Revised 22nd.April 2019

Tagrisso Tablets
Clinical Experience Investigation (All patients investigation) Protocol

1. Objective

Clinical experience investigation (CEI) is to be conducted to confirm the following to characterise safety and efficacy of Tagrisso Tablets (hereinafter referred to as "the product") in actual clinical use.

(1) Incidence of adverse drug reactions (ADRs) in actual clinical use

(2) Factors which may affect safety and efficacy of the product (especially analysis of the incidence and risk factors of interstitial lung disease [ILD] events)

(3) Information of ADRs not expected from "Precautions for Use" of the JPI

Based on approval condition, this CEI should be conducted with all patients after the launch until accumulation of data from a predetermined number of patients for all patients.

2. Safety specification

The following are the specific safety concerns to be investigated:

Interstitial lung disease, QT prolongation, Liver disorder, Haematotoxicity, Cardiac disorder (excluding QT interval prolongation), Infectious diseases, Thromboembolism, Corneal disorder, Safety in patients with liver impairment

3. CEI protocol

3.1 Target number of patients and rationale

Target number of patients: 3000 patients (evaluable for the analysis) who received TAGRISSO for the approved indication of "EGFR T790M mutation positive inoperable or recurrent non-small cell lung cancer that is resistant to EGFR tyrosine kinase inhibitor"

Rationale: Based on clinical trial experience of Japanese patients, it is not anticipated that an ILD incidence rate for a low risk group of a risk factor for ILD will be below 4%. Under the assumptions that a ratio of subjects between a low and high risk group of a risk factor for ILD is 3:1, an ILD incidence rate for a low risk group of a risk factor for ILD is approximately 4%, and an odds ratio between a high and a low risk groups of a risk factor for ILD is 2.0, approximately 2200 patients will be needed to ensure the power of 90% to detect a risk factors of ILD with two-sided significance level of 5%. However, taking into account possible variability in a ratio of patients in a low and high risk group of a risk factor for ILD, for example, it is deemed preferable to enroll greater number of patients than 2200 patients. With these the planned number of subjects to be enrolled is set to be 3000 patients.

3.2 Investigation subjects

All patients treated with the product will be enrolled in the investigation.

3.3 Observation period

12 months

Data for the first 3 months will be collected in the first Case Report Form (CRF), and those for the rest of the period (from 3 months onwards) will be collected in the second CRF.

3.4 Planned number of investigation sites by department

Approximately 650 sites, mainly departments of pulmonary medicine

3.5 Investigation method

All patients investigation will be conducted using the central registration method.

1) The Medical Representative (MR) in charge of this investigation will explain the objective, subjects, methods and other things of this investigation to the doctor in charge of this investigation at the investigational site, and request for this investigation to the head of the site (such as hospital director). The contract will be concluded in writing.
   Tagrisso should be delivered to the medical institutions where the contract of all-patient investigation can be concluded. In principle, the drug should be delivered after the contract is concluded.
2) This is an all-patient investigation using central registration method. The investigation items will be collected using EDC (Electronic Data Capture) via internet, in principle. [redacted] At the institutions where EDC is not available, paper CRF will be used, and MR will deliver the registration form and CRF to the investigator after the contract is concluded.
3) When the investigator decides to start administration of Tagrisso to patients who are applicable to the above "3.2 Patients subject to this investigation", the investigator will send the information for the patient's registration via [redacted] or FAX. Patients who are subject to this investigation but have received the drug before the contract is concluded must also be investigated after the contract is concluded.
4) After receiving the information for registration, the investigator will be informed that the patient is registered.
5) The investigator will observe the patients according to the "3.3 Observation period". After the observation periods from the treatment start to 3 months and 12 months later are completed, data from prematurely discontinued cases should be transferred via [redacted] immediately after the discontinuation, and electronically signed. For the sites where paper forms are used, the forms should be completed after the observation periods, and given to MR.

6) The section that manages post-marketing investigation, etc., will prepare, at a later time, the all-patient investigation confirmation form based on the collected registration forms and CRFs, and MR will deliver the form to the investigator.
7) The investigator, once receive the all-patient investigation confirmation form, will confirm that the CRFs submitted by the investigator include all the patients treated, and give signature or name in print with Japanese seal on the all-patient investigation confirmation form, and give it to MR.

3.6 Planned investigation period

Registration period: MM/YYYY (product launch date) to the lifting of approval conditions

Once AstraZeneca KK can assume that the number of patients enrolled is expected to achieve the target number soon, we will stop asking medical institutions to enter information from new patients into CRFs based on the consultation results with PMDA. However, we will continuously enrol patients, and maintain the system/process where CRFs could be collected to obtain appropriate information where necessary by the time the PMDA' s judgement on approvability of TAGRISSO will be reported to the Committee on Drugs, as one of the approval conditions for all-patient investigation.

Nine months is expected to be required as the registration period to achieve the target number of patients of 3,000 in this investigation. The target 3000 patients are planned to be registered by the end of Feb 2017. All patients who start Tagrisso by the end of Feb 2017 are targets of collecting their CRFs.

Investigation period: MM/YYYY (product launch date) to the lifting of approval conditions

3.7 Investigation items

3.7.1 Investigation items

1. Items to be investigated in all patients

1) Information to identify individual patients

Identification number

2) Patient characteristics (baseline status)

Inpatient/outpatient, age, gender, date of first dosing, daily dose, reason for using the product, treatment line that the product is used for, T790M mutation, prior chemotherapy for primary disease, chest CT (yes/no), past or current history of ILD, smoking history, performance status (PS), prior lung surgery, prior lung radiation therapy, LVEF, height, weight, known allergy (yes/no), EGFR gene mutation test (EGFR gene mutation assay [yes/no], date of test, EGFR gene mutation status), medical history/concurrent disease (past or current history of hepatic dysfunction and its severity, past or current history of renal dysfunction and its severity, past or current history of ILD, past or current history /complication of asthma, past or current history /complication of COPD(including chronic bronchitis and emphysema), past or current history of other diseases), information regarding the diagnosis of primary disease (time of diagnosis of the cancer treated with the product, histological type at the time of diagnosis, location of the lesion treated with the product, clinical stage at the time of diagnosis, disease status)

3) Prior lung surgery

Name of surgery, date of surgery

4) Prior oxygen therapy
5) Pregnancy during the observation period (pregnancy [yes/no], lactation [yes/no])
6) Concomitant radiotherapy

   Irradiated site, first day of treatment, last day of treatment
7) Prior/concomitant chemotherapy for primary disease

   Treatment line, name of drug, route of administration, first day of treatment, last day of treatment
8) Changes in dose of the product

   Dosage per time/number of doses, date of changes in dosage and administration, reason for changes in dosage and administration
9) Continuation/discontinuation of the product (reason for discontinuation)
10) Assessment of response to the product

    Best overall response reported in each CRF, date of imaging that confirmed the best overall response
11) Progression

    Date of assessment, progression, PS
12) Data items reported for death cases

    Date of death, cause of death, causality between the product and death, autopsy (yes/no)
13) Adverse events

    Presence/absence of adverse events (AEs) [any undesirable or unintentional signs (including laboratory abnormalities), symptoms, or diseases whether or not considered causally related to the product] reported during the observation period

    However, deterioration of a pre-existing lung cancer lesion and lung cancer death should not be reported as an AE.

2. Items to be investigated in patients with an AE of ILD
   1) Initial findings suggesting ILD
   2) AE term**, start date, outcome, date of outcome, severity (CTCAE Grade), seriousness,* causality to the product, possible causes other than the product, and use of drugs to treat ILD

      * A serious adverse event (SAE) is defined as below based on the definition of "serious" in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (Notification No. 0328007 issued by the Safety Division, PFSB dated 28 March 2005):

      Any event that results in death, is life-threatening, results in persistent or significant disability/incapability, requires inpatient hospitalization or prolongation of existing hospitalization, is a medically important event or reaction, or is a congenital anomaly/birth defect

      ** For patients who discontinued the treatment due to an AE, all AEs observed within 28 days after the last dose will be followed up.
   3) Chest X-ray findings, chest CT findings
   4) Laboratory and clinical chemistry values
   5) Respiratory function test
   6) Infection test

7) Physical examination, clinical symptoms
8) Other tests
9) Concomitant drugs used to treat medical conditions other than primary disease
10) Comments on time course/causality of ILD

3. Items to be investigated in patients with an AE other than ILD
1) AE term**, start date, outcome, date of outcome, severity (CTCAE Grade), seriousness,* causality to the product, possible causes other than the product, concomitant drug considered to be causally related to the AE and laboratory abnormalities associated with the AE
2) Comments on time course/causality of AEs other than ILD

4. Other

In the event that the use of the product in pregnant or nursing women has been confirmed during the observation period of the CEI, delivery and newborns will be followed up.

< Observation schedule>

	Baseline	Start of treatment	At completion of 3-month observation period[a,b]	At completion of 12-month observation period[a,b]	Treatment discontinuation[a,c]	ILD (yes): at outcome assessment	AE other than ILD (yes): at outcome assessment
1. Items to be investigated in all patients	←	—	—	—	→ ○	○	○
(1) Information to identify individual patients		○					
(2) Patient characteristics		○					
(3) Prior lung surgery	←	→					
(4) Prior oxygen therapy	←	→					
(5) Pregnancy during the observation period		←	—	→			
(6) Concomitant radiotherapy		←	—	→			
(7) Prior/concomitant chemotherapy for primary disease	←	—	—	→			
(8) Changes in dose of the product		←	—	→	○	○	○
(9) Continuation/discontinuation of the product		←	—	→	○	○	○
(10) Assessment of response to the product		←	→	← →	○		
(11) Progression		←	→	← →	○		
(12) Death cases		←	—	→	○	○	○
(13) AEs		←	—	→	○		
2. Items to be investigated in patients with an AE of ILD		←	—	→		○	
3. Items to be investigated in patients with an AE other than ILD		←	—	→			○

a Only for patients followed up under routine clinical practice.

b The date of completion of 3-month observation period is defined as the day which is within ±2 weeks of and the closest to the last day of the observation period. In case that no visit has been made within ±2 weeks of the last day of the observation period, the date of last visit before the last day of the observation period will serve as the date of completion of 3-month observation period.
The date of completion of 12-month observation period is defined as the day which is within ±4 weeks of and the closest to the last day of the observation period. In case that no visit has been made within ±4 weeks of the last day of the observation period, the date of last visit before the last day of the observation period will serve as the date of completion of 12-month observation period.

c Date of treatment discontinuation is defined as the date of the last visit on treatment during the observation period or the next day of the last dose.

3.7.2 Key investigation items

The incidence of the following events will be investigated as key investigation items.

- ILD and QT prolongation, liver disorder, Haematotoxicity
- Cardiac disorder (excluding QT interval prolongation), infectious disease, thromboembolism, and corneal disorder
- Grade 3 or greater events of diarrhoea, skin disorder, and paronychia

Rationale:

- ILD: The Phase II combined analysis showed that 5/80 Japanese patients (6.3%) developed ILD, and it is highly likely that once ILD occurs, it may lead to serious outcome.
- QT interval prolongation: Although the Phase II combined analysis did not show serious cases,., the results from non-clinical and clinical studies suggest that QT interval prolongation in clinical practice.
- Liver disorder: The Phase II combined analysis showed that 32/411 overall population (7.8%) reported liver disorder, and it is necessary to pay careful caution to the occurrence of liver disorder in patient who will receive TAGRISSO.
- Haematotoxicity: The Phase II combined analysis showed that 40/80 Japanese patients (50.0%) reported haematological toxicity, and it is necessary to pay careful caution to the occurrence of haematological toxicity in patient who will receive TAGRISSO.
- Cardiac disorder (excluding QT interval prolongation): The Phase II combined analysis showed that 5/411overall population (1.2%) reported cardiac disorder and it is necessary to pay careful caution to the occurrence of cardiac disorder in patient who will receive TAGRISSO.
- Infectious diseases: The Phase II combined analysis showed that 21/411overall population (5.1%) reported infectious diseases and it is necessary to pay careful caution to the occurrence of infectious diseases in patient who will receive TAGRISSO.
- Thromboembolism: The Phase II combined analysis showed that 4/411overall population (1.0%) reported thromboembolism and it is necessary to pay careful caution to the occurrence of thromboembolism in patient who will receive TAGRISSO.
- Corneal disorder: The Phase II combined analysis showed that 2/411overall population (0.5%) reported corneal disorder and it is necessary to pay careful caution to the occurrence of t corneal disorder in patient who will receive TAGRISSO.
- Grade 3 or greater events of Diarrhoea, Skin disorder, Paronychia: These were the most common ADRs in clinical studies (mostly Grade 1 or 2).

3.8 Items to be analysed and analysis method

Details of the definition of analysis sets and analysis method will be provided in the Analysis Plan.

1) Analysis sets
    1)Safety analysis set
    2)Efficacy analysis set
2) Items for analysis
    1) Items regarding patient disposition

Number of registered patients, number of patients whose CRF are collected, number of patients in the safety analysis set, number of patients in the efficacy analysis set, number of patients excluded from the investigation (total and by reason for exclusion), number of discontinued patients (total and by reason for discontinuation)

2) Items regarding patient characteristics

Inpatient/outpatient, age, gender, reason for using the product, treatment line that the product is used for, EGFR gene mutation test, chest CT (yes/no), smoking history, PS, prior lung radiation therapy, height, weight, known allergy, medical history/concurrent disease, information regarding the diagnosis of primary disease, pregnancy (yes/no), lactation (yes/no), etc.

3) Items regarding treatment

Prior lung surgery, prior oxygen therapy, concomitant radiotherapy, prior/concomitant chemotherapy for primary disease, treatment with the product

4) Items regarding safety

ADRs (especially analysis of the incidence and risk factors of ILD events), SAEs

5) Items regarding efficacy

Number and ratio of patients by best overall response and by the presence/absence of progression at 3 months and 12 months after start of treatment (or at discontinuation of treatment)

3) Interim analysis

An interim analysis will be conducted one and a half year after launch based on the fixed data collected on CRFs because it is important to provide the information to the health care professionals as soon as possible

3.9 Organisation responsible for conducting CEI

Organisation responsible for conducting the CEI is the same as the one shown in the Attachment (2) to the Risk Management Plan.

3.10 Name and address of the cnotract acceptor (if any) who perform part of CEI-related duties and the scope of contracted duties

Business trustee

Address: (Omit)

Name:(Omit)

Content: (Omit)

4. Additional measure which may be implemented according to the result of the CEI and classification to determine the launch of the measure

At each milestone, the risk management plan will be reviewed. The review includes:

- Examination on necessity to revise the CEI protocol and on whether there is a new safety specification or not.
- Examination on necessity to develop a risk minimisation activity for the new safety specification.
- Examination on necessity of revision of the risk minimisation activity for the current safety specification.

5. Milestones for assessment of the schedule of the CEI and the collected data or for reporting to the PMDA

Milestones

At the time of J-PSUR submission, interim analysis (scheduled date; Dec. 2017) , and end of the CEI (scheduled date; Feb. 2019)

6. Other requirements

1) Revision of protocol

During the investigation period, progress in the investigation, number of dropouts, incidence of unlisted/serious ADRs, substantial increase in the incidence rate of specific ADRs, validity of investigation items, etc. should be continuously kept track of, and the protocol should be reviewed and revised as needed.

Furthermore, when approval for partial changes in Dosage and Administration or Indications has been obtained (except in case that a new re-examination period has been set) during the CEI of the product or on other relevant occasions, the protocol should also be revised as appropriate based on evaluation of the need for protocol revision.

2) Measures to be taken to deal with any issues or questions

In case that the occurrence of ADRs unexpected from the Precautions for Use is suggested; substantial increase in the incidence of ADRs is noticed, any safety or efficacy issue that was not identified before marketing has been raised, the occurrence of unusual ADRs is suggested, etc., the necessity of a special clinical experience investigation and a post-marketing clinical study should be assessed in order to detect or confirm the causes and to verify suppositions, etc. drawn from investigation.

7. Attachements（Omit）

Contract correspondence
Implementation guidance
Registration form
CRF1
CRF2