FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	Dose Optimization Study of Idelalisib in Follicular Lymphoma
Name of Test Drug:	Idelalisib (IDL; Zydelig®; GS-1101)
Dose and Formulation:	Idelalisib 150-mg or 100-mg tablets
Indication:	Follicular Lymphoma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-313-1580
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	101254 2015-000366-66
ClinicalTrials.gov Identifier:	NCT02536300
Study Start Date:	14 January 2016 (first participant screened)
Study End Date:	27 September 2022 (last participant last visit for the primary endpoint and for this report)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Sponsor Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	25 March 2023
Previous Report Date:	07 December 2017

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-313-1580
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: Dose Optimization Study of Idelalisib in Follicular Lymphoma

Investigators: Multicenter study

Study Centers: 1 site in Australia, 1 site in Canada, 6 sites in the United Kingdom, 2 sites in Israel, and 34 sites in Europe

Publications: There were no publications at the time of this clinical study report (CSR).

Study Period:

14 January 2016 (first participant screened)
27 September 2022 (last participant last visit for the primary endpoint and for this report)

Phase of Development: Phase 3

Study Objectives:

The primary objective of this study was as follows:

- To establish a safe and effective dosing regimen of idelalisib (IDL; Zydelig®; GS-1101) in participants with relapsed or refractory follicular lymphoma (FL) who have no other therapeutic options

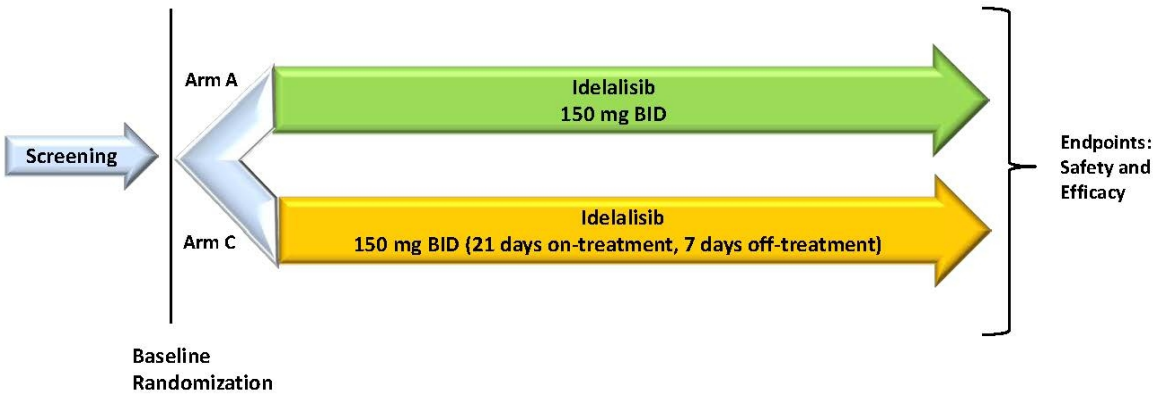
The secondary objectives of this study were as follows:

- To evaluate the overall response rate (ORR)
- To evaluate the progression-free survival (PFS), duration of response (DOR), and overall survival (OS)
- To evaluate the overall safety profile of IDL
- To determine the pharmacokinetics (PK) of IDL and its major metabolite (GS-563117)

Methodology: This was a randomized, open-label, multicenter study. Participants were randomized in a 1:1 ratio to the following treatment arms (per Protocol Amendment 5) (Synopsis Figure 1):

- Arm A: IDL 150 mg administered twice daily continuously
- Arm C: IDL 150 mg administered twice daily in 28-day cycles with 21 days on-treatment and 7 days off-treatment (intermittent dosing schedule)

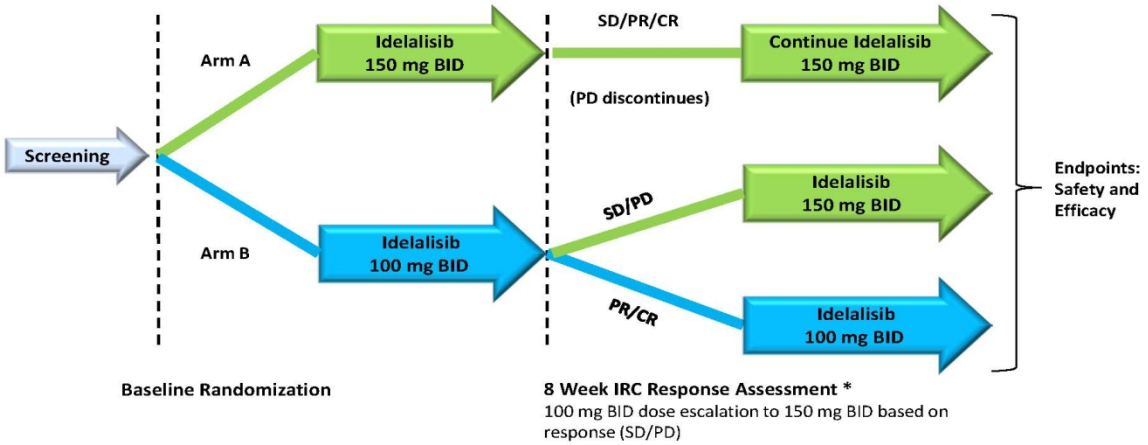
Synopsis Figure 1. Study Schema per Protocol Amendment 5



BID = twice daily

The original protocol for this study included an Arm B (IDL 100 mg administered twice daily continuously) (Synopsis Figure 2). Based on the preliminary efficacy analysis indicating that Arm B appeared unlikely to meet the requirement of ORR ≥ 50%, the sponsor, having received regulatory feedback, decided to discontinue Arm B per Protocol Amendment 5.

Synopsis Figure 2. Study Schema Prior to Protocol Amendment 5



* Unblinding and dose modifications may occur at any time during study participation if the IRC Assessment confirms progressive disease.

BID = twice daily; CR = complete response; IRC = independent review committee; PD = progressive disease; PR = partial response; SD = stable disease

In accordance with Protocol Amendment 6, participants enrolled prior to implementation of Protocol Amendment 5 and who were still receiving blinded treatment were unblinded at the time of Protocol Amendment 6 implementation. These participants, previously randomized in a blinded manner to either Arm A (IDL 150 mg twice daily) or Arm B (IDL 100 mg twice daily), continued at the randomized dose level if they were still on treatment. Based on the 8-week blinded independent review committee (IRC) response assessment, participants

with stable disease (SD) or progressive disease (PD) were unblinded in both arms. Participants with a partial response (PR) or complete response (CR) maintained the blind and continued at the randomized dose level. Participants randomized to 100 mg twice daily with SD or PD had the option to be dose escalated to 150 mg twice daily. Participants randomized to 150 mg twice daily with SD continued open-label IDL at 150 mg twice daily and those with PD were discontinued from study treatment. These same unblinding and dose modification principles were applied at any time throughout study participation when disease progression was suspected and confirmed by IRC assessment.

Clinic visits occurred at screening; Day 1; every 2 weeks through Week 12; every 4 weeks through Week 24; at Weeks 32, 36, 40, and 48; and every 12 weeks thereafter through the end of study. Participants were assessed for safety at each visit. Additional visits were required between protocol-specified visits for laboratory testing only.

Participants Enrolled per Protocol Amendments 5 and 6:

Participants were assessed for FL disease status by continuous use of a single radiographic imaging method including positron emission tomography-computed tomography (PET-CT), computed tomography (CT), or magnetic resonance imaging (MRI) at screening and at Weeks 12, 24, 36, 48, 60, and 84 until IRC documented disease progression, and at the end of treatment (EOT) visit (unless radiographic assessments were performed within the 4 weeks prior to the EOT visit). After Week 84, radiographic assessments were performed at the discretion of the investigator. Screening CT/PET-CT/MRI could be performed within 6 weeks prior to the first dose. Subsequent scans could be done within 1 week prior to the clinic visit.

Participants Enrolled Prior to Protocol Amendment 5:

Same as above except that FL disease status was assessed at Weeks 8, 16, 24, and every 24 weeks thereafter until disease progression.

Assessment of Coronavirus Disease Impact:

Changes in study conduct (eg, any changes in study visit schedules, missed visits, or participant discontinuations that may have led to missing information) and duration of those changes due to restrictions related to the COVID-19 pandemic were included under the appropriate protocol amendment/administrative letter. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 pandemic control measures that were not included in a protocol amendment or administrative letter are described in the study's Coronavirus Outbreak Crisis Management Plan (Appendix 16.1.1).

This study was conducted as a United States (US) Food and Drug Administration postmarketing requirement to verify the clinical benefit of Zydelig monotherapy in patients with relapsed or refractory FL and small lymphocytic lymphoma (SLL). Due to challenges in recruiting participants, the sponsor made the decision to withdraw the indications for both FL and SLL in the US, and terminate the study.

Number of Participants (Planned and Analyzed):

Planned: 266 participants per Protocol Amendment 5

The sample size was originally planned to include 240 participants randomized in a 1:1 ratio to Arm A (IDL 150 mg twice daily) or Arm B (IDL 100 mg twice daily). As per Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 participants into Arm B. As per Protocol Amendment 5, 120 participants each were to be randomized into Arm A and Arm C.

Analyzed: 96 participants

- All Enrolled Analysis Set: 96 participants (Arm A: 47; Arm B: 27; Arm C: 22)
- Intent-to-Treat (ITT) Analysis Set: 96 participants (Arm A: 47; Arm B: 27; Arm C: 22)
- Safety Analysis Set: 95 participants (Arm A: 47; Arm B: 27; Arm C: 21)
- PK Analysis Set: 95 participants (Arm A: 47; Arm B: 27; Arm C: 21)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Participants met all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female ≥ 18 years of age
2) Histologically confirmed diagnosis of B-cell FL, and grade limited to 1, 2, or 3a based on criteria established by the World Health Organization 2008 classification of tumors of hematopoietic and lymphoid tissues
3) Relapsed or refractory FL and had received at least 2 lines of prior therapy for FL and had no other available therapeutic options. Note: rituximab maintenance was not routinely considered a separate line of therapy when it was given as part of the prior rituximab-containing regimen given over a number of cycles followed by maintenance. Rituximab monotherapy could be considered a separate line of therapy when disease relapse occurred between the initiation of rituximab monotherapy and the preceding line of therapy. If there were any ambiguities about eligibility, the site consulted with the medical monitor.
4) Ann Arbor Stage 2 (noncontiguous), 3, or 4 disease per Lugano Classification
5) Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy as determined by IRC, (defined as the presence of ≥ 1 lesion that measured ≥ 1.5 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by PET-CT, CT, or MRI)
6) Adequate performance status (such as Eastern Cooperative Oncology Group [ECOG] Performance Status of ≤ 2 or Karnofsky Performance Status of ≥ 60)
7) Required baseline laboratory data (within 4 weeks prior to start of study therapy) as mentioned in the protocol

8) For female participants of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse per protocol
9) For male participants of reproductive potential having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception during heterosexual intercourse per protocol
10) Lactating females had to agree to discontinue nursing
11) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for *Pneumocystis jirovecii* pneumonia
12) Evidence of a signed informed consent indicating that the participant is aware of the neoplastic nature of their disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

Exclusion Criteria:

Participants who met any of the following exclusion criteria were not to be enrolled in this study:

1) History of lymphoid malignancy other than FL (eg, diffuse large B-cell lymphoma). Note: biopsy documentation of the absence or presence of high-grade lymphoma was not required
2) Known history of, or clinically apparent, central nervous system (CNS) lymphoma or leptomeningeal lymphoma. Note: imaging documentation of the absence or presence of CNS disease was not required
3) Known presence of intermediate or high-grade myelodysplastic syndrome. Note: intermediate or high-grade myelodysplasia was defined as the presence of ≥ 5% bone marrow blasts; karyotypic abnormalities other than normal, Y deletion, 5q deletion, or 20q deletion; or ≥ 2 lineages of cytopenias due to myelodysplasia
4) Known history of serious allergic reaction including anaphylaxis or Stevens-Johnson syndrome/toxic epidermal necrolysis
5) History of a nonlymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to enrollment, or any other cancer or malignancy that had been in complete remission for ≥ 5 years
6) Evidence of ongoing systemic infection (eg, bacterial, fungal, viral) at the time of enrollment
7) Known history of drug-induced liver injury, chronic active hepatitis B virus, chronic active hepatitis C virus, alcoholic liver disease, nonalcoholic steatohepatitis, cirrhosis of the liver, portal hypertension, primary biliary cirrhosis, or ongoing extrahepatic obstruction caused by cholelithiasis

8) History of or ongoing drug-induced pneumonitis
9) History of or ongoing inflammatory bowel disease
10) Known HIV infection
11) Cytomegalovirus (CMV): ongoing infection, treatment, or specifically CMV antiviral prophylaxis within 28 days prior to the screening visit CMV test
12) Presence of any condition that could, in the opinion of the investigator, compromise the participant's ability to participate in the study, such as history of substance abuse, alcoholism, or a psychiatric condition
13) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation
14) Ongoing immunosuppressive therapy, including systemic corticosteroids (> 10 mg prednisone or equivalent/day) with the exception of the use of topical, enteric, or inhaled corticosteroids as therapy for comorbid conditions or systemic corticosteroids for autoimmune anemia and/or thrombocytopenia
15) Concurrent participation in another therapeutic clinical study
16) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the participant or impair the assessment of study results
17) Prior treatment with phosphatidylinositol 3-kinase inhibitors

Duration of Treatment: IDL was to be administered until a participant met the criteria for discontinuation of study drug, as described in the protocol, such as disease progression, unacceptable toxicity, substantial noncompliance with study procedures or study drug, initiation of another systemic anticancer or experimental therapy, or withdrawal from the study.

Test Product, Dose, Mode of Administration, and Batch No.: Arm A: IDL 150-mg tablets were to be taken twice daily orally starting on Day 1 and administered continuously.

Arm C: IDL 150-mg tablets were to be taken twice daily orally starting on Day 1 and administered continuously for 21 days, followed by 7 days of no study drug, within each 28-day cycle.

Dose reduction to 100 mg twice daily was available, if required for both the arms.

The original protocol for this study included an Arm B (IDL 100-mg tablets twice daily orally starting on Day 1 and administered continuously), which was closed to enrollment as of Protocol Amendment 5.

Investigational product specifications are provided in Synopsis Table 1.

Synopsis Table 1. GS-US-313-1580: Summary of Investigational Product (Test Drug)

	IDL Tablets	
Strength (mg)	100 mg	150 mg
Batch No.	CV1702B1	CV1308B2
	VCXV	CV1602B1
	YWTY	THSP
	CV1901B1	CV1603B2
	CV2001A1	CV1603B1
	CV1304D2	CV1603B3
	CV1601B1	ZPMF
	PCZC	—
	ZMPC	—
Expiration date	November 2019	September 2017
	October 2019	April 2019
	August 2022	July 2019
	August 2022	April 2020
	August 2022	April 2021
	May 2017	April 2021
	April 2019	January 2023
	April 2018	—
	January 2023	—
Manufacturer/Supplier	Patheon Inc. 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada	
Site of release in Europe	Fisher Clinical Services UK Ltd. Langhurstwood Road Horsham West Sussex RH12 4QD, UK Gilead Sciences Ireland UC IDA Business & Technology Park Carrigtohill, Co. Cork, Ireland	

IDL = idelalisib; UK = United Kingdom

Reference Therapy, Dose, Mode of Administration, and Batch No.:

Prior to Protocol Amendment 5, while the study was still blinded, IDL 100-mg or 150-mg tablets were combined with matching 150-mg or 100-mg placebo tablets, respectively, in each blister card to ensure the blind was maintained. As of Protocol Amendments 5 and 6, this was an open-label, randomized study and no reference therapy (placebo) was used. Reference therapy specifications are provided in Synopsis Table 2.

Synopsis Table 2. GS-US-313-1580: Summary of Reference Therapy (Placebo)

	Placebo-to-Match IDL Tablets	
Strength (mg)	100 mg Placebo	150 mg Placebo
Batch No.	CV1307B2	CV1306B2
	CV1501B2	CV1502B2
	CV1501B3	CV1502B3
	CV1802B2	CV1803B2
	—	CV1803B3
Expiration date	June 2018	June 2018
	February 2020	February 2020
	February 2020	February 2020
	September 2023	September 2023
	—	September 2023
Manufacturer/Supplier	Patheon Inc. 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada	
Site of release in Europe	Fisher Clinical Services UK Ltd. Langhurstwood Road Horsham West Sussex RH12 4QD, UK Gilead Sciences Ireland UC IDA Business & Technology Park Carrigtohill, Co. Cork Ireland	

IDL = idelalisib; UK = United Kingdom

Due to restrictions related to the COVID-19 pandemic, changes in study visit schedules may have occurred that necessitated alternative secure delivery methods of study drug as described in the Coronavirus Outbreak Crisis Management Plan (Appendix 16.1.1). In all cases, existing regulatory requirements for maintaining investigational product accountability remained and were addressed and documented.

Criteria for Evaluation:

Efficacy:

Efficacy parameters were summarized and listed by treatment arms based on the ITT Analysis Set. The analyses were conducted using the IRC assessments based on standardized criteria {Cheson 2007}.

Primary Endpoint:

- ORR, defined as the proportion of participants who achieve a PR or CR

Secondary Endpoints

- DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by IRC or death from any cause
- ORR by Week 24, defined as the proportion of participants who achieve a PR or CR by Week 24
- PFS, defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause
- OS, defined as the interval from randomization to death from any cause

Safety:

All adverse events (AEs) were listed. The focus of AE summarization was on treatment-emergent adverse events (TEAEs). Safety analyses were conducted using the Safety Analysis Set, unless otherwise specified.

Primary Endpoint:

- Incidence of Grade ≥ 4 TEAEs

Secondary Endpoints:

- Overall safety profile of IDL, including the incidence of AEs and clinically significant laboratory abnormalities, severity, timing, and relationship to IDL of any AEs; serious adverse events (SAEs); or AEs leading to interruption, reduction, or discontinuation of IDL; time to onset of AEs of interest (AEIs) defined as the interval from the start of IDL treatment to the first documentation of start of AEI.

Pharmacokinetics:

Secondary Endpoint:

- IDL trough (predose) and peak (1.5-hour samples) plasma concentrations assessed by validated bioanalytical method

Blood samples for PK assessment of IDL were collected from participants at predose and at 1.5 hours after IDL dose administration at baseline, Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48.

Statistical Methods:

The final study analysis was conducted when all enrolled participants had discontinued the study.

Analysis Data Set:

The All Enrolled Analysis Set included all participants who received a study participant identification number after screening and was used for participant enrollment summary and data listings, unless otherwise specified.

The ITT Analysis Set included all participants who were randomized regardless of whether they received any study drug and was used in the analysis of participant characteristics and efficacy.

The Safety Analysis Set included all participants who received at least 1 dose of study drug and was used in the analyses of safety variables as well as study treatment administration.

The PK Analysis Set included data from participants in the Safety Analysis Set who had received the study drug and had at least 1 sample with detectable drug concentration.

An IRC reviewed blinded radiographic data and pertinent clinical data in order to provide independent expert evaluation of tumor status. The findings of the IRC were considered primary for analyses of the primary efficacy endpoint and other tumor control endpoints.

Efficacy:

Primary Endpoint:

For the primary efficacy analysis, ORR was evaluated by treatment arm using the IRC assessments in the ITT Analysis Set. Participants who did not have sufficient baseline or on-study tumor assessment to characterize response were counted as nonresponders. Estimates and the corresponding 95% confidence intervals (CIs) based on the Clopper-Pearson exact method were provided.

Secondary Endpoints:

The ORR by Week 24 and corresponding 95% CIs were evaluated by treatment arm using the IRC assessments in the ITT Analysis Set.

The time-to-event efficacy endpoints including PFS, DOR, and OS were analyzed using the Kaplan-Meier method in the ITT Analysis Set, and the analyses of DOR included participants who achieved a PR or CR.

Pharmacokinetics:

The plasma concentrations of IDL and its primary metabolite at predose and at 1.5 hours postdose at each relevant clinic visit were summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, percentage coefficient of variation, standard deviation, median, minimum, and maximum).

Safety:

Safety was assessed via incidence of AEs, clinical laboratory tests, and concomitant medications. Information regarding study drug administration, study drug compliance, and other safety variables was summarized by treatment arm.

For the primary safety endpoint, the number and percentage of participants who experienced at least 1 ≥ Grade 4 TEAE were listed and summarized by treatment arm. The severity, timing, relationship to study drug, and drug interruptions for all TEAEs were summarized.

Due to disruption in study conduct as a result of the COVID-19 pandemic, some efficacy and/or safety assessments were not conducted and the handling of these protocol deviations is described in the Statistical Analysis Plan in Appendix 16.1.9. Additionally, to monitor and assess participant safety until the participant could return to the site for their regular follow-up per protocol, virtual study visits, and local laboratories were implemented, as required.

SUMMARY OF RESULTS:

The data presented in this final CSR reflect safety, efficacy, and PK data as of the data cutoff date of 27 September 2022 (study end date).

Participant Disposition and Demographics:

Of the 145 participants screened, 96 participants were randomized to the study (Section 15.1, Table 3). Of these, 95 participants received at least 1 dose of study drug (IDL) and were included in the Safety Analysis Set. All the 96 participants (100%) discontinued the study drug (only 95 participants had received at least 1 dose of study drug) and the study. The most common reasons for discontinuation of the study drug in Arm A and Arm B were AE (27 participants [57.4%]; 13 participants [48.1%], respectively) and PD (13 participants [27.7%]; 7 participants [25.9%], respectively). The most common reasons for discontinuation of study drug in Arm C were PD and study terminated by sponsor (7 participants [31.8%], each) followed by AE (3 participants [13.6%]). The most common reasons for discontinuation of study in Arm A and Arm B were investigator's discretion (17 participants [36.2%]; 11 participants [40.7%], respectively) and PD (11 participants [23.4%]; 7 participants [25.9%]), respectively. The most common reasons for discontinuation of study in Arm C were study terminated by sponsor (7 participants [31.8%]) and PD (6 participants [27.3%]).

Overall, the median (first quartile [Q1], third quartile [Q3]) age of participants was 65 (57, 73) years, with an age range of 32 to 89 years (Section 15.1, Table 4). Overall, approximately half of the participants were male (53.7%); 24 participants (51.1%) in Arm A, 14 participants (51.9%) in Arm B, and 13 participants (61.9%) in Arm C. Overall, the majority of the participants were White and identified as not Hispanic or Latino (89.5%, each). Overall, the median (Q1, Q3) baseline body mass index was 25.9 (23.7, 28.2) kg/m^2. At study entry, 50 participants (52.6%), had an ECOG performance score of 0 (22 participants [46.8%] in Arm A, 18 participants [66.7%] in Arm B, and 10 participants [47.6%] in Arm C) and 36 participants (37.9%) had an ECOG performance score of 1 (17 participants [36.2%] in Arm A, 9 participants [33.3%] in Arm B, and 10 participants [47.6%] in Arm C).

A summary of participants who discontinued study drug due to COVID-19 pandemic-related matters is provided in Section 15.1, Table 10.10. A by-participant listing of study drug discontinuations due to COVID-19 pandemic-related matters is provided in Appendix 16, Listing 9.7. None of these discontinuations affected the overall quality or interpretation of the study data.

A by-participant listing of missed and virtual study visits due to restrictions related to the COVID-19 pandemic is provided in Appendix 16, Listing 20.3. None of these missed or virtual study visits affected the overall quality or interpretation of the study data.

By-participant listings of important and nonimportant protocol deviations due to COVID-19 pandemic-related study disruptions are provided in Appendix 16, Listings 20.1 and 20.2, respectively. None of these pandemic-related protocol deviations affected the overall quality or interpretation of the study data.

Efficacy Results:

Primary Endpoint:

Overall Response Rate:

Based on the ITT Analysis Set, the ORR (95% CI) was 38.3% (24.5%, 53.6%) for Arm A, 44.4% (25.5%, 64.7%) for Arm B, and 40.9% (20.7%, 63.6%) for Arm C (Synopsis Table 3).

Synopsis Table 3. GS-US-313-1580: Overall Response Rate by IRC Assessment (ITT Analysis Set)

	IDL 150 mg BID Arm A (N = 47)	IDL 100 mg BID Arm B (N = 27)	IDL 150 mg BID INT Arm C (N = 22)
Best Overall Response			
CR	2 (4.3%)	1 (3.7%)	1 (4.5%)
PR	16 (34.0%)	11 (40.7%)	8 (36.4%)
SD	15 (31.9%)	12 (44.4%)	6 (27.3%)
PD	4 (8.5%)	1 (3.7%)	3 (13.6%)
NE	0	0	0
Discontinued before reaching the first assessment (NA1)	0	0	0
No baseline assessment (NA2)	10 (21.3%)	2 (7.4%)	4 (18.2%)
ORR (95% CI)[a]	38.3% (24.5%, 53.6%)	44.4% (25.5%, 64.7%)	40.9% (20.7%, 63.6%)
Responders (CR+PR)	18	12	9
Nonresponders (SD+PD+NE+NA1+NA2)	29	15	13
ORR (95% CI) at Week 24[a]	36.2% (22.7%, 51.5%)	33.3% (16.5%, 54.0%)	27.3% (10.7%, 50.2%)
Responders (CR+PR)	17	9	6
Nonresponders (SD+PD+NE+NA1+NA2)	30	18	16

BID = twice daily; CI = confidence interval; CR = complete response; IDL = idelalisib; IRC = independent review committee; ITT = intent to treat; NE = not estimable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
ORR is defined as the proportion of participants who achieve a CR or PR.
a 95% CI for ORR is based on Clopper-Pearson exact method.
Source: Section 15.1, Table 6

Secondary Endpoints:

Duration of Response:

Duration of response is summarized in Synopsis Table 4 and Section 15.1, Figure 3. The median (95% CI) DOR was 27.1 (7.7, not estimable) months in Arm A (N = 18), 18.0 (2.7, not estimable) months in Arm B (N = 12), and 5.7 (0.3, not estimable) months in Arm C (N = 9).

Time to Response

Time to response is summarized in Synopsis Table 4. The median (Q1, Q3) time to response was 2.3 (1.8, 3.7) months, with a range of 1.6 to 9.9 months in the Arm A (N = 18); 1.9 (1.7, 9.2) months, with a range of 1.6 to 38.8 months for Arm B (N = 12); and 3.8 (2.8, 6.1) months, with a range of 2.5 to 13.8 months for Arm C (N = 9).

Synopsis Table 4. GS-US-313-1580: Duration of Response - IRC Assessment (ITT Analysis Set)–Participants With Complete Response or Partial Response Achieved

	IDL 150 mg BID Arm A (N = 18)	IDL 100 mg BID Arm B (N = 12)	IDL 150 mg BID INT Arm C (N = 9)
Number (%) of participants with events	6 (33.3%)	6 (50.0%)	5 (55.6%)
Disease progression	4 (22.2%)	3 (25.0%)	3 (33.3%)
Death	2 (11.1%)	3 (25.0%)	2 (22.2%)
Number (%) of participants censored	12 (66.7%)	6 (50.0%)	4 (44.4%)
Discontinued study	8 (44.4%)	3 (25.0%)	4 (44.4%)
Missed ≥ 2 consecutive tumor assessments	3 (16.7%)	1 (8.3%)	0
Received new anticancer treatment	1 (5.6%)	2 (16.7%)	0
Kaplan-Meier estimate of DOR (months) (95% CI)[a]			
Q1	7.9 (1.2, 27.1)	14.1 (2.7, 18.0)	1.7 (0.3, 5.8)
Median	27.1 (7.7, NE)	18.0 (2.7, NE)	5.7 (0.3, NE)
Q3	NE (14.2, NE)	40.9 (14.7, NE)	NE (2.8, NE)
Time to response (months)[b]			
N	18	12	9
Mean (StD)	3.3 (2.41)	7.3 (11.43)	5.5 (3.78)
Median	2.3	1.9	3.8
Q1, Q3	1.8, 3.7	1.7, 9.2	2.8, 6.1
Min, Max	1.6, 9.9	1.6, 38.8	2.5, 13.8

BID = twice daily; CI = confidence interval; CR = complete response; DOR = duration of response; IDL = idelalisib; IRC = independent review committee; ITT = intent to treat; NE = not estimable; PR = partial response; Q1 = first quartile; Q3 = third quartile; StD = standard deviation
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
a DOR (months) = (date of first event or censoring - date of first documented {CR or PR} + 1)/30.4375
b Time to response (months) = (date of first documented {CR or PR} - date of randomization + 1)/30.4375
Source: Section 15.1, Table 8

Overall Response Rate at Week 24

Based on the ITT Analysis Set, the ORR at Week 24 (95% CI) was 36.2% (22.7%, 51.5%) for Arm A, 33.3% (16.5%, 54.0%) for Arm B, and 27.3% (10.7%, 50.2%) for Arm C (Synopsis Table 3).

Progression-Free Survival

Analysis of PFS as assessed by the IRC based on the ITT Analysis Set is summarized in Synopsis Table 5 and Section 15.1, Figure 1.

A total of 19 participants (40.4%) in Arm A, 14 participants (51.9%) in Arm B, and 14 participants (63.6%) in Arm C experienced a PFS event.

The median (95% CI) PFS was 9.8 (5.5, 28.7) months for participants in the Arm A, 19.4 (13.9, 23.3) months for participants in Arm B, and 8.3 (2.9, 8.7) months for Arm C.

Synopsis Table 5. GS-US-313-1580: Progression-Free Survival - IRC Assessment (ITT Analysis Set)

	IDL 150 mg BID Arm A (N = 47)	IDL 100 mg BID Arm B (N = 27)	IDL 150 mg BID INT Arm C (N = 22)
Number (%) of participants with events	19 (40.4%)	14 (51.9%)	14 (63.6%)
Disease progression	12 (25.5%)	7 (25.9%)	10 (45.5%)
Death	7 (14.9%)	7 (25.9%)	4 (18.2%)
Number (%) of participants censored	28 (59.6%)	13 (48.1%)	8 (36.4%)
Discontinued study	15 (31.9%)	5 (18.5%)	5 (22.7%)
Missed ≥ 2 consecutive tumor assessments	3 (6.4%)	4 (14.8%)	0
Received new anticancer treatment	5 (10.6%)	3 (11.1%)	1 (4.5%)
Alive with no on-study tumor assessments	5 (10.6%)	1 (3.7%)	2 (9.1%)
Kaplan-Meier estimate of PFS (months) (95% CI)			
Q1	5.3 (2.7, 8.3)	13.9 (2.0, 19.4)	3.1 (1.2, 8.1)
Median	9.8 (5.5, 28.7)	19.4 (13.9, 23.3)	8.3 (2.9, 8.7)
Q3	28.7 (11.1, NE)	23.3 (19.4, NE)	9.5 (8.3, NE)
Kaplan-Meier estimate of PFS rate (95% CI)			
At Week 24	67.8% (49.1%, 80.9%)	87.4% (65.7%, 95.8%)	70.0% (45.1%, 85.3%)

BID = twice daily; CI = confidence interval; IDL = idelalisib; IRC = independent review committee; ITT = intent to treat; NE = not estimable; PFS = progression-free survival; Q1 = first quartile; Q3 = third quartile
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
PFS (months) = (date of event or censoring - date of randomization + 1)/30.4375, and the 95% CI is derived using log-log transformation.
Source: Section 15.1, Table 7

Overall Survival

The OS analysis was performed using the ITT Analysis Set, which included all available survival information during the study (Synopsis Table 6 and Section 15.1, Figure 2). Twenty participants (42.6%) in Arm A, 12 participants (44.4%) in Arm B, and 6 participants (27.3%) in Arm C died during the study. The median (95% CI) OS was 28.7 (14.0, not estimable) months in Arm A, not estimable (23.3, not estimable) months in Arm B, and not estimable (13.9, not estimable) months in Arm C.

Synopsis Table 6. GS-US-313-1580: Overall Survival -(ITT Analysis Set)

	IDL 150 mg BID Arm A (N = 47)	IDL 100 mg BID Arm B (N = 27)	IDL 150 mg BID INT Arm C (N = 22)
Number (%) of participants with events (death)	20 (42.6%)	12 (44.4%)	6 (27.3%)
Number (%) of participants censored (discontinued study)	27 (57.4%)	15 (55.6%)	16 (72.7%)
Kaplan-Meier estimate of OS (months) (95% CI)			
Q1	11.4 (4.4, 20.8)	20.1 (7.1, 39.1)	13.9 (1.2, NE)
Median	28.7 (14.0, NE)	NE (23.3, NE)	NE (13.9, NE)
Q3	NE (44.0, NE)	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimate of OS rate (95% CI)			
At Week 24	88.7% (74.9%, 95.1%)	100.0% (100.0%, 100.0%)	85.2% (60.8%, 95.0%)

BID = twice daily; CI = confidence interval; IDL = idelalisib; ITT = intent to treat; NE = not estimable; OS = overall survival; Q1 = first quartile; Q3 = third quartile
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
OS (months) = (date of death or censoring - date of randomization + 1)/30.4375, and the 95% CI is derived using log-log transformation.
Source: Section 15.1, Table 9

Pharmacokinetics Results:

A statistical summary of IDL and its metabolite in the 3 treatment arms is provided in Section 15.1, Table 12.1. In general, the plasma concentrations of IDL and its metabolite appeared to be at steady state by Week 4 in the 100 mg twice daily (Arm B) and 150 mg twice daily (Arm A) dosing groups. The mean IDL concentrations at predose and 1.5 hours postdose following 150 mg twice daily administration (Arm A) were higher than that in the 100 mg twice daily (Arm B) dosing group. The plasma concentrations in the 150 mg twice daily (Arm A) dosing group with 21 days on-and 7 days off-treatment schedule (Arm C) were consistent with the plasma concentrations in 150 mg twice daily (Arm A) dosing group during the continuous dosing window but reduced during the drug holiday.

Safety Results:

Extent of Exposure:

Exposure to IDL ranged from 0.4 to 33.5 months (median of 4.7 months) in Arm A, 0.7 to 63.6 months (median of 7.9 months) in Arm B, and 0.4 to 24.6 months (median of 8.4 months) in Arm C (Section 15.1, Table 5). A total of 41 participants (87.2%) in Arm A, 20 participants (74.1%) in Arm B, and 14 participants (66.7%) in Arm C had at least 1 dose modification or interruption.

Adverse Events:

All AEs and laboratory abnormalities presented in this report were treatment-emergent and are referred to as AEs and laboratory abnormalities throughout this report. Additionally, the relationship of AEs to study drug are investigator assessed.

In total, 90 participants (94.7%) (45 participants [95.7%] in Arm A; 26 participants [96.3%] in Arm B; and 19 participants [90.5%] in Arm C) experienced at least 1 AE during the study (Synopsis Table 7). Overall, 78 participants (82.1%) had at least 1 Grade ≥ 3 AE, 74 participants (77.9%) experienced AEs considered as related to IDL, and 30 participants (31.6%) had 1 or more SAE considered as related to IDL. Overall, 45 participants (47.4%) experienced AEs leading to IDL discontinuation, 56 participants (58.9%) experienced AEs leading to temporary interruption of IDL, and 5 participants (5.3%) experienced AEs leading to study discontinuation. Eight participants (8.4%) experienced AEs leading to death. Overall, the most frequently reported AEs (by preferred term [PT]) were diarrhea (41 participants [43.2%]), neutropenia (26 participants [27.4%]), rash (22 participants [23.2%]), and pyrexia (21 [21.1%] participants) (Section 15.1, Table 10.2.2).

Synopsis Table 7. GS-US-313-1580: Treatment-Emergent Adverse Events: Overall Summary (Safety Analysis Set)

Number (%) of Participants With Any	IDL 150 mg BID Arm A (N = 47)	IDL 100 mg BID Arm B (N = 27)	IDL 150 mg BID INT Arm C (N = 21)	Total (N = 95)
TEAE	45 (95.7%)	26 (96.3%)	19 (90.5%)	90 (94.7%)
TEAE with Grade 4 or higher	15 (31.9%)	12 (44.4%)	8 (38.1%)	35 (36.8%)
TEAE with Grade 3 or higher	41 (87.2%)	25 (92.6%)	12 (57.1%)	78 (82.1%)
TEAE related to IDL	38 (80.9%)	25 (92.6%)	11 (52.4%)	74 (77.9%)
TE serious AE	31 (66.0%)	19 (70.4%)	11 (52.4%)	61 (64.2%)
TE serious AE related to IDL	16 (34.0%)	11 (40.7%)	3 (14.3%)	30 (31.6%)
TEAE leading to discontinuation of IDL	28 (59.6%)	13 (48.1%)	4 (19.0%)	45 (47.4%)
TEAE leading to temporary interruption of IDL	32 (68.1%)	18 (66.7%)	6 (28.6%)	56 (58.9%)
TEAE leading to study discontinuation	2 (4.3%)	3 (11.1%)	0	5 (5.3%)
TEAE leading to death	2 (4.3%)	2 (7.4%)	4 (19.0%)	8 (8.4%)

AE = adverse event; BID = twice daily; IDL = idelalisib; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
Adverse events were coded according to MedDRA Version 25.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by The Common Terminology Criteria for Adverse Events Version 5.0.
Source: Section 15.1, Table 10.1

Overall, 35 participants (36.8%) had at least 1 Grade ≥ 4 AE: 15 participants (31.9%) in Arm A, 12 participants (44.4%) in Arm B, and 8 participants (38.1%) in Arm C. The most common Grade ≥ 4 AEs (by PT) were neutropenia (14 participants [14.7%]), alanine aminotransferase (ALT) increased (4 participants [4.2%]), and thrombocytopenia (3 participants [3.2%]); (Synopsis Table 8).

Synopsis Table 8. GS-US-313-1580: Grade 4 or Higher Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	IDL 150 mg BID Arm A (N = 47)	IDL 100 mg BID Arm B (N = 27)	IDL 150 mg BID INT Arm C (N = 21)	Total (N = 95)
Number (%) of participants with any Grade 4 or higher treatment-emergent adverse event	15 (31.9%)	12 (44.4%)	8 (38.1%)	35 (36.8%)
Neutropenia	6 (12.8%)	5 (18.5%)	3 (14.3%)	14 (14.7%)
Thrombocytopenia	3 (6.4%)	0	0	3 (3.2%)
Alanine aminotransferase increased	2 (4.3%)	2 (7.4%)	0	4 (4.2%)
Aspartate aminotransferase increased	1 (2.1%)	1 (3.7%)	0	2 (2.1%)
COVID-19	1 (2.1%)	0	1 (4.8%)	2 (2.1%)
Coronavirus pneumonia	1 (2.1%)	0	0	1 (1.1%)
Drug-induced liver injury	1 (2.1%)	0	0	1 (1.1%)
Hepatotoxicity	1 (2.1%)	0	0	1 (1.1%)
Hypercalcaemia of malignancy	1 (2.1%)	0	0	1 (1.1%)
Squamous cell carcinoma	1 (2.1%)	0	0	1 (1.1%)
Stevens-Johnson syndrome	1 (2.1%)	0	0	1 (1.1%)
Abdominal infection	0	0	1 (4.8%)	1 (1.1%)
Acute kidney injury	0	1 (3.7%)	0	1 (1.1%)
Acute myeloid leukaemia	0	1 (3.7%)	0	1 (1.1%)
Anaemia	0	0	1 (4.8%)	1 (1.1%)
COVID-19 pneumonia	0	0	1 (4.8%)	1 (1.1%)
Diarrhoea	0	1 (3.7%)	0	1 (1.1%)
Febrile neutropenia	0	1 (3.7%)	0	1 (1.1%)
Hyperglycaemia	0	1 (3.7%)	0	1 (1.1%)
Neutropenic sepsis	0	0	1 (4.8%)	1 (1.1%)
Pleural effusion	0	0	1 (4.8%)	1 (1.1%)
Sepsis	0	1 (3.7%)	0	1 (1.1%)

AE = adverse event; BID = twice daily; COVID 19 = coronavirus disease 2019; IDL = idelalisib; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
Arm A = IDL 150 mg BID; Arm B = IDL 100 mg BID; Arm C = IDL 150 mg BID INT (21 days on-treatment, 7 days off-treatment). Arm B closed to enrollment as of Protocol Amendment 5.
Adverse events were coded according to MedDRA Version 25.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation. Multiple AEs were counted only once per participant for the highest severity grade for each PT. Preferred terms were presented by the descending order of incidence in Arm A.
Source: Section 15.1, Table 10.4

Serious Adverse Events and Deaths

Overall, 61 participants (64.2%) experienced at least 1 SAE during the study: Arm A, 31 participants (66.0%); Arm B, 19 participants (70.4%); and Arm C, 11 participants (52.4%) (Section 15.1, Table 10.8). Serious AEs considered related to IDL were experienced by 16 participants (34.0%), 11 participants (40.7%), and 3 participants (14.3%), in Arm A, B, and C, respectively (Section 15.1, Table 10.9). Overall, the most common SAEs were diarrhea (13 participants [13.7%]); and COVID-19, pneumonia, and acute kidney injury (4 participants [4.2%], each) (Section 15.1, Table 10.8). Overall, the most common SAEs considered related to IDL were diarrhea (12 participants [12.6%]), colitis (3 participants [3.2%]), and pneumonia (3 participants [3.2%]) (Section 15.1, Table 10.9).

Overall, 8 participants (8.4%) experienced 1 or more AEs leading to death (Section 15.1, Table 10.7), and there were 38 (40.0%) deaths in total (Arm A 20 participants [42.6%]; Arm B 12 participants [44.4%]; and Arm C 6 participants [28.6%]) (Section 15.1, Table 10.13).

Adverse Events of Interest

Analysis of AEIs and time to onset of AEIs was not performed.

Laboratory Abnormalities

The following postbaseline Grade 4 hematology laboratory abnormalities were reported: neutrophils decreased (5 participants [10.6%]); platelet count decreased (3 participants [6.4%]) and neutrophils, segmented decreased (2 participants [4.3%]) in Arm A; neutrophils decreased (3 participants [11.1%]), and neutrophils, segmented decreased (2 participants [7.4%]) in Arm B; and neutrophils decreased and neutrophils, segmented decreased (2 participants [10.0%]; each) in Arm C (Section 15.1, Table 11.1).

The following postbaseline Grade 4 chemistry laboratory abnormalities were reported: alanine aminotransferase (ALT) increased (3 participants [6.4%]), aspartate aminotransferase (AST) increased and hyperuricemia (2 participants [4.3%], each); hypercalcemia, hyperglycemia, and hypokalemia (1 participant [2.1%]; each); and nonfasting hyperglycemia (1 participant [3.0%]) in Arm A; ALT increased (2 participants [7.4%]), hyperglycemia (1 participant [3.7%]), and non-fasting hyperglycemia (1 participant [4.5%]) in Arm B; and hyperuricemia (1 participant [5.3%]) in Arm C (Section 15.1, Table 11.2).

COVID-19 and SARS-CoV-2 infection-related AEs are summarized in Section 15.1, Table 10.2.1. A by-participant listing of participants with confirmed and suspected SARS-CoV-2 infection is provided in Appendix 16, Listing 20.4.

CONCLUSIONS: The study was terminated early (after enrollment of 96 participants); therefore, the primary objective of the study to establish a safe and effective dosing regimen of IDL in participants with relapsed or refractory FL who have no other therapeutic options could not be determined. The overall conclusions from this study are as follows:

- The primary endpoint, ORR (95% CI) was 38.3% (24.5%, 53.6%) for Arm A, 44.4% (25.5%, 64.7%) for Arm B, and 40.9% (20.7%, 63.6%) for Arm C.
- Fifteen participants (31.9%) in Arm A, 12 participants (44.4%) in Arm B, and 8 participants (38.1%) in Arm C had Grade ≥ 4 AE.
- Overall, the most frequently reported AEs (by PT) were diarrhea, neutropenia, rash, and pyrexia; all known adverse drug reactions of IDL. The safety findings were consistent with the established safety profile of IDL.