Summary Report of Benefit-Risk Assessment

TABRECTA FILM-COATED TABLET 150 MG, 200 MG

NEW DRUG APPLICATIONS

Active Ingredient(s)	Capmatinib
Product Registrant	Novartis (Singapore) Pte Ltd
Product Registration Number	SIN16350P, SIN16351P
Application Route	Abridged evaluation
Date of Approval	22 October 2021

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A INTRODUCTION

Tabrecta is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.

The active substance, capmatinib, is an oral highly selective and potent inhibitor of the MET receptor tyrosine kinase. Capmatinib inhibits MET-mediated phosphorylation and downstream signalling such as the PI3K/Akt and MAPK/ERK pathways, as well as proliferation and survival of MET-dependent cancer cells.

Tabrecta is available as film-coated tablets containing 150mg and 200mg of capmatinib as capmatinib dihydrochloride monohydrate. Other ingredients in the tablet core are microcrystalline cellulose, mannitol, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide, and sodium lauril sulfate. The ingredients in the film coating are hypromellose, titanium dioxide, macrogol 4000, talc and iron oxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, capmatinib dihydrochloride monohydrate, is manufactured at Novartis Ringaskiddy Limited, Cork, Ireland. The drug product, Tabrecta is manufactured at Novartis Pharma Produktions GmbH, Wehr, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Novartis Ringaskiddy Limited was adequate to support the approved storage condition and re-test period. The packaging is a polyethylene (PE) bag or in a PE bag from continuous PE liner. The PE bag is then placed into an additional PE bag and stored in metal drum. The drug substance is approved for storage at or below 25°C with a re-test period of 18 months.

Drug product:
The tablet is manufactured using a wet granulation approach, followed by film-coating. The process is considered to be a standard process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is a polychlorotrifluoro ethylene/ polyvinyl chloride with a heat sealable lacquered aluminium foil blister (PCTFE/PVC-Alu) containing 12 tablets/blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of capmatinib in the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation was based on 1 pivotal study (Study A2201/ Study GEOMETRY mono-1), and supported by 1 dose response study (Study CINC280X2102) as well as real-world evidence (RWE) from Study CINC280X2401.

Study CINC280X2102 was a Phase 1, open-label, multi-centre, non-randomised, single-arm, dose escalation study with an expansion phase. Based on the safety, pharmacodynamics, bioavailability and efficacy data from the escalation phase, the maximum tolerated dose of capmatinib was determined to be 400mg twice daily and was selected for further investigation in the Phase 2 study. The escalation phase was followed by an expansion phase which enrolled 55 subjects with MET-dysregulated NSCLC, out of which 4 subjects were identified with MET-mutated NSCLC. Of the 4 subjects 1 achieved complete response (CR), 2 achieved partial response (PR) and 1 had stable disease (SD). As per Blinded Independent Review Committee (BIRC) assessment, the duration of response (DOR) for the subject who achieved CR was 16.8 months, and that for the 2 subjects with PR was 2.1 months and 2.0 months, respectively. The progression free survival (PFS) was 18.6 months for the subject with CR, 3.8 months, 3.9 months for the 2 subjects with PR, and 3.0 months for the subject with SD based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Study A2201 is a Phase 2, ongoing, single-arm, non-randomised, open-label, multi-cohort study conducted in patients with wild-type EGFR and ALK rearrangement negative advanced or metastatic (stage IIIB or IV) NSCLC harbouring MET mutations (detected by reverse transcriptase-polymerase chain reaction [RT-PCR]) and/or amplification (detected by fluorescent in-situ hybridisation [FISH]). Subjects with MET exon 14 skipping mutations were enrolled in Cohort 4 and Cohort 5b, and those with MET amplification without MET mutations were enrolled in Cohorts 1a, 1b, 2, 3 and Cohort 5a. All subjects in Cohorts 1a, 1b, 2, 3 and 4 must have failed 1 or 2 prior lines of systemic therapy in advanced stage, subjects in Cohort 6 must have failed one line of systemic therapy for advanced/metastatic disease, while subjects enrolled in Cohorts 5a, 5b, and 7 were treatment-naïve for advanced disease. The indication sought in the application was based on Cohorts 4 (previously treated patients) and 5b (treatment-naïve patients).

All the patients in the study were treated with capmatinib 400 mg twice daily until the subject experienced a disease progression event according to RECIST 1.1 as determined by the

investigator and confirmed by the BIRC. Dose reductions were allowed as per the dose reduction schedule, and for each subject, a maximum of 2 dose level modifications were allowed after which the subject discontinued from the treatment.

The primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of subjects with a best overall response (BOR) of CR or PR by BIRC assessment. The key secondary efficacy endpoints were PFS as determined by the BIRC and investigator, time to response (TTR), overall survival (OS) and DOR calculated as the time from the date of the first documented CR or PR by the BIRC to the first documented progression or death due to any cause. In the pre-treated subjects in Cohort 4, a pre-specified ORR ≥ 35% with a lower bound of the 95% confidence limit of > 25% was considered to reflect clinically relevant efficacy. For treatment-naïve subjects in Cohort 5b, an ORR ≥ 55% with a lower bound of the 95% confidence limit > 35% was considered as clinically relevant efficacy.

The primary analysis comprised 97 subjects with 69 patients in Cohort 4 (MET mutated, pre-treated) and 28 patients in Cohort 5b (MET mutated, treatment-naïve). The median study follow-up was 22.5 months (range: 12.4 to 36.1) and 16.8 months (range: 10.3 to 24.9) for Cohorts 4 and 5b, respectively. The median age of the subjects was 71 years (range: 49-90). There was a higher proportion of women (59.8%) and 37.1% of the population were ex-smokers. The majority of subjects had good ECOG status at baseline (99.0% had ECOG PS 0 or 1). In Cohort 4, majority of the subjects (88.4%) had received platinum-based chemotherapy (irrespective of the line) prior to entering the study, whereas Cohort 5b included only subjects who had not received prior systemic chemotherapy

The primary efficacy endpoint of ORR by BIRC assessment were 40.6% (95% CI: 28.9, 53.1) in Cohort 4 and 67.9% (95% CI: 47.6, 84.1) in Cohort 5b, respectively. Consistent results were observed with the assessment by investigator, with 42.0% (95% CI: 30.2, 54.5) and 60.7% (95% CI: 40.6, 78.5) in Cohort 4 and Cohort 5b, respectively. The results met the pre-defined criteria for clinically relevant efficacy.

Similarly, for the median DOR, the BIRC assessment of 9.72 months (95% CI: 5.55, 12.98) and 12.58 months (95% CI: 5.55, 25.33) in Cohort 4 and Cohort 5b, respectively, were consistent with that by the investigator, 8.31 months (95% CI: 5.45, 12.06) and 13.83 months (95% CI: 4.27, 25.33) in Cohort 4 and Cohort 5b, respectively.

Tumour responses to capmatinib were observed with a TTR per BIRC of approximately 7 weeks, with 82.1% and 68.4% of responders achieving response within 2 months of initiating treatment in Cohort 4 and Cohort 5b, respectively. The median PFS by BIRC was 5.42 months (95% CI: 4.17, 6.97) and 9.69 months (95% CI: 5.52, 13.86) in Cohort 4 and Cohort 5b, respectively; and by the investigator was 4.80 months (95% CI: 4.11, 7.75) and 11.14 months (95% CI: 5.52, 15.24) in Cohort 4 and Cohort 5b, respectively. Median OS was 13.57 months (95% CI: 8.61, 21.19) and 15.24 months (95% CI: 12.22, NE) in Cohort 4 and Cohort 5b, respectively.

Summary of key efficacy results (15 Apr 2019 cutoff)

	Cohort 4 (MET mutated, pre-treated) N = 69	**Cohort 5b (MET mutated, treatment-naïve) N = 28**
Primary endpoint		
ORR (CR + PR), BIRC Exact binomial 95% CI	28 (40.6%) [28.9, 53.1]	19 (67.9%) [47.6, 84.1]
Complete response (CR)	0 (0.0%)	1 (3.6%)
Partial response (PR)	28 (40.6%)	18 (64.3%)

Stable disease (SD)	25 (36.2%)	8 (28.6%)
Non-CR/non-PD	1 (1.4%)	0 (0.0%)
Progressive disease (PD)	6 (8.7%)	1 (3.6%)
Not evaluable (NE)	9 (13.0%)	0 (0.0%)
Key secondary endpoints		
PFS per BIRC		
No. of events, n (%)	55 (79.7%)	17 (60.7%)
Median PFS (months) [95% CI]	5.42 [4.17, 6.97]	9.69 [5.52, 13.86]
OS		
No. of events, n (%)	44 (63.8%)	13 (46.4%)
Median OS, months [95% CI]	13.57 [8.61, 21.19]	15.24 [12.22, NE]
DOR per BIRC		
No. of events, n (%)	20 (71.4%)	10 (52.6%)
Median DOR, months [95% CI]	9.72 [5.55, 12.98]	11.14 [5.55, NE]
Median DOR, months [95% CI] *28 Oct 2019 cutoff date	9.72 [5.55, 12.98]	12.58 [5.55, 25.33]

The supporting RWE from Study CINC280X2401 was based on retrospective chart collection from 157 subjects with MET mutated advanced or metastatic NSCLC treated with MET inhibitor as compared with standard-of-care therapies including chemotherapy and immunotherapy in various lines of therapy. MET inhibiting class included drugs like cabozantinib, crizotinib, emibetuzumab, ficlatuzumab, foretinib, glesatinib, merestinib, onartuzumab, rilotumumab, sitravatinib, tepotinib, and tivantinib. The analysis showed that OS was improved in MET inhibitor-treated subjects (median OS of 25.4 months, 95% CI: 18.8, 40.9) compared to those who did not receive MET inhibitors (10.7 months, 95% CI: 7.8, 14.4). This study provided supportive evidence of the survival benefit with MET inhibitors in this patient population.

Clinical outcomes of patients receiving MET inhibitors versus patients who did not receive MET inhibitors, and standard-of-care agents

Overall survival of patients receiving MET inhibitors versus patients who did not receive MET inhibitors		
	Received MET inhibitor (N = 49)	**Did not receive MET inhibitor (N = 108)**
Median OS (months) [95% CI]	25.4 [18.8, 40.9]	10.7 [7.8, 14.4]

Clinical outcomes of patients receiving different standard-of-care agents				
	First-line		**Second- or third-line**	
	Chemotherapy (N = 61)	**Immunotherapy (N = 12)**	**Chemotherapy (N = 9)**	**Immunotherapy (N = 16)**
Median OS (months) [95% CI]	9.1 [7.5, 18.9]	18.4 [1.5, 18.4]	13.2 [3.0, 42.7]	11.9 [2.1, NE]
	Chemotherapy (N = 86)	**Immunotherapy (N = 17)**	**Chemotherapy (N = 22)**	**Immunotherapy (N = 24)**
Median PFS (months) [95% CI]	5.1 [3.3, 6.9]	2.6 [1.0, 6.9]	2.8 [1.2, 5.0]	3.1 [1.9, 4.1]
ORR (CR + PR)	25.6%	35.3%	13.6%	16.7%

Study A2201 met its primary endpoint in terms of BIRC-assessed ORR in both the pre-treated (Cohort 4) and treatment-naïve (Cohort 5b) subjects with MET-mutated NSCLC. The results of the secondary endpoints supported the primary endpoint. The ORR observed in the first-line setting of 67.9% was comparable to that seen with other approved targeted therapies, while the ORR in the second-line setting of 40.6% was numerically better than that known for the current standard of care such as docetaxel, atezolizumab, nivolumab and pembrolizumab (9 - 20%).

The benefit of treatment with MET inhibitors compared against treatment regimens without MET inhibitors in patients with MET mutated advanced or metastatic NSCLC observed in Study CINC280X2401 further supports the use of capmatinib in this patient population. While the overall data was considered promising, given the small sample size of Cohorts 4 and 5b in

Study A2201, the final results from a larger sample size of the on-going study are required to be submitted post-approval in order to confirm the observed benefit.

D ASSESSMENT OF CLINICAL SAFETY

The safety data reviewed was primarily based on the results from Study A2201 (n = 348), supplemented by data from 6 pooled studies (n=555) conducted in all solid tumour subjects who had received capmatinib monotherapy (Study A2201, Study X1101, Study X2102, Study A2108, Study A2103 and Study A2105).

Study name	Study Description
A2201	Phase II, multicentre study of capmatinib in adult subjects with EGFR wild-type, ALK-negative locally advanced or metastatic NSCLC (N=334), including also MET mutated NSCLC.
X1101	Phase I study of capmatinib in Japanese subjects with advanced solid tumours
X2102	Phase I open-label dose escalation study with expansion to assess the safety and tolerability of capmatinib in subjects with MET dependent advanced solid tumours
A2103	Phase I, multicentre, open-label, single-sequence drug-drug interaction study to assess the effect of capmatinib on the pharmacokinetics of midazolam and caffeine in subjects with MET-dysregulated advanced solid tumours
A2105	Phase I, multicentre, open-label, single-sequence drug-drug interaction study to assess the effect of capmatinib on the pharmacokinetics of digoxin and rosuvastatin in subjects with MET-dysregulated advanced solid tumours
A2108	Multicentre, open label, Phase I dose escalation study to evaluate the pharmacokinetics, safety, and tolerability of capmatinib tablet formulation with food in subjects with MET dysregulated advanced solid tumours

The median duration of exposure to capmatinib in Study A2201 as of the data cut-off date on 18 Sep 2019 was 15.4 weeks, and 34 subjects (9.8%) had received capmatinib for ≥72 weeks.

Summary of AEs (last three columns contain data with 18 Sep 2019 cutoff)

AE	Study A2201 Cohort 4 (n = 69) 15 Apr 2019 cutoff	Study A2201 Cohort 5b (n = 28) 15 Apr 2019 cutoff	Study A2201 All subjects (n = 348)	Pooled analyses All NSCLC (n = 433)	Pooled analyses All solid tumour (n = 555)
Any AE					
All grades	68 (98.6%)	28 (100%)	340 (97.7%)	425 (98.2%)	546 (98.4%)
Grade 3/4	50 (72.5%)	20 (71.4%)	231 (66.4%)	291 (67.2%)	349 (62.9%)
Treatment-related AE					
All grades	60 (87.0%)	27 (96.4%)	297 (85.3%)	371 (85.7%)	471 (84.9%)
Grade 3/4	33 (47.8%)	15 (53.6%)	128 (36.8%)	157 (36.3%)	179 (32.3%)
SAE					
All grades	35 (50.7%)	13 (46.4%)	172 (49.4%)	214 (49.4%)	263 (47.4%)
Grade 3/4	29 (42.0%)	11 (39.3%)	142 (40.8%)	175 (40.4%)	212 (38.2%)
Treatment-related SAE					
All grades	12 (17.4%)	4 (14.3%)	44 (12.6%)	54 (12.5%)	61 (11.0%)
Grade 3/4	8 (11.6%)	4 (14.3%)	30 (8.6%)	37 (8.5%)	42 (7.6%)
Discontinuations due to AE					
All grades	14 (20.3%)	6 (21.4%)	56 (16.1%)	71 (16.4%)	82 (14.8%)
Grades 3/4	8 (11.6%)	5 (17.9%)	35 (10.1%)	46 (10.6%)	52 (9.4%)
Deaths* *Due to reasons not related to study indication	2 (2.9%)	2 (7.1%)	11 (3.2%)	16 (3.7%)	26 (4.7%)

The incidences of adverse event (AE) and serious AEs observed in Study A2201 were similar between the NSCLC and all solid tumour populations.

In Study A2201, AEs were reported in 98.6% of subjects in Cohort 4 and all subjects in Cohort 5b, and the most frequently reported AEs were peripheral oedema (51.1%), nausea (43.7%),

vomiting (28.2%), and increased blood creatinine (25.0%). The most common grade 3/4 AEs (in ≥ 5% of subjects), irrespective of study drug relationship, were peripheral oedema (8.9%), dyspnoea (6.6%), increased ALT (6.0%), and increased lipase (5.7%).

The serious adverse events (SAEs) reported in ≥ 2% of all subjects were: dyspnoea (6.6%), pneumonia (4.9%), general physical health deterioration (3.7%), pleural effusion (3.4%), vomiting (2.3%), and nausea (2.0%). A total of 11 deaths were attributed to SAEs (cardiac arrest [in 2 subjects], atrial fibrillation, hepatitis, pneumonia, pneumonia bacterial, pneumonitis, organizing pneumonia, respiratory distress, sepsis, and septic shock [one subject each]). Four of these deaths (cardiac arrest, hepatitis, organizing pneumonia, pneumonitis) were reported as treatment-related by the investigator. These subjects had other confounding factors including thoracic radiotherapy prior to study entry and concomitant therapy contributing to the SAE. Fifty-six subjects (16.1%) had AEs which led to permanent discontinuation of study treatment irrespective of study drug relation, with 10.1% (35 subjects) experiencing grade 3/4 AEs leading to permanent discontinuation of study treatment.

Overview of AESI (Safety set)

	Data cutoff 15 Apr 2019						**Data cutoff 18 Sep 2019**	
	Cohort 4 (2nd/3rd line, MET mutated, n = 69)		Cohort 5b (treatment-naïve, MET mutated, n = 28)		All subjects n = 334		All subjects n = 348	
AESI	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hepatotoxicity	17 (24.6)	8 (11.6)	8 (28.6)	3 (10.7)	94 (28.1)	32 (9.6)	101 (29.0)	35 (10.1)
Renal dysfunction	24 (34.8)	0	10 (35.7)	0	89 (26.6)	1 (0.3)	91 (26.1)	1 (0.3)
Central nervous system toxicity	14 (20.3)	0	4 (14.3)	0	62 (18.6)	3 (0.9)	64 (18.4)	3 (0.9)
Pancreatitis	9 (13.0)	8 (11.6)	5 (17.9)	3 (10.7)	41 (12.3)	26 (7.8)	43 (12.4)	28 (8.0)
Interstitial lung disease/ pneumonitis	7 (10.1)	3 (4.3)	2 (7.1)	2 (7.1)	15 (4.5)	6 (1.8)	15 (4.3)	6 (1.7)
QTc interval prolongation	1 (1.4)	0	2 (7.1)	0	10 (3.0)	3 (0.9)	10 (2.9)	3 (0.9)
Photosensitivity	0	0	0	0	1 (0.3)	0	1 (0.3)	0
Teratogenicity	0	0	0	0	0	0	0	0
Drug-drug interactions with strong CYP3A4 inducers*	0	0	0	0	0	0	0	0

A subject with multiple severity grades for an AE was only counted under the maximum grade.
*Any subject receiving treatment with strong inducers of CYP3A4 and could not be discontinued ≥1 week prior to the start of treatment with capmatinib and for the duration of the study was to be excluded from the study.
MedDRA version 22.0, CTCAE version 4.03, Case Retrieval Strategy version 17-May-2019

The AEs of special interest (AESIs) with capmatinib were hepatotoxicity (29.0%), renal dysfunction (26.1%), central nervous system toxicity (18.4%), pancreatitis (12.4%), interstitial lung disease (ILD)/pneumonitis (4.3%), QTc interval prolongation (2.9%), and photosensitivity (0.3%).

ILD/pneumonitis is a class effect for tyrosine kinase inhibitors (TKIs) including MET inhibitors. There were 15 subjects with ILD/pneumonitis-related AEs, 12 subjects had pneumonitis and 3 subjects had ILD, of which 6 were of grade 3 in severity. The remaining 9 subjects experienced grade 1/2 events and there was no grade 4 event. Most of these subjects (10 of 15 subjects) had prior immunotherapy and/or radiotherapy as confounding factors and/or had progressive disease at the onset of ILD/pneumonitis. Eight subjects discontinued study drug due to these AEs. One fatal event of ILD/pneumonitis was reported. The median time to first occurrence of

grade 3/4 ILD/pneumonitis AEs was 1.38 months and the median duration of these first occurrence of grade 3/4 ILD/pneumonitis AEs was 0.44 months.

Hepatotoxicity AEs were reported in 101 subjects, among these 6 subjects had SAEs and 35 subjects had grade 3/4 AEs. The most common were increased alanine aminotransferase, increased aspartate aminotransferase, hypoalbuminemia, increased gamma-glutamyltransferase, and increased blood alkaline phosphatase. About 2% of subjects required study drug discontinuation, 3.4% of the subjects required dose adjustment, and 7.2% subjects required dose interruption. TKIs are known to cause hepatotoxicity, and these events could be exacerbated by the underlying liver metastases seen in metastatic NSCLC.

Renal dysfunction was reported in 91 subjects, of which 68 subjects had treatment-related events, and most of the events were of grades 1/2 severity. CNS toxicity (seizures, epilepsy) was reported in 64 subjects and in 3 of the subjects the severity was grade 3. No discontinuation due to CNS toxicity was reported. Pancreatitis-grouped AEs (elevated pancreatic enzymes) were reported in 43 subjects, of which 28 reported grade 3/4 events.

The safety profile was generally consistent with the mechanism of action of TKIs. The AESIs of ILD/pneumonitis, hepatotoxicity, renal dysfunction, pancreatitis, CNS toxicity and photosensitivity were the main safety risks associated with capmatinib. Relevant information on ILD/pneumonitis and hepatotoxicity with respect to dosage modification, warnings and precautions have been included in the product label. The adverse events section has also adequately described the AESIs including those that were less commonly observed (renal dysfunction, pancreatitis, CNS toxicity, and photosensitivity). Overall safety profile of capmatinib for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation was considered acceptable for the intended patient population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

MET-mutated NSCLC is a rare condition and is more prevalent in the elderly population with multiple related comorbidities, representing a difficult-to-treat population. MET mutation is mutually exclusive from other established molecular drivers tested and may constitute 2-3% of NSCLC patients. The prognosis with standard therapies for metastatic NSCLC population with MET-mutations is poorer compared to those without MET mutations. Capmatinib is a first-in class drug targeting MET exon 14 skipping mutations in NSCLC subjects.

The efficacy of capmatinib in the treatment of metastatic NSCLC patients with MET exon 14 skipping mutations was demonstrated in the pivotal Study A2201 with an ORR of 67.9% (95% CI: 47.6, 84.1) and 40.6% (95% CI: 28.9, 53.1) in treatment-naïve and pre-treated MET mutated metastatic NSCLC patients, respectively. The ORR observed both in the first-line setting and the second-line setting was generally higher than that observed in naïve first-line platinum recipients (30.7%) and second/third-line immunotherapy recipients (19.0%) or second/third-line single-agent chemotherapy recipients (16.7%) in metastatic NSCLC subjects with MET mutations in the RWE study. The observed ORR was also comparable to that seen with other approved targeted therapies for first-line setting, while the ORR in the second-line setting was numerically better than that known for the current standard of care and was considered clinically meaningful.

The results of the secondary endpoints supported the primary endpoint. The observed responses were durable with a median DOR of 9.72 months (95% CI: 5.55, 12.98) in the pre-

treated subjects and 12.58 months (95% CI: 5.55, 25.33) in the treatment-naïve subjects. Median PFS was 5.42 months (95% CI: 4.17, 6.97), and 9.69 months (95% CI: 5.52, 13.86) in the pre-treated and treatment-naïve cohorts, respectively. Median OS was 13.57 months (95% CI: 8.61, 21.19) in the pre-treated population and 15.24 months (95% CI: 12.22, NE) in the treatment-naïve population. Although OS and PFS could not be contextualised due to the lack of a comparator arm, they were comparable to the current available treatment options for advanced NSCLC which was reassuring.

The supporting RWE study showed that patients with MET mutated advanced or metastatic NSCLC had a greater survival benefit when treated with MET inhibitors compared against platinum-based therapy and immunotherapy, regardless of whether patients were treatment naïve or received prior lines of treatment. The findings supported the use of capmatinib in this patient population.

The safety profile of capmatinib for patients with metastatic NSCLC with a MET exon 14 skipping mutation were characterised by peripheral oedema, nausea, vomiting, and increased blood creatinine. The AESIs of ILD/pneumonitis and hepatotoxicity were the major safety risks associated with capmatinib and have been highlighted in dosage modification, warnings and precautions, and adverse events sections of the proposed product insert. Considering that the patients will be managed by oncologists with expertise in manging the treatment-related toxicities, and given the rare condition with poor prognosis with limited treatment options, the safety profile was considered acceptable for the treatment population.

Overall, the benefits in terms of improved ORR and durable response with capmatinib in the treatment of adult patients with metastatic NSCLC with MET exon 14 skipping mutations outweighed the risks associated with the treatment, subject to further results from a larger sample size and with more mature data from the pivotal Study A2201 to confirm the efficacy benefit.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tabrecta for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation was deemed favourable and approval of the product registration was granted on 22 Oct 2021, subject to confirmation of clinical benefit from the updated results of the pivotal Study A2201.

APPROVED PACKAGE INSERT AT REGISTRATION