

## NON-INTERVENTIONAL STUDY INTERIM REPORT SYNOPSIS

**Title:** A multinational active safety surveillance study of crizotinib in Europe and the United States (US).

**Date of Synopsis:** 21 September 2016

**Keywords:** Crizotinib, erlotinib, ceritinib, lung cancer, non-small cell.

**Rationale and background:** Crizotinib, an orally administered selective ATP competitive small molecule inhibitor of the anaplastic lymphoma kinase (ALK), has been approved multinationally, including in the United States (US) in August 2011 and Europe in June 2013, for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC). To supplement the data obtained within the clinical development program, this post-authorization safety study (PASS) was designed to evaluate the safety and effectiveness of crizotinib in the real-world setting in Europe and the US.

**Research question and objectives:** The objective of this study is to evaluate the safety and effectiveness of crizotinib in patients with lung cancer in the real world setting. The primary objective was to estimate the incidence and incidence proportion over an approximately 3-year period of observation for hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and vision disorders among patients with lung cancer receiving crizotinib dispensation. The secondary objective is to estimate the incidence rate and incidence proportion over an approximately 3-year period of observation for renal cysts, edema, leukopenia, neuropathy, malignant melanoma, GI perforation, cardiac failure, and photosensitivity among lung cancer patients receiving crizotinib dispensation/prescription. Incidence rates and proportions of the same endpoints are calculated for patients receiving dispensation of ceritinib, erlotinib, and gefitinib in order to provide context to the findings.

For this Second Interim Report using data from national and regional healthcare databases, the primary objective in the US, Denmark and Sweden was to estimate the cumulative incidence and incidence rate of hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and vision disorders among patients with lung cancer receiving a dispensation crizotinib. In Finland and in the Netherlands, the primary objective was to describe demographics and/or concomitant medication and comorbidity of patients receiving a dispensation of crizotinib because of limited data and/or inadequate follow-up for the crizotinib study group to allow for evaluation of the study endpoints.

This Second Interim Report does not include data on ceritinib in Sweden, Denmark, Finland and PHARMO in the Netherlands since it was not approved for use in Europe during the interim study report period.

**Study design:** This is a non-interventional, active safety surveillance study using existing healthcare data sources from the US, Denmark, Sweden, Finland and the Netherlands.

**Setting:** The study population for the Second Interim Report included patients receiving dispensations of crizotinib, erlotinib, gefitinib or ceritinib between 1 September 2011 to 31 December 2014 in Optum Research Database in the US, between 1 June 2013 and 30 November 2014 in administrative and national registries in Denmark, between 1 January 2013 and 31 December 2014 in administrative and national registries in Sweden, between 1 April 2014 and 31 December 2014 in administrative and national registries in Finland, and between 1 January 2014 and 31 August 2015 in PHARMO Database Network in the Netherlands.

**Subjects and study size:** Overall, 248 patients with a dispensation of crizotinib, 1,905 patients with a dispensation of erlotinib or gefitinib, and 20 patients having a dispensation of ceritinib were included in the Second Interim Report.

**Variables and data sources:** Primary endpoints for the study are hepatotoxicity, pneumonitis/interstitial lung disease (ILD), QTc prolongation related events, bradycardia, and vision disorder. Secondary endpoints are renal cysts, edema, leukopenia, neuropathy, malignant melanoma, gastrointestinal (GI) perforation, photosensitivity, and mortality and overall survival. Data sources for the Second Interim Report included the national and regional healthcare databases in the US, Denmark, Sweden, Finland and the Netherlands.

**Results:** Results of the Second Interim Report from each country were presented below.

## US

A total of 857 eligible patients were included in the report. Of these patients, 171 had an index dispensing of crizotinib and 686 had an index dispensing of erlotinib. The median age was 53.5 years (IQR: 48.0-61.0) for crizotinib study drug group and 61.0 years (IQR: 55.0-66.0) for erlotinib study drug group. The median time from first observed lung cancer diagnosis to the index drug dispensation was 5 months (IQR: 1 to 12) for crizotinib and 8 months (IQR: 2 to 17) for erlotinib. Crizotinib and erlotinib study drug groups were comparable with respect to the Charlson comorbidity index, presence of brain metastases, preexisting hepatic impairment, and liver cirrhosis. Relative to erlotinib study drug group, crizotinib study drug group was less likely to have baseline diagnoses for renal impairment, chronic lung disease, chronic obstructive pulmonary disease, and diabetes.

For the primary endpoints, the 3-year cumulative incidences of bradycardia and hepatotoxicity were comparable between crizotinib and erlotinib study drug groups. The 3-year cumulative incidences of prolongation of QTc interval and vision disorder in crizotinib study drug group (34.5% and 9.4%, respectively) were higher than that in erlotinib study drug group (24.1% and 3.3%, respectively). The 3-year cumulative incidences of Pneumonitis/ILD and bradycardia in crizotinib study drug group were lower (19.4% and 8.2%, respectively) compared to that in erlotinib study drug group (24.5% and 10.2%, respectively). Incidence rates per 100 person years in crizotinib and erlotinib study drug groups, respectively, were 9.4 (95% CI: 4.3 - 17.9) and 11.9 (95% CI: 8.5 - 16.1) for bradycardia, 2.8 (95% CI: 0.8 - 7.2) and 5.0 (95% CI: 3.3 - 7.3) for hepatotoxicity, 20.8 (95% CI: 12.3 - 32.9) and 31.7 (95% CI: 25.9 - 38.5) for pneumonitis, 43.6 (95% CI:

27.6-65.4) and 28.2 (95% CI: 21.6-36.2) for prolonged QTc, and 10.3 (95% CI: 5.5 - 17.7) and 4.1 (95% CI: 2.5 - 6.3) for vision disorders.

For the secondary endpoints, relative to erlotinib study drug group, crizotinib study drug group had lower cumulative incidence of photosensitivity (0.6% in crizotinib study drug group, 9.5% in erlotinib study drug group), neuropathy (23.9% in crizotinib study drug group, 26.8% in erlotinib study drug group), leukopenia (11.0% in crizotinib study drug group, 15.5% in erlotinib study drug group), and all-cause death (9.1% in crizotinib study drug group, 15.3% in erlotinib study drug group), and higher cumulative incidence of edema (27.9% in crizotinib study drug group, 15.6% in erlotinib study drug group). Incidence rates of the secondary endpoints between crizotinib and erlotinib study drug groups showed similar patterns as cumulative incidences. The 6-month survival probability was 96% for the crizotinib group and 88% for the erlotinib group, and the 12-month survival probability was 87% for the crizotinib group and 83% for the erlotinib group.

### Denmark

There are no data on gefitinib in the Second Interim Report from Denmark since gefitinib was not identifiable via available administrative and national registries. During the report period, there were 34 patients with a record of an in-hospital dispensation of crizotinib and 458 with a record of an in-hospital dispensation of erlotinib, all of whom had history of primary lung cancer. Women accounted for 64.7% of the crizotinib-treated primary lung cancer patients and for 53.9% of the erlotinib-treated primary lung cancer patients. Median (quartiles) age at the index date was 60.6 (50.5, 66.2) years in the crizotinib group; and 68.1 (62.0, 74.0) years in the erlotinib group. Median time from the primary lung cancer diagnosis to the index date was 2.5 months in the crizotinib group and 9.5 months in the erlotinib group. Patients in the crizotinib group were less likely than patients in the erlotinib group to have a history of chronic obstructive pulmonary disease (COPD) (2.9% vs. 10.0%), brain metastases (5.9% vs. 9.8%), or pre-existing renal impairment was (2.9% vs. 6.6%), and more likely to have pre-existing hepatic impairment (5.9% vs. 1.5%). In the crizotinib group, 29/34 (85.3%) of the patients had a record of the ALK-rearrangement. Majority of the patients in both crizotinib (70.6%) and erlotinib (62.2%) groups had Stage IV tumor at diagnosis.

For primary endpoints, there were no incident cases of bradycardia, hepatotoxicity or vision disorder in the crizotinib group. One-year cumulative incidences of prolongation of QTc and pneumonitis/ILD in the crizotinib group were 3.7% (95% CI: 0.3, 15.9) and 3.6% (95% CI: 0.3, 15.4), respectively. In the erlotinib group, 1-year cumulative incidences of primary endpoints ranged from 0.2% (95% CI: 0.0, 1.2) for hepatotoxicity and 6.2% (95% CI: 4.1, 8.8) for pneumonitis/ILD. Incidence rates of prolongation of QTc and pneumonitis/ILD in the crizotinib group were 39.9 (95% CI: 1.0, 222.5) per 1,000 person-years and 43.5 (95% CI: 2.1, 241.6) per 1,000 person-years, respectively. In the erlotinib group, incidence rates of primary endpoints ranged from 3.7 (95% CI: 0.1, 20.6) per 1,000 person-years for hepatotoxicity to 106.4 (95% CI: 68.8, 157.0) per 1,000 person-years for pneumonitis/ILD.

For secondary endpoints, there were no incident cases of renal cysts, leukopenia, photosensitivity, malignant melanoma, or GI perforation in the crizotinib group. The

one-year cumulative incidences of edema and neuropathy in the crizotinib group were 2.9% (95% CI: 0.2, 13.0) and 15.6% (95% CI: 5.7, 30.0), respectively. In the erlotinib group, 1-year cumulative incidences of the secondary endpoints ranged from 0.2% (95% CI: 0.0, 1.2) for malignant melanoma and gastrointestinal perforation to 8.9% (95% CI: 6.4, 11.9) for neuropathy. The incidence rates of edema and neuropathy in the crizotinib group were 33.8 (95% CI: 0.9, 188.3) per 1,000 person-years and 187.8 (95% CI: 97.2, 385.4) per 1,000 person-years, respectively. In the erlotinib group, incidence rates of secondary endpoints ranged from 3.8 (95% CI: 0.1, 20.9) per 1,000 person-years for malignant melanoma to 152.8 (95% CI: 109.2, 218.1) per 1,000 person-years for neuropathy. The one-year overall survival was higher in the crizotinib group compared to that in the erlotinib group: 64% (95% CI: 45%, 78%) vs. 30% (95% CI: 26%, 35%).

### Sweden

A total of 575 patients from Sweden were eligible and included in this Second Interim Report. Of the eligible patients, 25 patients had a dispensation of crizotinib, 499 patients had a dispensation of erlotinib, 51 patients had a dispensation of gefitinib, and 21 patients had dispensations of erlotinib and gefitinib. Patients in the crizotinib study drug group were younger than the patients in the other study drug groups on the index date (median age: 63 years vs. 68.0-69.0 years, respectively). While 60% of the patients in the crizotinib study drug group were male, the corresponding proportion was 39-47% in other study drug groups. Time since lung cancer diagnosis was longer for the crizotinib study drug group (30.7 months) compared with the erlotinib study drug group (15.4 months) or the gefitinib study drug group (12.0 months). Compared to the other study drug groups, the proportion of patients with pre-existing hepatic impairment and brain metastases in the crizotinib study drug group was higher but the proportion of patients having chronic lung disease, diabetes and pre-existing renal impairment in the crizotinib study drug group was lower.

In the crizotinib study drug group, there were no incident events for hepatotoxicity, prolongation of QTc interval and pneumonitis/ILD. The one-year cumulative incidence of bradycardia in the crizotinib study drug group was 4.0% (95% CI: 0.1%, 20.4%). The corresponding one-year cumulative incidence for the erlotinib study drug group was 0.2% (95% CI: 0%, 1.1%). The two other study drug groups had no incident events for bradycardia. The incidence rates of bradycardia in the crizotinib study drug group and the erlotinib study drug group were 63.3 per 1,000 person-years (95% CI: 1.6 - 352.5) and 6.2 per 1,000 person-years (95% CI: 0.08 - 22.3), respectively. Among patients in the crizotinib study drug group the one-year cumulative incidence of vision disorder was 5.3% (95% CI: 0.1%, 26.0%). The corresponding one-year cumulative incidence for the gefitinib study drug group, the erlotinib study drug group, and the gefitinib and erlotinib combination study drug group was 2.1% (95% CI: 1.0%, 11.3%), 1.8% (95% CI: 0.8%, 3.5%) and 5.6% (95% CI: 0.1%, 27.3%), respectively. The incidence rates of vision disorder in the crizotinib study drug group, the gefitinib study drug group, the erlotinib study drug group, and the gefitinib and erlotinib combination study drug group were 76.8 per 1,000 person-years (95% CI: 1.9 – 427.6), 30.9 per 1,000 person-years (95% CI: 0.08 – 171.9), 30.8 per 1,000 person-years (95% CI: 14.1 – 58.4) and 109.7 per 1,000 person-years (95% CI: 2.8 – 611.1), respectively.

There were no incident events for any secondary endpoints (ie, renal cysts, edema, leukopenia, neuropathy, malignant melanoma, GI perforation, and photosensitivity) among crizotinib exposed patients. In the crizotinib group all-cause mortality during one year follow-up was 20.0% (95% CI: 6.8%, 40.7%). All of them were reported as lung cancer specific mortality. The corresponding all-cause mortality for the gefitinib study drug group, the erlotinib study drug group, and the gefitinib and erlotinib combination study drug group was 35.3% (95% CI: 22.4%, 49.9%), 59.3% (95% CI: 54.9%, 63.7%) and 38.1% (95% CI: 18.1%, 61.6%), respectively. The median survival time from the index date was 293 days for the crizotinib study drug group, and the corresponding median survival time for the gefitinib study drug group, the erlotinib study drug group, and the gefitinib and erlotinib combination study drug group was 507, 206, and 280 days, respectively. It should be noted that the follow-up time for the patients in the crizotinib group was less than one-year while the follow-up time for patients in other groups was greater than one year but less than two years. The different follow up time was because crizotinib was approved in Europe in 2013 while erlotinib and gefitinib were approved in Europe in 2005 and 2009, respectively.

### Finland

During the report period, nine patients with a record of dispensation of crizotinib (8 lung cancer and 1 patient with other cancer), 108 with a record of dispensation of erlotinib, and 19 with a record of dispensation of gefitinib were included. The proportion of women was 75.0% in the crizotinib group, 52.8% in the erlotinib group and 57.9% in the gefitinib group. Patients in the crizotinib group were younger than the patients in the erlotinib and gefitinib groups at the index date (mean age  $54.9 \pm 14.0$ ,  $68.6 \pm 8.9$ , and  $70.4 \pm 11.0$ , respectively). Median time from lung cancer diagnosis to start of treatment was 25.6 months (interquartile range: 17.5-36.0) in the crizotinib group, 8.5 months (interquartile range: 4.6-20.5) in the erlotinib group, and 1.7 months (interquartile range: 1.1-4.4) in the gefitinib group.

The proportion of patients with brain metastases was 12.5% in the crizotinib group, 4.6% in the erlotinib group and 5.3% in the gefitinib group. The proportion of patients with pre-existing renal impairment was 0% in the crizotinib group, 13.0% in the erlotinib group and 10.5% in the gefitinib group. The chronic obstructive pulmonary disease (COPD) was 0% in the crizotinib group, 15.7% in the erlotinib group and 10.5% in the gefitinib group. The proportion of patients used steroids was 87.5% in the crizotinib group, 68.5% in the erlotinib group and 21.1% in the gefitinib group. The proportion of patients used ophthalmologicals was 50.0% in the crizotinib group, 11.1% in the erlotinib group and 10.5% in the gefitinib group.

### The Netherlands

Fourteen eligible patients were identified from the PHARMO Out-patient Pharmacy Database: 1 with a dispensation of crizotinib, 13 with a dispensation of erlotinib; none with a dispensation of gefitinib or ceritinib. Most out-patient users of erlotinib were female (69%) and their mean ( $\pm$ SD) age was 65 ( $\pm$ 10) years. Fifty-eight eligible patients were identified from the In-patient Pharmacy Database: 8 with a dispensation of crizotinib, 26 with a dispensation of erlotinib, 24 with a dispensation of gefitinib and none with a dispensation of ceritinib. Most in-patient users of crizotinib, erlotinib or gefitinib were female (63%, 69%

and 71%, respectively). The mean ( $\pm$ SD) age was 61 ( $\pm$ 10) for crizotinib users, 66 ( $\pm$ 11) for erlotinib users and 66 ( $\pm$ 8) for gefitinib users.

**Discussion:** Results from the Second Interim Report were based on data available from national and regional healthcare databases in the US, Denmark, Sweden, Finland, and the Netherlands. Relative to the other study drug groups, the crizotinib study drug group was younger, had a higher proportion of patients with pre-existing hepatic impairment, and had a lower percent of patients with pre-existing renal impairment. Incidences of primary and secondary endpoints by study groups were estimated separately in the US, Denmark and Sweden. For primary endpoints, the incidence of hepatotoxicity and pneumonitis/ILD in the crizotinib study drug group was either comparable or lower than that in other study drug groups. The incidence of other primary endpoints in study drug groups varied by country. For secondary endpoints, the incidence of leukopenia, neuropathy, and photosensitivity in the crizotinib study drug group was lower compared to the other study drug groups. The survival probability in crizotinib study drug group was higher than that in the other study drug groups except data from Sweden. This was because crizotinib was approved in Europe in 2013 while erlotinib and gefitinib were approved in Europe in 2005 and 2009, respectively. Thus, the overall follow-up time for patients in the crizotinib group in Sweden during this interim report period was less than that in other study drug groups. The incidence of other secondary endpoints in study drug groups differed by country. Due to differing molecular target, clinical characteristics of patients, comorbidities, and reliance on unadjusted measures of occurrence, direct comparisons between study drug groups should be made with caution. Therefore, observed numerical differences, or lack thereof, may be attributed to differing clinical characteristics of patients and comorbidities, between patients within the different drug groups and may not reflect differences in risk and benefits of study drugs.

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