Summary Report of Benefit-Risk Assessment

TANSTRIVE HARD CAPSULES 40MG AND 80MG

NEW DRUG APPLICATION

Active Ingredient(s)	Selpercatinib
Product Registrant	DKSH Singapore Pte. Ltd.
Product Registration Number	SIN16990P, SIN16991P
Application Route	Abridged evaluation
Date of Approval	24 April 2024

Table of Contents

A INTRODUCTION

Tanstrive is indicated for the following:

- Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (*RET*) gene fusion.
- Treatment of adult and paediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, who require systemic therapy.
- Treatment of adult and paediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Tanstrive contains selpercatinib, which is a selective *RET* tyrosine kinase inhibitor. Certain *RET* fusion proteins and activating point mutations can drive tumorigenic potential through hyperactivation of downstream signalling pathways leading to uncontrolled cell proliferation. Selpercatinib demonstrated anti-tumour activity in cells harbouring constitutive activation of *RET* proteins resulting from gene fusions and mutations.

Tanstrive is available as hard capsules containing 40 mg or 80 mg of selpercatinib. Other ingredients in the capsule fill are microcrystalline cellulose and colloidal silicon dioxide. Ingredients of the 40 mg capsule shell include gelatin, titanium dioxide, ferric oxide black, and black ink. Ingredients of the 80 mg capsule shell include gelatin, titanium dioxide, FD&C blue #1, and black ink. The black ink is composed of shellac, potassium hydroxide, and ferric oxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, selpercatinib, is manufactured at Eli Lilly Kinsale Limited, Cork, Ireland. The drug products, Tanstrive Hard Capsule 40mg and 80mg, are manufactured at Lilly del Caribe Inc., Puerto Rico, USA.

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 has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 30°C with a re-test period of 24 months. The packaging is double low-density polyethylene liners placed in a laminated foil liner. As an alternative, the drug substance may also be packed

in a linear low-density polyethylene (LLDPE) primary liner placed in a laminated foil liner. Each liner will be individually cable tied or sealed and placed in a container.

Drug product:

The capsules are manufactured using a dry blending approach followed by encapsulation, which is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with 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 cold form aluminium foil sealed blister with aluminium foil lidding, containing 7 capsules per blister, and 4 blisters per carton.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy data supporting the use of selpercatinib in the treatment of NSCLC, MTC and thyroid cancer was primarily derived from the pivotal study LIBRETTO-001 (LOXO-RET-17001). Study LIBRETTO-001 was a Phase 1/2, ongoing, multicentre, open-label, single-arm study to evaluate the anti-tumour activity of selpercatinib in patients with advanced or metastatic solid tumours, including *RET* fusion-positive NSCLC, *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.

Phase 1 of the study determined that the maximum tolerated dose was 160 mg twice daily. In Phase 2, patients were enrolled into 5 cohorts based on tumour type, type of *RET* alteration and prior treatment. All patients received selpercatinib 160 mg twice daily until disease progression or unacceptable toxicity.

The primary endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by independent radiology review committee (IRC). The secondary efficacy endpoints included duration of response (DOR), progression free survival (PFS) and overall survival (OS).

<u>NSCLC</u>

The study enrolled patients with locally advanced or metastatic *RET* fusion-positive NSCLC who had received prior platinum-based chemotherapy (Cohort 1) or who were treatment-naïve (Cohort 2). As of the initial data cut-off of 17 June 2019, 105 previously treated and 39 treatment-naïve patients with *RET* fusion-positive NSCLC were treated with selpercatinib 160 mg twice daily. Among patients with *RET* fusion-positive NSCLC who were previously treated,

the median age was 61 years (range: 23 to 81) and the median number of prior systemic therapies was 3 (range: 1 to 15). For treatment-naïve patients, the median age was 61 years (range: 23 to 86).

In previously treated patients, the primary endpoint of ORR based on RECIST v1.1 by IRC assessment was 61.9% (65/105; 95% CI: 51.9, 71.2) as of the 17 June 2019 data cut-off, and this was maintained at the updated analysis comprising 247 patients (data cut-off 15 June 2021) with an ORR of 61.1% (151/247; 95% CI: 54.7, 67.2). The ORR results were similar (50.0% to 71.2%) irrespective of number of prior treatments.

In treatment-naïve patients, the primary endpoint of ORR by IRC assessment was 92.3% (12/13; 95% CI: 64.0, 99.8) at the initial data cut-off, and this was maintained at the updated analysis comprising 69 patients (data cut-off 15 June 2021), with an ORR of 84.1% (58/69; 95% CI: 73.3, 91.8).

Summary of Key Efficacy Endpoints for NSCLC

Endpoints	Previously Treated NSCLC		Treatment-naïve NSCLC	
	Data cut-off		Data cut-off	
	17 Jun 2019 (N=105)	15 Jun 2021 (N=247)	17 Jun 2019 (N=13)	15 Jun 2021 (N=69)
ORR, n (%)	65 (61.9)	151 (61.1)	12 (92.3)	58 (84.1)
(95% CI)	(51.9, 71.2)	(54.7, 67.2)	(64.0, 99.8)	(73.3, 91.8)
CR, n (%)	1 (1.0)	18 (7.3)	0	4 (5.8)
Median DOR (months) (95% CI)	12.5 (10.3, NR)	28.6 (20.4, NR)	NR	20.2 (13.0, NR)
Median duration of response follow-up (months)	8.1	21.2	7.5	20.3
Median PFS (months) (95% CI)	13.9 (10.9, NR)	24.9 (19.3, NR)	NR	22.0 (13.8, NR)
Median OS (months)	NR	NR	NR	NR

ORR: Objective response rate, CR: Complete response, DOR: Duration of response, PFS: Progression-free survival, OS: Overall survival, NR: Not reached

The ORR observed with selpercatinib in patients with *RET* fusion-positive NSCLC who were previously treated or treatment-naïve (61.1% to 92.3%) was numerically higher than that reported for non-selective treatments (16% to 47%) and was considered clinically meaningful. Given the single-arm design and limited sample size in the LIBRETTO-001 study, further confirmation of clinical efficacy would be required.

A Phase 3 study LIBRETTO-431 comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab as initial treatment of advanced or metastatic *RET* fusion-positive nonsquamous NSCLC is currently ongoing. Interim results demonstrated an improvement in the primary efficacy endpoint PFS by BICR for selpercatinib compared to the control arm (24.8 months [95% CI: 16.9, NE] vs 11.2 months [95% CI: 8.8, 16.8]), corresponding to a HR of 0.46 (95% CI 0.31, 0.70; p<0.001) This study is required to be submitted as a post-approval registration condition to further confirm the overall benefit of selpercatinib in *RET* fusion-positive NSCLC.

RET-mutant MTC

The study enrolled patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib and/or vandetanib (Cohort 3) or were naïve to cabozantinib and vandetanib (Cohort 4).

As of the initial data cut-off of 17 June 2019, 55 patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib and 88 patients who were cabozantinib and vandetanib treatment-naïve were treated with selpercatinib 160 mg twice daily. Among patients with *RET*-mutant MTC previously treated with cabozantinib and/or vandetanib, the median age was 57 years (range: 17 to 84) and the median of prior systemic therapies was 2 (range: 1 to 8). One third (33%) of the patients had received vandetanib, 24% had received cabozantinib and 44% had previously received both cabozantinib and vandetanib. Among patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve, the median age was 58 years (range: 15 to 82). Three adolescent patients (aged 15 to 17 years) with MTC were also enrolled in this study.

In MTC patients who had received 1 or more lines of prior cabozantinib or vandetanib, the primary endpoint of ORR based on RECIST v1.1 by IRC assessment was 63.6% (35/55; 95% CI: 49.6, 76.2) at the initial data cut-off (17 June 2019), and this was maintained at the updated analysis comprising 55 patients (data cut-off 16 December 2019) with an ORR of 69.1% (38/55; 95% CI: 55.2, 80.9). The ORR results were similar (66.7% to 70.8%) among *RET*-mutant MTC patients irrespective of type of prior treatments. The secondary endpoints of median DOR, PFS and OS were not reached. At the latest data cut-off (13 January 2023) consisting of a total of 152 patients, the ORR was 77.6% (118/152; 95% CI: 70.2, 84.0).

In MTC patients who were cabozantinib or vandetanib treatment-naïve, the ORR results were comparable to that observed in the previously treated patients. The primary endpoint of ORR by IRC assessment was 70.5% (31/44; 95% CI: 54.8, 83.2) at the initial data cut-off, and this was maintained at the updated analysis comprising 88 patients (data cut-off 16 December 2019) with an ORR of 72.7% (64/88; 95% CI: 62.2, 81.7). At the latest data cut-off (13 January 2023) with a total of 143 patients, the ORR was 82.5% (118/143; 95% CI: 75.3, 88.4).

Summary of Key Efficacy Endpoints for MTC

Endpoints	Previously Treated *RET*-Mutant MTC		Treatment-naïve *RET*-Mutant MTC	
	Data cut-off		Data cut-off	
	17 Jun 2019 (N=55)	16 Dec 2019 (N=55)	17 Jun 2019 (N=44)	16 Dec 2019 (N=88)
ORR, n (%)	35 (63.6)	38 (69.1)	31 (70.5)	64 (72.7)
(95% CI)	(49.6, 76.2)	(55.2, 80.9)	(54.8, 83.2)	(62.2, 81.7)
CR, n (%)	3 (5.5)	5 (9.1)	2 (4.5)	10 (11.4)
PR, n (%)	32 (58.2)	33 (60.0)	29 (65.9)	54 (61.4)
Median DOR (months) (95% CI)	NR	NR	NR	22.0 (NR, NR)
Median duration of response follow-up (months)	9.2	14.1	7.2	7.8
Median PFS (months) (95% CI)	NR	NR	NR	23.6 (NR, NR)
Median OS (months)	NR	NR	NR	NR

ORR: Objective response rate, CR: Complete response, PR: Partial response, DOR: Duration of response, PFS: Progression-free survival, OS: Overall survival, NR: Not reached

While cross-study comparisons have limitations, the ORR observed with selpercatinib in patients with *RET*-mutant MTC who were previously treated or cabozantinib/vandetanib naïve (63.6% to 82.5%) was numerically higher than that reported with vandetanib or cabozantinib (28% to 45%). The high ORR (>60%) observed in this study was considered clinically meaningful. Nevertheless, given the single-arm design and limited sample size in the LIBRETTO-001 study, further confirmation of clinical efficacy would be required.

A Phase 3 LIBRETTO-531 study is currently ongoing and is expected to provide confirmatory clinical evidence for the use of selpercatinib in *RET*-mutant MTC. This study is a randomised, open-label study comparing selpercatinib to physician's choice of either cabozantinib or vandetanib in 291 patients with advanced *RET*-mutant MTC as first-line therapy. The primary endpoint of this study was PFS assessed by blinded independent central review (BICR). The results from the interim analysis of this study demonstrated improvement in BICR-assessed PFS in the selpercatinib arm compared to the control arm. The median PFS in the selpercatinib arm was not reached, as compared to 16.8 months (95% CI: 12.2, 25.1) in the control arm. This corresponded to a hazard ratio (HR) of 0.280 (95% CI: 0.165, 0.475; p<0.0001). The ORR reported in this study (69.4%) was comparable to that observed in the treatment-naïve patients in the LIBRETTO-001 study (70.5% at the initial data cut-off).

The positive PFS results from this Phase 3 study further supports the clinical relevance of the ORR data observed in the LIBRETTO-001 study, and updated data from the LIBRETTO-531 study is required to confirm the efficacy and safety of selpercatinib in the treatment of *RET*-mutant MTC.

Efficacy in Adolescents

The use of selpercatinib for the treatment of *RET*-mutant MTC in adolescents aged 12 to 17 years was supported by pharmacokinetic (PK) and efficacy data from an ongoing paediatric study LIBRETTO-121. This is a Phase 1/2, multicentre, open-label study in paediatric patients (N= 27 as of data cut-off of 13 January 2023) with advanced solid or primary central nervous system (CNS) tumours with *RET* alteration.

Available PK results from 19 patients 12 to 20 years of age were observed to be comparable to those obtained in the adult population from the LIBRETTO-001 study, demonstrating similar exposure between the treatment populations. Limited ORR results by IRC assessment from 5 MTC patients aged 12 to 17 years were also available from this paediatric study. The ORR in these patients was 40% (2/5; 95% CI: 5.3, 85.3), which was lower than that reported in the adult studies (63.6% to 82.5%). Of the 5 MTC patients enrolled in the study, 3 had non-measurable disease at baseline, who would be considered responders only if they have complete response (CR). Hence, the inclusion of these patients in the calculation of ORR contributed to the conservative estimate of the ORR which appeared to be lower than the adult ORR results. For the remaining 2 patients with measurable disease, both achieved partial response (PR).

Efficacy results in adolescents 12 to 17 years old with *RET*-mutant MTC (LIBRETTO-121)

Endpoints	Overall (N=5) n (%)
ORR by IRC assessment (confirmed CR or PR), n (%)	2 (40.0)
(95% CI)	(5.3, 85.3)
CR, n (%)	0
PR, n (%)	2 (40.0)
SD, n (%)	1 (20.0)
SD16+, n (%)	1 (20.0)
PD, n (%)	0
Not evaluable, n (%)	1 (20.0)

ORR: Objective response rate, CR: Complete response, PR: Partial response, SD: Stable disease, SD16+: Stable disease lasting 16 or more weeks, PD: Progressive disease

In the LIBRETTO-001 study, there was also limited efficacy data (data cut-off 13 January 2023) in 3 adolescent patients aged 15 to 17 years with *RET*-mutant MTC. Two patients reported PR, with durations of response of 49.1 and 50.7 months, and 1 patient reported SD.

While the overall data in adolescents was limited due to the small patient numbers, the available PK data and preliminary ORR from 2 MTC patients with measurable disease from the ongoing paediatric study provided reasonable evidence to support the extrapolation of efficacy given the similar pathophysiology of *RET*-driven disease in adults and adolescents. Additional data from the ongoing paediatric study is required to be submitted to further support the efficacy of selpercatinib in this patient population.

RET Fusion-Positive Thyroid Cancer

The clinical efficacy of selpercatinib in treatment of patients with advanced *RET* fusion-positive thyroid cancer was evaluated in radioactive iodine (RAI)-refractory patients who were systemic therapy-naïve or had previously received sorafenib and/or lenvatinib in the LIBRETTO-001 study (Cohorts 1 and 2).

As of the initial data cut-off (17 June 2019), 27 patients with *RET* fusion-positive thyroid cancer were treated with selpercatinib 160 mg twice daily. The median age was 54 years (range: 20 to 88) and all patients (100%) had a history of metastatic disease. Of the 27 patients, 19 had received prior systemic therapy other than RAI and represented 4 different thyroid histologies including papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1). The other 8 patients (all papillary) received no other prior systemic therapy other than RAI. There were no adolescents with *RET* fusion-positive thyroid cancer enrolled in this study.

The primary endpoint of ORR based on RECIST v1.1 by IRC assessment was 86.7% (13/15; 95% CI: 59.5, 98.3) in previously treated thyroid cancer patients, and this was maintained at the updated analysis comprising 19 patients (data cut-off 16 December 2019) with an ORR of 78.9% (15/19; 95% CI: 54.4, 93.9). The secondary endpoints of median PFS and median DOR were 20 months and 18.43 months, respectively, while the median OS was not reached. At the latest data cut-off (13 January 2023) with a total of 41 patients, the ORR was 85.4% (35/41; 95% CI: 70.8, 94.4).

The ORR in treatment-naïve *RET* fusion-positive thyroid cancer was comparable to the previously treated population. For the 3 patients with treatment-naïve *RET* fusion-positive thyroid cancer, the ORR by IRC was 100% (3/3; 95% CI: 29.2, 100.0) at the initial data cut-off,

and this was maintained at the updated analysis comprising 8 patients (data cut-off 16 December 2019) with an ORR of 100% (8/8; 95% CI: 63.1, 100). At the latest data cut-off (13 January 2023) in 24 patients, the ORR was 95.8% (23/24; 95% CI: 78.9, 99.0).

Summary of Key Efficacy Endpoints (*RET* fusion-positive thyroid cancer)

Endpoints	Previously treated *RET* fusion-positive thyroid cancer		Treatment-naïve *RET* fusion-positive thyroid cancer	
	Data cut-off		Data cut-off	
	17 Jun 2019 (N=15)	16 Dec 2019 (N=19)	17 Jun 2019 (N=3)	16 Dec 2019 (N=8)
ORR, n (%)	13 (86.7)	15 (78.9)	3 (100)	8 (100)
(95% CI)	(59.5, 98.3)	(54.4, 93.9)	(29.2, 100)	(63.1, 100)
CR, n (%)	0	1 (5.3)	1 (33.3)	1 (12.5)
PR, n (%)	13 (86.7)	14 (73.7)	2 (66.7)	7 (87.5)
Median DOR (months) (95% CI)	NR	18.43 (7.6, NR)	NR	NR
Median duration of response follow-up (months)	12.09	17.51	5.55	7.67
Median PFS (months) (95% CI)	NR	20.07 (9.4, NR)	NR	NR
Median OS (months)	NR	NR	NR	NR

Subgroup analyses of the primary endpoint by histology type at the 13 January 2023 data cut-off demonstrated consistently high ORR for patients with anaplastic (3/4 or 75%), Hurthle Cell (1/1 or 100%), papillary (48/54 or 88.9%) or poorly differentiated (6/6 or 100%) thyroid cancer. The range of histology types was considered sufficiently representative of the disease in the clinical setting.

The observed ORR (78.9% to 100%) was numerically higher than that reported with current standard of therapy including lenvatinib (65%), sorafenib (12%) and cabozantinib (9%). Notwithstanding the limitations of the non-comparative study and the small sample size, the high ORR was considered clinically meaningful.

Efficacy in Adolescents

The extension of efficacy from adults to adolescent patients with *RET* fusion-positive thyroid cancer was based on the same scientific considerations supporting the use of selpercatinib in adolescents with *RET*-mutant MTC. Limited ORR results by IRC assessment from 8 thyroid cancer patients aged 12 to 17 years were available from the ongoing paediatric study LIBRETTO-121. The ORR in these patients was 62.5% (5/8; 95% CI: 24.5, 91.5), with 2 out of 8 (25%) achieving CR, and 3 (37.5%) achieving PR. Of these 8 patients, 5 had measurable disease at baseline, and all of them achieved CR or PR.

Efficacy results in adolescents 12 to 17 years old with *RET* fusion-positive thyroid cancer (LIBRETTO-121)

Endpoints	Overall (N=8) n (%)
ORR by IRC assessment (confirmed CR or PR), n (%)	5 (62.5)
(95% CI)	(24.5, 91.5)
CR, n (%)	2 (25.0)
PR, n (%)	3 (37.5)

Based on the data presented, the results supported the efficacy of selpercatinib for the treatment of adults with *RET* fusion-positive NSCLC, as well as adults and adolescents aged 12 years and above with *RET* fusion-positive thyroid cancer and *RET*-mutant MTC.

D ASSESSMENT OF CLINICAL SAFETY

The overall safety population comprised a total of 531 patients enrolled in the LIBRETTO-001 study who had received at least one dose of selpercatinib, including 253 patients with NSCLC, 226 patients with *RET*-mutant MTC and 27 patients with *RET* fusion-positive thyroid cancer. Of these, 93.4% received at least one dose of 160 mg twice daily.

Summary of safety (LIBRETTO-001)

	***RET* fusion-positive NSCLC (N=253) n (%)**	***RET*-mutant MTC (N=226) n (%)**	**All patients (N=531) n (%)**
Any TEAE			
All	244 (96.4)	224 (99.1)	519 (97.7)
Related	218 (86.2)	193 (85.4)	451 (84.9)
Grade 3 or 4 TEAE All Related	 127 (50.2) 70 (27.7)	 114 (50.4) 53 (23.5)	 271 (51.0) 132 (24.9)
SAE All Related	 80 (31.6) 21 (8.3)	 59 (26.1) 11 (4.9)	 161 (30.3) 33 (6.2)
TEAE leading to treatment discontinuation			
All	11 (4.3)	5 (2.2)	19 (3.6)
Related	4 (1.6)	4 (1.8)	9 (1.7)
Fatal TEAE	9 (3.6)	4 (1.8)	15 (2.8)

*Data cut-off 17 June 2019

In the overall safety population, 97.7% of patients reported treatment-emergent adverse events (TEAEs). The most commonly reported TEAEs were dry mouth (32.2%), diarrhoea (31.3%), hypertension (28.8%), AST increased (27.5%), ALT increased (25.6%), fatigue (24.3%), and constipation (21.8%). The most commonly reported Grade 3 or 4 TEAEs included hypertension (13.9%; 8.1% related), ALT increased (8.5%; 7.0% related), AST increased (6.4%; 4.5% related), and hyponatremia (5.1%; 0.4% related). Overall, 132 patients (24.9%) had at least 1 Grade 3 or 4 TEAE considered related to selpercatinib.

Serious AEs (SAEs) were reported in 30.3% of patients, of which 6.2% were considered related to selpercatinib. The most commonly reported SAEs included AST and ALT increased (2.1%; 1.5% related), pneumonia (2.1%; 0 related), dyspnoea (1.7%; 0 related), and hyponatremia (1.5%; 0 related). TEAEs leading to treatment discontinuation were reported in 19 patients (3.6%). The most common TEAEs leading to discontinuation were ALT increased, hypersensitivity, hypoxia and sepsis (0.4% each). A total of 15 patients (2.8%) experienced fatal TEAEs, which included disease progression, cardiac arrest, respiratory failure, sepsis, cardio-respiratory arrest, cerebrovascular accident, postprocedural haemorrhage, haemoptysis, cerebral haemorrhage, and multiorgan dysfunction syndrome. None of these events were considered related to selpercatinib.

The adverse events of special interest (AESIs) with selpercatinib included AST/ALT increased, hypertension, QT prolongation and haemorrhagic events. AST increases were reported in 27.5% of patients, and ALT increases in 25.6% of patients. Most of these events were of Grade 1 or 2 in severity. No patients on study met the Hy's Law criteria for drug-induced liver injury. Dose modification recommendations have been included in the product label to mitigate this AE.

Treatment-emergent hypertension was reported in 29.3% of patients, half of whom (14.1%) had Grade 3 or 4 events. SAEs of hypertension were reported in 5 (0.9%) patients. Hypertension was managed through the addition or adjustment of concomitant antihypertensive medications and dose modifications in the study. Twenty-one patients (4.0%) had their selpercatinib dose interrupted and 6 patients (1.1%) had doses reduced. No patient permanently discontinued treatment due to hypertension.

QT prolongation was reported in 13.4% of patients. Most AEs were Grade 1 or 2 events (9.8%), and 3.6% were reported as Grade 3 events. Dose modifications in the study included dose interruptions (1.9% of patients) and dose reductions (2.6%). No patients discontinued selpercatinib due to QT prolongation. There were also no reports of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation or ventricular flutter. Warnings and recommendations on monitoring and clinical management of QT prolongation have been included in the product label.

Grade ≥3 haemorrhagic events occurred in 3.1% of patients, including 4 (0.5%) patients with fatal haemorrhagic events: two cases of cerebral haemorrhage, and one case each of tracheostomy site haemorrhage and haemoptysis. All deaths were considered unrelated to selpercatinib by the investigator. Warnings to discontinue selpercatinib permanently in patients with severe or life-threatening haemorrhage have been included in the product label.

Overall, the safety profile of selpercatinib in adults was consistent with the known AEs associated with *RET* tyrosine kinase inhibitors. To manage the toxicities associated with the treatment, the product label has included recommendations on dose modifications and warnings to mitigate the identified safety risks.

Safety in Adolescents

In the juvenile rat toxicity studies, selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses equivalent to or greater than adult human exposure at the clinical dose of 160 mg twice daily. In the clinical setting, physeal dysplasia could potentially impact patients with open growth plates resulting in decreased growth velocity in late puberty. Based on the limited safety data in adolescents 12 to 17 years of age (27 patients across *RET*-altered tumour types in LIBRETTO-121), three cases of epiphysiolysis were reported in patients aged 14 to 16 years with MTC. These events were confounded by underlying disease conditions (scoliosis, poor growth, hypothyroidism) and a causal association with selpercatinib has not be determined.

Given the uncertainty of the impact on growth and development in adolescent patients, warnings and recommendations on monitoring growth plates in adolescent patients with open growth plates are provided in the product label.

E ASSESSMENT OF BENEFIT-RISK PROFILE

NSCLC

RET fusions are oncogenic drivers in 1-2% of NSCLC and are associated with a high risk of brain metastases. Standard first-line systemic non-targeted therapy in patients with advanced, non-resectable NSCLC include platinum chemotherapy and/or immunotherapy with a checkpoint inhibitor. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis would generally have 5-year survival rates ranging from 10% to <1% for Stage 4 disease.

In the pivotal study LIBRETTO-001, relatively large treatment effects with high ORR were demonstrated in previously treated or treatment-naïve patients with *RET*-fusion positive NSCLC (62% to 92.3%). The ORR results were similar (50% to 71.2%) irrespective of prior treatments. These results were considered clinically meaningful.

The safety profile of selpercatinib in patients with *RET* fusion-positive NSCLC is generally consistent with the known AEs associated with *RET* inhibition. Notable TEAEs of concern included hepatic toxicity, hypertension, QT prolongation and haemorrhage, which have been adequately described in the package insert.

Overall, considering the limited treatment options, the benefits of selpercatinib were considered to outweigh the risks for the treatment of *RET* fusion-positive NSCLC in adults. The final results from the Phase 1/2 study LIBRETTO-001 and the Phase 3 study LIBRETTO-431 would be required to confirm the efficacy and safety of selpercatinib in the treatment of NSCLC.

MTC and TC

Adults

MTC represents 5% to 10% of all thyroid cancers and accounts for 13.4% of all thyroid cancer-related deaths. Kinase-activating *RET* alterations are present in more than 95% of hereditary cases and approximately 50% of sporadic MTC cases. Only 20% of patients with distant metastases at diagnosis survive 10 years after diagnosis. Metastatic MTC is managed with resection, radiation or systemic therapies including non-selective treatments such as cabozantinib and vandetanib.

As for *RET* fusion-positive thyroid cancer, *RET* gene fusions have been identified in approximately 6% to 9% of papillary thyroid cancer (PTC) and approximately 6% of poorly differentiated thyroid cancer. The clinical course of *RET* fusion-positive PTC is heterogeneous, varying from some tumours being cured by surgical resection to aggressive cancers associated with metastases and high mortality. Currently, there is no registered treatment for *RET* fusion-positive thyroid cancer in Singapore.

In the pivotal study LIBRETTO-001, clinically meaningful ORR has been demonstrated in previously treated or treatment-naïve patients with *RET*-mutant MTC (63.6% to 82.5%) and *RET* fusion-positive thyroid cancer (78.9% to 100%). The high ORR was consistent across the subgroups including analyses by prior lines of therapies and thyroid cancer histologies. In addition, the interim Phase 3 data in first-line MTC from the ongoing LIBRETTO-531 study demonstrated significant improvement in PFS compared to cabozantinib/vandetanib (HR: 0.280, 95% CI: 0.165, 0.475; p<0.0001).

The safety profile of selpercatinib in patients with *RET*-mutant MTC or *RET* fusion-positive thyroid cancer is generally consistent with the known AEs associated with *RET* inhibition.

While there were limitations to the dataset, in particular the small sample size and the non-comparative study design, the ORR observed with selpercatinib was considered promising, and the favourable results were supported by the interim PFS results from the Phase 3 study LIBRETTO-531. The safety profile was acceptable for the target population. Taken together, in view of the rarity of *RET*-mutant MTC and *RET* fusion-positive thyroid cancer as well as the limited treatment options, the benefit-risk profile of selpercatinib in the adults with *RET*-mutant MTC and *RET* fusion-positive thyroid cancer was considered favourable.

The final results from the Phase 1/2 study LIBRETTO-001 and the Phase 3 study LIBRETTO-531 would be required to confirm the efficacy and safety of selpercatinib in the treatment of *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.

Adolescents

MTC in children and adolescents may be more aggressive than that in adults and may have a worse prognosis. In clinical setting, children and adolescents patients are treated in the same manner as adults, with initial thyroidectomy then re-resection, radiation, or systemic therapy with recurrent disease.

In comparison to adults, *RET*-fusion thyroid cancer in paediatric patients, of which PTC accounts for approximately 90%, is often aggressive and presents at an advanced stage disease at the time of diagnosis. Treatment options for paediatric patients with *RET*-mutant MTC or *RET* fusion-positive thyroid cancer are limited, typically involving surgical resection and RAI. Hence, there is an unmet medical need for new therapies in this patient population.

There was limited data on the use of selpercatinib in the adolescent population, which was derived from preliminary ORR results from a small number of adolescent patients with *RET*-mutant MTC or *RET* fusion-positive thyroid cancer (5 MTC and 8 thyroid cancer patients). Nonetheless, considering the biological and PK similarity between adult patients and adolescent patients, the observed efficacy in adults could reasonably be extrapolated to adolescent patients. Physeal dysplasia has been observed in juvenile animal toxicity studies, hence a potential risk on bone growth in adolescent patients with open growth plates could not be ruled out. The product label has included recommendations to monitor growth plates in adolescent patients and to interrupt or discontinue therapy based on severity of growth plate abnormalities and individual benefit-risk assessment. The product label was strengthened to indicate the limited efficacy and safety data in adolescents 12 years and older.

Overall, considering the unmet medical need due to the life-threatening nature of the disease and the lack of treatment options, the benefits of selpercatinib in adolescents 12 years and above, which are expected to be similar to the adult population where a consistently high ORR was achieved, were considered to outweigh the risks for the treatment of *RET*-mutant MTC and *RET* fusion-positive thyroid cancer.

The final results from the paediatric study LIBRETTO-121 would be required to further support the efficacy and safety of selpercatinib in the adolescent population.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tanstrive for the requested indications in *RET* fusion-positive NSCLC, *RET*-mutant MTC and *RET* fusion-positive thyroid cancer was deemed favourable, and approval of the product registration was granted on 24 April 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

NAME OF THE MEDICINAL PRODUCT

Tanstrive Hard Capsules 40mg (contains 40mg selpercatinib)

Tanstrive Hard Capsules 80mg (contains 80mg selpercatinib)

1 INDICATIONS AND USAGE

1.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

TANSTRIVE is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion.

1.2 *RET*-Mutant Medullary Thyroid Cancer

TANSTRIVE is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation who require systemic therapy.

1.3 *RET* Fusion-Positive Thyroid Cancer

TANSTRIVE is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with TANSTRIVE based on the presence of a *RET* gene fusion (NSCLC or thyroid cancer) or specific *RET* gene mutation (MTC) in tumor specimens *[see Clinical Studies (14)]*.

2.2 Important Administration Instructions

TANSTRIVE may be taken with or without food unless coadministered with a proton pump inhibitor (PPI) *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage

The recommended dosage of TANSTRIVE based on body weight is:

- Less than 50 kg: 120 mg
- 50 kg or greater: 160 mg

Take TANSTRIVE orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity. Swallow the capsules whole. Do not crush or chew the capsules.

Do not take a missed dose if it is less than 6 hours until next scheduled dose.

If vomiting occurs after TANSTRIVE administration, do not take an additional dose and continue to the next scheduled time for the next dose.

2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents

Avoid concomitant use of a PPI, a histamine-2 (H2) receptor antagonist, or a locally-acting antacid with TANSTRIVE *[see Drug Interactions (7.1)]*. If concomitant use cannot be avoided:

- Take TANSTRIVE with food when coadministered with a PPI.
- Take TANSTRIVE 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- Take TANSTRIVE 2 hours before or 2 hours after administration of a locally-acting antacid.

2.5 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended TANSTRIVE Dose Reductions for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily

Permanently discontinue TANSTRIVE in patients unable to tolerate three dose reductions. The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended TANSTRIVE Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	Grade 3 or Grade 4	• Withhold TANSTRIVE and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence.

Interstitial Lung Disease/ Pneumonitis *[see Warnings and Precautions (5.2)]*	Grade 2	• Withhold TANSTRIVE until resolution. • Resume at a reduced dose. • Discontinue TANSTRIVE for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	• Discontinue TANSTRIVE for confirmed ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.3)]*	Grade 3	• Withhold TANSTRIVE for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	• Discontinue TANSTRIVE.
QT Interval Prolongation *[see Warnings and Precautions (5.4)]*	Grade 3	• Withhold TANSTRIVE until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.
	Grade 4	• Discontinue TANSTRIVE
Hemorrhagic Events *[see Warnings and Precautions (5.5)]*	Grade 3 or Grade 4	• Withhold TANSTRIVE until recovery to baseline or Grade 0 or 1. • Discontinue TANSTRIVE for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions	All Grades	• Withhold TANSTRIVE until resolution of the event. Initiate corticosteroids.

[see Warnings and Precautions (5.6)]		• Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids.
Hypothyroidism *[see Warnings and Precautions (5.9)]*	Grade 3 or Grade 4	• Withhold TANSTRIVE until resolution to Grade 1 or baseline. • Discontinue TANSTRIVE based on severity.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or Grade 4	• Withhold TANSTRIVE until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

2.6 Dosage Modifications for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with TANSTRIVE. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the TANSTRIVE dose as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume TANSTRIVE at the dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.1)]*.

Table 3: Recommended TANSTRIVE Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Current TANSTRIVE Dosage	Recommended TANSTRIVE Dosage	
	Moderate CYP3A Inhibitor	Strong CYP3A Inhibitor
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

2.7 Dosage Modification for Severe Hepatic Impairment

Reduce the recommended dosage of TANSTRIVE for patients with severe hepatic impairment as recommended in Table 4 *[see Use in Specific Populations (8.7)]*.

Table 4: Recommended TANSTRIVE Dosage for Severe Hepatic Impairment

Current TANSTRIVE Dosage	Recommended TANSTRIVE Dosage
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 40 mg: gray opaque capsule imprinted with “Lilly”, “3977” and “40 mg” in black ink.
- 80 mg: blue opaque capsule imprinted with “Lilly”, “2980” and “80 mg” in black ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious hepatic adverse reactions occurred in 3% of patients treated with TANSTRIVE. Increased AST occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased ALT occurred in 55% of patients, including Grade 3 or 4 events in 12% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 6weeks (range: 1 day to 3.4 years) and increased ALT was 5.8 weeks (range: 1 day to 2.5 years).

Monitor ALT and AST prior to initiating TANSTRIVE, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue TANSTRIVE based on the severity *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with TANSTRIVE. ILD/pneumonitis occurred in 1.8% of patients who received TANSTRIVE, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold TANSTRIVE and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue TANSTRIVE based on severity of confirmed ILD *[see Dosage and Administration (2.5)]*.

5.3 Hypertension

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient *[see Adverse Reactions (6.1)]*. Overall, 6.3% had their dose interrupted and 1.3% had their dose reduced for hypertension.

Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate TANSTRIVE in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating TANSTRIVE. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue TANSTRIVE based on the severity *[see Dosage and Administration (2.5)]*.

5.4 QT Interval Prolongation

TANSTRIVE can cause concentration-dependent QT interval prolongation *[see Clinical Pharmacology (12.2)]*. An increase in QTcF interval to >500 ms was measured in 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% of patients *[see Adverse Reactions (6.1)]*. TANSTRIVE has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating TANSTRIVE and during treatment.

Monitor the QT interval more frequently when TANSTRIVE is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue TANSTRIVE based on the severity *[see Dosage and Administration (2.5)]*.

5.5 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with TANSTRIVE. Grade ≥3 hemorrhagic events occurred in 3.1% of patients treated with TANSTRIVE, including 4

(0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n = 2), tracheostomy site hemorrhage (n = 1), and hemoptysis (n=1).

Permanently discontinue TANSTRIVE in patients with severe or life-threatening hemorrhage *[see Dosage and Administration (2.5)]*.

5.6 Hypersensitivity

Hypersensitivity occurred in 6% of patients receiving TANSTRIVE, including Grade 3 hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.

If hypersensitivity occurs, withhold TANSTRIVE and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume TANSTRIVE at a reduced dose and increase the dose of TANSTRIVE by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity *[see Dosage and Administration (2.5)]*. Continue steroids until patient reaches target dose and then taper. Permanently discontinue TANSTRIVE for recurrent hypersensitivity.

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 0.6% of patients with medullary thyroid carcinoma receiving TANSTRIVE *[see Adverse Reactions (6.1)]*. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.8 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, TANSTRIVE has the potential to adversely affect wound healing.

Withhold TANSTRIVE for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of TANSTRIVE after resolution of wound healing complications has not been established.

5.9 Hypothyroidism

TANSTRIVE can cause hypothyroidism. Hypothyroidism occurred in 13% of patients treated with TANSTRIVE; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC *[see Adverse Reactions (6.1)]*.

Monitor thyroid function before treatment with TANSTRIVE and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold TANSTRIVE until clinically stable or permanently discontinue TANSTRIVE based on severity *[see Dosage and Administration (2.5)]*.

5.10 Embryo-Fetal Toxicity

Based on data from animal reproduction studies and its mechanism of action, TANSTRIVE can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TANSTRIVE and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TANSTRIVE and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease / Pneumonitis *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.4)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.7)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.8)]*
- Hypothyroidism *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to TANSTRIVE as a single agent at 160 mg orally twice daily evaluated in 796 patients with advanced solid tumors in LIBRETTO-001 *[see Clinical Studies (14)]*. Among the 796 patients who received TANSTRIVE, 84% were exposed for 6 months or longer and 73% were exposed for greater than one year. Among these patients, 96% received at least one dose of TANSTRIVE at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 51% were male; and 69% were White, 23% were Asian, 5% were

Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (45%), MTC (40%), and non-medullary thyroid carcinoma (7%).

Serious adverse reactions occurred in 44% of patients who received TANSTRIVE. The most frequent serious adverse reactions (≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n = 6), respiratory failure (n = 5), hemorrhage (n = 4), pneumonia (n = 3), pneumonitis (n = 2), cardiac arrest (n=2), sudden death (n = 1), and cardiac failure (n = 1).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TANSTRIVE. Adverse reactions resulting in permanent discontinuation in ≥0.5% of patients included increased ALT (0.6%), fatigue (0.6%), sepsis (0.5%), and increased AST (0.5%).

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received TANSTRIVE. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, diarrhea, and hypertension.

Dose reductions due to an adverse reaction occurred in 41% of patients who received TANSTRIVE. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema.

The most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

Table 5 summarizes the adverse reactions in LIBRETTO-001.

Table 5: Adverse Reactions (≥20%) in Patients Who Received TANSTRIVE in LIBRETTO-001

Adverse Reaction	**TANSTRIVE (n = 796)**	
	Grades 1-4# (%)	**Grades 3-4** (%)
Gastrointestinal		
Diarrhea[1]	47	5*
Dry Mouth	43	0
Abdominal pain[2]	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular		
Hypertension	41	20
General		
Edema[3]	49	0.8*
Fatigue[4]	46	3.1*
Arthralgia	21	0.3*
Skin		
Rash[5]	33	0.6*
Nervous System		
Headache[6]	28	1.4*
Respiratory		

Cough[7]	24	0
Dyspnea[8]	22	3.1
Investigations		
Prolonged QT interval	21	4.8*
Blood and Lymphatic System		
Hemorrhage[9]	22	2.6

[1] Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, gastrointestinal hypermotility, anal incontinence.

[2] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, epigastric discomfort, gastrointestinal pain.

[3] Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, generalized edema, genital edema.

[4] Fatigue includes fatigue, asthenia, malaise.

[5] Rash includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, butterfly rash, exfoliative rash, rash follicular, rash generalized, rash vesicular.

[6] Headache includes headache, sinus headache, tension headache.

[7] Includes cough, productive cough, upper airway cough syndrome.

[8] Includes dyspnea, dyspnea exertional, dyspnea at rest.

[9] Hemorrhage includes hemorrhage, epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, hemorrhage subcutaneous, spontaneous

hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, conjunctival hemorrhage, disseminated intravascular coagulation, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic stroke, hemorrhoidal hemorrhage, hepatic hemorrhage, hepatic hematoma, intraabdominal hemorrhage, laryngeal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, post procedural hemorrhage, postmenopausal hemorrhage, pelvic hematoma, periorbital hematoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retinal hemorrhage, retroperitoneal hematoma, scleral hemorrhage, skin hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, vessel puncture site hematoma.

* Only includes a grade 3 adverse reaction.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Clinically relevant adverse reactions in ≤15% of patients who received TANSTRIVE include hypothyroidism (13%); hypersensitivity (6%); interstitial lung disease/pneumonitis, chylothorax, chylous ascites or tumor lysis syndrome (all < 2%).

Table 6 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 6: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TANSTRIVE in LIBRETTO-001

	TANSTRIVE[1]	
Laboratory Abnormality	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Chemistry		
Increased AST	59	11
Decreased calcium	59	5.7

Increased ALT	56	12
Decreased albumin	56	2.3
Increased glucose	53	2.8
Increased creatinine	47	2.4
Decreased sodium	42	11
Increased alkaline phosphatase	40	3.4
Increased total cholesterol	35	1.7
Increased potassium	34	2.7
Decreased glucose	34	1.0
Decreased magnesium	33	0.6
Increased bilirubin	30	2.8
Hematology		
Decreased lymphocytes	52	20
Decreased platelets	37	3.2
Decreased hemoglobin	28	3.5
Decreased neutrophils	25	3.2

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 765 to 791 patients.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Increased Creatinine

In healthy subjects administered TANSTRIVE 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3)]*.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on TANSTRIVE

Acid-Reducing Agents

Concomitant use of TANSTRIVE with acid-reducing agents decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce TANSTRIVE anti-tumor activity.

Avoid concomitant use of PPIs, H2 receptor antagonists, and locally-acting antacids with TANSTRIVE. If coadministration cannot be avoided, take TANSTRIVE with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid) *[see Dosage and Administration (2.4)]*.

Strong and Moderate CYP3A Inhibitors

Concomitant use of TANSTRIVE with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of TANSTRIVE adverse reactions, including QTc interval prolongation.

Avoid concomitant use of strong and moderate CYP3A inhibitors with TANSTRIVE. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the TANSTRIVE dosage and monitor the QT interval with ECGs more frequently *[see Dosage and Administration (2.6), Warning and Precautions (5.4)]*.

Strong and Moderate CYP3A Inducers

Concomitant use of TANSTRIVE with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce TANSTRIVE anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with TANSTRIVE.

7.2 Effects of TANSTRIVE on Other Drugs

CYP2C8 and CYP3A Substrates

TANSTRIVE is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of TANSTRIVE with CYP2C8 and CYP3A substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of TANSTRIVE with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Certain P-gp Substrates

TANSTRIVE is a P-gp inhibitor. Concomitant use of TANSTRIVE with P-gp substrates increases their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of TANSTRIVE with P-gp substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling.

7.3 Drugs that Prolong QT Interval

TANSTRIVE is associated with QTc interval prolongation *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.2)]*. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action *[see Clinical Pharmacology (12.1)]*, TANSTRIVE can cause fetal harm when administered to a pregnant woman. There are no available data on TANSTRIVE use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥100 mg/kg [approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

8.2 Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with TANSTRIVE and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, TANSTRIVE can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TANSTRIVE *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with TANSTRIVE and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with TANSTRIVE and for 1 week after the last dose.

Infertility

TANSTRIVE may impair fertility in females and males of reproductive potential *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

There are limited data in paediatric patients 12 years and older with *RET*-mutant MTC or *RET* fusion-positive thyroid cancer. The safety and effectiveness of TANSTRIVE have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of TANSTRIVE have not been established in pediatric patients for other indications *[see Indications and Usage (1)]*.

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, animals were dosed daily with selpercatinib from post-natal day 21 to day 70 (approximately equivalent to a human child to late adolescent). Selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone modeling, resulting in decreased femur length and with reduction in bone mineral density.

Selpercatinib also induced reversible hypocellularity of bone marrow in males at ≥30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily), and reversible alterations of dentin composition at ≥50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Irreversible, dose-dependent degeneration of testicular germinal epithelium, with vacuolation of Sertoli cells and corresponding depletion of spermatozoa in the epididymides, was also observed at ≥ 30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily) and affected male reproductive performance at 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Females exhibited delay in attainment of vaginal patency, a marker of sexual maturity, at 125 mg/kg (approximately 4 times the adult human exposure at the clinical dose of 160 mg twice daily); this affect was associated with lower mean body weight. Similar effects in irregular thickening of growth plates in adult rats and minipigs, and tooth dysplasia and malocclusion, resulting in tooth loss in adult rats were observed in repeat dose studies of up to 13-week duration with selpercatinib.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of 796 patients who received TANSTRIVE, 34% (268 patients) were ≥65 years of age and 9% (74 patients) were ≥75 years of age. No overall differences were observed in the safety or effectiveness of TANSTRIVE between patients who were ≥65 years of age and younger patients.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal disease (ESRD) *[see Clinical Pharmacology (12.3)]*.

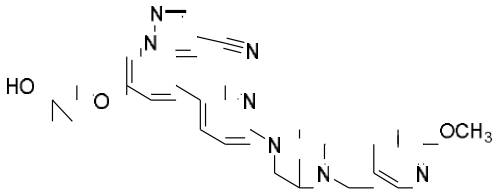
8.7 Hepatic Impairment

Reduce the dose when administering TANSTRIVE to patients with severe [total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST] hepatic impairment *[see Dosage and Administration (2.7)]*. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for TANSTRIVE-related adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Selpercatinib is a kinase inhibitor. The molecular formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and the molecular weight is

525.61 g/mol. The chemical name is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6- diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile. Selpercatinib has the following chemical structure:



Selpercatinib is a white to light yellow powder that is slightly hygroscopic. The aqueous solubility of selpercatinib is pH dependent, from sparingly soluble at low pH to practically insoluble at neutral pH.

TANSTRIVE (selpercatinib) is supplied as 40 mg or 80 mg hard gelatin capsules for oral use. Each capsule contains inactive ingredients of microcrystalline cellulose and colloidal silicon dioxide. The 40 mg capsule shell is composed of gelatin, titanium dioxide, ferric oxide black

and black ink. The 80 mg capsule shell is composed of gelatin, titanium dioxide, FD&C blue #1 and black ink. The black ink is composed of shellac, potassium hydroxide and ferric oxide black.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selpercatinib is a kinase inhibitor. Selpercatinib inhibited wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC_{50} values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. In cellular assays, selpercatinib inhibited RET at approximately 60-fold lower concentrations than FGFR1 and 2 and approximately 8-fold lower concentration than VEGFR3.

Certain point mutations in *RET* or chromosomal rearrangements involving in-frame fusions of *RET* with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET proteins resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived *RET* fusion positive tumor.

12.2 Pharmacodynamics

Exposure-Response Relationship

Selpercatinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

The effect of TANSTRIVE on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90%

confidence interval: 12.1 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients after administration of 160 mg twice daily. The increase in QTc was concentration-dependent.

12.3 Pharmacokinetics

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily [0.06 to 1.5 times the maximum recommended total daily dosage].

Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold. Mean steady-state selpercatinib [coefficient of variation (CV%)] C_{max} was 2,980 (53%) ng/mL and AUC_{0-24h} was 51,600 (58%) ng*h/mL.

Absorption

The median t_{max} of selpercatinib is 2 hours. The mean absolute bioavailability of TANSTRIVE capsules is 73% (60% to 82%) in healthy subjects.

Effect of Food

No clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy subjects.

Distribution

The apparent volume of distribution (V_{ss}/F) of selpercatinib is 191 L.

Protein binding of selpercatinib is 96% in vitro and is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Elimination

The apparent clearance (CL/F) of selpercatinib is 6 L/h in patients and the half-life is 32 hours following oral administration of TANSTRIVE in healthy subjects.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma.

Excretion

Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged).

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (27 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (15 years to 92 years), sex, or mild, moderate, or severe renal impairment (eGFR ≥15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Patients with Hepatic Impairment

The selpercatinib $AUC_{0\text{-}INF}$ increased by 7%, 32%, and 77% in subjects with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST), moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, respectively, compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton-Pump Inhibitors (PPI): Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when TANSTRIVE was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when TANSTRIVE was administered with food (Table 7).

Table 7: Change in Selpercatinib Exposure After Coadministration with PPI

	Selpercatinib $AUC_{0\text{-}INF}$	**Selpercatinib C_{max}**
TANSTRIVE fasting	Reference	Reference
TANSTRIVE fasting + PPI	↓ 69%	↓ 88%
TANSTRIVE with a high-fat meal[1] + PPI	↑ 2%	↓ 49%
TANSTRIVE with a low-fat meal[2] + PPI	No change	↓ 22%

[1] High-fat meal: approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1,000 calories total.

[2] Low-fat meal: approximately 390 calories and 10 g of fat

H2 Receptor Antagonists: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after the TANSTRIVE dose (administered fasting).

Strong CYP3A Inhibitors: Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib $AUC_{0\text{-}INF}$ by 133% and C_{max} by 30%.

Moderate CYP3A Inhibitors: Coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC by 60-99% and C_{max} by 46-76%.

Strong CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib $AUC_{0\text{-}INF}$ by 87% and C_{max} by 70%.

Moderate CYP3A Inducers: Coadministration of multiple doses of bosentan or efavirenz (moderate CYP3A inducers) is predicted to decrease the selpercatinib AUC by 40-70% and C_{max} by 34-57%.

Weak CYP3A Inducers: Coadministration of multiple doses of modafinil (weak CYP3A inducer) is predicted to decrease the selpercatinib AUC by 33% and C_{max} by 26%.

CYP2C8 Substrates: Coadministration of TANSTRIVE with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide $AUC_{0\text{-}INF}$ by 188% and C_{max} by 91%.

CYP3A Substrates: Coadministration of TANSTRIVE with midazolam (sensitive CYP3A substrate) increased the midazolam $AUC_{0\text{-}INF}$ by 54% and C_{max} by 39%.

P-glycoprotein (P-gp) Substrates: Coadministration of TANSTRIVE with dabigatran (P-gp substrate) increased the dabigatran $AUC_{0\text{-}INF}$ by 38% and C_{max} by 43%.

P-gp Inhibitors: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with a single dose of rifampin (P-gp inhibitor).

MATE1 Substrates: No clinically significant differences in glucose levels were observed when metformin (MATE1 substrate) was coadministered with selpercatinib.

In Vitro Studies

CYP Enzymes: Selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Selpercatinib inhibits MATE1 and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1 *[see Adverse Effects (6.1)]*.

Selpercatinib is a substrate for P-gp and BCRP, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with selpercatinib. Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive in the in vivo micronucleus assay in rats at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily.

In general toxicology studies, male rats and minipigs exhibited testicular degeneration which was associated with luminal cell debris and/or reduced luminal sperm in the epididymis at selpercatinib exposures approximately 0.4 (rat) and 0.1 (minipig) times the clinical exposure by AUC at the recommended human dose. In a dedicated fertility study in male rats, administration of selpercatinib at doses up to 30 mg/kg/day (approximately twice the clinical exposure by AUC at the 160 twice daily dose) for 28 days prior to cohabitation with untreated females did not affect mating or have clear effects on fertility. Males did, however, display a dose-dependent increase in testicular germ cell depletion and spermatid retention at doses ≥3 mg/kg (~0.2 times the clinical exposure by AUC at the 160 twice daily dose) accompanied by altered sperm morphology at 30 mg/kg.

In a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). While selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level in females with some viable embryos there were increases in post-implantation loss. In a 3-month general toxicology study in minipigs, there were findings of decreased or absent corpora lutea at a selpercatinib dose of 15 mg/kg (approximately 0.3 times to the human exposure by AUC at the 160 mg twice daily clinical dose). Corpora luteal cysts were present in the minipig at selpercatinib doses ≥2 mg/kg (approximately 0.07 times the human exposure by AUC at the 160 mg twice daily clinical dose).

14 CLINICAL STUDIES

14.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of TANSTRIVE was evaluated in patients with advanced *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with locally advanced (stage III who were not candidates for surgical resection or definitive chemoradiation) or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) or other local testing methods. Adult patients received TANSTRIVE 160 mg orally twice daily until unacceptable toxicity or disease progression; patients enrolled in the dose escalation phase were permitted to adjust their dose to 160 mg twice daily. The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

RET Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 247 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001.

The median age was 61 years (range: 23 to 81); 57% were female; 44% were White, 48% were Asian, 4.9% were Black, and 2.8% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3%) and 97% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1–15); 58% had prior anti-PD-1/PD-L1 therapy. *RET* fusions were detected in 94% of patients using NGS (84.6% tumor samples; 9.3% blood or plasma samples), 4.0% using FISH, 1.6% using PCR and 0.4% by other local testing methods.

Efficacy results for previously treated *RET* fusion-positive NSCLC are summarized in Table 8.

Table 8: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

	TANSTRIVE (n = 247)
Overall Response Rate[1] (95% CI)	61% (55%, 67%)
Complete response	7.3%
Partial response	54%
Duration of Response	
Median in months (95% CI)	28.6 (20, NE)
% with ≥ 12 months[2]	63%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

For the 144 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 63% (95% CI: 54%, 70%) and the median DOR was 28.6 months (95% CI: 14.8, NE).

Among the 247 patients with previously treated *RET* fusion-positive NSCLC, 16 had measurable CNS metastases at baseline as assessed by BIRC. One patient received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 14 of these 16 patients; 39% of responders had an intracranial DOR of ≥ 12 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 69 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001.

The median age was 63 years (range 23 to 92); 62% were female; 70% were White, 19% were Asian, and 6% were Black. ECOG performance status was 0-1 (94%) or 2 (6%) and 99% of patients had metastatic disease. *RET* fusions were detected in 91% of patients using NGS (60.9% tumor samples; 30.4% in blood), 7.2% using FISH and 1.4% using PCR.

Efficacy results for treatment naïve *RET* fusion-positive NSCLC are summarized in Table 9.

Table 9: Efficacy Results in LIBRETTO-001 (Treatment-Naïve *RET* Fusion-Positive NSCLC)

	TANSTRIVE (n =69)
Overall Response Rate[1] (95% CI)	84% (73%, 92%)
Complete response	5.8%
Partial response	78%
Duration of Response	
Median in months (95% CI)	20.2 (13, NE)
% with ≥12 months[2]	50%

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response NE = not estimable

Among the 69 patients with treatment-naïve *RET* fusion-positive NSCLC, 5 had measurable CNS metastases at baseline as assessed by BIRC. Two patients received RT to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 5 patients; 38% of responders had an intracranial DOR of ≥ 12 months.

14.2 *RET*-Mutant Medullary Thyroid Cancer

The efficacy of TANSTRIVE was evaluated in patients with *RET*-mutant MTC enrolled in a multicenter, open-label, multi- cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib or vandetanib (or both) and patients with advanced or

metastatic *RET*-mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts.

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC who had previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. ECOG performance status was 0-1 (95%) or 2 (5%) and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 – 8). *RET* mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synonymous, frameshift or nonsense *RET* mutations; the specific mutations used to identify and enroll patients are described in Table 10.

Table 10: Mutations used to Identify and Enroll Patients with *RET*-Mutant MTC in LIBRETTO-001

RET Mutation Type[1]	**Previously Treated (n = 55)**	**Cabozantinib/ Vandetanib Naïve (n = 88)**	**Total (n = 143)**
M918T	33	49	82
Extracellular cysteine mutation[2]	7	20	27
V804M or V804L	5[4]	6	11
Other[3]	10	13	23

1 Somatic or germline mutations; protein change.

2 Extracellular cysteine mutations involving cysteine residues 609, 611, 618, 620, 630, and 634

[3] Other included: K666N (1), D631_L633delinsV (2), D631_L633delinsE (5), D378_G385delinsE (1), D898_E901del (2), A883F (4), E632_L633del (4), L790F (2), T636_V637insCRT(1), D898_E901del + D903_S904delinsEP (1).

[4] One patient also had a M918T mutation

Efficacy results for *RET*-mutant MTC are summarized in Table 11.

Table 11: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	TANSTRIVE (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥6 months[2]	76

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

Efficacy was evaluated in 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve enrolled into a cohort of LIBRETTO-001.

The median age was 58 years (range: 15 to 82) with two patients (2.3%) aged 12 to 16 years; 66% were male; and 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3.4%). All patients (100%) had metastatic disease and 18% had received 1 or 2 prior systemic therapies (including 8%

kinase inhibitors, 4.5% chemotherapy, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). *RET* mutation status was detected in 77.3% of patients using NGS (75.0% tumor samples; 2.3% blood samples), 18.2% using PCR, and 4.5% using an unknown test. The mutations used to identify and enroll patients are described in Table 10.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 12.

Table 12: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

	TANSTRIVE (n = 88)
Overall Response Rate[1] (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%

Duration of Response	
Median in months (95% CI)	22.0 (NE, NE)
% with ≥6 months[2]	61

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response

NE = not estimable

14.3 *RET* Fusion-Positive Thyroid Cancer

The efficacy of TANSTRIVE was evaluated in patients with advanced *RET* fusion-positive thyroid cancer enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 27 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with *RET* fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both, in separate cohorts.

The median age was 54 years (range 20 to 88); 52% were male; 74% were White, 11% were Hispanic/Latino, 7.4% were Asian, and 3.7% were Black. ECOG performance status was 0-1 (89%) or 2 (11%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (78%), poorly differentiated thyroid cancer (11%), anaplastic thyroid cancer (7%) and Hurthle cell thyroid cancer (4%). Patients had received a median of 3 prior therapies (range 1–7). *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples.

Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 13.

Table 13: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	TANSTRIVE	**TANSTRIVE**

	Previously Treated (n = 19)	**Systemic Therapy Naïve (n = 8)**
Overall Response Rate[1] (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥6 months[2]	87	75

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response

NE = not estimable

16 HOW SUPPLIED/STORAGE AND HANDLING

TANSTRIVE (selpercatinib) capsules are supplied in blister strip cold forming aluminium foil (CFAF) sealed with aluminium foil lidding, in carton of 28 capsules:

40 mg: Gray opaque, imprinted with “Lilly”, “3977” and “40 mg” in black ink

80 mg: Blue opaque, imprinted with “Lilly”, “2980” and “80 mg” in black ink

Do not store above 30° C.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients that ILD/ pneumonitis can occur and to contact their healthcare provider immediately for signs or symptoms of ILD including new or worsening cough or shortness of breath *[see Warnings and Precautions (5.2)]*.

Hypertension

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings *[see Warnings and Precautions (5.3)]*.

QT Prolongation

Advise patients that TANSTRIVE can cause QTc interval prolongation and to inform their healthcare provider if they have any QTc interval prolongation symptoms, such as syncope *[see Warnings and Precautions (5.4)]*.

Hemorrhagic Events

Advise patients that TANSTRIVE may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding [*see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to monitor for signs and symptoms of hypersensitivity reactions, particularly during the first month of treatment *[see Warnings and Precautions (5.6)]*.

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS *[see Warnings and Precautions (5.7)]*.

Risk of Impaired Wound Healing

Advise patients that TANSTRIVE may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.8)]*.

Hypothyroidism

Advise patients that TANSTRIVE can cause hypothyroidism and to immediately contact their healthcare provider for signs or symptoms of hypothyroidism *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the possible risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during the treatment with TANSTRIVE and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with TANSTRIVE and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TANSTRIVE and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that TANSTRIVE may impair fertility *[see Use in Specific Populations (8.4), Nonclinical Toxicology (13.1)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription

medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, proton pump inhibitors, H2 receptor antagonists, and antacids while taking TANSTRIVE.

If PPIs are required, instruct patients to take TANSTRIVE with food. If H2 receptor antagonists are required, instruct patients to take TANSTRIVE 2 hours before or 10 hours after the H2 receptor antagonist. If locally-acting antacids are required, instruct patients to take TANSTRIVE 2 hours before or 2 hours after the locally-acting antacid *[see Drug Interactions (7.1, 7.2)]*.

18 PRODUCT OWNER

Eli Lilly and Company, Indianapolis, IN 46285, USA

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