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Trodelvy® (sacituzumab govitecan-hziy) Safety Analyses by EAIRs in Pretreated HR+/HER2- mBC

This document is in response to your request for information regarding the safety of Trodelvy® (sacituzumab govitecan-hziy [SG]) in patients with pretreated hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2- mBC).

Gilead continually assesses safety data from all sources for unidentified drug reactions and updates the product label information accordingly to reflect the safety profile of SG. Because case reports of potential adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

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The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at:
https://www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.pdf

Summary

Relevant Product Labeling[1,2]

SG is indicated for the treatment of adult patients with unresectable locally advanced or metastatic hormone-receptor positive/human epidermal growth factor receptor 2-negative breast cancer (IHC 0, IHC 1+ or IHC 2+/ISH–) who have received endocrine-based therapy and ≥2 additional systemic therapies in the metastatic setting.

Safety Analyses: Exposure Adjusted Incidence Rates (EAIRs)

Two phase 3 studies compared the safety and efficacy of SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle, with chemotherapy treatment of physicians' choice (TPC) in patients with pretreated HR+/HER2- mBC.[3-5]

TROPiCS-02, included 543 patients who were previously treated with ≥1 taxane, ≥1 endocrine therapy, and ≥1 cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) in any setting, and who had received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease.[3]
An exploratory post hoc safety analysis assessed EAIRs (the relationship between treatment exposure and adverse event [AE] frequency).[4]

- EAIRs were similar between treatment groups for Grade ≥3 treatment-emergent adverse events (TEAEs) including neutropenia, febrile neutropenia, leukopenia, anemia, and fatigue, serious adverse events (SAEs), TEAEs that led to discontinuation, and death.

The EAIR for dose delay favored TPC. EAIRs were lower for SG vs TPC, for TEAEs that led to dose reduction and higher with SG vs TPC for Grade ≥3 diarrhea.[4]

EVER-132-002, included 331 Asian patients who were previously treated with ≥1 endocrine therapy and ≥1 taxane in any setting, and who had received ≥2 and ≤4 prior chemotherapy regimens in the metastatic setting. Prior use of CDK4/6i was not mandatory.[5]

- EAIRs for any-grade and Grade ≥3 TEAEs were similar between treatment groups. EAIRs were also similar between groups for serious TEAEs, TEAEs that led to treatment discontinuation and TEAEs that led to death. Compared with TPC, the EAIR that led to dose interruption was higher with SG, whilst the EAIR for TEAEs that led to dose reduction was lower.[6]

Background Information on EAIRs

In clinical studies, AEs are commonly reported as absolute incidence rates; however, these rates do not account for treatment exposure. It is recognized that longer treatment exposure may lead to higher incidences of AEs.[7] As the median treatment exposure in TROPiCS-02 was longer for SG vs TPC (4.1 vs 2.3 mo),[3] a post hoc safety analysis assessed the relationship between treatment exposure and the frequency of AEs using time-at-risk EAIR.[4] This relationship was also examined in the EVER-132-002 trial.[6]

EAIR is defined as the number of patients with ≥1 specific AE divided by total exposure time (patient years of exposure [PYE]) among patients in the respective treatment group at risk of an initial occurrence of the event. For patients who experienced specific AEs, exposure was measured from the date of first dose up to the date of first AE onset. For patients who did not experience an AE, exposure was measured from the date of first dose up to data cutoff (if still on study treatment) or up to last dose (if discontinued study treatment).[4,6]

EAIRs that are similar between treatment groups are reflected by an EAIR difference that includes 0 in the 95% CI. A positive EAIR difference and 95% CI indicates higher EAIR in the SG group, while a negative EAIR difference and 95% CI indicates higher EAIR in the TPC group.[4,6]

EAIR considers the potential risk for an AE within PYE, however, this assumes a constant rate of time to first AE, which is not always true in clinical practice.[7]

Safety Analyses: EAIRs

TROPiCS-02 Study in Pretreated HR+/HER2- mBC

TROPiCS-02, an open-label, randomized, multicenter phase 3 study compared the safety and efficacy of SG with TPC in patients with HR+/HER2- mBC who were previously treated with ≥1 taxane, ≥1 endocrine therapy, and ≥1 CDK4/6i in any setting, and who had received ≥2 and ≤4 prior chemotherapy regimens for metastatic disease.[3]

First interim safety analysis

A total of 543 patients were randomized and 517 patients received ≥1 dose of study drug (safety population).[3] The median treatment duration of patients was 4.1 (0.03–24.2) vs 2.3

(0.03–22.3) mo for SG and TPC, respectively. See Table 1 for absolute incidence rates of treatment-related adverse events (TRAEs) of special interest.

Table 1. TROPiCS-02 First Interim Safety Analysis: Absolute Incidence Rates of TRAEs[3,4]

		SG (n=268)	TPC (n=249)
TRAEs of special interest, n (%)	Neutropenia[a]	188 (70)	134 (54)
	Diarrhea[a]	152 (57)	41 (16)
	Neuropathy	23 (9)	38 (15)
	Febrile neutropenia	14 (5)	11 (4)
	Interstitial lung disease	0	2 (1)

[a]Neutropenia and diarrhea were managed with dose reductions and supportive care.

Post hoc safety analysis: EAIRs[4]

An exploratory post hoc safety analysis assessed the relationship between treatment exposure and AE frequency. To calculate the risk of an AE, time-at-risk EAIR was evaluated to consider patient exposure to specific AEs. Table 2 and Table 3 present EAIRs (reported as patients with ≥1 event per 1 PYE) and EAIR differences with absolute incidence rates. Please note that due to the exploratory nature of this post hoc analysis, all results presented in Table 2 and Table 3 should be considered nominal.

Absolute incidence rates for TEAEs that led to dose reduction were similar for SG and TPC; however, the rate was lower for SG when adjusted for treatment exposure (Table 2). EAIRs were similar between the two groups for Grade ≥3 TEAEs, SAEs, TEAEs that led to discontinuation, and death, but the absolute incidence of AEs was higher for SG. The EAIR for dose delay favored the TPC group.

Table 2. TROPiCS-02 Post Hoc Safety Analysis: Overall Safety Summary[4]

		SG (n=268)	TPC (n=249)	EAIR Difference vs TPC (95% CI)
TEAEs that led to dose reduction	n (%)	89 (33)	82 (33)	−0.6 (−1.05 to −0.19)
	PYE	85.8	50.1	
	EAIR (95% CI)	1.04 (0.83–1.28)	1.64 (1.3–2.03)	
TEAEs that led to dose delay	n (%)	178 (66)	109 (44)	0.67 (0.002–1.33)
	PYE	57.1	44.6	
	EAIR (95% CI)	3.12 (2.67–3.61)	2.44 (2.01–2.95)	
Grade ≥3 TEAEs	n (%)	198 (74)	149 (60)	0.15 (−0.72 to 0.99)
	PYE	49.2	38.5	
	EAIR (95% CI)	4.02 (3.48–4.62)	3.87 (3.28–4.55)	
SAEs	n (%)	74 (28)	47 (19)	−0.03 (−0.32 to 0.24)
	PYE	103.6	63	
	EAIR (95% CI)	0.71 (0.56–0.9)	0.75 (0.55–0.99)	
TEAEs that led to treatment discontinuation	n (%)	17 (6)	11 (4)	−0.02 (−0.15 to 0.1)
	PYE	123.8	72	
	EAIR (95% CI)	0.14 (0.08–0.22)	0.15 (0.08–0.27)	
TEAEs that led to death	n (%)	6 (2)[a]	0	0.05 (−0.01 to 0.11)
	PYE	123.9	72	
	EAIR (95% CI)	0.05 (0.02–0.11)	0 (0–0.05)	

[a]One patient experienced a TRAE that led to death (septic shock due to neutropenic colitis). AEs not considered to be treatment related that led to death in the remaining 5 patients included the following: arrhythmia, COVID-19 pneumonia, pulmonary embolism, pneumonia, and nervous system disorder (each, n=1).

Compared with TPC, the incidence of Grade ≥3 diarrhea remained higher for SG when adjusted for treatment exposure (Table 3). EAIRs were similar between treatment groups for Grade ≥3 neutropenia, despite the absolute incidence being higher for SG vs TPC. In addition, the Grade ≥3 EAIRs of febrile neutropenia, leukopenia, anemia, and fatigue were similar between groups.

Table 3. TROPiCS-02 Post Hoc Safety Analysis: Most Common Grade ≥3 TEAEs With an Absolute Incidence ≥5% for SG, EAIRs, and EAIR Differences[4]

Grade ≥3 TEAEs		SG (n=268)	TPC (n=249)	EAIR Difference vs TPC (95% CI)
Neutropenia	n (%)	138 (51)	96 (39)	0.03 (-0.53 to 0.56)
	PYE	67.3	47.5	
	EAIR (95% CI)	2.05 (1.72–2.42)	2.02 (1.64–2.47)	
Diarrhea	n (%)	27 (10)	3 (1)	0.19 (0.08–0.3)
	PYE	116.2	71.8	
	EAIR (95% CI)	0.23 (0.15–0.34)	0.04 (0.01–0.12)	
Leukopenia	n (%)	23 (9)	15 (6)	-0.03 (-0.18 to 0.11)
	PYE	118.6	68.3	
	EAIR (95% CI)	0.19 (0.12–0.29)	0.22 (0.12–0.36)	
Anemia	n (%)	20 (7)	9 (4)	0.04 (-0.09 to 0.16)
	PYE	118.5	71.3	
	EAIR (95% CI)	0.17 (0.1–0.26)	0.13 (0.06–0.24)	
Febrile neutropenia	n (%)	16 (6)	11 (4)	-0.02 (-0.16 to 0.09)
	PYE	119.7	69.8	
	EAIR (95% CI)	0.13 (0.08–0.22)	0.16 (0.08–0.28)	
Fatigue	n (%)	16 (6)	8 (3)	0.03 (-0.1 to 0.13)
	PYE	115.3	71.1	
	EAIR (95% CI)	0.14 (0.08–0.23)	0.11 (0.05–0.22)	

EVER-132-002 Study in Pretreated HR+/HER2- mBC

EVER-132-002, a phase 3 study, compared the efficacy and safety of SG 10 mg/kg IV on Days 1 and 8 of a 21-day treatment cycle to TPC in 331 Asian patients with HR+/HER2- mBC who were previously treated with ≥1 endocrine therapy and ≥1 taxane in any setting and had received ≥2 and ≤4 prior chemotherapy regimens in the metastatic setting. Prior use of CDK4/6i was not mandatory.[5]

Safety analysis: absolute incidence rates[5]

The median treatment duration of patients in the safety population was 5.1 (0.03–24.9) and 3.3 (0.03–28.1) mo for SG and TPC, respectively. The most common any-grade TEAEs in the SG group were neutropenia, anemia, leukopenia, alopecia, and nausea (Table 4).

Table 4. EVER-132-002: Absolute Incidence Rates of the Most Common Any-Grade TEAEs[5]

		SG (n=165)	TPC (n=164)
Any-grade TEAEs, n (%)	Neutropenia	145 (88)	128 (78)
	Anemia	117 (71)	91 (55)
	Leukopenia	113 (68)	104 (63)
	Alopecia	103 (62)	66 (40)
	Nausea	95 (58)	52 (32)

Safety analysis: EAIRs[5,6]

EAIRs for any-grade and Grade ≥3 TEAEs were similar between treatment groups. EAIRs were also similar between groups for serious TEAEs, TEAEs that led to treatment discontinuation, and TEAEs that led to death. Compared with TPC, the EAIR that led to dose interruption was higher with SG, whilst the EAIR for TEAEs that led to dose reduction was lower (Table 5).

Table 5. EVER-132-002: Overall Safety Summary by EAIR[6]

		SG (n=165)	TPC (n=164)	EAIR Difference vs TPC (95% CI)
Any-grade TEAE	PYE	2.5	2.8	7.55 (-6.36 to 21.65)
	EAIR (95% CI)	67.04 (57.2–78.08)	59.49 (50.73–69.32)	
Grade ≥3 TEAEs	PYE	27.1	23.4	0.12 (-1.15 to 1.37)
	EAIR (95% CI)	4.99 (4.18–5.9)	4.87 (4.02–5.85)	
TEAEs that led to treatment discontinuation	PYE	88.7	58.7	-0.05 (-0.17 to 0.05)
	EAIR (95% CI)	0.06 (0.02–0.13)	0.1 (0.04–0.22)	
TEAEs that led to dose interruption	PYE	39.8	40.3	1.18 (0.51 to 1.86)
	EAIR (95% CI)	2.81 (2.32–3.38)	1.64 (1.27–2.08)	
TEAEs that led to dose reduction	PYE	65.9	43.4	-0.58 (-1 to -0.2)
	EAIR (95% CI)	0.64 (0.46–0.86)	1.22 (0.91–1.6)	
TEAEs that led to death	PYE	88.5	58.6	-0.01 (-0.09 to 0.05)
	EAIR (95% CI)	0.011 (0–0.06)	0.02 (0–0.1)	
Treatment-emergent SAEs	PYE	76.8	56.3	-0.074 (-0.35 to 0.18)
	EAIR (95% CI)	0.5 (0.35–0.68)	0.57 (0.39–0.8)	
Most common TEAEs[a]				
Neutropenia	PYE	16.7	17.4	1.31 (-0.63 to 3.28)
	EAIR (95% CI)	8.69 (7.33–10.22)	7.38 (6.15–8.77)	
Anemia	PYE	37	37.1	0.71 (-0.07 to 1.5)
	EAIR (95% CI)	3.16 (2.62–3.79)	2.46 (1.98–3.01)	
Leukopenia	PYE	33.3	27.6	-0.37 (-1.36 to 0.61)
	EAIR (95% CI)	3.4 (2.8–4.09)	3.76 (3.08–4.56)	
Alopecia	PYE	32.6	33.1	1.16 (0.37 to 1.97)
	EAIR (95% CI)	3.16 (2.58–3.83)	1.99 (1.54–2.53)	
Nausea	PYE	44.8	44.7	0.95 (0.41 to 1.51)
	EAIR (95% CI)	2.12 (1.71–2.59)	1.16 (0.87–1.53)	
Thrombocytopenia	PYE	74.7	46.4	-0.81 (-1.2 to -0.46)
	EAIR (95% CI)	0.44 (0.3–0.62)	1.25 (0.95–1.62)	
AST increased	PYE	72.5	42	-0.64 (-1.08 to -0.23)
	EAIR (95% CI)	0.74 (0.56–0.97)	1.83 (1.05–1.78)	

[a]The 5 most common TEAEs from each treatment group were included.

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Gilead Sciences Inc. Placeholder for local label.
3. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2022;40(29):3365-3376.
4. Tolaney SM, Schmid P, Bardia A, et al. Exposure-adjusted incidence rates of adverse events from the phase 3 TROPiCS-02 study of sacituzumab govitecan vs treatment of physician's choice

in HR+/HER2- metastatic breast cancer [Poster: P3-07-08]. San Antonio Breast Cancer Symposium (SABCS); December 6-10, 2022; San Antonio, TX.
5. Xu B, Wang S, Yan M, et al. Sacituzumab govitecan in HR+/HER2- metastatic breast cancer: the randomized phase 3 EVER-132-002 trial. *Nat Med.* 2024;30(12):3709-3716.
6. Xu B, Wang S, Yan M, et al. Sacituzumab govitecan in HR+/HER2- metastatic breast cancer: the randomized phase 3 EVER-132-002 trial [Extended Data]. *Nat Med.* 2024;30(12):3709-3716.
7. Zhou Y, Ke C, Jiang Q, Shahin S, Snapinn S. Choosing appropriate metrics to evaluate adverse events in safety evaluation. *Ther Innov Regul Sci.* 2015;49(3):398-404.

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the Trodelvy US Prescribing Information available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.pdf.

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