice to further treatment. A subject’s participation in the study was discontinued at any time at the discretion of the investigators. Justifiable reasons for the investigator to discontinue a subject from the study may include, but were not limited to, the following:

- Adverse event (AE): clinical or laboratory events occurred that, in the medical judgment of the investigator, were grounds for discontinuation, for the best interest of the subject. This included serious and non-serious AEs regardless of relation to study drug.
- Withdrawal of consent: the subject requested withdrawal from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for his or her withdrawal, it was recorded in the case report form (CRF).
- Lost to Follow-up: the subject stopped coming for visits and study personnel were unable to contact the subject.
- Pregnancy: women who became pregnant during the study were withdrawn from the treatment at the earliest opportunity. Any pregnancy was followed to its conclusion and the neonate was evaluated, as appropriate.
- Concomitant therapy: the subject needed to receive any therapy that was incompatible with the study medication or continued study participation.
- Lack of efficacy: a subject who had not found an effective dose after 14 days of treatment in the open, Dose-Titration Phase or at any time during the study.
- Other: the subject was terminated for a reason other than those listed above, such as theft or loss of study drugs or termination of the study by the sponsor. The reason, if provided, was recorded on the CRF.

When a subject decided to withdraw after the administration of the investigational product(s), or when the investigators decided to withdraw the subject, all efforts were made to complete and reported the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject’s withdrawal was made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason, date, and time for the withdrawal were noted in the CRF. If the reason for withdrawal was a clinical AE or an abnormal laboratory test result, monitoring was continued until the outcome was evident. The specific event or test result(s) were recorded in the CRF. The sponsor reserved the right to terminate the trial at any time.

**Basic regulatory principles**

The study was carried out properly in accordance with regulatory guidelines (e.g., International Conference on Harmonization [ICH] E6-Good Clinical Practice [GCP]) was coordinated and used in accordance with the protocol. If there were any discrepancies, an explanation for those had been provided.

**Randomization and Dosing**

The subjects were screened and randomized. Fentanyl citrate nasal spray was dispensed in a multi dose vial where dosing is 1 or 2 sprays. Each spray contains 100 µg. Subjects were instructed to self-administer the doses by trained site staff in the correct standard administration technique.

**Recording of adverse reactions and events**

All AEs reported by the subject or observed by the study staff was recorded in the CRF. The following information regarding each AE was obtained: date and time of onset and resolution (duration), intensity, whether it was serious, any required treatment or action taken, outcome, relationship to the investigational product, and whether the AE caused withdrawal from the study.
Serious adverse reactions/events

Adverse reaction
An adverse reaction is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected adverse reaction
An unexpected adverse reaction is an adverse reaction the nature and severity of which is not consistent with the trial

Suspected unexpected serious adverse reaction (SUSAR)
Where the adverse reaction is unexpected and serious it may be termed a suspected unexpected serious adverse reaction (SUSAR).

Serious adverse event (SAE), serious adverse reaction or unexpected serious adverse reaction
A serious adverse event (SAE), serious adverse reaction or unexpected serious adverse reaction means any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death.
- Is life-threatening. The term “life-threatening” in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event.
- Require inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.

Any laboratory test result that meets the criteria for an SAE or SUSAR, in the absence of appropriate and/or adequate clinical diagnosis, should be reported as an SAE or SUSAR, unless the result is considered normal for the current trial subject population.

Vital signs
Vital sign parameters include measurements of heart rate, systolic and diastolic blood pressure, and respiration rate. Before vital signs were measured, the subject was in the supine position for at least 5 minutes. All these measurements were performed within one hour of the scheduled time so as not to interfere with dosing of the drug. The actual time of measurement was recorded in the CRF. In case of any abnormality in vital signs before dosing, medical opinion was taken.

Physical examination
A physician performed a physical and systemic examination for the presence of abnormalities in general appearance, lungs, cardiovascular system, abdomen, skin and extremities.

Study procedure
This was an open-label study conducted at multiple centers worldwide. Open-label means the condition where both the physician and the participating subjects know the treatment receiving.

Main study
Cancer subjects who experienced on average, but not necessarily every day, 1 to 4 episodes of BTCP daily over 2 weeks while taking at least 60 mg per day of oral morphine (or equivalent opioid) for their underlying cancer pain were eligible to enroll.

For the newly enrolled subjects, the main study consists of 4 phases:

- Screening Phase (up to 10 days).
- Open, dose-Titration Phase (up to a maximum of 14 days).
- Open-Label Treatment Phase (16 weeks).
- End-Of-Treatment Phase (should occur 1 to 14 days after last dose).

The total duration of the individual subject participation in the main study was up to approximately 5 months.

Extension Period
In order to provide subjects who were gaining clinical benefit from the use of Fentanyl citrate nasal spray with access to the treatment following their participation in the main study, they entered the Extension Period.

**STUDY SCHEMATIC REPRESENTATION**

For newly enrolled subjects

<table>
<thead>
<tr>
<th>Screening phase (Up to 10 days)</th>
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<tbody>
<tr>
<td>Open-label dose titration phase (Up to a maximum of 14 days)</td>
</tr>
<tr>
<td>Open-label treatment phase (Up to 16 weeks)</td>
</tr>
<tr>
<td>End-of-Treatment visit (Should occur 1 to 14 days after last dose)</td>
</tr>
<tr>
<td>Extension period visits (As clinically indicated)</td>
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</table>

**RESULTS AND DISCUSSION**

The results showed significant difference in Pain within five minutes of Dosing. Improvements in Pain Maintained Throughout Pain Episode. Breakthrough cancer pain affected up to 95% of all cancer patients and was characterized by sudden, unpredictable episodes of intense pain that occurred despite background pain medication. This pain was rapid in onset, often reaching maximum intensity in five minutes with duration of 30-60 minutes.

Fentanyl citrate nasal spray was aimed at providing a fast, effective and convenient treatment for the breakthrough cancer pain - sudden, unpredictable episodes of intense pain that occurred despite background pain medication and which affected up to 95% of cancer patients with pain. Fentanyl was a highly effective opioid analgesic and was seen as the drug of choice for breakthrough cancer pain. However, there remained a need for a presentation that provided fast and reliable onset of action coupled with ease of use and high patient acceptability.

The subject’s acceptability assessment, including over all pain relief, pain intensity, were assessed using a 4- point scale.
The pie diagram and histogram revealed that nearly 60 percentage of the patients got pain relief within 15 minutes. At the 60 minutes, nearly complete pain relief was achieved.

After the administration of the Fentanyl, the pain intensity significantly decreased in cancer patients. Demographic and histogram data revealed that nearly 79 % of pain intensity decreased within 15 minutes of administration.

**Adverse events**

Demographic and medical data showed that only 18.5% of patients suffered from headache, 25.9% of patients suffered from dizziness, 25.9% of patients suffered from nausea and 33.3% of patients suffered from constipation.

**SUMMARY AND CONCLUSION**

Opioid analgesics are the mainstay of pharmacotherapy for severe pain because of their unparalleled efficacy, but they can also present difficulties involving adverse effects, tolerance, and dosing regimens. Cancer patients taking regular medication for their pain often still have episodes of severe pain that ‘break through’ despite their background pain treatment. Fentanyl is a strong, short-acting pain killer often used to treat this ‘breakthrough’ pain. Breakthrough pain, defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain, is typically treated with oral opioids, such as morphine. The effective treatment of breakthrough pain in cancer subjects is not a fully met medical need, as oral dose forms can take a longer time to relieve pain and injections are not acceptable to many subjects.

Current treatments for breakthrough cancer pain (BTCP) work too slowly to meet the fast onset of most BTCP episodes, they continue to act longer than the episode of pain lasts and so can have unwanted side effects due to this ‘over treatment’ of the pain episode. In addition most cancer patients have oral problems which make taking pain relief...
medication by mouth uncomfortable for the patient. The nasal route has the potential to deliver the drug rapidly, and is safe and convenient for most subjects. Of the Opioid drugs available, Fentanyl is a suitable candidate for nasal administration in a reasonable dose volume. Fentanyl is a well-established and characterized drug, with many years of clinical use. Its side-effect profile is well documented, and is qualitatively similar to that of other Opioid analgesics. Results of a Phase 3 clinical trial demonstrated positive results with a fentanyl citrate nasal spray in all measures of pain control assessed in a chronic cancer pain population. Fentanyl citrate nasal spray utilizes a new delivery technology designed to produce a more rapid and efficient absorption of medicine. The medication is designed to help patients with a common, yet under treated, component of chronic pain called breakthrough pain, which is characterized by its fast onset. According to the investigators- “Helping patients get better control of their pain requires that clinicians adequately address breakthrough pain. For breakthrough pain, you need a medication that comes closer to matching the rapid onset of the pain episodes and has a relatively short duration of action. Based on the results of the Phase 3 clinical trials, fentanyl citrate nasal spray appears to have that profile.”

The open label randomized trial evaluated fentanyl citrate nasal spray in chronic pain patients with cancer-related breakthrough pain. Patients with cancer who were already receiving various around-the-clock opioid medications for persistent pain, and had one to four episodes of breakthrough pain a day that were controlled with a short-acting oral opioid. After the initial dose titration phase, predefined dosing regimens that would expose each individual patient to fentanyl citrate nasal spray during the course of the study. Patients had the option to use their prior supplemental opioid for any breakthrough pain episode that did not respond within 15 minutes of fentanyl citrate administration.

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