Economic Analysis of Inpatient Severe Adverse Events-Related Expenditures in Metastatic Solid Tumor Patients Exposed to Larotrectinib or Entrectinib

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BACKGROUND

- Larotrectinib is the first FDA-approved oral, CNS-active, selective tropomyosin receptor kinase (TRK) inhibitor that directly targets signaling proteins that play an important role in cellular communication and tumor growth.[1,2]
- Larotrectinib is well tolerated, demonstrates a favorable safety profile, and has shown durable antitumor activity in adult and pediatric patients with TRK fusion cancer.[3]
- Entrectinib, a multikinase inhibitor that targets TRK, ROS1, and ALK, was recently approved for the treatment of adult TRK fusion cancer.[4]
- As entrectinib also targets ROS1 and ALK in addition to TRK, off-target adverse events (AEs) may be seen; AEs noted specifically in the warnings/precautions section of the prescribing information of several previously approved ALK/ROS1 inhibitors to-date include severe interstitial lung disease/pneumonitis, bradycardia, and hepatotoxicity.[4–9]
- Given that larotrectinib and entrectinib are the first two tumor agnostic TRK inhibitors available in the US, we compared the incidence and inpatient cost of severe adverse events (SAEs) that occurred in the clinical trials secondary to larotrectinib or entrectinib in unresectable or metastatic solid tumor patients.

OBJECTIVES

- To estimate inpatient costs associated with SAEs secondary to TRK inhibitor therapies (larotrectinib and entrectinib) in unresectable or metastatic solid tumor patients.

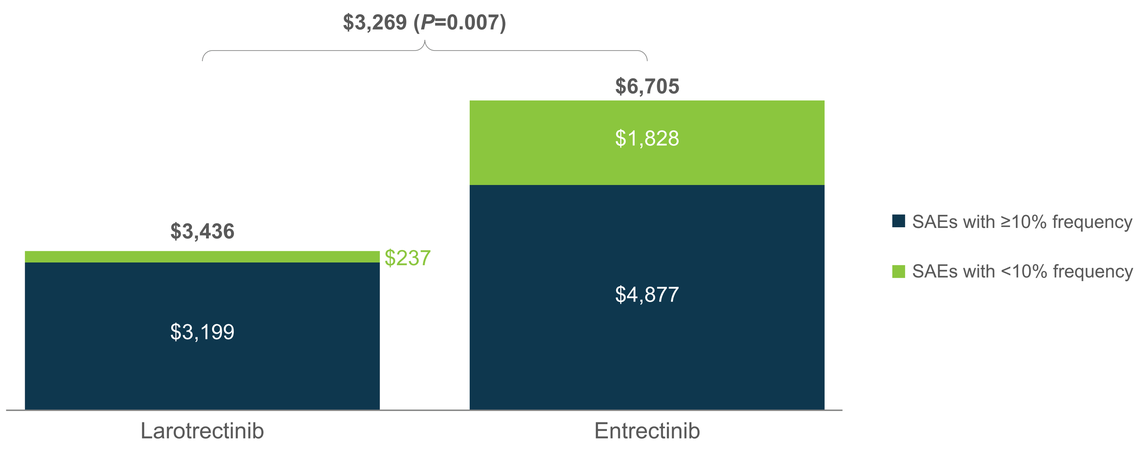
METHODS

- An economic analysis was conducted utilizing two sources of data:
  - SAE (defined as grade 3 or grade 4 non-laboratory AEs per Common Terminology Criteria for Adverse Events v4.03 for larotrectinib, v4.0 for entrectinib) rates from the respective TRK inhibitor prescribing information (PI) as listed in AE tables, Warnings and Precautions sections, and other PI sections
  - SAE inpatient costs identified from the 2016 Healthcare Utilization Project Nationwide (HCUP) Inpatient Sample data costs were adjusted to 2019 USD
- Total SAE-related costs per intervention represented the aggregate of individual SAE-related prevalence-weighted costs.
  - Incidence-adjusted cost per SAE = [grade 3 SAE (%) + grade 4 SAE (%)] / 100 * cost per SAE ($)
- Costs were stratified by low incidence (occurring in <10% of patients) and high incidence SAEs (occurring in ≥10% of patients).

RESULTS

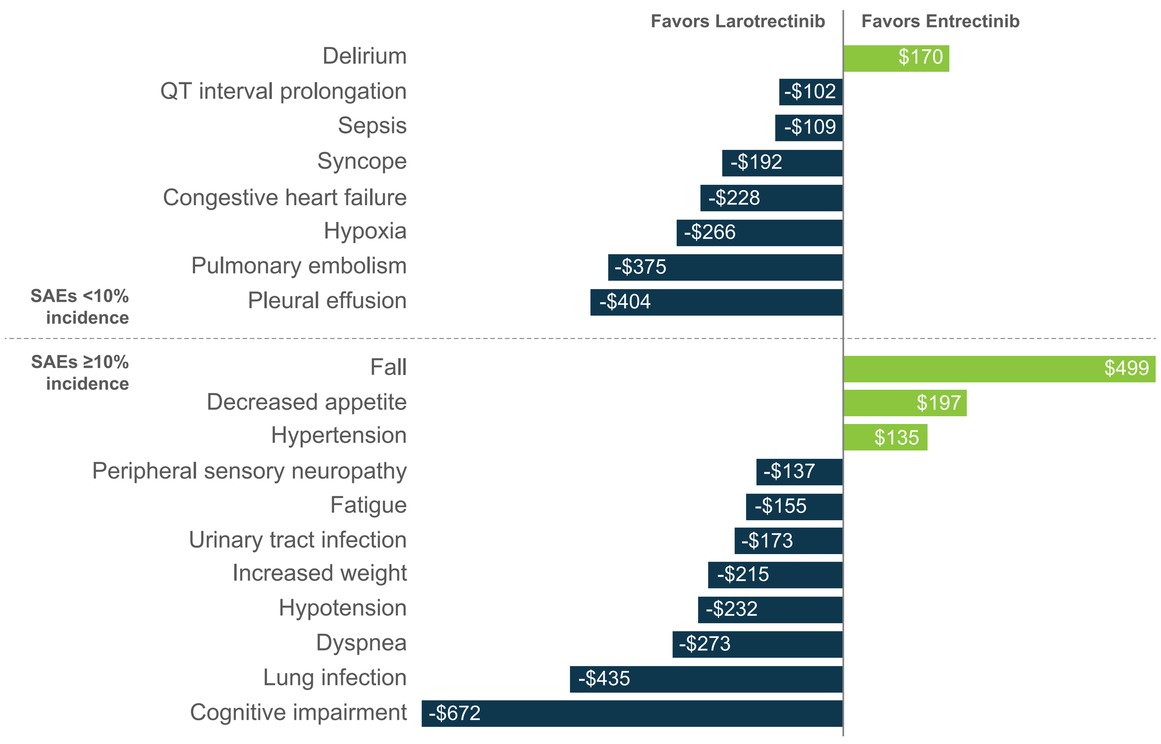
- Fifty-seven SAEs were included. SAEs that most impacted cost differences between larotrectinib and entrectinib are cognitive impairment, falls, lung infection, pleural effusion, pulmonary embolism, dyspnea, hypoxia, and hypotension.
- **Figure 1** illustrates the total incidence-adjusted costs per SAE for larotrectinib and entrectinib which equaled $3,436 for larotrectinib and $6,705 for entrectinib.
- Larotrectinib was associated with a cumulative incidence-adjusted SAE cost savings of $3,269 per patient when compared with entrectinib (*P*=0.007).
- For SAEs occurring in ≥10% of patients (high incidence), the subtotal sum of incidence-adjusted costs per SAE equaled $3,199 for larotrectinib and $4,877 for entrectinib.
- For SAEs occurring in <10% of patients (low incidence), the subtotal sum of incidence-adjusted costs per SAE equaled $237 for larotrectinib and $1,828 for entrectinib.

Figure 1. Overall Larotrectinib vs Entrectinib SAE Cost by SAE Frequency



- When stratified by low and high incidence SAE groups, larotrectinib compared to entrectinib was cost saving ($1,591 and $1,678 saved per patient, respectively).
- Cognitive impairment and pleural effusion contributed most to the cost differential between larotrectinib and entrectinib in the high incidence SAE group (-$672) and low incidence SAE group ($-404), respectively (**Figure 2**).

Figure 2. Larotrectinib vs Entrectinib Incidence-Adjusted Cost per SAE



Note: Incidence-adjusted cost per SAEs with >$100 absolute difference between larotrectinib and entrectinib are reported.

- SAEs that contributed >$100 absolute cost difference between larotrectinib and entrectinib for SAEs with ≥10% incidence are shown in **Table 1** and SAEs <10% incidence are shown in **Table 2**.

Table 1. Larotrectinib vs Entrectinib Cost Differential for Incremental-Adjusted Cost per SAE: ≥10% Incidence

	Cost per Event (2019 USD)	SAE, %		Cost Differential, $ (negative values favor larotrectinib)
		Larotrectinib	Entrectinib	
Cognitive impairment	14,931	0.0	4.5	-672
Fall	49,861	1.0	0.0	499
Lung infection	7,253	0.0	6.0	-435
Dyspnea	6,815	2.0	6.0	-273
Hypotension	8,271	0.0	2.8	-232
Increased weight	7,180	4.0	7.0	-215
Decreased appetite	11,578	2.0	0.3	197
Urinary tract infection	7,521	0.0	2.3	-173
Fatigue	7,772	3.0	5.0	-155
Peripheral sensory neuropathy	12,493	0.0	1.1	-137
Hypertension	6,771	2.0	0.0	135

Table 2. Larotrectinib vs Entrectinib Cost Differential for Incremental-Adjusted Cost per SAE: <10% Incidence

	Cost per Event (2019 USD)	SAE, %		Cost Differential, $ (negative values favor larotrectinib)
		Larotrectinib	Entrectinib	
Pleural effusion	13,020	0.0	3.1	-404
Pulmonary embolism	11,038	0.0	3.4	-375
Hypoxia	7,837	0.0	3.4	-266
Congestive heart failure	9,896	0.0	2.3	-228
Syncope	7,691	0.0	2.5	-192
Delirium	8,490	2.0	0.0	170
Sepsis	18,084	0.0	0.6	109
QT interval prolongation	11,038	0.0	0.6	-102

LIMITATIONS

- Abnormal grade 3-4 laboratory values were excluded from the analysis because they were unlikely to result in hospitalization.
- These cost estimations do not take into account the possibility of patient exhibition of multiple cases of a given SAE; therefore, it is likely that these cost estimates are underestimated.
- Trial population data describing SAEs may differ from real-world data characterizing more diverse or otherwise contrasting patient populations.
- Additionally, cost data utilized from the HCUP National (Nationwide) Inpatient Sample may not necessarily reflect those costs to various health systems or to third-party payers.

CONCLUSIONS

- Larotrectinib demonstrates a less economically burdensome SAE profile compared to entrectinib in the treatment of unresectable or metastatic solid tumors from an inpatient cost perspective and when comparing incidence-adjusted costs in non-laboratory SAE.
- Areas in which larotrectinib demonstrated the most significant SAE-related savings over entrectinib included those related to cognitive disorders, pulmonary disorders, and cardiometabolic disorders.
- Future real-world analyses should be conducted in order to better characterize AE-related economic burden, including that related to less severe AEs and AE-related medical expenditures not captured within inpatient datasets.

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