**A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF FENTANYL ETHYPHARM FOR BREAKTHROUGH PAIN IN OPIOID-TREATED PATIENTS WITH CANCER**

S. Novotna1, K. Valentova2, E. Richterova3, S. Harabisova4, F. Trinquet5, ETHYFYL study group

1 Vysokomětická nemocnice, Vysoko Myto, 2 Nemocnice s poliklinikou v Semilce, Semily, 3 Ambulance lechy chronique bolesti a paliativni mediciny, Hradec Kralove, 4 Metstiska nemocnice Ostrava, Ostrava, Czech Republic, 5 Ethypharm, Saint Cloud, France.

**BACKGROUND**

Oromucosal fentanyl is currently used/recommended for the treatment of breakthrough pain (BTP) in opioid treated patients with cancer (Caseani et al. Lancet Oncol 2012; 13: e68-69). Ethypharm developed an oromucosal formulation of fentanyl supravalsalvalable to oral transmucosal fentanyl citrate with a ratio of 1.5, a higher early systemic exposure and a shorter Tmax (time of maximum plasma concentration) (Data on file Ethypharm). Five dosages were developed: 133, 267, 400, 533 and 800 µg.

**OBJECTIVES**

The primary objective was to assess the clinical effectiveness of Fentanyl Ethypharm when used to relieve BTP episodes in opioid-treated cancer patients. The secondary objectives were to assess:

- The safety and tolerability of Fentanyl Ethypharm
- The efficacy of Fentanyl Ethypharm on the neuropathic component of BTP

**METHODS**

Methodology

This was a prospective, multicentre study designed with 2 different periods:

- A first open-label escalating dose titration period to identify an optimal dose which should provide adequate pain relief of 2 consecutive BTP episodes with an acceptable level of adverse effects.
- A second randomized, double-blind, cross over and placebo-controlled period to assess the efficacy and safety of Fentanyl Ethypharm. Patients were assigned to one of 13 sequences of 9 tablets (6 Fentanyl Ethypharm tablets of the dose identified during the open titration and 3 placebo tablets).

A maximum of 4 BTP episodes per day could be treated with the study drug. Patients were authorized to take their usual rescue medication if adequate analgesia was not obtained after 15-30 minutes.

**RESULTS**

**Patient disposition**

93 patients were enrolled by 21 investigators (ETHYFYL study group) in Czech Republic.

**Baseline characteristics**

The Safety population was defined as all patients that received at least one dose of Fentanyl Ethypharm. The modified Intent To Treat (mITT) population was defined as all randomized patients who received at least one dose of Fentanyl Ethypharm and one dose of placebo and provided at least one baseline and post-baseline PI score for each of the two doses.

**Optimal dose identified during the open titration period**

<table>
<thead>
<tr>
<th>Dose (µg)</th>
<th>Safety population N=91</th>
<th>mITT population N=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>133 µg</td>
<td>35.9%</td>
<td>30.8%</td>
</tr>
<tr>
<td>267 µg</td>
<td>30.8%</td>
<td>14.1%</td>
</tr>
<tr>
<td>400 µg</td>
<td>30.8%</td>
<td>12.8%</td>
</tr>
<tr>
<td>533 µg</td>
<td>30.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>800 µg</td>
<td>35.9%</td>
<td></td>
</tr>
</tbody>
</table>

66.7% of the patients had identified the optimal dose as 133 and 267 µg.

**Efficacy**

654 episodes of BTP were treated during the double-blind period in the mITT population.

- **Sum of Pain Intensity Differences (SPID)**
  - SPID at 30 minutes was significantly in favour of Fentanyl Ethypharm compared to placebo (p<0.0001). This significant difference was observed from 6 minutes to 60 minutes post dose.


**ClinicalTrials.gov Identifier:** NCT01842893

This trial was sponsored by Ethypharm.

*Fentanyl Ethypharm is licensed to Grunenthal as Recevil for selected European countries.*

**Financial disclosure:** The investigators (ETHYFYL study group) received fees from Ethypharm for enrolling patients in the study. F. Trinquet is an employee of Ethypharm.