2 SYNOPSIS

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

Title of Study: A Phase 2, Randomized, Open-Label Study of Trilaciclib Administered with First-Line Platinum-Based Chemotherapy and Avelumab Maintenance Therapy in Patients with Untreated, Locally Advanced or Metastatic Urothelial Carcinoma (PRESERVE 3)

Coordinating Investigator: N/A

Study sites: 55 centers in 5 countries (France, Georgia, Hungary, Spain, and the United States [US])

Publications:

Studied period (years):	**Phase of development:**
Date first patient enrolled: 08 September 2021 Date last patient completed: 01 March 2024	2

Objectives:

Objective		Endpoints	
Type	**Description**	**Protocol Defined**	**In aCSR**
Primary			
Efficacy	To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	PFS during the overall study	Yes
Secondary			
Efficacy	To evaluate the anti-tumor efficacy of trilaciclib compared to a control group	ORR defined as the proportion of patients who had an objective response (unconfirmed or confirmed) per RECIST v1.1 (Chemotherapy Period, Maintenance Period, Overall Treatment Period)	Yes [a] (Maintenance Period not analyzed [b])
		DCR defined as the proportion of patients with best overall response of confirmed CR or PR, or stable disease per RECIST v1.1 (Maintenance Period, Overall Treatment Period)	Yes [a] (Maintenance Period not analyzed [b])
		DOR per RECIST v1.1 (Overall Treatment Period)	Yes [a]
		PFS (Maintenance and Survival Follow-up Periods)	Yes
		Probability of survival at Month 16	No [b]
		OS (Maintenance and Survival Follow-up Periods, during the overall study)	Yes [a]
Efficacy	To evaluate the myeloprotective effects of trilaciclib when combined with platinum-based chemotherapy compared with chemotherapy alone:		
	– To assess the effects of trilaciclib on the neutrophil lineage compared to a control group	Duration of severe (Grade 4) neutropenia (DSN) in Cycle 1	Yes
		Occurrence of severe (Grade 4) neutropenia (SN)	
		Occurrence of febrile neutropenia AEs	No [b]
		Occurrence of G-CSF administration	

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Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

Objective		Endpoints	
Type	– **Description**	**Protocol Defined**	**In aCSR**
Secondary *(continued)*			
Efficacy	– To assess the effects of trilaciclib on the RBC lineage compared to a control group	Occurrence of Grade 3 or 4 decreased hemoglobin laboratory values	No [b]
		RBC transfusions on or after Week 5 (occurrence and number of transfusions)	
		Occurrence of ESA administration	
	– To assess the effects of trilaciclib on the platelet lineage compared to a control group	Occurrence of Grade 3 or 4 decreased platelet count laboratory values	No [b]
		Platelet transfusions (occurrence and number of transfusions)	
	– To assess the effects of trilaciclib on hospitalizations due to chemotherapy-induced myelosuppression compared to a control group	Occurrence and number of hospitalizations due to chemotherapy-induced myelosuppression	No [b]
	– To assess the effects of trilaciclib on chemotherapy dosing compared to a control group	All-cause dose reductions (occurrence and number of reductions)	No [b]
		All-cause cycle delays (occurrence and number of delays)	
Safety	To assess the safety and tolerability of trilaciclib compared to a control group	Occurrence and severity of AEs by NCI-CTCAE v5.0	Yes
		Trilaciclib AESIs	
		Avelumab AESIs	
		Changes in laboratory parameters (hematology and serum chemistry), vital signs and electrocardiogram (ECG) [c] parameters	
		Grade 3 or 4 abnormalities in serum chemistry laboratory parameters	
		Occurrence of trilaciclib dose delays and infusion interruptions	
		Occurrence of chemotherapy dose reductions	
		Occurrence of chemotherapy dose delays and infusion interruptions	
		Occurrence of avelumab dose delays and infusion interruptions	No [d]
Exploratory			
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI

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Objective		Endpoints	
Type	**Description**	**Protocol Defined**	**In aCSR**
Exploratory *(continued)*			
CCI	CCI CCI CCI	CCI CCI CCI	
CCI	CCI CCI CCI CCI CCI CCI	CCI	CCI
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Methodology:

This was a Phase 2, multicenter, randomized, open-label study evaluating the safety and efficacy of trilaciclib administered with platinum-based chemotherapy followed by trilaciclib administered with avelumab maintenance therapy compared with platinum-based chemotherapy followed by avelumab maintenance therapy in patients receiving first-line treatment for advanced/metastatic urothelial carcinoma. Patients were randomly assigned (1:1) to one of two treatment arms:

- Arm A – platinum-based chemotherapy followed by avelumab maintenance therapy
- Arm B – trilaciclib plus platinum-based chemotherapy followed by trilaciclib plus avelumab maintenance therapy

The study included 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase began on the day of randomization and completed at the End of Treatment Visit. Survival Follow-up assessments occurred every 3 months after the End of Treatment Visit (including assessments at Month 17 Day 1).

A Data Monitoring Committee (DMC) monitored accumulating safety and anti-tumor response data with the first meeting planned when approximately 10 patients treated with trilaciclib + cisplatin or 10 patients treated with trilaciclib + carboplatin have completed at least 2 cycles of study treatment, whichever occurred first.

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
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Standard of care platinum-based chemotherapy (with or without the addition of trilaciclib) was administered intravenously (IV) in 21-day cycles and standard of care avelumab maintenance therapy (with or without the addition of trilaciclib) was administered IV in 14-day cycles.

There were two stratification factors for randomization: presence of visceral metastasis (yes or no) at randomization, and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin).

Patients enrolled in the study were eligible to receive 4-6 cycles of platinum-based chemotherapy, and patients without progressive disease (PD) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines (i.e., with an ongoing complete response [CR], partial response [PR], or stable disease) after platinum-based chemotherapy were eligible to receive avelumab maintenance therapy until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever came first.

An End of Treatment Visit occurred approximately 14 days following a patient's last dose of study drug. Safety Follow-up Visits (which may have been a phone call) occurred 30 days after the last dose of study drug and 90 days after the last dose of avelumab. Patients were followed for survival approximately every 3 months (including an assessment at Month 17 Day 1) after the End of Treatment Visit. Survival Follow-up Visits may have been done via telephone, email, or clinic visit. Unless otherwise decided by the Sponsor, the study was to continue until at least 60% of patients enrolled in the study have died. However, the study was terminated by the Sponsor on 01 March 2024 and results are summarized in this abbreviated clinical study report (aCSR).

Number of patients (planned and analyzed): Approximately 90 patients were planned in this study and 92 patients were analyzed.

Diagnosis and main criteria for inclusion:

Patients were ≥18 years of age at the time of signing the informed consent with locally advanced or metastatic urothelial carcinoma and were receiving first line treatment and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients had documented, locally advanced (T4b, any N; or any T, N 2-3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra). Patients had measurable disease as defined by RECIST v1.1, considered eligible to receive platinum-based chemotherapy and avelumab maintenance therapy, and no prior systemic therapy in the inoperable, locally advanced, or metastatic setting. A treatment-free interval > 12 months between the last perioperative/adjuvant treatment administration and the date of recurrence was required in order to be considered treatment-naïve in the metastatic setting. Patients had tumor tissue available from a metastatic or locally recurrent urothelial carcinoma lesion (archival or fresh biopsy). Patients also had adequate organ function as demonstrated by the laboratory values.

Test product dose and mode of administration:

Trilaciclib

In each chemotherapy cycle at Day 1 and Day 8, a dose of trilaciclib 240 mg/m^2 reconstituted and diluted in 250 mL of dextrose 5% in water or normal saline (sodium chloride solution 0.9%) was administered as a 30-minute IV infusion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy was administered. If administration of platinum-based chemotherapy was skipped or discontinued, trilaciclib was also skipped or discontinued.

In each avelumab maintenance cycle at Day 1, a dose of trilaciclib 240 mg/m^2 reconstituted as described above was administered as a 30-minute IV infusion completed within 4 hours prior to the start of avelumab on each day avelumab was administered. If administration of avelumab maintenance therapy was delayed or skipped, then

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Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
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trilaciclib was administered as scheduled. If administration of avelumab maintenance therapy was permanently discontinued, trilaciclib was also permanently discontinued.

Duration of treatment: Patients enrolled in the study were eligible to receive 4-6 cycles of platinum-based chemotherapy followed by avelumab maintenance therapy (with or without trilaciclib) until disease progression, unacceptable toxicity, withdrawal of consent, Investigator decision, or the end of the trial, whichever came first. In specific circumstances, study treatment may have continued beyond disease progression with approval from the Medical Monitor.

Reference therapy and dose and mode of administration:

Platinum-based Chemotherapy

Gemcitabine 1000 mg/m^2 by IV infusion on Day 1 and Day 8 of each 21-day chemotherapy cycle.

Cisplatin eligible: cisplatin 70 mg/m^2 administered IV on Day 1 of each 21-day chemotherapy cycle. Gemcitabine was administered before cisplatin.

Cisplatin ineligible: carboplatin using Calvert formula with a target area under the curve (AUC)=4.5 administered IV on Day 1 of each 21-day chemotherapy cycle. Gemcitabine was administered before carboplatin.

Patients were allowed to switch from cisplatin to carboplatin chemotherapy if they became ineligible for cisplatin due to toxicity, or from carboplatin to cisplatin chemotherapy in the event that patient became eligible to receive cisplatin. Changes in protocol chemotherapy were not allowed for the reason of suspected or confirmed disease progression by RECIST v1.1.

Other platinum-based chemotherapies, such as methotrexate/carboplatin/vinblastine for example, were not permitted in this study.

Avelumab Maintenance Therapy

Avelumab 800 mg administered IV on Day 1 of each 14-day maintenance cycle as a 60-minute infusion. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab was mandatory for the first 4 infusions. Premedication were administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Criteria for evaluation:

Efficacy:

Anti-tumor efficacy assessments included PFS, ORR (unconfirmed and confirmed), DCR, DOR, and OS. Tumor response criteria were based on RECIST v1.1. Myelosuppression endpoints (DSN and SN) were assessed based on hematology assessments, myelosuppression-related adverse event (AE) details, dose reductions/delays and supportive care interventions (including transfusions). Further details are provided in SAP Section 8.1.1 and Section 8.1.2. This aCSR focuses on PFS during the overall study and during the Maintenance and Survival Follow-up Periods as well as myelosuppression endpoints DSN and SN.

Safety:

Safety was evaluated by monitoring AEs, clinical laboratory test results (hematology, clinical chemistry), vital sign measurements (blood pressure, heart rate, and oral body temperature), 12 lead safety ECG results, dose modifications, and physical examination findings. Further details are provided in SAP Section 9.1.

Pharmacokinetics:

The pharmacokinetics (PK) of trilaciclib and metabolites, cisplatin and avelumab were determined using a non-linear mixed effects modeling approach. These results were summarized in a separate report.

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

Pharmacodynamics:

Pharmacodynamics were planned to have been assessed using peripheral blood and tumor biopsies to evaluate potential markers of response and resistance, including immune markers. However, these analyses were not conducted due to the termination of the study.

Statistical Methods:

Efficacy and safety data collected from this study were summarized by Chemotherapy Period, Maintenance Period, Overall Treatment Period, during the overall study, or Survival Follow-up Period depending on the category of the data to be summarized (see Section 7.7.1 for definitions of study periods).

Table 2 summarizes the treatment groups and analysis periods as they relate to the protocol, tabular summaries, and text discussions in this aCSR.

Analysis Populations:

Analysis Population	**Definition and Use**
ITT	Defined as all randomized patients. Analyses for the ITT population were conducted based on the randomly assigned treatment regardless of whether the patient received any study treatment or was compliant with the protocol. Unless otherwise specified, the ITT population was the primary population for all efficacy analyses.
Response Evaluable	Defined as those patients who were in the ITT population and received at least one dose of any study drug, had measurable (target) tumor lesion(s) at baseline tumor assessment, and had at least one of the following: (1) at least 1 post-baseline tumor assessment; (2) discontinued treatment because of clinical progression prior to their first post baseline tumor scan; (3) died due to disease progression prior to their first post-baseline tumor scan. Analyses using the Response Evaluable population were conducted on the basis of the randomly assigned treatment. It was the primary analysis population for efficacy endpoints evaluating tumor responses.
Safety	Defined as all randomized patients who received at least one dose of any study drug. Analyses using the safety population was conducted on the basis of the actual treatment received at Day 1 of Cycle 1 in chemotherapy period. Unless otherwise specified, all safety data analyses for the chemotherapy period and overall treatment period were performed based on this population.
Maintenance	Defined as all randomized patients who received at least one dose of any study drug during the maintenance period. Unless otherwise specified, all analyses using this population were based on the treatment group as initially assigned at randomization. That is, in Arm A (Chemotherapy/Avelumab) or Arm B (trilaciclib + chemotherapy/avelumab).

Efficacy:

Unless otherwise specified, all efficacy analyses were performed on the ITT population. Treatment effect on PFS was evaluated based on the number of events as stated in SAP Section 1.3 and was not limited to treatment phase (e.g., Chemotherapy Period, Maintenance period, or Survival Follow-Up).

There were two stratification factors for randomization: presence of visceral metastasis (yes or no) at randomization and initial platinum-based chemotherapy to be administered (cisplatin or carboplatin; Chemo Type). Both stratification factors were included in the statistical analysis models to assess trilaciclib's anti-tumor efficacy.

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

The family-wise Type 1 error rate of 2-sided 0.2 was only applied for the primary endpoint. For secondary efficacy endpoints, nominal p-value and 95% CIs were generated as the reference for judging strength of the evidence and the precision of point estimation.

Analysis for Primary Efficacy Endpoint – Progression-Free Survival during the Study

The treatment effect for PFS was primarily evaluated using a stratified log-rank test accounting for the two stratification factors. The magnitude of treatment effect, HR (Arm B vs. Arm A) along with its 80% CI was estimated using a Cox proportional hazard model controlling for the same factors as included in the stratified log-rank test. Kaplan-Meier estimates were provided for the survival probability along with their 95% CIs.

Analysis for Secondary Efficacy Endpoint – PFS in Maintenance and Survival Follow-up Periods

PFS in the Maintenance and Survival Follow-up Periods was calculated for patients in the Maintenance population.

For the derivation of timepoint responses in the maintenance and survival follow-up periods, the last non-missing tumor assessment during Chemotherapy Period was used as the baseline to derive tumor response status (hereafter referred to as maintenance baseline).

PFS in the Maintenance and Survival Follow-up Periods was defined as the time (months) from date of first dose of study drug in maintenance period to the date of the first documented disease progression or death in the absence of PD for those who had a PFS event during Maintenance and Survival Follow-up Periods. For those who did not have any PFS event, PFS was censored. Specifically, PFS in the Maintenance and Survival Follow-up Periods was calculated as (date of PFS event or censoring – date of first dose of study drug in Maintenance Period + 1)/ 30.4375.

Analysis for Secondary Efficacy Endpoint – DSN in Cycle 1

Treatment effect on DSN in Cycle 1 was evaluated using nonparametric analysis of covariance (ANCOVA). In this analysis, the rank-transformed (within each stratum) DSN values were analyzed by an ANCOVA model with the terms of treatment and Chemo Type (initial platinum-based chemotherapy to be administered). Rank-transformed baseline ANC (within each stratum) was included as a covariate in the model. In addition, the group-difference in DSN in Cycle 1 (Trila+Chemo – Chemo), its standard error and 95% CI was generated and reported from a Satterthwaite t-test and presented.

Analysis for Secondary Efficacy Endpoint – Occurrence of SN During Chemotherapy Period

The occurrence of SN was a binary variable. The number and percentage of patients with at least one occurrence of SN during Chemotherapy Period was summarized by treatment group.

The treatment effect was evaluated using a modified Poisson regression model. The model included the factors of treatment and Chemo Type as the fixed effect and corresponding baseline value as a covariate when applicable. The variable duration of Chemotherapy Period among patients was adjusted by using the log-transformed duration of Chemotherapy Period (in the unit of cycles or weeks) as the offset variable in the model. A 2-sided p-value, adjusted relative risk (aRR, Arm B vs. Arm A) and its 95% CI were generated from the modified Poisson regression model and reported. Baseline ANC was used as a covariate in the model. The duration of Chemotherapy Period that was used to construct an offset variable in the model was the number of cycles in Chemotherapy Period.

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

Safety:

Safety data were summarized using descriptive statistics by treatment group and for overall patients when appropriate. No inferential statistical comparisons for between-group differences were made.

Adverse Events

AEs were defined as those AEs occurring on or worsening in severity after the first dose of any study drug (i.e., the conventional treatment-emergent AEs) and were collected in the study database as follows:

- For the Overall Treatment Period, AEs were reported from the first dose of any study drug until 30 days after the last dose of study drug (for patients who did not enter maintenance) or from the first dose of any study drug until 90 days after the last dose of study drug during the Maintenance Period (for patients who entered maintenance).
- For the Chemotherapy Period, AEs were reported from the first dose of any study drug until 30 days after the last dose of study drug during the Chemotherapy Period.
- For the Maintenance Period, AEs were reported from the first dose of any maintenance study drug until 90 days after the last dose of study drug during Maintenance Period.

Serious adverse events (SAEs) thought to be related to a study specific procedure were also collected between the time the patient signed the informed consent and the first dose of any study drug.

AEs were coded from verbatim text to PT and grouped by primary SOC according to MedDRA version 26.1. The severity (toxicity grades 1-5) of AEs were graded according to the NCI CTCAE version 5.0 by the Investigator.

Trilaciclib Adverse Events of Special Interest

AEs of special interest (AESI) for trilaciclib were identified, reflecting either the findings in the AEs from the previous studies of trilaciclib or class effects for CDK 4/6 inhibitors. AESI for trilaciclib were identified by searching MedDRA PTs based on the Customized MedDRA Queries as detailed in SAP Appendix 2.

Specifically, trilaciclib AESI included the following 5 categories:

- Injection site reaction/Phlebitis/Thrombophlebitis
- Acute drug hypersensitivity reaction
- Hepatotoxicity
- Interstitial lung disease/Pneumonitis
- Embolic and thrombotic events, venous

Clinical Laboratory Data

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables were graded according to NCI CTCAE criteria, Version 5.0 or later. The determination of CTCAE grade for each measurement was based on the collected laboratory values and did not involve clinical judgement. Abnormal hepatic laboratory values were defined including any occurrence among all on-treatment, post-baseline assessments including scheduled and unscheduled values. Hy's Law was evaluated as defined in SAP Section 9.3.2.

Vital Signs

Vital signs including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, and body temperature will be measured according to Schedule of Assessments in SAP Appendix 1. SAP Table 11 lists the criteria for potentially clinically significant vital signs.

SUMMARY – CONCLUSIONS

Efficacy Results:

Overall, this study did not demonstrate that treatment with trilaciclib could provide improved anti-tumor efficacy or myeloprotective efficacy in patients receiving first-line and maintenance treatment for advanced/metastatic urothelial carcinoma.

PFS

The primary endpoint (PFS during the overall study in the ITT population) was not met as differences in median PFS during the overall study were not statistically significantly different between Trila+Chemo/Avel and Chemo/Avel groups, with an HR of 0.94 (80% CI: 0.69, 1.29) and two-sided p-value of 0.885. Results from analyses of secondary endpoints of anti-tumor efficacy were consistent with the primary endpoint showing no statistically significant differences between groups for PFS or OS during the Maintenance and Survival Follow-up Periods or between groups for OS, ORR, DCR, or DOR during the Overall Treatment Period.

DSN and SN

Evaluations of myeloprotective efficacy also failed to show significant differences between groups. DSN at Cycle 1 showed a treatment difference (Trila+Chemo – Chemo) of -0.3 days (95% CI: -1.3, 0.7; p=0.743), and the occurrence of SN during the Chemotherapy Period event rate aRR (Trila+Chemo vs Chemo) was 0.621 (95% CI: 0.148, 2.607; p=0.515).

Safety Results:

Treatment with trilaciclib (240 mg/m^2) and platinum-based chemotherapy (gemcitabine+cisplatin or gemcitabine+carboplatin) followed by trilaciclib and avelumab maintenance therapy was generally safe and well-tolerated in patients receiving first-line treatment for advanced/metastatic urothelial carcinoma. Overall, with the exception of SAEs during the Chemotherapy Period, the safety profiles of trilaciclib in the Safety population during the Chemotherapy Period and in the Maintenance population during the Maintenance Period were generally consistent. While incidences of AEs, Grade ≥3 AEs, SAEs, AEs leading to discontinuation of study drug, and AESIs were higher among patients in the Chemotherapy Period relative to the Maintenance Period, these observations were shown with and without trilaciclib treatment and most likely reflect toxicities associated with platinum-based chemotherapies. During the Chemotherapy Period, SAEs were reported at higher incidences among patients treated with trilaciclib, a difference that was not observed during the Maintenance Period. Trilaciclib treatment combined with platinum-based chemotherapy also resulted in numerically more patients having renal AEs and SAEs during the Chemotherapy Period than during the Maintenance Period.

Safety conclusions from analyses of the Chemotherapy Period (Safety population) and the Maintenance Period (Maintenance population) are summarized below. During the Chemotherapy Period, conclusions are based on comparison of the overall groups (Trila+Chemo vs Chemo alone), unless differences across individual chemotherapy groups were clinically meaningful.

Chemotherapy Period

- During the Chemotherapy Period, the median duration of exposure and median number of cycles were similar in the Trila+Chemo group (15.4 weeks and 4.0 cycles) and the Chemo alone group (14.9 weeks and 4.0 cycles).
- Overall, during the Chemotherapy Period, the proportion of patients with any study drug modifications was similar between the Trila+Chemo and Chemo alone groups (57.8% vs 63.8%).
- Overall, >90% of patients experienced at least 1 AE during the Chemotherapy Period, including 95.6% in the Trila+Chemo group and 95.7% in the Chemo alone group.
- The most common AE PTs (ie, those occurring in ≥20% of patients in either overall group) during the Chemotherapy Period were anemia, nausea, neutropenia, asthenia, decreased appetite, constipation, thrombocytopenia, and fatigue.
    - Of these, nausea and decreased appetite occurred in higher proportions of patients in the Trila+Chemo group (46.7% and 28.9%, respectively) than in the Chemo alone group (36.2% and 19.1%, respectively).
- Similar proportions of patients reported AEs Grade ≥3 during the Chemotherapy Period in the Trila+Chemo (60.0%) and Chemo alone (70.2%) groups.

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

- The most common AE Grade ≥3 PTs (ie, those occurring in ≥20% of patients in either overall group) were anemia and neutropenia, which occurred in similar proportions of patients in the Trila+Chemo group (28.9% and 20.0%, respectively) and Chemo alone group (27.7% and 23.4%, respectively).

- The proportions of patients with AEs related to any study drug during the Chemotherapy Period were similar in the Trila+Chemo (88.9%) and Chemo alone (91.5%) groups.
  - The most common trilaciclib-related AE PT (ie, those occurring in ≥20% of patients overall) was nausea.
  - Two patients (9.52%) in the Trila/Gem+Carb group had trilaciclib-related AEs (asthenia and platelet count decreased) that led to discontinuation of trilaciclib.
- The following renal and hematologic AEs were potentially clinically meaningful during the Chemotherapy Period:
  - The proportions of patients with AEs in the Renal and urinary disorders SOC were higher in the Trila+Chemo group (33.3%) compared with the Chemo alone group (19.1%). This difference with trilaciclib treatment was observed in both the gemcitabine/cisplatin and gemcitabine/carboplatin chemotherapy groups.
  - The following renal AEs were reported more frequently in the Trila+Chemo group relative to Chemo alone group: renal failure (11.1% vs 0%), acute kidney injury (6.67% vs 2.13%), blood creatinine increased (6.67% vs 4.26%), and renal impairment (4.44% vs 0%).
  - The following Grade 3 renal AEs were reported more frequently in the Trila+Chemo group relative to the Chemo alone group: acute kidney injury (6.67% vs 0%), renal failure (2.22% vs 0%), and blood creatinine increased (2.22% vs 0%). None of these events were Grade 4.
  - The following hematologic AEs were reported in lower proportions of patients in the Trila+Chemo group compared with the Chemo alone group: neutrophil count decreased (8.89% vs 19.1%) and platelet count decreased (8.89% vs 21.3%).
  - The following Grade 3 hematologic AEs were reported in the Trila+Chemo and Chemo alone groups: neutrophil count decreased (4.44% vs 12.8%) and platelet count decreased (2.22% vs 6.38%). No patients in the Trila+Chemo group and 2.13% of patients in the Chemo alone group had Grade 4 AEs of neutrophil count decreased. Grade 4 platelet count decreased AEs were reported in 4.44% of patients in the Trila+Chemo group and 10.6% of patients in the Chemo alone group.
  - No AEs of acute kidney injury, renal failure, renal impairment, blood creatinine increased, or platelet count decreased were considered related to trilaciclib treatment. A trilaciclib-related AE of neutrophil count decreased was reported in 4.17% of patients in the Trila/Gem+Cis group and 0% of patients in the Trila/Gem+Carb group.
- PPD , which began on Day 80 during the Chemotherapy Period. The event was not considered related to any study medication. No other patients died secondary to an AE during the Chemotherapy Period or the Maintenance Period.
- A higher proportion of patients reported SAEs during the Chemotherapy Period in the Trila+Chemo group (35.6%) compared with the Chemo alone group (21.3%).
  - SAE PTs reported for >2 patients in Trila+Chemo or Chemo alone groups included urinary tract infection (6.67% vs 2.13%) and acute kidney injury (6.67% vs 0%).

- Few patients had AEs that led to discontinuation of any study drug during the Chemotherapy Period with similar proportions in the Trila+Chemo group (17.8%) and the Chemo alone group (10.6%).
    - Acute kidney injury was the only AE that led to discontinuation of any study drug reported for >1 patient and occurred in 6.67% of patients in the Trila+Chemo group and 2.13% of patients in the Chemo alone group.
- Few patients had AESIs during the Chemotherapy Period, with numerically more patients having AESIs in the Trila+Chemo group (6 patients [13.3%]) than in the Chemo alone group (2 patients [4.26%]).
    - Embolic and thrombotic events, venous was the only AESI category with >2 patients overall, which included 6.67% of patients in the Trila+Chemo group and 2.13% of patients in the Chemo alone group.
    - Pulmonary embolism was the only AESI PT reported for >2 patients overall, which included 6.67% of patients in the Trila+Chemo group and 2.13% of patients in the Chemo alone group.
    - A non-serious Grade 1 AESI of injection site reaction was reported for 1 patient (2.22%) in the Trila+Chemo group.
    - No AESIs of hepatotoxicity or interstitial lung disease/pneumonitis were observed.
- The majority of clinical chemistry and hematology laboratory abnormalities during the Chemotherapy Period were Grade 1 or Grade 2 with few patients experiencing any Grade ≥3 abnormalities during the Chemotherapy Period.
- During the Chemotherapy Period, the proportions of patients who experienced postbaseline clinical chemistry or hematology laboratory abnormalities were similar between the Trila+Chemo group and the Chemo alone group, with the following exceptions for Grade ≥3 abnormality differences (≥10%) between groups:
    - The proportions of Grade ≥3 lymphocyte abnormalities were higher in the Trila+Chemo group (31.1%) compared with the Chemo alone group (17.0%). Differences in the incidence of lymphocyte abnormalities were mostly driven by differences observed among patients treated with gemcitabine+carboplatin, as Grade ≥3 lymphocyte abnormalities were higher in the Trila/Gem+Carb group (38.1%) compared with the Gem+Carb group (13.0%).
    - The proportion of Grade ≥3 platelet abnormalities was lower in the Trila+Chemo group (11.1%) compared with the Chemo alone group (25.5%).
    - Similar proportions of patients in the Trila+Chemo group and the Chemo alone group reported Grade ≥3 creatinine or eGFR abnormalities. However, the proportion of patients with Grade 3 eGFR abnormalities was higher in the Trila/Gem+Cis group (13.0%) compared with the Gem+Cis group (0%), while the opposite was observed among gemcitabine+carboplatin groups (0% in the Trila/Gem+Carb group and 17.4% in the Gem+Carb group). The proportion of Grade ≥3 eGFR abnormalities were lower in the Trila/Gem+Carb group (5.26%) compared with the Gem+Carb group (17.4%).
- No patients were considered possible Hy's Law cases during the Chemotherapy Period.
- There were no clinically significant changes in vital signs during the Chemotherapy Period.

<u>Maintenance Period</u>

- During the Maintenance Period, the median duration of exposure and median number of cycles were shorter in the Trila+Avel group (16.1 weeks and 5.0 cycles) relative to the Avel alone group (18.1 weeks and 9.0 cycles).
- Overall, during the Maintenance Period, the proportion of patients with any study drug modifications was similar between the Trila+Avel and Avel alone groups (43.3% vs 48.3%).
- Overall, ≥80% of patients experienced at least 1 AE during the Maintenance Period, including 80.0% in the Trila+Avel group and 82.8% in the Avel alone group.
- No AE PTs met the criteria for most common (ie, those occurring in ≥20% of patients in either group) during the Maintenance Period.
    - AE PTs with a ≥10% difference in the Trila+Avel group compared with the Avel alone group included urinary tract infection (16.7% vs 3.45%) and anemia (26.7% vs 3.45%).

Name of Sponsor/Company: G1 Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product: G1T28 (trilaciclib dihydrochloride)		
Name of Active Ingredient: G1T28 (trilaciclib dihydrochloride)		

- A similar proportion of patients reported AEs Grade ≥3 during the Maintenance Period in the Trila+Avel group (30.0%) and the Avel alone group (20.7%).
    - No AE Grade ≥3 PTs met the criteria for most common (ie, those occurring in ≥20% of patients in either group). A higher proportion of patients reported Grade ≥3 anemia in the Trila+Avel group (10.0%) compared with the Avel alone group (0%).
- The proportions of patients with AEs related to either study drug during the Maintenance Period were similar in the Trila+Avel (43.3%) and Avel alone (37.9%) groups.
    - A total of 30.0% of patients reported trilaciclib-related AEs. No PTs were reported for >1 patient and none led to discontinuation of trilacilib.
- No patients experienced AEs leading to death during the Maintenance Period.
- Similar proportions of patients in the Trila+Avel group (20.0%) and the Avel alone group (17.2%) reported SAEs during the Maintenance Period.
    - The only SAE PT reported for >1 patient was pyelonephritis acute in the Trila+Avel group (6.67%).
- A non-serious AE of renal failure in 1 patient in the Trila+Avel group led to discontinuation of avelumab during the Maintenance Period; no other AEs leading to discontinuation were reported during the Maintenance Period
- Few patients had AESIs during the Maintenance Period, with similar proportions in the Trila+Avel group (3.33%) and Avel alone group (6.90%).
    - No AESI category had >1 patient in either group, and no AESIs of hepatotoxicity, interstitial lung disease/pneumonitis, or embolic and thrombotic events were observed.
- The majority of clinical chemistry and hematology laboratory abnormalities during the Maintenance Period were Grade 1 or Grade 2 with few patients experiencing any Grade ≥3 abnormalities.
- During the Maintenance Period, the proportions of patients who experienced postbaseline clinical chemistry or hematology laboratory abnormalities were similar between the Trila+Avel group and the Avel alone group, with the following exceptions for Grade ≥3 abnormality differences (≥10%) between groups:
    - The proportions of Grade 3 and Grade ≥3 eGFR abnormalities were higher in the Trlia+Avel group (18.5% for each) compared with the Avel alone group (7.14% for each).
- No patients were considered possible Hy's Law cases during the Maintenance Period.
- There were no clinically significant changes in vital signs during Maintenance Period.

Conclusions:

Treatment with trilaciclib (240 mg/m^2) and platinum-based chemotherapy followed by trilaciclib and avelumab maintenance therapy did not result in improved anti-tumor efficacy (as measured by PFS, OS, ORR, DCR, and DOR) or provide myeloprotective efficacy (as measured by DSN and SN) in patients receiving first-line treatment for advanced/metastatic urothelial carcinoma. While this treatment regimen was generally safe and well-tolerated, renal AEs in patients treated with trilaciclib combined with platinum-based chemotherapy may represent a possible safety signal in this patient population.

Date of the report: 07 June 2024