Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer

SUPPLEMENTAL DATA

Methods

Patients

The key inclusion criterion was a World Health Organization status of 0 to 2. Patients may have received prior local palliative radiation, surgery, chemotherapy, or investigational therapy provided that the last treatment was given at least 28 days prior to randomization. Exclusion criteria included significant cardiac, hematopoietic, hepatic, or renal dysfunction, an unmeasurable QTcF correction or QTcF >450 ms at screening, and history of arrhythmia. Patients were not permitted to take concomitant medications that are known to be associated with torsades de pointes or potent inducers of CYP3A4 function.

Measurable disease was defined as at least one lesion, not irradiated within 12 weeks of the date of randomization, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), and which is suitable for accurate repeated measurements. Measurable lesions with calcifications were not assessed as target lesions unless no other measurable lesion was available.

Study design and treatment

In Part B of the study, blinding for patients was removed at 14 months and the treatment options were as follows: patients receiving vandetanib 300 mg/day were given the option to continue vandetanib at 300 mg/day; patients receiving vandetanib 150 mg/day were given the option to stay on vandetanib at 150 mg/day or to increase the dose to 300 mg/day (provided they had no dose reductions as a result of an adverse event [AE] or QT prolongation). Patients receiving a reduced dose of vandetanib in Part A could continue to receive vandetanib at the same dose in Part B (100 mg for patients randomized to the 150 mg arm or 200 mg for patients randomized to the 300 mg arm).

Patients with dose escalation from 150 mg/day in Part A to 300 mg/day in Part B received additional visits to assess safety (weeks 3 and 8, and after the first dose in Part B). Patients receiving vandetanib with objective disease progression within 14 months on blinded treatment in Part A were also given the option to receive vandetanib in Part B with dosing as described above according to the last dose they received in Part A. No further dose escalations were permitted in Part B.

Patients were followed for efficacy only during the double-blind randomized phase (Part A) of the study. Safety evaluations were continued during Part B for a total period of 2 years following randomization in Part A or for 60 days following permanent discontinuation of vandetanib, if prior to 2 years. Following the final safety analysis, patients could continue to receive open-label vandetanib (depending on the availability of commercial supply) as long as, in the investigator's opinion, the patient was continuing to receive clinical benefit.

Statistical methods

Estimates of the objective response rate (ORR) within the first 14 months following randomization were calculated with two-sided exact 95% confidence intervals (CIs). The Wilson score method was used for calculation of the CIs. A sensitivity analysis of ORR was performed using the per-protocol analysis set. A waterfall plot representing the individual patients' best percentage change from baseline in tumor size during the first 14 months was presented by treatment arm. Population pharmacokinetic analyses were performed using non-linear, mixed-effects modelling.

For Parts A and B, absolute and change from baseline for each of the electrocardiogram (ECG) parameters were summarized using univariate statistics. Summaries of incidence of QTcF prolongation, period until recovery from QTcF prolongation, QTcF prolongation, and time to first QTcF prolongation (days) were produced.

Results

Pharmacokinetics – Part A

Mean plasma concentrations of vandetanib, as expected, were higher in the group of patients receiving vandetanib 300 mg. Mean maximum plasma concentration at steady state (C_{maxss}) was estimated to be 486 ng/mL for the 150 mg group, and 885 ng/mL for the 300 mg group. Mean area under the plasma concentration time curve at steady state (AUC_{ss}) was estimated to be 8250 ng.h/mL for the 150 mg group and 14804 ng.h/mL for the 300 mg group. Clearance was similar for the 150 mg group (10.4 L/h) and the 300 mg group (11.1 L/h).

Safety – Parts A and B

Deaths

Five patients died during Part A of the study (all in the vandetanib 300 mg group); three deaths were related to the disease under investigation, and two patients experienced AEs leading to death (one AE of epilepsy and one AE of pulmonary embolism). The death in the patient with an AE of epilepsy was also related to the disease under investigation. Eight patients died during Part B of the study (five patients initially randomized to vandetanib 150 mg in Part A, and three patients initially randomized to vandetanib 300 mg; all eight patients received vandetanib 300 mg in Part B). Six deaths were related to the disease under investigation and two patients experienced AEs leading to death (one AE of acute cardiac failure and one event of laryngeal hemorrhage). The patient who died from acute cardiac failure was initially randomized to vandetanib 300 mg in Part A; this patient had normal ejection fraction throughout Part B of the study and no reports of hypertension. The patient with laryngeal hemorrhage was initially randomized to vandetanib 150 mg in Part A. This laryngeal hemorrhage was related to an inflammatory lesion in the larynx rather than related to malignancy, and was not considered to be related to the study drug. None of the deaths in Part A or Part B were considered related to vandetanib.

Clinical laboratory evaluation, vital signs and ECG changes

For Part A, all means were within normal laboratory reference ranges, except for hemoglobin and lactate hydrogenase. Laboratory parameter values did not differ markedly between the vandetanib 150 and 300 mg dose groups. Calcium levels were

generally at the low end of the normal reference ranges for the safety population. Clinically important changes in Common Terminology Criteria for Adverse Events (CTCAE) grade occurred in approximately 5% of patients, in whom a CTCAE grade change of ≥2 was recorded. Urinalysis showed that a small number of patients in both groups experienced anomalies in occult blood, glucose, and protein levels. Although values outside the normal ranges were recorded for a small number of patients for the majority of laboratory parameters, these are not considered to be clinically significant.

In Part B, the majority of changes in mean values for hematology and clinical chemistry variables were not considered clinically significant. Mean percentage change from baseline to the final analysis visit (week 108) was high (13503.20%) for thyrotropin in the 300 mg group.

No abnormal left ventricular ejection fraction (LVEF) findings were reported in either dose group in Part A. In Part B, one patient had an LVEF of <40%; this patient had a baseline LVEF value of 45% in Parts A and B, which reduced to 35% at week 24 in Part B. This patient was initially randomized to vandetanib 300 mg and received open-label vandetanib 300 mg in Part B, which was later reduced to 200 mg because of an AE of decreased ejection fraction.

The number of abnormalities in clinical laboratory parameters (hematological, clinical chemistry, and urinalysis), vital signs, ECGs, and LVEF data were not of clinical concern, with the majority considered to be consistent with the known safety profile of vandetanib or the patients' underlying disease.