This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

SPONSOR is committed to publicly disclosing all medical research results that are significant to patients, health care providers or payers-whether favorable or unfavorable to the SPONSOR product-in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.
Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1. ABSTRACT

Title:

Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

Keywords:

Breakthrough pain, Instanyl, Risk Minimization Measures (RMMs), Educational Materials (EM), Post-authorization safety study (PASS).

Rationale and Background:

Instanyl® (intranasal fentanyl) is an opioid analgesic indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain, marketed throughout the European Union (EU) since 20 July 2009.

This PASS is designed to evaluate the changes in knowledge and self-reported behavior of targeted prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs, including the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors.

Research Question and Objectives:

Research questions:

Are the updated EM effective in:

- Increasing the knowledge of prescribers about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose and medication errors?
- Increasing compliance of self-reported behavior with Instanyl® label?

Objectives:

The overall objective of this study is to measure the changes in understanding and self-reported behavior of Instanyl® prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs.

Specifically, the study objectives are:

- To assess prescribers' awareness of the updated EM;
- To assess the changes in prescribers' knowledge and understanding of the key information contained in the updated EMs, including risks of off-label use, misuse, abuse, diversion, medication error, addiction, overdose, and death

- To assess the changes in prescribers' self-reported behavior in prescribing in accordance with approved indication
- To assess the reasons for off-label prescription
- To assess whether prescribers are fully aware about the profile of patients at risk of misuse and addiction

Study Design:

Two cross-sectional surveys among prescribers who are current and potential prescribers of Instanyl® in France, the Netherlands and Poland, before and after the implementation of the updated EMs. The pre-EM survey was conducted before the distribution of the updated EMs, which is defined as the baseline period, and occurred in June 2022. Approximately 5 months following the distribution of the updated EMs, in November 2022 the second survey (post-EM survey) was conducted (i.e., post-EM distribution period), and results of both surveys are presented in this Final Report. Both surveys were self-administered via the web (i.e., Internet), and applied the same questionnaire to assess Instanyl® prescribers' knowledge and self-reported behavior with respect to off-label use, misuse, abuse, addiction, overdose and death. In addition, a questionnaire asking about receipt and reading of the updated EMs was applied to the post-EM survey. Both questionnaires ask whether the prescribers consulted other sources of information about Instanyl®.

Setting:

The surveys were conducted through a web questionnaire among prescribers who are current and potential prescribers of Instanyl® in France, the Netherlands and Poland before and after the distribution of the updated EMs.

Physicians and Study Size, Including Dropouts:

Physicians [redacted], active in clinical practice and with valid contact details who met the following inclusion criteria could be enrolled: specialists of any of those medical specialties targeted for the EMs as agreed with each national competent authority, who have prescribed Instanyl® in the previous 12 months (pre-EM) or since the distribution of updated EMs (post-EM) and who intend to prescribe Instanyl® in the following months after each survey.

The following exclusion criteria were applied using the screening questions at the beginning of the web questionnaire: physicians who may have a conflict of interest (i.e., prescribers employed by regulatory bodies, pharmaceutical industries); inactive or retired prescribers; physicians who did not prescribe Instanyl® in the previous 12 months (pre-EM) or since the

updated EMs (post-EM) and did not foresee treating a patient with Instanyl® in the following 12 months, regardless of whether they had ever prescribed Instanyl®.

For each study country, the survey included physicians identified and recruited from OneKey™ lists. A pragmatic split was proposed to allocate a sufficient size to the less represented strata of the sample, since a variance of the number of physicians in the countries was expected. The results of both surveys presented in this final report were weighted back according to the real proportion of physicians from OneKey™ database lists to allow the representativeness of the overall sample. The total target sample considering France, the Netherlands and Poland was 259 physicians for each survey.

Variables and Data Sources:

Primary data collection surveys were conducted through a web questionnaire that collected information on self-reported Instanyl® prescribing behavior in the past 12 months, knowledge about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. Awareness of the updated EMs were also assessed in the post-EM survey.

Results:

Physicians' participants:

In total, for the pre-EM survey, 277 physicians prescribing Instanyl® participated, of which 97 (35.0%) were from France, 109 (39.3%) from the Netherlands, and 71 (25.6%) from Poland. For the post-EM survey, 263 physicians prescribing Instanyl® participated, of which 94 (35.7%) were from France, 101 (38.4%) from the Netherlands, and 68 (25.9%) from Poland. A higher participation rate was observed in the pre-EM survey compared to the post-EM survey.

Descriptive data:

Physicians who participated in the post-EM survey were found to be older in comparison to those in the pre-EM survey. In the overall weighted sample, 56.8% (n=157/277) of physicians in the pre-EM survey were aged 31-49 years (post-EM survey: 13.1%; n=34/263). In contrast, the proportion of physicians aged 50 years or over was 20.1% (n=56/277) in the pre-EM survey, and 54.1% (142/263) in the post-EM survey. Moreover, in the overall weighted sample, a lower proportion of physicians who work in hospital/clinic-based setting was observed in the post-EM survey (24.6%) compared to the pre-EM survey (33.5%) and in community-based private practice setting (45.9% and 50.6%, respectively). In the post-EM survey, physicians reported relying more on unofficial sources of information in addition to scientific literature or conferences.

Prescribers' awareness, knowledge, and behavior are described below. At an aggregated level, i.e., for all prescribers considered as a whole (or a sub-group of prescribers), each criteria success threshold was achieved if at least 80% of prescribers responded correctly at least 80% of the questions of the criterion.

Awareness of updated EMs:

The threshold of 80% awareness of updated EMs at an aggregated level was neither reached overall, by specialty, nor at country level, with only 11.5% (95% Confidence Interval [95% CI]: 7.7%-15.4%, n=30/263) of physicians having met the success threshold for this criterion. From the overall sample, 24.1% (n=63/263) of physicians responded having received any educational material since the updated EM (Appendix Table 37), of which 65.6% (n=42/63) had received or downloaded the physicians guide to prescribing or the Instanyl® prescribing checklist, and 25.6% (n=16/63) reported having received or downloaded both EM. From prescribers who reported having received it, 92.8% (n=39/42) declared having read the Instanyl® prescribing checklist or the Physician's guide to prescribing. For this question, only the response "either the Instanyl® prescribing checklist or the physician's guide to prescribing" was considered for the physician score, which may have contributed to the low proportion of successful physicians.

Prescriber Knowledge:

The success threshold of at least 80% for the knowledge criterion was neither achieved at the aggregated level nor on a country level in the pre-EM or post-EM survey. Nevertheless, in the post-EM survey unweighted sample, a higher proportion of physicians scored 60%-80% of points than in the pre-EM survey (55.9% vs. 50.2% in pre-EM survey), indicating some improvements in the physicians' knowledge about Instanyl®. In fact, weighted results of the key topics related to knowledge criteria indicated that physicians performed better in the post-EM survey compared to the pre-EM survey in many statements regarding the approved indication, and presented a more conservative responses for recommended posology, and risks for opioid disorders.

Prescriber Behavior:

The success in the behavior criterion at the aggregated level was neither achieved overall nor on country level in the pre-EM and post-EM surveys (threshold of at least 80%). Overall, the weighted percentage of successful prescribers in the behavior criterion was 23.0% (95% CI: 18.1%- 28.0%, n=64/277) in the pre-EM survey and 11.2% (95% CI: 7.4%- 15.0%, n=29/263) in the post-EM survey. However, some improvements in self-reported behavior were observed in the post-EM survey compared to the pre-EM survey. For instance, a lower proportion of

physicians that presented a low level of knowledge (i.e., scored 40%-60% of the number of total points) (42.2% in the pre-EM survey, vs. 29.9% in the post-EM survey) was observed, as well as a higher proportion of physicians that presented a moderate level of knowledge (i.e., scored 60%-80% of the total points) (24.2% in the pre-EM survey vs. 38.3% in the post-EM survey). Moreover, the weighted results of the key topics related to the behavior criteria indicated that physicians performed better in the post-EM survey for many statements, as well as presented a more conservative and careful profile, by selecting for instance, an initial dose lower than the recommended, and a longer time between doses than recommended, which also may indicate some effectiveness of the updated EM.

Off-label prescription:

The most frequent reason for off-label prescription of Instanyl® was "fast relief of pain" in both pre-EM and post-EM surveys. However, off-label prescription of Instanyl® for fast relief of pain was less frequently observed in the post-EM survey for non-cancer patients with background pain (84.3% vs. 90.5% in pre-EM survey) and more frequently observed for cancer patients with uncontrolled background pain (96.4% vs. 86.9% in pre-EM survey). The reason "other routes of administration were not possible" was less frequently selected in the post-EM survey for prescriptions to other patients, i.e., uncontrolled background pain in cancer patients (49.7% vs. 57.1% in the pre-EM survey), breakthrough pain in non-cancer patients (52.6% vs. 57.0% in the pre-EM survey), and background pain in non-cancer patients (53.9% vs. 84.0% in the pre-EM survey). The reason "patient or caregiver's request" was also less frequently reported in the post-EM survey than in the pre-EM survey for pediatric patients ((33.7% vs. 78.4% in the pre-EM survey), as well as for uncontrolled background pain in cancer patients (27.7% vs. 36.5% in the pre-EM survey), and background pain in non-cancer patients (20.2% vs. 40% in the pre-EM survey).

Profile of patients at risk of misuse and addiction:

Awareness of the profile of patients at risk for misuse and addiction in the weighted sample was 18.0% (13.5%-22.6%) in the pre-EM and 20.6% (15.7%-25.5%) in the post-EM survey, and thus success in awareness of the profile of patients at risk of misuse or addiction was not achieved in either of the surveys (threshold of at least 80%). Considering each statement, higher percentages in the knowledge on communicating the risks to patients/caregivers, on the diagnostic criteria, and on patients at risk for misuse or addiction were observed, with an absolute increase of 19.2% in correctly identifying that "patients taking psychiatric medication are at risk" (49.7% in the pre-EM vs. 68.9% in the post-EM survey), an increase of 7.8% in correctly identifying "patients with personal or family history of substance use are at risk" (61.2% in the pre-EM survey vs. 69.0% in the post-EM survey); an increase of 4.1% in

correctly identifying that "tobacco users are at risk" (27.9% in the pre-EM survey vs. 32.0% in the post-EM survey). Results may indicate that the updated EM may have been effective in increasing, to some extent, the physician's knowledge about Instanyl®, even without achieving the aggregated threshold of success at this criterion.

Comparison between physicians who met the success threshold and physicians who did not meet the success threshold:

Physicians who met the success threshold regarding the awareness of EM were most commonly oncologists/oncoradiologists. Physicians who did not meet the success threshold regarding the awareness of EM and regarding the self-behavior criteria were most commonly general practitioners, from the Netherlands, and had treated fewer patients with the drug since the distribution of EM. Additional analysis showed that physicians who met the success threshold regarding awareness of the updated EM also met the success threshold in the self-behavior criterion, but not with regards to knowledge. Participating in both pre-EM and post-EM surveys did not seem to have an impact on the awareness of updated EM, knowledge, self-reported behavior, reasons for off-label prescription, or awareness of the profile of patients at risk of misuse of abuse.

Discussion:

The overall objective of this study was successfully met as it aimed to measure changes in understanding and self-reported behavior of Instanyl® prescribers regarding Instanyl® off-label use and the key information contained in the updated EM.

The updated EM were designed to increase physicians' awareness of Instanyl® and to reduce off-label use and risks. The key messages are intended to explain the approved indication and off-label use of Instanyl®, highlighting the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. However, results from the 2 surveys indicated that the updated EM were neither effective in increasing the percentage of physicians successful in the criteria of knowledge, nor increasing compliance in self-reported behavior regarding Instanyl®. Nevertheless, some results observed in the post-EM survey may be indicators of effectiveness of the updated EM. In the current study, an additional 8.1% of physicians (about 80%) in the post-EM survey correctly responded that Instanyl® should only be prescribed to patients already receiving opioid therapy. Moreover, 9 out of 10 physicians in the post-EM survey reported compliant behavior, prescribing Instanyl® to patients with cancer that were all on ongoing maintenance opioid therapy. Concerning improvements for reducing the risk of abuse, 6.2% fewer physicians reported prescribing Instanyl® off-label for fast relief of pain to

non-cancer patients with background pain and 10% fewer physicians reported having prescribed Instanyl® for the management of musculoskeletal disorders pain, such as for back pain, fibromyalgia, arthritis, after the distribution of the updated EM. For this study, the period between the distribution of the updated EM and the post-EM survey was 5 months, which may have been too short for physicians to assimilate the updated knowledge and behaviors into daily practice. [redacted]. Nevertheless, the benefit-risk profile of this product remains unchanged by the results of this study and remains positive.

Takeda is currently launching DoseGuard, an improved Instanyl® nasal spray with several additional features supporting patient safety and removing the current Instanyl® multi-dose nasal spray from the market. Instanyl® multi-dose nasal spray will be completely removed from the European market within a period of 9-12 months from the first launch of DoseGuard (no later than until July 2024). Educational materials for Instanyl DoseGuard have been reviewed with the aim of providing adequate instructions for the efficient use of DoseGuard. [redacted].

Marketing Authorization Holder(s): Takeda Pharmaceutical Company Limited

Name and Affiliations of Principal Investigator: [redacted], Germany.