



Trodelvy® (sacituzumab govitecan-hziy)

Incidence and Management of Hypersensitivity and IRRs in mBC

This document is in response to your request for information regarding hypersensitivity and infusion-related reactions (IRRs) with Trodelvy® (sacituzumab govitecan-hziy [SG]).

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 a causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

This document summarizes data for SG monotherapy (10 mg/kg IV on Days 1 and 8 of a 21-day treatment cycle) from phase 2 and 3 clinical studies, with a focus on patients with mBC.

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The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at:

www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling¹

Prior to each dose of SG, premedication for prevention of infusion reactions is recommended. Premedicate with antipyretics and histamine-1 (H1) and histamine-2 (H2) blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.

The recommended dosage modifications for IRRs are provided in Table 1.

Table 1. Dosage Modifications for IRRs¹

Severity	Dose Modification
Grade 1–3 IRRs	Slow infusion rate or interrupt the infusion
Grade 4 IRRs	Permanently discontinue SG

Administer the first infusion over 3 hours. Observe patients during the infusion and for ≥30 minutes following the initial dose for signs or symptoms of IRRs.

Administer second and subsequent infusions over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for ≥30 minutes after infusion.

SG is contraindicated in patients who have experienced a severe hypersensitivity reaction to SG.

SG can cause serious hypersensitivity reactions including life-threatening anaphylactic reactions. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, and skin reactions.

Hypersensitivity reactions occurred in 28% of patients treated with SG, with 13% occurring within 24 hours of dosage. Grade 3 to 4 hypersensitivity occurred in 1.5% of patients treated with SG, with 0.4% of these occurring within 24 hours of dosage. The incidence of hypersensitivity reactions leading to permanent discontinuation of SG was 0.4%. The incidence of anaphylactic reactions was <0.1%.

Premedication for infusion reactions in patients receiving SG is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering SG.

Closely monitor patients for hypersensitivity and IRRs during each SG infusion and for ≥30 minutes after completion of each infusion.

Permanently discontinue SG for Grade 4 IRRs.

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness, dizziness, chills, rigors, wheezing, pruritus, flushing, rash, hypotension, or fever that occur during or at any time following the infusion.

Incidence of Hypersensitivity and IRRs: Pooled Safety Analyses

A total of 1354 patients from four studies (ASCENT-03,² ASCENT,³ TROPiCS-02,⁴ and IMMU-132-01⁵) were included in a pooled safety analysis. These studies included 641 patients with mTNBC (in a 1L or 2L+ setting) and 322 patients with pretreated HR+/HER2-mBC; 391 patients had other tumor types. The median (range) treatment duration of SG was 4.9 (0–63) mo.¹

- Hypersensitivity reactions were reported in 28% of patients treated with SG, with 13% occurring within 24 hours of dosage. Grade 3–4 hypersensitivity was reported in 1.5% of patients treated with SG with 0.4% of these occurring within 24 hours of dosage. The incidence of hypersensitivity reactions leading to permanent discontinuation of SG was 0.4%. The incidence of anaphylactic reaction was <0.1%.

A total of 969 patients, with either mTNBC treated in the 2L+ setting or pretreated HR+/HER2-mBC, were included in a pooled analysis of clinical studies in the NA/EU (ASCENT,³ TROPiCS-02,⁴ IMMU-132-01⁵) and Asia (EVER-132-001,⁶ EVER-132-002,⁷ and ASCENT-J02⁸) regions. The median duration of treatment (range) in the NA/EU and Asia groups were 4.6 (<0.1–62.6) and 5.2 mo (<0.1–24.9), respectively.⁹

- Time to onset of hypersensitivity, a treatment emergent adverse event (TEAE) of interest, was similar between groups. Time to onset (range) of any grade and Grade ≥3 hypersensitivity in the NA/EU group was 31 days (1–854) and 65 days (1–317), respectively. In the Asia group it was 30 days (1–598) and 0 days, respectively.¹⁰

Incidence of Hypersensitivity and IRRs: SG Clinical Studies

In ASCENT-03, a study in 1L mTNBC,² hypersensitivity TEAEs that occurred on the day of or 1 day after infusion were reported by 7.6% (n=21) vs 12.3% (n=34) of patients in the SG vs chemotherapy treatment of physician's choice (TPC) arms, respectively. Grade ≥3 hypersensitivity was reported by 1.4% (n=4) of patients in the TPC arm; there were no reports in the SG arm.¹¹

In ASCENT, in patients with mTNBC treated in the 2L+ setting,³ any-grade and Grade ≥3 hypersensitivity events occurring within 24 hours of dosing were reported in 34.1% and 1.7% of patients in the SG arm vs 20.5% and 1.3% of patients in the arm that received TPC, respectively.¹²

In TROPiCS-02, in patients with pretreated HR+/HER2- mBC,⁴ hypersensitivity TEAEs occurring on the day of or 1 day after infusion were reported in 26.5% (n=71) of patients in the SG arm vs 19.3% (n=48) of patients in the TPC arm.¹³

In ASCENT-07, a study in 1L post-ET HR+/HER2- mBC, any-grade hypersensitivity was 14% with SG and 9% with TPC; Grade ≥3 was <1% in both arms.¹⁴

In IMMU-132-01, in patients with metastatic epithelial cancer, the incidence of hypersensitivity reactions of any grade within 24 hours of dosing was 37.6%.^{5,12}

Pooled SG Safety Analyses

Safety Analysis in Patients With Multiple Epithelial Tumors

A total of 1354 patients from four studies (ASCENT-03,² ASCENT,³ TROPiCS-02,⁴ and IMMU-132-01⁵) were included in a pooled safety analysis. These studies included 641 patients with mTNBC (in a 1L or 2L+ setting) and 322 patients with pretreated HR+/HER2- mBC; 391 patients had other tumor types (Figure 1). The median (range) treatment duration of SG was 4.9 (0–63) mo.¹

Figure 1. Pooled Clinical Studies: Patients With Multiple Epithelial Tumors¹⁻⁵

ASCENT, Phase 3 An open label, randomized, confirmatory study in patients with refractory or relapsed mTNBC who had received ≥2 prior chemotherapy regimens, ≥1 for metastatic disease	TROPiCS-02, Phase 3 An open-label, randomized, study in patients with HR+/HER2- mBC who had received ≥1 taxane, ≥1 endocrine therapy, and ≥1 CDK4/6i in any setting and 2–4 prior chemotherapy regimens for metastatic disease
SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle, N=1354 (mTNBC, n=641; HR+/HER2- mBC, n=322; other tumor types, n=391) Continue treatment until loss of clinical benefit or unacceptable toxicity	
ASCENT-03, Phase 3 An open-label, randomized study in patients with previously untreated, locally advanced, inoperable or mTNBC who are not candidates for PD-(L)1 inhibitor therapy	IMMU-132-01, Phase 1/2 A single-arm, open-label basket study in patients with numerous metastatic epithelial cancers (including TNBC, HR+/HER2- BC) who had relapsed after or were refractory to ≥1 prior therapy for metastatic disease

Abbreviation: CDK4/6i=cyclin-dependent 4/6 inhibitor

Hypersensitivity and IRRs¹

In this pooled safety population, hypersensitivity reactions were reported in 28% of patients treated with SG, with 13% occurring within 24 hours of dosage. Grade 3–4 hypersensitivity was reported in 1.5% of patients treated with SG with 0.4% of these occurring within 24 hours of dosage. The incidence of hypersensitivity reactions leading to permanent discontinuation of SG was 0.4%. The incidence of anaphylactic reaction was <0.1%.

Safety Analysis in Patients With mBC

A pooled analysis of clinical studies in the NA/EU (ASCENT,³ TROPiCS-02,⁴ IMMU-132-01⁵) and Asia (EVER-132-001,⁶ EVER-132-002,⁷ and ASCENT-J02⁸) regions, evaluated SG in 969 patients with either mTNBC or HR+/HER2- mBC; TEAEs were analyzed by region, NA/EU and Asia.⁹

Hypersensitivity

Hypersensitivity, a TEAE of interest, was similar between the NA/EU and Asia groups in terms of time to onset.⁹ Hypersensitivity included preferred terms of hypersensitivity (Standardised MedDRA Query [SMQ] [broad, narrow]) and anaphylactic reactions (SMQ [broad, narrow]) and only includes events with onset dates on day of or 1 day after dose. The median time to onset of hypersensitivity was defined as time from the first dose of study drug to the first event of hypersensitivity. The times to onset of any-grade and Grade ≥ 3 hypersensitivity for both groups are shown in Table 2.¹⁰

Table 2. Pooled Safety in mBC: Time to Onset of Hypersensitivity¹⁰

	Time to Onset	
	Any Grade	Grade ≥ 3
NA/EU; Median (range), days	31 (1-854)	65 (1-317)
Asia; Median (range), days	30 (1-598)	0

SG Clinical Studies

ASCENT-03 Study in 1L mTNBC

ASCENT-03, an ongoing, global, open-label, randomized, phase 3 study, is comparing the efficacy and safety of SG vs TPC (gem + carbo, paclitaxel, or nab-paclitaxel), as 1L treatment in patients (N=558) with previously untreated, locally advanced, inoperable or mTNBC who are not candidates for programmed death-(ligand) 1 [PD-(L)1] inhibitor therapy.² The median (range) duration of SG treatment at the final PFS analysis was 8.3 (<0.1–28.7) mo.^{2,15}

Hypersensitivity TEAEs that occurred on the day of or 1 day after infusion were reported by 7.6% (n=21) vs 12.3% (n=34) of patients in the SG vs TPC arms, respectively. Grade ≥ 3 hypersensitivity was reported by 1.4% (n=4) of patients in the TPC arm; there were no reports in the SG arm. Hypersensitivity TEAEs that were deemed treatment related were reported in 5.5% (n=15) vs 11.2% (n=31) of patients in the SG vs TPC arms, respectively. Median duration of hypersensitivity in ASCENT-03 for patients who received SG was 8 days.¹¹

ASCENT Study in 2L+ mTNBC

Patients received a median of seven treatment cycles of SG, with a median treatment duration (range) of 4.4 (0.03–22.9) mo.¹⁶ Premedication with antipyretics and histamine 1 and 2 (H1 and H2) blockers for prevention of IRRs was recommended. Corticosteroids (50 mg of hydrocortisone or its equivalent orally or IV) could be added if needed.¹⁶ No frequency data are available regarding pre-infusion medication use for prevention of IRRs.³ SG was administered as a slow IV infusion (Table 3).¹⁷

Table 3. ASCENT: Infusion Rate Guidelines¹⁷

Infusion Rate ^a	First Infusion	Subsequent Infusions
Initial rate (first 15 minutes)	≤50 mg/hr	100–200 mg/hr
Incremental rate (advance every 15–30 minutes)	50 mg/hr	100–200 mg/hr
Maximum recommended rate	500 mg/hr	1000 mg/hr

^aThese suggested infusion rate guidelines were for patients who remained stable in the absence of hypersensitivity or infusion-related events.

Permanent termination of infusion was advised for Grade ≥3 IRRs. In instances of moderate (Grade 2) infusion toxicity, the infusion was stopped for ≥15 minutes or until symptoms resolved and then resumed at a slower infusion rate, if the patient was stable. For mild (Grade 1) toxicity, the remaining infusion rate was slowed. Infusion toxicity must have resolved to Grade ≤1 prior to a patient receiving the next scheduled infusion.¹⁷

Hypersensitivity and IRRs¹²

In the SG vs TPC arms, any-grade hypersensitivity that occurred within 24 hours of dosing was reported by 34.1% vs 20.5% of patients in the safety population, respectively (Table 4), and serious hypersensitivity occurred in 0.4% vs 1.3% of patients. Hypersensitivity did not lead to permanent discontinuation of study drug or to dose reduction in either study arm. Hypersensitivity led to treatment interruption in 1.2% of patients in the SG arm and 0.4% of patients in the TPC arm. The most frequent hypersensitivity events were cough (SG, 7.4%; TPC, 6.7%) and dyspnea (SG, 7%; TPC, 6.7%). No cases of anaphylactic reactions were reported.

Table 4. ASCENT: Incidence of Hypersensitivity¹²

Incidence, %	SG (n=258)			TPC (n=224)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hypersensitivity ^a	34.1	1.7	0	20.5	1.3	0

^a Hypersensitivity reactions occurred within 24 hours of dosing.

See Table 5 for time to onset and duration of hypersensitivity.

Table 5. ASCENT: Time to Onset and Duration of Hypersensitivity¹²

	SG (n=258)		TPC (n=224)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Time to first event of hypersensitivity, median, days ^a	42	110	25	15
Duration of hypersensitivity, median, days ^b	18.5	5	13	4

^aDefined as time from the first dose of study drug to the first event.

^bCalculated as the last date of hypersensitivity event minus the onset date +1.

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

In the SG arm (n=268), patients received a mean (range) of 8.2 (1–35) treatment cycles over a median (range) duration of 4.1 (0.03–24.2) mo.⁴

Patients were excluded for known hypersensitivity to or intolerance of either of the study drugs or any of the excipients. Premedication to prevent infusion reactions, including antipyretics and H1 and H2 blockers, was recommended before SG infusion. Corticosteroids (50 mg hydrocortisone or equivalent orally or IV) could be administered prior to subsequent infusions as needed. In the TPC group, use of premedication (ie, antipyretics, H1 blockers, and H2 blockers) for prevention of IRRs and medications for prevention and treatment of chemotherapy-induced nausea, vomiting, and diarrhea for patients was based on the

investigator's discretion. IRRs were defined as symptoms that occurred within the first 6 hours after SG administration and could occur at any cycle.¹⁸

Hypersensitivity TEAEs that occurred on the day of or 1 day after infusion were reported by 26.5% (n=71) vs 19.3% (n=48) of patients in the SG vs TPC arms, respectively. Hypersensitivity TEAEs that were deemed treatment related were reported in 16.4% (n=44) vs 10.4% (n=26) of patients in the SG vs TPC arms, respectively. The median time to onset of the first event of hypersensitivity was 29 days vs 19 days in the SG vs TPC arms, respectively; median time to onset of the first event of Grade ≥ 3 hypersensitivity was 51 days vs 26 days.¹³

ASCENT-07 Study in 1L Post-ET in HR+/HER2- mBC¹⁴

ASCENT-07, an on-going, global, open-label, randomized, phase 3 study (N=690), compares the efficacy and safety of SG vs TPC (capecitabine, paclitaxel, or nab paclitaxel) in patients with HR+/HER2- (IHC 0, IHC 1+, IHC2+/ISH-) locally advanced, inoperable, or mBC who have received prior ET. The median (range) duration of SG treatment at the PFS analysis was 8.3 mo (0–22.1).

Any-grade hypersensitivity was 14% with SG and 9% with TPC; Grade ≥ 3 was $<1\%$ in both arms. The most common any-grade TEAEs that led to treatment discontinuation included IRR ($<1\%$) in the TPC group.

IMMU-132-01 Study in Metastatic Epithelial Cancer

Patients who had a history of anaphylactic reaction to irinotecan or Grade ≥ 3 gastrointestinal toxicity to prior irinotecan were excluded from the study.⁵

All patients who received ≥ 1 dose of SG were included in the overall safety population (OSP; N=495). During the study, pre-infusion medications were given at the discretion of the investigator. In the OSP, 85.7% (n=424) of patients received pre-infusion medications.⁵

No data are available regarding the frequency of administration of pre-infusion medications for prevention of IRRs specifically. Within 24 hours of infusion, hypersensitivity reactions were reported in 37.6% of patients. The most frequent hypersensitivity events were cough (11.3%), dyspnea (10.3%), and rash (9.3%). One case of anaphylactic reaction occurred in a patient treated with SG 10 mg/kg.¹²

Fifty-two (96.3%) patients in the HR+/HER2- mBC cohort received pre-infusion medications, including dexamethasone, fosaprepitant, and palonosetron.¹⁹ Three (3%) patients in the mTNBC cohort (n=108) experienced Grade ≥ 3 hypersensitivity events that were associated with the infusion of monoclonal antibodies.²⁰

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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at:

www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Follow-Up

For any additional questions, please contact Trodelvy Medical Information at:

 1-888-983-4668 or  www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety  1-800-445-3235, option 3 or

 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by  1-800-FDA-1088 or  MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or  www.accessdata.fda.gov/scripts/medwatch

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