1. ABSTRACT

Title

A Cross-sectional Survey to Evaluate Physician Knowledge of Safety Messages Included in the Physician Education Booklet (PEB) for IMLYGIC®

- **Keywords**

IMLYGIC; talimogene laherparepvec; melanoma; risk minimisation; survey

- **Rationale and Background**

Talimogene laherparepvec (IMLYGIC®) is an oncolytic viral drug to treat unresectable and metastatic melanoma. To ensure safe administration and handling, IMLYGIC was authorised with additional risk minimisation measures (RMMs) in Europe, which include a controlled distribution programme and educational material targeted for physicians and patients. For physicians, the primary additional RMM is the Physician Education Booklet (PEB).

This post-authorisation safety study (PASS, category 3) was initiated to assess the effectiveness of the information provided in the PEB.

- **Research Question and Objectives**

The primary objective was to evaluate physicians' knowledge of the key messages included in the IMLYGIC PEB among physicians who completed the required IMLYGIC training. The secondary objectives were to evaluate physicians' receipt and reading of the IMLYGIC PEB among physicians who completed the required IMLYGIC training, and to evaluate physicians' understanding of the requirements to distribute the Patient Information Leaflet (PIL), Patient Safety Brochure, and Patient Alert Card.

- **Study Design**

This was a multi-national, non-interventional, cross-sectional survey study.

- **Setting**

The target population was physicians who completed the required IMLYGIC training in Austria, Germany, the Netherlands, and the United Kingdom.

- **Subjects and Study Size, Including Dropouts**

Eligible physicians must have completed the controlled distribution programme training and must have provided permission to share their responses in aggregate with national competent regulatory authorities. A total of 129 invitations were sent to physicians, of which 12 failed delivery. Among the remaining 117 invited physicians, 18 physicians completed the eligibility questions, giving a survey response rate of 15.4% (18/117). Of these respondents, 1 (5.6%) was ineligible. Of the 17 eligible physicians, 15 completed all of the primary and secondary endpoint questions and these physicians comprised the primary analysis set for this report. The 17 physicians who completed at least 1 of the primary or secondary endpoint questions comprise the secondary analysis set for this report.

- **Variables and Data Sources**

The survey questionnaire was developed to evaluate physicians' knowledge of the key messages, and levels of receipt and reading, of the PEB and to evaluate physicians understanding of requirements to distribute the Patient Information Leaflet (PIL), Patient Safety Brochure, and Patient Alert Card.

- **Results**

The study invited 117 physicians to participate in the survey. The overall response rate was 15.3% (n=18/117) and ranged from 6.1% in Germany to 23.8% in the United Kingdom. Of the 18 respondents, 1 physician did not meet study eligibility criteria. Among the respondents, 15 of 17 physicians (88.2%) responded to all the primary and secondary endpoint questions (questions 1-17) and comprised the primary analysis set. The primary effectiveness endpoints were analysed in 6 key message domains

For Domain #1 (knowledge of the risk of disseminated herpetic infection in immunocompromised individuals), 4 survey items were mapped to key messages on the knowledge of risk of disseminated herpetic infection in immunocompromised individuals. The respondents generally had a high level of knowledge ranging from 73.3% to 100%. Knowledge that disseminated herpetic infection in immunocompromised individuals is a potential side effect/complication associated with IMLYGIC was the lowest of the 4 items (73.3%). In addition, all physicians knew the risks and benefits of treatment should be considered before administering IMLYGIC to patients receiving immunosuppressive agents.

For Domain #2 (knowledge of the risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs), 7 survey items were mapped to key messages on the knowledge of the risk of accidental exposure or transmission of IMLYGIC to close contacts or HCPs. Knowledge levels for the 7 items ranged from 33.3% to 100%. Knowledge was lowest for the item IMLYGIC-treated patients should avoid sharing cutlery and drinking vessels for the duration of IMLYGIC treatment and for 30 days after (33.3%). Less than half of physicians had knowledge that IMLYGIC-treated patients should use barrier protection (eg, with a latex condom) during sexual intercourse for the duration of IMLYGIC treatment and for 30 days after (46.7%). Knowledge levels were >70% for all other items in Domain #2. All physicians had knowledge the IMLYGIC-treated patients should avoid sharing injection needles, razor blades, and toothbrushes for the duration of IMLYGIC treatment and for 30 days after.

For Domain #3 (knowledge of the risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wild-type herpes in patients), 2 survey items were mapped to key messages on the knowledge of risk of symptomatic herpetic infection due to latency and reactivation of IMLYGIC or wild-type herpes in patients. Less than half of physicians knew that patients' treatment with acyclovir will interfere with the effectiveness of IMLYGIC for patients receiving IMLYGIC who develop herpetic infections (46.7%). Whereas, the majority of physicians (80%) knew that herpetic infections in treated patients is a side effect/complication associated with IMLYGIC.

For Domain #4 (knowledge regarding IMLYGIC use in pregnancy), 3 survey items were mapped to key messages on the knowledge regarding IMLYGIC use in pregnancy. Levels of knowledge were 60% for knowledge of foetal exposure to IMLYGIC from viral shedding and transmission through the placenta is a potential side effect/complication associated with IMLYGIC; 80% for knowledge that there is a potential risk to the foetus or neonate if exposed to IMLYGIC during pregnancy or during birth, and 93.3% for

knowledge that women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC.

For Domain #5 (knowledge of the safe use and handling of IMYLIGIC), 9 survey items were mapped to key messages on the knowledge regarding the safe use and handling of IMLYGIC. Knowledge levels ranged from 13.3% to 100%. Knowledge was lowest for the item that it is not necessary for exposed individuals to prophylactically take acyclovir in the event of exposure of IMLYGIC to broken skin or needle-stick (13.3%). One-third of physicians knew that close contacts of patients who are immunocompromised should not clean a patient's injection sites even if they wear protective gloves (33.3%). Only half of physicians knew that it is not necessary to avoid any form of ungloved direct contact with patients treated with IMLYGIC (53.3%). Two-third of physicians knew that HCPs who are pregnant should not prepare and administer IMLYGIC (66.7%). For the remaining 5 items, knowledge levels were 93.3% to 100%.

For Domain #6 (knowledge of the important accompanying patient materials), only 1 survey item was mapped to the key message on the knowledge of the important accompanying patient materials. All physicians acknowledged being given the IMLYGIC Patient Information Leaflet, Patient Safety Brochure, and Patient Alert Card to give to their patients who receive IMLYGIC.

The secondary effectiveness endpoints were analysed in 2 domains. For the first domain on the physicians' levels of receipt and reading of the IMLYGIC PEB, 2 survey items were mapped. The majority of the respondents (86.7%) reported that they received the IMLYGIC PEB and all respondents reported that they read "all" or "some" of the IMLYGIC PEB. For the second domain, 1 item was mapped to physician's understanding of the requirements to distribute the Patient Safety Brochure and Patient Alert Card. All respondents reported that they always distribute the IMLYGIC Patient Information Leaflet, Patient Safety Brochure, and Patient Alert Card to patients when they receive their first IMLYGIC injection.

The exploratory objective evaluated the physicians' composite knowledge for all 6 primary endpoints. The majority of the respondents (86.7%) answered 17-25 of 26 items correctly. No respondents answered all items correctly, nor did any the respondents answer fewer than 10 items correctly. Due to the small sample size, the analysis of knowledge levels stratified by country or sub-groups was not performed.

- **Discussion**

Based on the results of this study, it appears that the physicians participating in this survey had generally good knowledge of the key messages included in the IMLYGIC PEB. However, these results should be interpreted with caution due to the small number of physicians who participated in this survey. Generally, levels of receipt and reading of the IMLYGIC PEB among physicians completing the survey was high, as was their understanding of the requirements to distribute patient-directed materials to patients.

- **Marketing Authorization Holder(s)**

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