GILEAD | Medical Information

Trodelvy® (sacituzumab govitecan-hziy) Incidence and Management of Diarrhea in Patients With mBC

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and the incidence and management of diarrhea in patients with metastatic breast cancer (mBC).

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 and real-world studies, with a focus on patients with 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.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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 Labeling[1]

SG can cause severe diarrhea. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold SG until resolved to ≤ Grade 1 and reduce subsequent doses.

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of SG as described in Tables 1 and 2 of the US FDA-approved prescribing information. Do not re-escalate the SG dose after a dose reduction for adverse reactions has been made.

Incidence and Management of Diarrhea: Pooled Safety Analyses

A total of 1063 patients from four studies (ASCENT,[2] TROPiCS-02,[3] TROPHY-U-01[4], and IMMU-132-01[5]) were included in this analysis.[6] These studies included patients with mTNBC treated in the 2L+ setting and patients with pretreated HR+/HER2- mBC. The median (range) treatment duration of SG was 4.1 (0–63) mo.[1]

- Any-grade treatment-emergent diarrhea, Grade ≥3 diarrhea, and diarrhea that led to treatment discontinuation were reported for 64%, 11%, and 1% of patients treated with SG, respectively.[6] Grade ≥3 diarrhea was more common in patients with *UGT1A1 *28/*28* GT (15%) than in those with other GTs (**1/*1*, 8%; **1/*28*, 12%).[6] *UGT1A1* testing is not required as per the product label.[1]
- Median onset of any-grade and Grade ≥3 diarrhea occurred at approximately 2 wk from treatment initiation and resolved in approximately 1 wk.[6]
- Antidiarrheal treatment was administered to 477 patients (70%); loperamide ± other antidiarrheals were used by 90% of these patients. Loperamide was advised for non-infectious diarrhea at onset.[7-9] For unresolved diarrhea after 24 h, opium tincture and diphenoxylate/atropine were recommended.[8] Subcutaneous octreotide was recommended for persistent diarrhea, and premedication with atropine was recommended for patients who experienced cholinergic response, including diarrhea, to SG.[7-9] Additional supportive measures and dietary modifications were recommended.[6-8]

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 NA/EU (ASCENT,[2] TROPiCS-02,[3] and IMMU-132-01[5]) and Asia (EVER-132-001,[10] EVER-132-002,[11] and ASCENT-J02[12]) regions. The median (range) duration of treatment in the NA/EU and Asia groups were 4.6 (<0.1–62.6) mo and 5.2 (<0.1–24.9) mo, respectively.[13]

- Across NA/EU (n=688) and Asia (n=281), rates of any-grade and Grade ≥3 diarrhea were higher in NA/EU than in Asia (63% vs 48% and 10% vs 6%, respectively); these rates remained generally stable over time.[13]
- Any-grade treatment-emergent diarrhea was more frequent in patients with the *UGT1A1 *28/*28* GT vs **1/*1* or **1/*28* GTs, regardless of region.[13,14] No patients with the *28/*28 GT in the Asian region reported Grade ≥3 events compared with 18% in the NA/EU region.[14]
- Diarrhea was among the most common TEAEs leading to discontinuation in NA/EU (<1%) but not in Asia.[13]
- Time to onset of any-grade diarrhea was similar between NA/EU and Asia (median: 13 d vs 15 d, respectively), although Grade ≥3 events occurred earlier in Asia (13 d vs 19 d).[14]
- Loperamide was the most commonly used antidiarrheal. Of the patients who received an antidiarrheal during SG treatment, a higher percentage in NA/EU vs Asia received loperamide (89% vs 49%, respectively) and atropine (20% vs 5%). More patients in Asia vs NA/EU received other antidiarrheal treatment: 73% vs 23%, respectively.[13]

Incidence and Management of Diarrhea: SG Clinical Studies in mBC

In ASCENT, a study in 2L+ mTNBC, the incidence of Grade ≥3 treatment-related diarrhea was 10% with SG vs <1% with TPC.[2] A post-hoc analysis showed that neither OS nor PFS was adversely impacted by Grade ≥2 diarrhea. One patient discontinued SG due to Grade 2 diarrhea, which was considered unrelated to study drug.[15]

In ASCENT-03, a study in 1L mTNBC:

- Grade ≥3 treatment-emergent diarrhea was reported by 9% and 1% of patients in the SG (n=275) and chemotherapy TPC (n=276) arms, respectively.[16] In the SG arm, diarrhea led to dose reduction in 15 patients (5%) and to treatment discontinuation in 1 patient (<1%). In the TPC arm, diarrhea led to dose reduction in 3 patients (1%), and no patients required treatment discontinuation.[17]

- A total of 137 and 35 patients received antidiarrheal treatment in the SG and TPC arms, respectively. In both treatment arms, loperamide was the most common treatment: SG, 90%; TPC, 77%. Overall, multiple antidiarrheals were used in 20% of patients who received any antidiarrheal treatment in both treatment arms.[17]

In TROPiCS-02, a study in pretreated HR+/HER2- mBC, the incidence of Grade ≥3 treatment-related diarrhea was 9% in patients treated with SG vs 1% of patients treated with TPC. Diarrhea was among the most common (≥2% incidence) serious TRAEs reported in SG-treated patients (5%).[3] Of the patients treated with SG, 68% received antidiarrheals/intestinal anti-inflammatory and anti-infective agents.[8] No information regarding treatment modifications, or diarrhea resolution, was provided.[3]

In ASCENT-07, a study in 1L post-ET HR+/HER2- mBC, any-grade treatment-emergent diarrhea occurred in 54% of SG-treated patients (n=449) and 31% of TPC-treated patients (n=232), with Grade ≥3 events reported in 7% and 2%, respectively. No information regarding treatment modifications, diarrhea resolution, or management was provided.[18]

In IMMU-132-01, a study in metastatic epithelial cancer,[5,19,20] the incidence of Grade ≥3 treatment-related diarrhea in the mTNBC cohort was 8%. Diarrhea was managed with routine supportive care per standard practice (ie, early intervention).[19] The incidence of Grade ≥3 treatment-related diarrhea in the HR+/HER2- mBC cohort was 7.4%; 1 patient discontinued SG due to Grade 3 treatment-related diarrhea/dehydration, which resolved 4 days later. Overall, 44.4% of patients received antipropulsives and 5.6% received antidiarrheal probiotics.[20]

PRIMED (N=50) evaluated the impact of primary prophylactic loperamide as management of diarrhea.[21]

- At the primary safety analysis (median follow-up, 4.3 mo), the incidence of Grade ≥2 diarrhea was 16% (n=8; *P*=0.084); thus, the second primary endpoint was not met.
- At the extended safety analysis (median follow-up, 9 mo), the incidence of any-grade diarrhea was 44% (n=22). Nine patients (18%) had Grade ≥2 diarrhea, 4% had Grade 3 diarrhea, and no cases of Grade 4 diarrhea were reported.
- Two patients discontinued due treatment-emergent Grade 2 enteritis and Grade 3 diarrhea.

Incidence and Management of Diarrhea: Real-World mBC Studies

An observational study assessed SG safety by *UGT1A1* GT in patients with mTNBC. Among patients with the **28/*28* GT (n=6), none received atropine premedication; diarrhea occurred in 50%, with 33% requiring dose reductions due to Grade ≥2 diarrhea; and no treatment interruptions were reported. Among patients with **1/*1* or **1/*28* GTs (n=75), 11% received atropine premedication, 17% experienced diarrhea, 11% required dose reductions, and 12% required treatment interruption.[22]

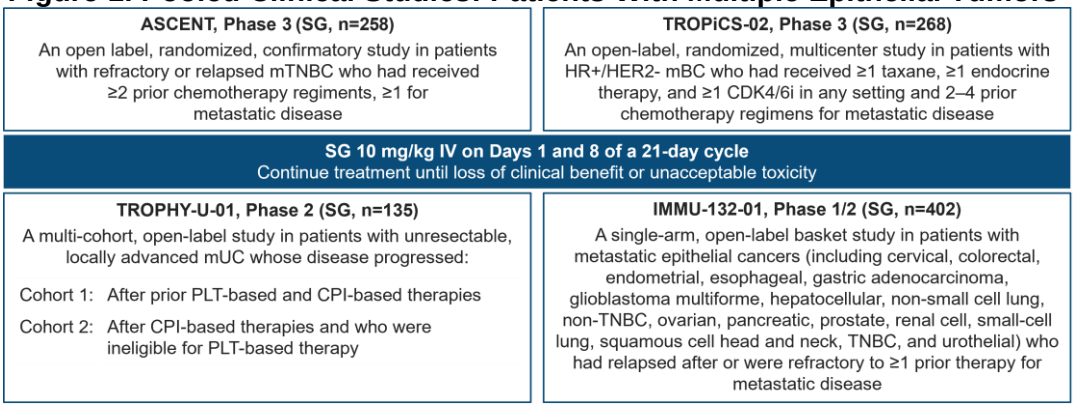
At 3 centers in Spain, 17 female patients with unresectable, locally advanced mTNBC or HR+/HER2- mBC were given atropine as a premedication to each SG infusion. The incidence of any-grade, Grade 1, and 2 treatment-emergent diarrhea was 41% (n=7), 35% (n=6), and 6% (n=1), respectively. Three patients required a dose reduction of SG. No discontinuations were due to TEAEs.[23]

Incidence and Management of Diarrhea: Pooled Safety Analyses

Safety Analysis in Patients With Multiple Epithelial Tumors

A pooled analysis examined exposure to SG in 1063 patients from four studies.[2-5] These studies included patients with mTNBC treated in the 2L+ setting and patients with pretreated HR+/HER2- mBC (Figure 1). The median (range) treatment duration of SG was 4.1 (0–63) mo.[6]

Figure 1. Pooled Clinical Studies: Patients With Multiple Epithelial Tumors[6]



Abbreviations: CPI=checkpoint inhibitor; mUC=metastatic urothelial cancer.

Baseline demographics and disease characteristics are summarized in Table 1.[6]

Table 1. Pooled Safety in Multiple Epithelial Tumors: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics		All Patients (N=1063)
Age, median (range), y		59 (27–90)
Sex, n (%)	Female	840 (79)
Race, n (%)	White/Black/Asian	826 (78)/55 (5)/38 (4)
	Other or unknown	144 (14)
ECOG PS, %	0/1	36/64
Time since metastatic disease diagnosis, median (range), mo		28.7 (-0.1 to 412.6)
Number of prior lines of systemic therapy, median (range), n		5 (1–17)
Presence of visceral metastasis, n (%)		882 (83)
UGT1A1 status, n (%)	**1/*1*	416 (39)
	**1/*28*	420 (40)
	**28/*28*	112 (11)
	Other/unknown	13 (1)/102 (10)

Diarrhea incidence, onset, and duration

Any-grade treatment-emergent diarrhea, Grade ≥3 diarrhea, and diarrhea that led to treatment discontinuation was reported for 64%, 11%, and 1% of patients treated with SG, respectively.[6]

Grade ≥3 diarrhea was more common in patients with *UGT1A1 *28/*28* GT (15%) than in those with other GTs (*1/*1*, 8%; *1/*28*, 12%).[6] *UGT1A1* testing is not required as per the product label.[1]

Median any-grade and Grade ≥3 diarrhea occurred approximately 2 wk after treatment initiation and resolved in approximately 1 wk (Table 2).[6]

Table 2. Pooled Safety in Multiple Epithelial Tumors: Time to Onset and Resolution of Diarrhea (N=1063)[6]

Time to Onset/Resolution, Median (Range), Wk	Time to Onset		Time to Resolution	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	1.9 (0.1–90)	2.1 (0.1–78.6)	1.1 (0.1–50)	1 (0.1–7.9)

Diarrhea management

SG-associated toxicities were assessed and managed in accordance with standard clinical/institutional practices and accepted treatment guidelines.[7,9,24]

Antidiarrheal medication

At the onset of non-infectious diarrhea, prompt initiation of loperamide 4 mg was advised, followed by 2 mg per episode (up to a dose of 16 mg/d). According to the ASCENT and IMMU-132-01 protocols, loperamide was to be discontinued 12 h after diarrhea had resolved and normal diet resumed; this was not required in TROPiCS-02.[7-9]

If diarrhea did not resolve after 24 h, the TROPiCS-02 protocol recommended that diphenoxylate/atropine be considered.[8] In addition, the TROPiCS-02 protocol also recommended opium tincture after 24 h.[8] For persistent diarrhea, subcutaneous octreotide (100–150 mcg three times daily) could be considered.[7-9]

Additional supportive measures included fluid and electrolyte substitution and oral antibiotics,[7-9] such as ciprofloxacin (for diarrhea that persisted >24 h, or in patients who exhibited fever with diarrhea). The ASCENT and IMMU-132-01 protocols specified a ciprofloxacin dose of 250 to 750 mg/12 h for 7 d.[7,9] In the study protocol for TROPiCS-02, several dietary modifications were recommended, including a bland diet, small frequent meals, adequate intake of clear liquids to maintain hydration, and discontinuation of lactose-containing foods/drinks and alcohol.[8]

Anticholinergic medication[7-9]

It was recommended that patients who experienced a cholinergic response to SG, including diarrhea, should receive premedications (eg, atropine) for future treatments.

Incidence of patients receiving any antidiarrheal medication[6]

Of the 681 patients who experienced any-grade diarrhea, 477 (70%) received antidiarrheal medication (Table 3); loperamide ± other antidiarrheals were used by 90% of these patients.

Table 3. Pooled Safety in Multiple Epithelial Tumors: Treatment of Diarrhea[6]

n (%)	Patients Who Received Any Antidiarrheal (n=477)
Any loperamide/any atropine	428 (90)/97 (20)
Loperamide alone/atropine alone	277 (58)/9 (2)
Other antidiarrheal alone	22 (5)
Multi-antidiarrheal regimen[a]	162 (34)

[a]Antidiarrheals with the same start or overlapping treatment dates were considered an antidiarrheal regimen.

Safety Analysis in Patients With mBC

A pooled analysis of clinical studies in the NA/EU (ASCENT,[2] TROPiCS-02,[3] and IMMU-132-01,[5]) and Asia (EVER-132-001,[10] EVER-132-002,[11] and ASCENT-J02[12]) regions, evaluated SG in 969 patients with either mTNBC treated in the 2L+ setting or pretreated HR+/HER2- mBC; TEAEs were analyzed by region, NA/EU and Asia. The median (range) duration of treatment in the NA/EU and Asia groups was 4.6 (<0.1–62.6) mo and 5.2 (<0.1–24.9) mo, respectively.[13]

Baseline age, sex, and BMI were generally similar in both groups; race data are presented in Table 4. Patients from Asia had a higher rate of ECOG PS 1 (67% vs 59%) and shorter time from metastatic diagnosis to randomization (25.2 vs 35.7 mo) vs NA/EU patients. UGT1A1 genotypes differed: NA/EU had more **1/*28* and **28/*28* GTs, while Asia had more **1/*1* and **1/*6* GTs.[13]

Table 4. Pooled Safety in mBC: Race by Region[13]

Region, n	Race, n (%)			
	White	Black	Asian	Other/Unknown
NA/EU (n=688)	517 (75)	41 (6)	26 (4)	104 (15)
Asia (n=281)	0	0	281 (100)	0

Diarrhea incidence and management

Higher rates of any-grade and Grade ≥3 diarrhea occurred in the NA/EU region than in the Asia region (Table 5); rates in both regions remained generally stable over time (through to approximately Weeks 69 and 72 in NA/EU and Asia, respectively). Diarrhea was one of the most common TEAEs that led to discontinuation in NA/EU (<1%) and was not among the most common TEAEs that led to discontinuation in Asia.[13] The median time to onset of any-grade diarrhea was similar between patients from NA/EU and Asia; however, the median time to onset of Grade ≥3 events was earlier in patients from Asia than in those from NA/EU (Table 5).[14]

Table 5. Pooled Safety in mBC: Diarrhea TEAEs and Time to Onset of Diarrhea[13,14]

		Overall (N=969)	
		NA/EU (n=688)	Asia (n=281)
Diarrhea TEAEs, n (%)	Any grade	430 (63)	134 (48)
	Grade ≥3	71 (10)	17 (6)
Time to onset of diarrhea, median (range), d	Any grade	13 (1–630)	15 (1–566)
	Grade ≥3	19 (4–550)	13 (10–316)

Among patients stratified by *UGT1A1* GT, the incidence of any-grade treatment-emergent diarrhea was higher in those with the **28/*28* GT than in those with the **1/*1* or **1/*28* GTs, regardless of region (Table 6).[13,14] No patients with the **28/*28* GT in the Asian region reported Grade ≥3 events compared with 18% in the NA/EU region.[14]

Table 6. Pooled Safety in mBC: Diarrhea TEAEs by *UGT1A1* Status in NA/EU and Asia[14]

		UGT1A1 GT: NA/EU			*UGT1A1* GT: Asia[a]		
		**1/*1* (n=285)	**1/*28* (n=272)	**28/*28* (n=71)	**1/*1* (n=147)	**1/*28* (n=32)	**28/*28* (n=4)
Diarrhea, n (%)	Any grade	169 (59)	171 (63)	52 (73)	61 (41)	19 (59)	3 (75)
	Grade ≥3	19 (7)	34 (13)	13 (18)	6 (4)	2 (6)	0

[a]In Asia, among the 65 patients with the **1/*6* GT, any-grade diarrhea TEAEs occurred in 35 patients (54%), and Grade ≥3 events occurred in 7 patients (11%).

Overall, loperamide was the most commonly used antidiarrheal. Of the patients who received an antidiarrheal during SG treatment, a higher percentage in the NA/EU region than in the Asia region received loperamide and atropine, while a higher percentage of patients in Asia vs patients in NA/EU received other antidiarrheal treatment (Table 7).[13]

Table 7. Pooled Safety in mBC: Treatment of Diarrhea[13]

Patients, n (%)	Patients Who Received an Antidiarrheal During SG Treatment		Patients Who Experienced Diarrhea and Received an Antidiarrheal During SG Treatment	
	NA/EU (n=343)	Asia (n=120)	NA/EU (n=298)	Asia (n=88)
Any loperamide	304 (89)	59 (49)	271 (91)	56 (64)
Any atropine	67 (20)	6 (5)	58 (19)	5 (6)
Other antidiarrheal	80 (23)	87 (73)	76 (26)	58 (66)

Incidence and Management of Diarrhea: SG Clinical Studies in mBC

ASCENT Study in 2L+ mTNBC

ASCENT (N=529) investigated the safety and efficacy of SG vs TPC (eribulin, vinorelbine, gemcitabine, or capecitabine) in patients with refractory or relapsed mTNBC.[2] Prophylactic antidiarrheals were not specified before SG doses in the protocol. In addition to treatment modifications (dose delay and/or reduction) and antidiarrheal therapy, SG was to be withheld in patients experiencing Grade ≥3 diarrhea at the time of scheduled treatment and resumed once symptoms had improved to Grade ≤1.[7] Patients received a median (range) of 7 (1–33) treatment cycles of SG, over a median (range) treatment duration of 4.4 mo (0.03–22.9).[25]

Safety

All-grade and Grade ≥3 treatment-related diarrhea were more frequent in patients treated with SG vs TPC (Table 8).[2]

Table 8. ASCENT: Incidence of Diarrhea TRAEs[2]

TRAE, %	SG (n=258)			TPC (n=224)		
	All-Grade	Grade ≥3	Grade 4	All-Grade	Grade ≥3	Grade 4
Diarrhea	153 (59)	27 (10)	0	27 (12)	1 (<1)	0

A post hoc subgroup analysis evaluated clinical outcomes according to the presence of Grade ≥2 diarrhea.[15] Of the 258 SG-treated patients, 81 had Grade ≥2 diarrhea. No Grade 5 diarrhea occurred. One patient discontinued the study due to Grade 2 diarrhea, which was considered unrelated to study drug. Neither OS nor PFS was adversely impacted by Grade ≥2 diarrhea. Select baseline characteristics, duration of treatment, and relative dose intensity in patients with and without Grade ≥2 diarrhea are shown in Table 9.[15]

Table 9. ASCENT: Select Baseline Characteristics, Duration of Treatment, and Relative Dose Intensity in Patients With and Without Grade ≥2 Diarrhea[15]

Variable	Grade ≥2 Diarrhea (n=81)	No Grade ≥2 Diarrhea (n=177)
Age, <65 y/≥65 y, n (%)	65 (80)/16 (20)	144 (81)/33 (19)
Race, White/Black/Asian/other, %	84/8/3/6	81/11/5/3
Visceral metastases at baseline, n (%)	68 (84)	145 (82)
Time from metastases to first dose, median (min, max), mo	19.5 (3.3, 98.8)	16.4 (-0.1, 191.4)
Prior systemic anticancer regimens, median (min, max), n	4 (2, 17)	4 (2, 11)
BMI at baseline, median (min, max), kg/m^2	27.7 (15.7, 49.3)	24.4 (15, 43.4)
Duration of treatment, median (min, max), wk	27.1 (0.9, 128.6)	17.4 (0.1, 106.4)
Relative dose intensity, median (min, max), %	97.7 (53.7, 105.5)	99.8 (56.8, 107.1)

Abbreviations: max=maximum; min=minimum.

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 (eg, gemcitabine + carboplatin, paclitaxel, or nab-paclitaxel) as 1L treatment in patients (N=558) with previously untreated, locally advanced, inoperable or mTNBC who were ineligible for PD-(L)1 inhibitor therapy.[16] Patients with active chronic inflammatory bowel disease or GI perforation that occurred <6 mo of enrollment were excluded. Prophylactic antidiarrheals were not specified before SG doses in the protocol. In addition to treatment modifications (dose delay and/or reduction), loperamide was recommended at the onset of treatment-related diarrhea, with escalation to additional agents if symptoms persisted >24 h.[26]

The median (range) duration of SG treatment at the final PFS analysis was 8.3 (<0.1–28.7) mo.[16]

Safety

In the SG arm, diarrhea was among the most commonly reported any-grade and Grade ≥3 TEAE (Table 10).[16]

Table 10. ASCENT-03: Any-Grade and Grade ≥3 Treatment-Emergent Diarrhea[16a]

TEAE, n (%)	SG (n=275)		TPC (n=276)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	148 (54)	25 (9)	55 (20)	2 (1)

[a]TEAEs began on or after the first dose date of study drug and ≤30 d after the last dose date of study drug (including crossover treatment if applicable) or the initiation of subsequent anticancer therapy, whichever occurred first. AEs were coded according to preferred terms in the Medical Dictionary for Regulatory Activities, version 27.1, and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Time to onset and duration of diarrhea[17]

The median time to onset of diarrhea was shorter for patients treated with SG than for those treated with TPC, and the median duration of diarrhea was generally comparable between treatment arms; these results should be interpreted with caution due to the small sample size (Table 11). Any-grade and Grade ≥3 diarrhea were most frequently reported early during SG treatment.

Table 11. ASCENT-03: Time to Onset and Duration of Diarrhea[17]

Diarrhea Outcomes	SG (n=275)				TPC (n=276)			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	n	Median (Range), d	n	Median (Range), d	n	Median (Range), d	n	Median (Range), d
Time to onset[a]	148	13 (1–427)	25	67 (6–356)	55	26 (1–296)	2	210 (110–310)
Duration[b]	130	6 (1–273)	24	6 (1–18)	48	6 (1–370)	2	1 (1–1)

[a]Defined as the time from the first dose date of study drug to the onset date of the first TEAE.
[b]Defined as the median duration among multiple preferred terms; within each preferred term, the duration is the median duration among multiple episodes (end date of TEAE – onset date of TEAE + 1 d for each episode).

Management of diarrhea[17]

Across treatment arms, most cases of diarrhea were Grade 1 or 2: SG, 45%; TPC, 19%.

A total of 137 (50%) and 35 (13%) patients received antidiarrheal treatment in the SG and TPC arms, respectively; loperamide was the most common treatment in both arms (SG, 90%; TPC, 77%). In both treatment arms, multi-antidiarrheal regimens were used in 20% of patients who received any antidiarrheal treatment. In the SG arm, diarrhea led to dose reduction in 15 patients (5%) and to treatment discontinuation in 1 patient (<1%). In the TPC arm, diarrhea led to dose reduction in 3 patients (1%), and no patients required treatment discontinuation.

Exploratory analysis: EAIRs[17]

EAIRs, defined as the number of patients with ≥1 specified TEAE per PYE, were calculated as the patients with a specific event divided by the total PYE in each arm. PYE was defined as the sum of each patient's time at risk (exposure duration). Due to the exploratory nature of this post hoc analysis, all results presented in Table 12 should be considered nominal.

The incidence of diarrhea remained higher for SG than for TPC when adjusted for treatment exposure. Additional EAIR data by treatment arm are presented in Table 12.

Table 12. ASCENT-03 Exploratory Safety Analysis: EAIRs[17]

TEAE	SG (n=275)		TPC (n=276)		EAIR Difference (95% CI)
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	
Diarrhea	148 (54)	1.42 (1.2–1.67)	55 (20)	0.41 (0.31–0.54)	1.01 (0.76–1.28)

Note: EAIR values <0 indicate a difference that favors SG, and values >0 indicate a difference that favors TPC.

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

TROPiCS-02 (N=543) investigated the safety and efficacy of SG vs TPC (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with pretreated HR+/HER2- mBC. In the overall safety population (n=517), patients received a mean (range) of 8.2 (1–35) SG cycles over a median (range) duration of 4.1 (0.03–24.2) mo.[3]

Safety

Among patients treated with SG (n=268) vs TPC (n=249), 68% vs 32% used antidiarrheals/intestinal anti-inflammatory and anti-infective agents.[3,8]

The incidence of any-grade, Grade 2, and Grade ≥3 treatment-related diarrhea was higher in patients treated with SG vs TPC (Table 13).[3] Grade 4 diarrhea occurred in 1% of patients treated with SG vs no patients treated with TPC.[8] Diarrhea was among the most common

(≥2% incidence) serious TRAEs with SG (5%).[3] The EAIR difference of any-grade diarrhea (incidence ≥10%) between SG and TPC was 2.29 (95% CI: 1.72–2.87) per PYE.[3,8]

Table 13. TROPiCS-02: Diarrhea TRAEs[3]

TRAE, n (%)	SG (n=268)			TPC (n=249)		
	Any Grade[a]	Grade 2[b]	Grade ≥3[b]	Any Grade[a]	Grade 2[b]	Grade ≥3b
Diarrhea	152 (57)	56 (21)	25 (9)	41 (16)	12 (5)	3 (1)

[a]TRAEs with an incidence ≥10%
[b]TRAEs with an incidence ≥5%

ASCENT-07 Study in 1L Post-ET in HR+/HER2- mBC[18]

ASCENT-07, an ongoing, global, open-label, randomized, phase 3 study (N=690) comparing the efficacy and safety of SG vs TPC (eg, capecitabine, paclitaxel, or nab-paclitaxel) in patients with HR+/HER2- (IHC 0, IHC 1+, IHC 2+/ISH-) locally advanced, inoperable, or mBC who have previously received ET. The median (range) duration of SG treatment at the PFS analysis was 8.3 (0–22.1) mo.

Overall, 449 patients treated with SG and 232 treated with TPC were included in the safety population. Any-grade treatment-emergent diarrhea occurred in 54% of SG-treated patients and 31% of TPC-treated patients, with Grade ≥3 events reported in 7% and 2%, respectively. No information regarding treatment modifications, diarrhea resolution, or management was provided.

IMMU-132-01 Study in Metastatic Epithelial Cancer

IMMU-132-01 investigated the safety and efficacy of SG in patients with metastatic epithelial cancers, including mTNBC and HR+/HER2- mBC.[5]

The mTNBC cohort (n=108) received a mean (range) of 9.6 (1–51) SG cycles, with a median (range) duration of exposure of 5.1 (0.03–36.1) mo.[19] The median (range) duration of treatment with SG was 4.6 (0–29.4) mo for the HR+/HER2- mBC cohort (n=54).[20]

Safety

In the mTNBC cohort, most diarrhea AEs were Grade 1 (Table 14); Grade 2 diarrhea was reported in 14% of patients, with no Grade 4 events observed. Serious diarrhea AEs occured in 3% of patients. Diarrhea was managed with standard supportive care (ie, early intervention).[19]

In the HR+/HER2- mBC cohort, diarrhea was among the most common all-grade and Grade ≥3 TRAEs (Table 14). Most treatment-related diarrhea was Grade 1 (27.8%) or Grade 2 (13%), and no Grade 4 treatment-related diarrhea was reported. Serious treatment-related diarrhea occurred in 1.9% of patients. One patient discontinued SG due to Grade 3 treatment-related diarrhea/dehydration, which resolved 4 days after discontinuation. Overall, 44.4% of patients received antipropulsives and 5.6% received antidiarrheal probiotics to manage GI toxicity.[20]

Table 14. IMMU-132-01: Incidence of Diarrhea AEs and TRAEs[19,20]

mTNBC Cohort (n=108)		HR+/HER2- Cohort (n=54)	
Diarrhea AEs, n (%)		Diarrhea TRAEs, n (%)	
All-Grade	Grade ≥3	All-Grade	Grade ≥3
67 (62)	9 (8)	NR (46.3)	NR (7.4)

PRIMED Study in mTNBC and HR+/HER2- mBC

PRIMED, an open-label, single arm, phase 2 study in 50 patients with unresectable locally advanced mTNBC (n=32) or HR+/HER2- mBC (n=18) treated with SG and primary prophylactic granulocyte colony-stimulating factor and loperamide, evaluated the incidence of neutropenia and diarrhea.[21] Patients received primary prophylactic loperamide (2 mg twice daily or 4 mg once daily on Days 2, 3, 4, 9, 10, and 11) during the first two SG cycles; additional loperamide was permitted thereafter at the healthcare provider's discretion. The primary endpoint was the incidence of either Grade ≥3 neutropenia or Grade ≥2 diarrhea during the first two treatment cycles. The study was considered to have had positive results if ≤14 patients (28%) had Grade ≥3 neutropenia or if ≤7 patients (14%) had Grade ≥2 diarrhea.[27] Patient baseline characteristics and prior treatments are summarized in Table 15.[21]

Table 15. PRIMED: Baseline Demographics, Disease Characteristics, and Prior Treatments[21]

Key Demographics and Characteristics and Prior Treatments		mTNBC (n=32)	HR+/HER2- mBC (n=18)	Overall (N=50)
Age, median (range), y		51 (31–74)	53.5 (37–72)	52 (31–74)
ECOG PS, n (%)	0/1	18 (56.2)/14 (43.8)	12 (66.7)/6 (33.3)	30 (60)/20 (40)
HER2 expression, n (%)	0	19 (59.4)	11 (61.1)	30 (60)
	1+	8 (25)	2 (11.1)	10 (20)
	2+/ISH [-]	5 (15.6)	5 (27.8)	10 (20)
Visceral disease, n (%)		20 (62.5)	15 (83.3)	35 (70)
Prior (neo)adjuvant chemotherapy, n (%)		19 (59.4)	5 (27.8)	24 (48)
Prior chemotherapy regimens for advanced disease, n (%)	0[a]	8 (25)	2 (11.1)	10 (20)
	1	18 (56.2)	11 (61.1)	29 (58)
	2	6 (18.8)	5 (27.8)	11 (22)
Most common (≥20% in any arm) active principle for previous anticancer treatment, n (%)	Taxane	32 (100)	18 (100)	50 (100)
	Anthracyclines	20 (62.5)	12 (66.7)	32 (64)
	Immunotherapy	11 (34.4)	0	11 (22)
	ET[b]	7 (21.9)	18 (100)	25 (50)
	CDK4/6i[b]	1 (3.1)	18 (100)	19 (38)

[a]Systemic treatment in the curative setting was considered as a line of therapy if development of unresectable locally advanced or metastatic disease occurred within 12 mo of chemotherapy or immunotherapy completion.
[b]The treatment of those in the TNBC arm with an endocrine therapy or CDK4/6i occurred when the patient's disease was not TNBC.

Safety

Primary safety analysis

The primary safety analysis had a median (range) follow-up time of 4.3 (0.2–8.6) mo. Results were reported for 50 patients during the first two cycles of SG: Grade ≥2 diarrhea, 8 patients (16%; *P*=0.084); thus, the second primary endpoint was not met (Table 16).[21]

Extended safety analysis

The extended safety analysis had a median (range) duration of follow-up of 9 (0.2–13.5) mo. At data cutoff, 9 patients (18%) continued treatment and 33 (66%) discontinued SG primarily due to disease progression. Twenty-nine patients (58%) received ≥1 dose of loperamide after Cycle 2 (median [range] duration, 5.6 [1.5–12.6] mo).[21]

The incidence of any-grade and Grade ≥2 diarrhea was 44% (n=22) and 18% (n=9), respectively, and no Grade 4 diarrhea or treatment-related serious AEs were reported (Table 16).[21,28] The overall rate of dose reductions and treatment interruptions were 22% and 50%, respectively. Four patients discontinued SG due to AEs; of these, 2 were SG-related: Grade 2 enteritis and Grade 3 diarrhea (Table 17).[21] An additional case of Grade ≥3 neutropenic colitis resulted in permanent SG discontinuation.[27] The average relative dose intensity of SG was 95%.[21]

Table 16. PRIMED: Diarrhea During First Two Cycles and Extended Safety Analysis[21,28]

Diarrhea, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥2	Grade 3	Grade ≥3	Grade 4
During first 2 cycles	17 (34)	NR	6 (12)	8 (16)[a]	2 (4)	NR	0
Extended safety analysis	22 (44)	13 (26)	7 (14)	NR	NR	2 (4)	NR

[a]Primary endpoint.

Table 17. PRIMED: Dose Reductions, Treatment Interruptions, and Discontinuations[21]

n (%)	Dose Reduction	Treatment Interruption	Permanent Discontinuation
During first 2 cycles	7 (14)	15 (30)	0
Extended safety analysis	11 (22)	25 (50)	4 (8)

Incidence and Management of Diarrhea: Real-World mBC Studies

Observational Study of SG Safety by *UGT1A1* GT[22]

An observational, descriptive, ambispective study in Spain evaluated the impact of *UGT1A1* GT on the safety and effectiveness of SG in patients with mTNBC. Outcomes were compared according to GT as follows: **28/*28* vs **1/*1* and**1/*28*. Overall, 81 patients were included in the analysis and had a mean (range) age of 54.5 (31–78) y; all patients had an ECOG PS ≤1, and 95% received SG in the 2L+ setting. Baseline characteristics were comparable between the *28/*28* vs **1/*1* and**1/*28* subgroups. A total of 6 patients had **28/*28* GT, and 75 had **1/*1* or **1/*28* GTs. A total of 8 patients (11%) with **1/*1* or **1/*28* GTs received atropine prior to administration of SG; none of the patients in the **28/*28* GT subgroup received atropine before SG.

Patients received a median (range) of 12 (1 to >30) doses of SG over a median (range) treatment duration of 6.2 (3.1–18.7) mo. Higher incidences of diarrhea were observed in patients with **28/*28* GT vs **1/*1* and**1/*28* GTs: 50% vs 17%, respectively (*P*=0.053). Dose interruptions due to diarrhea were NR in the **28/*28* GT subgroup compared with 12% of patients in the **1/*1* and**1/*28* GT subgroup (*P*=0.368). Dose reductions due to Grade ≥2 diarrhea were reported as follows: **28/*28*, n=2 (33%); **1/*1* and**1/*28*, n=29 (11%; *P*=0.104).

Real-World Safety of SG and Prophylactic Atropine Use[23]

At three Spanish centers, 17 female patients with unresectable, locally advanced mTNBC (n=13) or HR+/HER2- mBC (n=4) received atropine 0.5 mg subcutaneously as a premedication to each SG infusion, according to the approved indications in Spain. Select patient baseline characteristics are summarized in Table 18.

Table 18. Select Baseline Demographics and Disease Characteristics[23]

Key Demographics and Characteristics		SG + Atropine (N=17)
Age, median (range), y		50 (29–72)
ECOG PS, n (%)	0/1/2	2 (11.8)/9 (52.9)/6 (35.3)
Germline *BRCA* mutation, n (%)	Negative/positive	15 (88.2)/2 (11.8)
PD-L1 expression, n (%)	Negative/positive	3 (17.6)/14 (82.1)

Abbreviation: *BRCA*=breast cancer gene.

Of the 17 patients who received prophylactic atropine, overall, 7 patients developed any-grade diarrhea, 6 developed Grade 1 diarrhea, and 1 patient developed Grade 2 diarrhea. Constipation was NR as a common TEAE. Three patients each required a dose reduction of SG, and there were no discontinuations due to TEAEs.

References

1. TRODELVY® Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med.* 2021;384(16):1529-1541.
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. Loriot Y, Petrylak DP, Kalebasty AR, et al. TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: updated safety and efficacy outcomes. *Ann Oncol.* 2024;35(4):392-401.
5. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol.* 2021;32(6):746-756.
6. Rugo HS, Tolaney SM, Bardia A, et al. Pooled safety analysis of sacituzumab govitecan in multiple solid tumor types [Poster 3029]. Presented at: American Society of Clinical Oncology (ASCO); May 31-June 4, 2024; Chicago, IL.
7. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer [Protocol]. *N Engl J Med.* 2021;384(16):1529-1541.
8. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer [Supplementary Appendix]. *J Clin Oncol.* 2022;40(29):3365-3376.
9. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial [Protocol]. *Ann Oncol.* 2021;32(6):746-756.
10. Ma F, Wang S, Tong Z, et al. Overall survival results from EVER-132-001, a phase 2b single-arm study of sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer [Poster PO1-06-10]. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 5-9, 2023; San Antonio, TX.
11. 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.
12. Naito Y, Nakamura S, Kawaguchi-Sakita N, et al. Preliminary results from ASCENT-J02: a phase 1/2 study of sacituzumab govitecan in Japanese patients with advanced solid tumors. *Int J Clin Oncol.* 2024;29(11):1684-1695.
13. Rugo HS, Tolaney SM, Cortés J, et al. Sacituzumab govitecan in patients with metastatic breast cancer: pooled safety analysis of data from patients in North America, Europe, and Asia. *ESMO Open.* 2026;11(4).

14. Rugo HS, Tolaney SM, Cortés J, et al. Sacituzumab govitecan in patients with metastatic breast cancer: pooled safety analysis of data from patients in North America, Europe, and Asia [Supplementary appendix]. *ESMO Open.* 2026;11(4).
15. de Azambuja E, Jacobs F, Lambertini M, et al. Relationship of diarrhea and neutropenia events with outcomes in patients (pts) with metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG): post hoc analysis from the phase 3 ASCENT study [Poster 198P]. Presented at: European Society for Medical Oncology (ESMO BC); May 11-13 2023; Berlin, Germany.
16. Cortés J, Punie K, Barrios C, et al. Sacituzumab govitecan in untreated, advanced triple-negative breast cancer. *N Engl J Med.* 2025;393(19):1912-1925.
17. Hurvitz S, Bardia A, Tolaney SM, et al. Safety analysis of ASCENT-03, a phase 3 study of sacituzumab govitecan vs chemotherapy for previously untreated advanced triple-negative breast cancer in patients who are not candidates for PD-(L)1 inhibitors [Poster PS1-13-24]. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 9-12, 2025; San Antonio, TX.
18. Jhaveri K, Park YH, Barrios C, et al. Sacituzumab govitecan vs chemotherapy as first therapy after endocrine therapy in HR+/HER2- (IHC 0, 1+, 2+/ISH-) metastatic breast cancer: primary results from ASCENT-07. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 9-12, 2025; San Antonio, TX.
19. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med.* 2019;380(8):741-751.
20. Kalinsky K, Diamond JR, Vahdat LT, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. *Ann Oncol.* 2020;31(12):1709-1718.
21. Pérez-García JM, Gion M, Ruiz-Borrego M, et al. Prevention of sacituzumab govitecan-related neutropenia and diarrhea in patients with HER2-negative advanced breast cancer (PRIMED): an open-label, single-arm, phase 2 trial. *EClinicalMedicine.* 2025 Jun 18;85:103309.
22. do Pazo-Oubiña F, Del Rosario García B, Miarons M, et al. Impact of UGT1A1*28 allele on the safety and effectiveness of sacituzumab govitecan in metastatic triple-negative breast cancer: real-world evidence. *J Clin Med.* 2026;15(2):574.
23. Echarri MA, Santisteban M, Cardenas JD. Efficacy and safety of sacituzumab govitecan treatment with the addition of prophylactic atropine to prevent diarrhea to patients with metastatic breast cancer treated: a Spanish multicenter real-world study [Poster P1-06-12]. Presented at: San Antonio Breast Cancer Symposium (SABCS); December 10-13, 2024; San Antonio, TX.
24. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer [Protocol]. *J Clin Oncol.* 2022;40(29):3365-3376.
25. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer [Supplementary Appendix]. *N Engl J Med.* 2021;384(16):1529-1541.
26. Cortés J, Punie K, Barrios C, et al. Sacituzumab govitecan in untreated, advanced triple-negative breast cancer [Protocol]. *N Engl J Med.* 2025;393(19):1912-1925.
27. Pérez-García JM, Gion M, Ruiz-Borrego M, et al. Prevention of sacituzumab govitecan-related neutropenia and diarrhea in patients with HER2-negative advanced breast cancer (PRIMED): an open-label, single-arm, phase 2 trial [Supplementary Appendix]. *EClinicalMedicine.* 2025;85:103309.
28. Perez-Garcia JM, Gion M, Ruiz-Borrego M, et al. Prevention of sacituzumab govitecan-related neutropenia and diarrhea in patients with triple-negative or HR+/HER2- advanced breast cancer (PRIMED): a phase 2 trial [Poster 1101]. Presented at: American Society of Clinical Oncology (ASCO); May 31-June 4, 2024; Chicago, IL.

Abbreviations

1L=first-line
2L+=second-line and later
AE=adverse event
CDK4/6i=cyclin-dependent 4/6 inhibitor
EAIR=exposure-adjusted incidence rate
ECOG PS=Eastern Cooperative Oncology Group Performance Status
ET=endocrine therapy

EU=Europe
GT=genotype
HR+/HER2-=hormone receptor-positive/human epidermal growth factor receptor 2-negative
IHC=immunohistochemistry
ISH=in situ hybridization
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer
NA=North America
NR=not reported
OS=overall survival
PD-(L)1=programmed death (ligand) 1
PFS=progression-free survival
PYE=patient year of exposure
SG=sacituzumab govitecan-hziy
TEAE=treatment-emergent adverse event
TNBC=triple-negative breast cancer
TPC=treatment of physicians' choice
UGT1A1=uridine diphosphate glucuronosyl transferase family 1 member A1

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