Sponsor

Novartis

Generic Drug Name

BEZ235

Therapeutic Area of Trial

Advanced solid tumors (including advanced breast cancer)

Approved Indication

Investigational

Protocol Number

CBEZ235A2101

Title

A Phase I/Ib, multi-center, open-label study of BEZ235, administered orally on a continuous, daily-dosing schedule in adult patients with advanced solid malignancies, including patients with advanced breast cancer

Study Phase

Phase I/Ib

Study Start/End Dates

Study initiation date: 21-Dec-2006 (First patient first visit)

Study End date: 08-Jan-2013 (Last patient last visit)

Study Design/Methodology

This was a multi-center, open-label study of BEZ235 administered orally on a continuous daily dosing schedule (single agent and in combination with trastuzumab). The study included a dose escalation part (single agent and in combination with trastuzumab) and a dose expansion part (single agent and in combination with trastuzumab). During dose escalation, patients with advanced solid malignancies were enrolled into cohorts to establish the MTD of BEZ235. The dose escalation part was followed by a dose expansion part at the maximum tolerated dose (MTD) level for both the single agent and in combination with trastuzumab.

Centers

One center in Germany, one center in The Netherlands, one center in the UK, four centers in Spain, ten centers in the USA

Publication

None

Test Products, Doses, and Modes of Administration

BEZ235 was administered orally in the following dose forms:

- BEZ235 HGC: 5 mg, 25 mg or 100 mg hard gelatin capsules: starting dose of 10 mg/day
- BEZ235 SDS capsule A: 200 mg SDS 000 size capsules: starting dose of 400 mg/day
- BEZ235 SDS capsule B: 100 mg SDS 0 size capsules: starting dose of 800 mg/day
- BEZ235 SDS sachet: 200 mg and 400 mg SDS sachets: starting dose of 800 mg/day
- For the combination part, commercially available trastuzumab (Herceptin®) was used: starting dose was BEZ235 SDS 400 mg/day and 2 mg/kg weekly trastuzumab.

Statistical Methods

The data was summarized with regard to demography, baseline characteristics, efficacy, safety, biomarkers, and PK measurements, by dose level for each of the following subset of patients:

- BEZ235 HGC fasted
- BEZ235 HGC fed
- BEZ235 SDS capsule A
- BEZ235 SDS sachet
- BEZ235 SDS capsule B
- BEZ235 SDS in combination with trastuzumab

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, body mass index, body surface area, WHO performance status, tumor type, medical conditions, HER2/ER/PgR/EGFR status, Cowden Syndrome (CS), diagnosis and extent of cancer, etc., were listed individually by dose cohort and by patient, and were summarized using descriptive statistics i.e. n, mean, standard deviation, median, minimum and maximum for continuous variables and frequency counts for categorical variables. The dose limited toxicity (DLT) data (i.e. the presence or absence of DLT during Cycle 1) from all patients enrolled in the dose escalation part for estimation of MTDs and eligible for the dose-determining set were modeled via an adaptive Bayesian logistic regression model (BLRM). The dose escalation was guided by the escalation with overdose control (EWOC) principle. The disease control rate (DCR) and objective response rate (ORR) were presented by dose

cohort with exact 90% confidence intervals and summarized with counts and percentages. The single agent study arms + safety expansion arms were pooled. Kaplan-Meier estimates of the median progression free survival (PFS) and quartiles together with their 95% confidence intervals were presented. Estimates of the PFS at 3 and 6 months together with their 95% confidence intervals were also derived. All Response Evaluation Criteria in Solid Tumors (RECIST)-based analyses (DCR, ORR and PFS) were performed using the Investigator (local radiology) reported overall lesion responses.

All adverse events (AEs) recorded during the study were listed and summarized. The incidence of treatment-emergent adverse events (TEAEs) (new or worsening from baseline) was summarized by system organ class, severity (CTCAE, version 3.0), type of adverse event, and relation to the study drug by dose level. Deaths reportable as SAEs and non-fatal serious adverse events are listed by patient and tabulated by type of adverse event and dose level.

An analysis of variance (ANOVA) was performed on log-transformed AUCs and Cmax (Cycle 1 Day 1, 8 and 28) using a linear mixed-effect model to assess day effect, food intake status effect and dose proportionality. Inter- and intra-individual variability in systemic exposures was assessed. Descriptive graphical plots of individual plasma concentration as well as mean plasma concentration along with the corresponding time course were generated for safety and all relevant data.

All biomarker sample results obtained were listed by dose cohort or by study arm as appropriate. For selected biomarkers with results obtained at baseline and post-baseline, individual values as well as change from baseline or fold increase from baseline and pre-dose evaluations were summarized by means of descriptive statistics and graphs at each post baseline assessment.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Single agent dose escalation arm: Patients with histologically-confirmed advanced unresectable solid tumors, including CS patients who had progressed on (or not been able to tolerate) standard therapy within three months before screening visit or for whom no standard anticancer therapy existed.

Combination part:

- Patients with metastatic HER2+ breast cancer after failure of trastuzumab treatment. Eligible patients were to have tumors carrying molecular alterations of PIK3CA and/or phosphatase and tensin homolog (PTEN).

Single agent safety expansion arm: Patients with histologically-confirmed advanced unresectable solid tumors, including CS patients who had progressed on (or not been able to tolerate) standard therapy within three months before screening visit or for whom no standard anticancer therapy existed. Patients were to be pre-screened for molecular alterations affecting PIK3CA and/or PTEN. Patients with NSCLC were also to be pre-screened for EGFR mutation.

Exclusion Criteria:

- Patients who had brain metastases, which were progressive and/or requiring medical intervention for symptom control.
- Prior treatment with a PI3K inhibitor.
- Acute or chronic liver disease or renal disease.
- Acute or chronic pancreatitis.
- Patients with unresolved diarrhea ≥ CTCAE grade 2.
- Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
- Patients with diabetes mellitus requiring insulin treatment.
- Patients with known coagulopathies
- Patients with a history of photosensitivity reactions to other drugs.
- Any of the following ophthalmological findings:
    - Progressive eye disease that could lead to severe loss of visual acuity or visual field loss during the study period.
    - Inability to perform the ophthalmic procedures required in this protocol.
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
- Other protocol-defined inclusion/exclusion criteria applied.

Participant Flow

BEZ235 HGC group

Patient disposition by dose cohort, HGC Fast – FAS

Disposition reason	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
Patients treated								
Treatment discontinued	3 (100.0)	6 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	11 (100.0)	41 (100.0)
Primary reason for end of treatment								
Adverse Event(s)	0	0	0	0	0	0	3 (27.3)	3 (7.3)
Disease progression	3 (100.0)	6 (100.0)	3 (75.0)	5 (83.3)	5 (100.0)	6 (100.0)	8 (72.7)	36 (87.8)
Subject withdrew consent	0	0	1 (25.0)	1 (16.7)	0	0	0	2 (4.9)

Disposition reason	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
Percentage is based on N - Reason for treatment discontinuation is from CRF completion page								

Patient disposition by dose cohort, HGC Fed – FAS

Disposition reason	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
Patients treated					
Treatment discontinued	6 (100)	3 (100.0)	5 (100.0)	4 (100.0)	18 (100.0)
Primary reason for end of treatment					
Administrative problems	0	0	1 (20.0)	0	1 (5.6)
Adverse Event(s)	0	0	1 (20.0)	1 (25.0)	2 (11.1)
Disease progression	6 (100.0)	3 (100.0)	3 (60.0)	3 (75.0)	15 (83.3)
Percentage is based on N - Reason for treatment discontinuation is from CRF completion page					

BEZ235 SDS single agent group

Patient disposition by dose cohort SDS Caps A – FAS

	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Patients treated				
Treatment discontinued	5 (100)	6 (100)	11 (100.0)	22 (100.0)
Primary reason for end of Treatment				
Adverse Event(s)	0	0	1 (9.1)	1 (4.5)
Disease progression	4 (80.0)	6 (100.0)	10 (90.9)	20 (90.9)
Subject withdrew consent	1 (20.0)	0	0	1 (4.5)

Patient disposition by dose cohort SDS Sachet – FAS

	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Patients treated						
Treatment discontinued	6 (100.0)	10 (100.0)	24 (100.0)	14 (100.0)	7 (100)	61 (100)
Primary reason for end of treatment						
Adverse Event(s)	0	3 (30.0)	2 (8.3)	6 (42.9)	3 (42.9)	14 (23.0)
Disease progression	5 (83.3)	6 (60.0)	22 (91.7)	7 (50.0)	4 (57.1)	44 (72.1)
Subject withdrew consent	1 (16.7)	1 (10.0)	0	1 (7.1)	0	3 (4.9)

Patient disposition by dose cohort SDS Caps B – FAS

	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Patients treated		
Treatment discontinued	11(100.0)	11(100.0)
Primary reason for end of treatment		
Adverse Event(s)	4 (36.4)	4 (36.4)
Disease progression	7 (63.6)	7 (63.6)

BEZ235 SDS in combination with trastuzumab group

Patient disposition by dose cohort SDS + Trastuzumab

	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=10 n (%)	All SDS + T N=30 n (%)
Patients treated				
Treatment discontinued	3 (100.0)	17 (100.0)	10 (100.0)	30 (100.0)
Primary reason for end of treatment				
Adverse Event(s)	0	4 (23.5)	1 (10.0)	5 (16.7)
Disease progression	3 (100.0)	12 (70.6)	7 (70.0)	22 (73.3)
Subject withdrew consent	0	1 (5.9)	2 (20.0)	3 (10.0)

Baseline Characteristics

BEZ235 HGC group

Demographics at baseline by dose cohort, HCG Fast- FAS

	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
Age (Years)								
N	3	6	4	6	5	6	11	41
Mean	46.3	54.3	57.8	60.5	54.4	55.8	53.1	54.9
SD	10.07	13.11	10.50	8.41	8.96	5.81	10.53	9.79
Median	45.0	53.0	54.5	59.5	52.0	57.0	51.0	54.0
Min	37.0	40.0	49.0	50.0	48.0	49.0	41.0	37.0
Max	57.0	71.0	73.0	73.0	70.0	62.0	75.0	75.0
Age category (Years)								
<65	3 (100.0)	4 (66.7)	3 (75.0)	4 (66.7)	4 (80.0)	6 (100.0)	10 (90.9)	34 (82.9)
≥65	0	2 (33.3)	1 (25.0)	2 (33.3)	1 (20.0)	0	1 (9.1)	7 (17.1)
Sex								
Female	3 (100.0)	3 (50.0)	2 (50.0)	4 (66.7)	3 (60.0)	5 (83.3)	8 (72.7)	28 (68.3)
Male	0	3 (50.0)	2 (50.0)	2(33.3)	2 (40.0)	1 (16.7)	3 (27.3)	13 (31.7)
Race								
Black	0	1 (16.7)	0	0	0	0	0	1 (2.4)
Caucasian	3 (100.0)	5 (83.3)	4 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	11 (100.0)	40 (97.6)
Ethnicity								
Hispanic/Latino	0	0	1 (25.0)	0	0	0	6 (54.5)	7 (17.1)

	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
Other	3 (100.0)	6 (100.0)	3 (75.0)	6 (100.0)	5 (100.0)	6 (100.0)	5 (45.5)	34 (82.9)
Weight (kg)								
N	3	6	4	6	5	6	11	41
Mean	59.1	73.8	66.5	69.7	64.3	73.6	67.5	68.5
SD	12.96	15.88	11.40	21.92	13.94	23.46	14.31	16.34
Median	58.6	71.6	65.1	71.6	59.1	70.9	62.5	63.2
Min	46.4	56.9	55.0	39.0	50.0	47.0	50.0	39.0
Max	72.3	99.8	80.8	100.0	83.6	105.0	101.0	105.0
Height (cm)								
N	3	6	4	6	5	4	11	39
Mean	165.7	168.5	167.0	165.0	162.4	157.5	167.9	165.5
SD	5.86	11.91	9.90	15.94	5.59	19.33	11.64	11.89
Median	168.0	174.5	168.0	165.5	165.0	159.5	166.0	166.0
Min	159.0	150.0	154.0	139.0	155.0	132.0	155.0	132.0
Max	170.0	178.0	178.0	185.0	168.0	179.0	190.0	190.0
WHO performance status								
0	2 (66.7)	4 (66.7)	1 (25.0)	4 (66.7)	1 (20.0)	3 (50.0)	7 (63.6)	22 (53.7)
1	1 (33.3)	2 (33.3)	3 (75.0)	2 (33.3)	4 (80.0)	3 (50.0)	4 (36.4)	19 (46.3)
Presence of a Cowden syndrome								
No	3 (100.0)	6 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	6 (100.0)	11 (100.0)	41 (100.0)

Demographics at baseline by dose cohort, HCG Fed – FAS

	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
Age (Years)					
N	6	3	5	4	18
Mean	62.5	56.0	48.2	62.8	57.5
SD	14.79	24.02	12.36	10.69	15.15
Median	64.0	64.0	53.0	65.5	61.5
Min	43.0	29.0	31.0	48.0	29.0
Max	81.0	75.0	61.0	72.0	81.0
Age category (Years)					
<65	4 (66.7)	2 (66.7)	5 (100.0)	2 (50.0)	13 (72.2)
≥65	2 (33.3)	1 (33.3)	0	2 (50.0)	5 (27.8)
Sex					
Female	5 (83.3)	2 (66.7)	2 (40.0)	2 (50.0)	11 (61.1)
Male	1 (16.7)	1 (33.3)	3 (60.0)	2 (50.0)	7 (38.9)
Race					
Black	0	0	0	1 (25.0)	1 (5.6)
Caucasian	6 (100.0)	3 (100.0)	5 (100.0)	3 (75.0)	17 (94.4)
Ethnicity					
Hispanic/Latino	1 (16.7%)	2 (66.7)	2 (40.0)	2 (50.0)	7 (38.9)
Mixed Ethnicity	0	0	1(20.0)	0	1 (5.6)
Other	5 (83.3)	1 (33.3)	2 (40.0)	2 (50.0)	10 (55.6)
Weight (kg)					
N	6	3	5	4	18
Mean	70.8	63.5	82.6	75.7	73.9
SD	9.55	11.79	21.86	12.84	15.18
Median	69.6	58.0	79.3	72.0	70.1
Min	60.5	55.4	57.0	65.0	55.4
Max	85.0	77.0	106.8	93.6	106.8
Height (cm)					
N	5	3	5	4	17
Mean	166.2	161.3	172.4	171.5	168.4
SD	5.81	13.05	10.50	10.75	9.86
Median	167.0	160.0	176.0	170.0	170.0
Min	157.0	149.0	158.0	160.0	149.0
Max	172.0	175.0	182.0	186.0	186.0
WHO performance status					
0	3 (50.0)	0	2 (40.0)	2 (50.0)	7 (38.9)
1	3 (50.0)	3 (100.0)	3 (60.0)	2 (50.0)	11 (61.1)

	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
Presence of a Cowden syndrome					
No	6 (100.0)	3 (100.0)	4 (80.0)	4 (100.0)	17 (94.4)
Yes (genetically confirmed)	0	0	1 (20.0)	0	1 (5.6)

BEZ235 SDS single agent group

Demographics summary, by dose cohort SDS Caps A-FAS

Demographic Variable	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Age (Years)				
N	5	6	11	22
Mean	54.6	54.3	54.7	54.6
SD	5.77	10.54	13.31	10.83
Median	54.0	57.0	56.0	56.0
Min	47.0	34.0	32.0	32.0
Max	63.0	63.0	72.0	72.0
Age category (Years)				
<65	5 (100.0)	6 (100.0)	7 (63.6)	18 (81.8)
≥65	0	0	4 (36.4)	4 (18.2)
Sex				
Male	3 (60.0)	1 (16.7)	5 (45.5)	9 (40.9)
Female	2 (40.0)	5 (83.3)	6 (54.5)	13 (59.1)
Race				
Caucasian	5 (100.0)	4 (66.7)	10 (90.9)	19 (86.4)
Black	0	1 (16.7)	1 (9.1)	2 (9.1)
Asian	0	1 (16.7)	0	1 (4.5)
Ethnicity				
Other	5 (100.0)	5 (83.3)	11 (100.0)	21 (95.5)
Mixed Ethnicity	0	1 (16.7)	0	1 (4.5)
Weight (kg)				
N	5	5	9	19
Mean	81.2	63.1	80.3	76.0
SD	19.07	16.90	18.80	19.09
Median	77.5	63.0	80.0	73.0
Min	62.0	45.0	58.0	45.0
Max	110.0	87.5	109.5	110.0

Demographic Variable	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Height (cm)				
N	5	5	8	18
Mean	173.0	162.2	171.0	169.1
SD	8.72	7.36	9.93	9.56
Median	171.0	163.0	167.5	168.0
Min	163.0	150.0	161.0	150.0
Max	187.0	168.0	191.0	191.0
WHO performance status				
0	3 (60.0)	2 (33.3)	5 (45.5)	10 (45.5)
1	2 (40.0)	4 (66.7)	6 (54.5)	12 (54.5)
Presence of a Cowden syndrome				
No	5 (100.0)	6 (100.0)	11 (100.0)	22 (100.0)

Demographics summary, by dose cohort SDS Sachet-FAS

Demographic Variable	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Age (Years)						
N	6	10	24	14	7	61
Mean	57.7	54.0	59.5	56.6	55.0	57.2
SD	8.26	19.02	11.13	6.31	18.38	12.42
Median	59.0	62.5	60.5	55.5	54.0	58.0
Min	47.0	18.0	39.0	45.0	20.0	18.0
Max	70.0	70.0	82.0	73.0	81.0	82.0
Age category (Years)						
<65	5 (83.3)	7 (70.0)	16 (66.7)	13 (92.9)	6 (85.7)	47 (77.0)
≥65	1 (16.7)	3 (30.0)	8 (33.3)	1 (7.1)	1 (14.3)	14 (23.0)
Sex						
Male	1 (16.7)	5 (50.0)	11 (45.8)	3 (21.4)	4 (57.1)	24 (39.3)
Female	5 (83.3)	5 (50.0)	13 (54.2)	11 (78.6)	3 (42.9)	37 (60.7)
Race						
Caucasian	6 (100.0)	9 (90.0)	22 (91.7)	13 (92.9)	7 (100.0)	57 (93.4)
Black	0	1 (10.0)	0	1 (7.1)	0	2 (3.3)
Pacific islander	0	0	1 (4.2)	0	0	1 (1.6)
Other	0	0	1 (4.2)	0	0	1 (1.6)
Ethnicity						

Demographic Variable	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Hispanic/Latino	0	0	7 (29.2)	0	0	7 (11.5)
Other	6 (100.0)	10 (100.0)	17 (70.8)	14 (100.0)	7 (100.0)	54 (88.5)
Weight (kg)						
N	6	10	24	14	7	61
Mean	79.1	71.3	72.3	77.6	64.8	73.2
SD	22.97	14.27	16.40	25.55	15.00	18.94
Median	69.5	74.8	67.9	69.0	58.0	69.0
Min	58.5	53.4	49.0	55.0	51.5	49.0
Max	117.0	91.0	107.9	150.0	90.9	150.0
Height (cm)						
N	6	10	24	13	7	60
Mean	167.2	165.6	169.2	169.3	167.1	168.2
SD	10.94	8.37	9.70	11.61	4.34	9.43
Median	167.0	165.5	169.0	168.0	168.0	168.0
Min	154.0	148.0	152.0	150.0	160.0	148.0
Max	185.0	177.0	186.0	190.0	173.0	190.0
WHO performance status						
0	4 (66.7)	3 (30.0)	8 (33.3)	9 (64.3)	3 (42.9)	27 (44.3)
1	2 (33.3)	7 (70.0)	12 (50.0)	5 (35.7)	4 (57.1)	30 (49.2)
2	0	0	3 (12.5)	0	0	3 (4.9)
Missing	0	0	1 (4.2)	0	0	1 (1.6)
Presence of a Cowden syndrome						
No	6 (100.0)	10 (100.0)	24 (100.0)	14 (100.0)	7 (100.0)	61 (100.0)

Demographics summary, by dose cohort SDS Caps B-FAS

Demographic Variable	SDS Caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Age (Years)		
N	11	11
Mean	58.2	58.2
SD	11.21	11.21
Median	60.0	60.0
Min	29.0	29.0
Max	70.0	70.0
Age category (Years)		
<65	8 (72.7)	8 (72.7)

Demographic Variable	SDS Caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
≥ 65	3 (27.3)	3 (27.3)
Sex		
Male	6 (54.5)	6 (54.5)
Female	5 (45.5)	5 (45.5)
Race		
Caucasian	10 (90.9)	10 (90.9)
Asian	1 (9.1)	1 (9.1)
Ethnicity		
Hispanic/Latino	1 (9.1)	1 (9.1)
Other	10 (90.9)	10 (90.9)
Weight (kg)		
N	11	11
Mean	70.6	70.6
SD	11.32	11.32
Median	69.5	69.5
Min	51.0	51.0
Max	89.0	89.0
Height (cm)		
N	11	11
Mean	166.1	166.1
SD	7.89	7.89
Median	168.0	168.0
Min	150.0	150.0
Max	175.0	175.0
WHO performance status		
0	6 (54.5)	6 (54.5)
1	4 (36.4)	4 (36.4)
2	1 (9.1)	1 (9.1)
Presence of a Cowden syndrome		
No	11 (100.0)	11 (100.0)

Disease history, by dose cohort SDS Caps A- FAS

Disease history	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Primary site of cancer (group)				
Colon	2 (40.0)	0	4 (36.4)	6 (27.3)
Other	0	2 (33.3)	3 (27.3)	5 (22.7)
Breast	1 (20.0)	2 (33.3)	1 (9.1)	4 (18.2)
Lung	1 (20.0)	1 (16.7)	1 (9.1)	3 (13.6)
Ovary	0	1 (16.7)	1 (9.1)	2 (9.1)
Rectum	0	0	1 (9.1)	1 (4.5)
Skin melanoma	1 (20.0)	0	0	1 (4.5)
Primary site of cancer (details)				
Bone sarcoma	0	1 (16.7)	0	1 (4.5)
Breast	1 (20.0)	2 (33.3)	1 (9.1)	4 (18.2)
Cervix	0	1 (16.7)	0	1 (4.5)
Colon	2 (40.0)	0	4 (36.4)	6 (27.3)
Lung	1 (20.0)	1 (16.7)	1 (9.1)	3 (13.6)
Ovary	0	1 (16.7)	1 (9.1)	2 (9.1)
Rectum	0	0	1 (9.1)	1 (4.5)
Skin melanoma	1 (20.0)	0	0	1 (4.5)
Soft tissue sarcoma	0	0	1 (9.1)	1 (4.5)
Uterus	0	0	1 (9.1)	1 (4.5)
Other : axillary gland	0	0	1 (9.1)	1 (4.5)
Details of tumor histology/cytology				
Adenocarcinoma	3 (60.0)	2 (33.3)	5 (45.5)	10 (45.5)
Bronchioalveolar carcinoma	0	1 (16.7)	0	1 (4.5)
Endometrioid	0	0	1 (9.1)	1 (4.5)
Invasive ductal carcinoma	1 (20.0)	0	1 (9.1)	2 (9.1)
Melanoma	1 (20.0)	0	0	1 (4.5)
Sarcoma	0	2 (33.3)	0	2 (9.1)
Other :NSCLC	0	0	1 (9.1)	1 (4.5)
Other :ductal infiltrating	0	0	1 (9.1)	1 (4.5)
Other :invasive	0	0	1 (9.1)	1 (4.5)
Other :unknown	0	1 (16.7)	1 (9.1)	2 (9.1)
Histological grade				
Well differentiated	0	0	1 (9.1)	1 (4.5)
Moderately differentiated	3 (60.0)	1 (16.7)	5 (45.5)	9 (40.9)
Poorly differentiated	0	1 (16.7)	1 (9.1)	2 (9.1)
Unknown	2 (40.0)	4 (66.7)	4 (36.4)	10 (45.5)
Stage at initial diagnosis				

Disease history	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Stage I	0	1 (16.7)	0	1 (4.5)
Stage I b	0	1(16.7)	0	1(4.5)
Stage II	0	2 (33.3)	1 (9.1)	3 (13.6)
Stage II a	0	0	1 (9.1)	1 (4.5)
Stage III	2 (40.0)	0	4 (36.4)	6 (27.3)
Stage III b	0	0	1 (9.1)	1 (4.5)
Stage IV	3 (60.0)	1 (16.7)	4 (36.4)	8 (36.4)
Missing	0	1 (16.7)	0	1 (4.5)
Current extent of disease				
Stage III	0	0	1 (9.1)	1 (4.5)
Stage IV	5 (100.0)	6 (100.0)	10 (90.9)	21 (95.5)
Time since initial diagnosis of primary site (months)				
N	5	6	11	22
Mean	55.6	66.8	38.7	50.2
SD	46.15	41.03	16.80	33.11
Median	31.6	65.9	38.7	39.3
Min	12.2	19.5	17.0	12.2
Max	109.6	124.6	69.7	124.6
Time from initial diagnosis to first recurrence/relapse (months)				
N	5	6	11	22
Mean	9.0	39.0	13.7	19.5
SD	4.71	23.38	7.27	17.66
Median	9.9	30.9	13.2	13.8
Min	2.8	13.6	2.8	2.8
Max	15.4	69.3	28.0	69.3
Time from initial diagnosis to most recent recurrence/relapse (months)				
N	5	6	11	22
Mean	54.5	65.1	36.9	48.6
SD	46.11	41.47	17.14	33.35
Median	31.3	64.6	37.0	37.6
Min	10.3	16.2	15.1	10.3
Max	108.1	123.5	68.7	123.5
Time since most recent recurrence/relapse (months)				
N	5	6	11	22
Mean	1.1	1.7	1.8	1.6
SD	0.61	0.88	0.65	0.74
Median	1.0	1.4	1.9	1.6
Min	0.3	1.1	1.0	0.3

Disease history	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Max	1.9	3.4	3.4	3.4
Types of lesions at baseline				
Target only	1 (20.0)	1 (16.7)	2 (18.2)	4 (18.2)
Both target and non-target	4 (80.0)	5 (83.3)	9 (81.8)	18 (81.8)
HER2 status (1)				
HER2+	1 (20.0)	0	0	1 (4.5)
HER2-	0	2 (33.3)	1 (9.1)	3 (13.6)
ER status (1)				
ER+	0	2 (33.3)	0	2 (9.1)
ER-	1 (20.0)	0	1 (9.1)	2 (9.1)
PR status (1)				
PR+	0	1 (16.7)	0	1 (4.5)
PR-	1 (20.0)	1 (16.7)	1 (9.1)	3 (13.6)
HER2 status and ER status (1)				
HER2- ER+	0	2 (33.3)	0	2 (9.1)
HER2- ER-	0	0	1 (9.1)	1 (4.5)
HER2+ ER-	1 (20.0)	0	0	1 (4.5)

(1) For breast cancer patients only.
ER/PR: Estrogen receptor/Progesterone receptor
HER2: Human epidermal growth factor receptor 2
+/-: Positive/Negative

Disease history, by dose cohort SDS Sachet- FAS

Disease history	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Primary site of cancer (group)						
Other	1 (16.7)	4 (40.0)	6 (25.0)	4 (28.6)	5 (71.4)	20 (32.8)
Colon	3 (50.0)	3 (30.0)	6 (25.0)	2 (14.3)	1 (14.3)	15 (24.6)
Breast	2 (33.3)	1 (10.0)	5 (20.8)	4 (28.6)	0	12 (19.7)
Lung	0	0	5 (20.8)	3 (21.4)	0	8 (13.1)
Rectum	0	1 (10.0)	2 (8.3)	0	1 (14.3)	4 (6.6)
Ovary	0	1 (10.0)	0	1 (7.1)	0	2 (3.3)
Primary site of cancer (details)						
Bladder	0	0	0	0	1 (14.3)	1 (1.6)
Bone sarcoma	0	1 (10.0)	0	0	1 (14.3)	2 (3.3)

Disease history	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Breast	2 (33.3)	1 (10.0)	5 (20.8)	4 (28.6)	0	12 (19.7)
Cervix	0	0	2 (8.3)	0	0	2 (3.3)
Colon	3 (50.0)	3 (30.0)	6 (25.0)	2 (14.3)	1 (14.3)	15 (24.6)
Kidneys	0	1 (10.0)	1 (4.2)	3 (21.4)	0	5 (8.2)
Lung	0	0	5 (20.8)	3 (21.4)	0	8 (13.1)
Ovary	0	1 (10.0)	0	1 (7.1)	0	2 (3.3)
Prostate	0	1 (10.0)	0	0	0	1 (1.6)
Rectum	0	1 (10.0)	2 (8.3)	0	1 (14.3)	4 (6.6)
Salivary gland	0	0	0	0	2 (28.6)	2 (3.3)
Small intestine	0	0	1 (4.2)	0	0	1 (1.6)
Stomach	0	0	0	0	1 (14.3)	1 (1.6)
Other: endometrial	0	0	0	1 (7.1)	0	1 (1.6)
Other: endometrium	0	0	1 (4.2)	0	0	1 (1.6)
Other: ileum and liver	0	0	1 (4.2)	0	0	1 (1.6)
Other: thorax	0	1 (10.0)	0	0	0	1 (1.6)
Other: unknown primary	1 (16.7)	0	0	0	0	1 (1.6)
Details of tumor histology/cytology						
Adenocarcinoma	3 (50.0)	3 (30.0)	10 (41.7)	6 (42.9)	2 (28.6)	24 (39.3)
Carcinoid	0	0	1 (4.2)	0	0	1 (1.6)
Clear cell adenocarcinoma	0	1 (10.0)	0	1 (7.1)	0	2 (3.3)
DCIS (ductal carcinoma in situ)	0	0	1 (4.2)	0	0	1 (1.6)
Invasive ductal carcinoma	1 (16.7)	1 (10.0)	3 (12.5)	3 (21.4)	0	8 (13.1)
Invasive lobular carcinoma	1 (16.7)	0	1 (4.2)	1 (7.1)	0	3 (4.9)
Mucinous adenocarcinoma	0	0	1 (4.2)	0	0	1 (1.6)
Papillary serous	0	1 (10.0)	0	0	0	1 (1.6)
Sarcoma	0	0	0	0	1 (14.3)	1 (1.6)
Small Cell (neuroendocrine) carcinoma	0	2 (20.0)	0	0	0	2 (3.3)
Spindle cell	0	0	0	1 (7.1)	0	1 (1.6)
Squamous cell carcinoma	0	0	2 (8.3)	1 (7.1)	0	3 (4.9)
Other :Renal cell carcinoma T1 Nx Mx	0	0	1 (4.2)	0	0	1 (1.6)
Other:Stage IIIA, Grade III endometrial Carcinoma. 23% myometrial invasion and negative lymph nodes, with metastases in both ovaries	0	0	1 (4.2)	0	0	1 (1.6)
Other:adenoid cystic carcinoma	0	0	0	0	1 (14.3)	1 (1.6)

Disease history	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Other:clear cell sarcoma	0	0	1 (4.2)	0	0	1 (1.6)
Other:cystic adenoid	0	0	0	0	1 (14.3)	1 (1.6)
Other:ewing	0	1 (10.0)	0	0	1 (14.3)	2 (3.3)
Other:invasive urothelial carcinoma	0	0	0	0	1 (14.3)	1 (1.6)
Other:non-small cell	0	0	1 (4.2)	0	0	1 (1.6)
Other:non-small cell	0	0	1 (4.2)	0	0	1 (1.6)
Other:papillary serous adenocarcinoma	0	0	0	1 (7.1)	0	1 (1.6)
Other:synovial sarcoma	0	1 (10.0)	0	0	0	1 (1.6)
Not applicable:small cell carcinoma with focal squamous differentiation	1 (16.7)	0	0	0	0	1 (1.6)
Histological grade						
Well differentiated	0	2 (20.0)	3 (12.5)	2 (14.3)	1 (14.3)	8 (13.1)
Moderately differentiated	1 (16.7)	0	9 (37.5)	4 (28.6)	2 (28.6)	16 (26.2)
Poorly differentiated	2 (33.3)	1 (10.0)	5 (20.8)	4 (28.6)	1 (14.3)	13 (21.3)
Undifferentiated	0	2 (20.0)	0	0	0	2 (3.3)
Unknown	3 (50.0)	5 (50.0)	7 (29.2)	4 (28.6)	3 (42.9)	22 (36.1)
Stage at initial diagnosis						
Stage I	0	0	2 (8.3)	1 (7.1)	1 (14.3)	4 (6.6)
Stage I a	0	0	1 (4.2)	0	0	1 (1.6)
Stage II	0	0	0	1 (7.1)	1 (14.3)	2 (3.3)
Stage II a	0	1 (10.0)	2 (8.3)	0	1 (14.3)	4 (6.6)
Stage II b	0	1 (10.0)	1 (4.2)	4 (28.6)	1 (14.3)	7 (11.5)
Stage III	1 (16.7)	3 (30.0)	1 (4.2)	1 (7.1)	0	6 (9.8)
Stage III a	0	0	1 (4.2)	1 (7.1)	0	2 (3.3)
Stage III b	2 (33.3)	2 (20.0)	3 (12.5)	3 (21.4)	0	10 (16.4)
Stage IV	3 (50.0)	1 (10.0)	9 (37.5)	3 (21.4)	1 (14.3)	17 (27.9)
Stage IV b	0	0	4 (16.7)	0	0	4 (6.6)
Missing	0	2 (20.0)	0	0	2 (28.6)	4 (6.6)
Current extent of disease						
Stage III a	0	0	1 (4.2)	0	0	1 (1.6)
Stage III b	0	0	0	2 (14.3)	0	2 (3.3)
Stage IV	6 (100.0)	9 (90.0)	18 (75.0)	12 (85.7)	7 (100.0)	52 (85.2)
Stage IV a	0	0	1 (4.2)	0	0	1 (1.6)
Stage IV b	0	0	4 (16.7)	0	0	4 (6.6)
Missing	0	1 (10.0)	0	0	0	1 (1.6)
Time since initial diagnosis of primary site (months)						

Disease history	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
N	6	10	24	14	7	61
Mean	44.6	74.9	56.5	67.6	67.6	62.2
SD	24.12	48.54	46.35	51.42	42.49	45.39
Median	47.4	55.2	47.6	48.3	45.1	48.5
Min	8.5	33.1	5.7	22.6	27.4	5.7
Max	76.7	196.5	198.6	211.9	131.4	211.9
Time from initial diagnosis to first recurrence/relapse (months)						
N	5	10	21	14	7	57
Mean	10.1	25.3	23.9	28.7	37.5	25.8
SD	9.03	11.65	27.54	30.29	26.33	25.07
Median	7.5	25.1	18.4	18.9	21.7	19.2
Min	1.8	6.0	1.5	4.2	9.9	1.5
Max	24.0	40.1	122.6	108.0	80.5	122.6
Time from initial diagnosis to most recent recurrence/relapse (months)						
N	6	10	24	14	7	61
Mean	43.1	73.6	54.8	65.4	65.1	60.3
SD	24.28	48.78	46.39	52.12	41.74	45.54
Median	45.6	53.7	45.6	44.1	43.7	46.2
Min	7.1	32.3	4.9	21.8	26.0	4.9
Max	76.4	196.0	197.0	211.7	126.2	211.7
Time since most recent recurrence/relapse (months)						
N	6	10	24	14	7	61
Mean	1.6	1.3	1.7	2.3	2.6	1.9
SD	0.77	0.46	1.14	3.03	1.46	1.72
Median	1.4	1.4	1.7	1.5	2.6	1.5
Min	0.3	0.6	0.3	0.2	1.2	0.2
Max	2.4	1.9	5.2	12.5	5.3	12.5
Types of lesions at baseline						
Target only	1 (16.7)	0	3 (12.5)	2 (14.3)	1 (14.3)	7 (11.5)
Both target and non-target	5 (83.3)	10 (100.0)	21 (87.5)	12 (85.7)	6 (85.7)	54 (88.5)
HER2 status (1)						
HER2-	1 (16.7)	1 (10.0)	5 (20.8)	4 (28.6)	0	11 (18.0)
Missing	1 (16.7)	0	0	0	0	1 (1.6)
ER status (1)						
ER+	1 (16.7)	0	3 (12.5)	3 (21.4)	0	7 (11.5)
ER-	0	1 (10.0)	2 (8.3)	1 (7.1)	0	4 (6.6)
Missing	1 (16.7)	0	0	0	0	1 (1.6)
PR status (1)						

Disease history	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
PR+	1 (16.7)	0	1 (4.2)	3 (21.4)	0	5 (8.2)
PR-	0	1 (10.0)	4 (16.7)	1 (7.1)	0	6 (9.8)
Missing	1 (16.7)	0	0	0	0	1 (1.6)
HER2 status and ER status(1)						
HER2- ER+	1 (16.7)	0	3 (12.5)	3 (21.4)	0	7 (11.5)
HER2- ER-	0	1 (10.0)	2 (8.3)	1 (7.1)	0	4 (6.6)
Missing	1 (16.7)	0	0	0	0	1 (1.6)

(1) For breast cancer patients only.
ER/PR: Estrogen receptor/Progesterone receptor
HER2: Human epidermal growth factor receptor 2
+/-: Positive/Negative

Disease history, by dose cohort SDS Caps B- SDS Caps B

Disease history	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Primary site of cancer (group)		
Breast	1 (9.1)	1 (9.1)
Colon	4 (36.4)	4 (36.4)
Other	5 (45.5)	5 (45.5)
Ovary	1 (9.1)	1 (9.1)
Primary site of cancer (details)		
Breast	1 (9.1)	1 (9.1)
Colon	4 (36.4)	4 (36.4)
Oesophagus	1 (9.1)	1 (9.1)
Ovary	1 (9.1)	1 (9.1)
Uterus	1 (9.1)	1 (9.1)
Other : Endometrium	1 (9.1)	1 (9.1)
Other : heart	1 (9.1)	1 (9.1)
Other : mesothelioma	1 (9.1)	1 (9.1)
Details of tumor histology/ cytology		
Adenocarcinoma	5 (45.5)	5 (45.5)
Invasive lobular carcinoma	1 (9.1)	1 (9.1)
Papillary serous	1 (9.1)	1 (9.1)
Squamous cell carcinoma	1 (9.1)	1 (9.1)
Other :angiosarcoma	1 (9.1)	1 (9.1)

Disease history	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Other :serous carcinoma	1 (9.1)	1 (9.1)
Other :solid-papillary	1 (9.1)	1 (9.1)
Histological grade		
Well differentiated	1 (9.1)	1 (9.1)
Moderately differentiated	2 (18.2)	2 (18.2)
Poorly differentiated	2 (18.2)	2 (18.2)
Unknown	6 (54.5)	6 (54.5)
Stage at initial diagnosis		
Stage II a	2 (18.2)	2 (18.2)
Stage II b	2 (18.2)	2 (18.2)
Stage III	1 (9.1)	1 (9.1)
Stage III b	1 (9.1)	1 (9.1)
Stage IV	2 (18.2)	2 (18.2)
Stage IV a	1 (9.1)	1 (9.1)
Missing	2 (18.2)	2 (18.2)
Current extent of disease		
Stage IV	10 (90.9)	10 (90.9)
Stage IV b	1 (9.1)	1 (9.1)
Time since initial diagnosis of primary site (months)		
N	11	11
Mean	48.7	48.7
SD	31.73	31.73
Median	41.9	41.9
Min	11.3	11.3
Max	126.0	126.0
Time from initial diagnosis to first recurrence/relapse (months)		
N	11	11
Mean	21.5	21.5
SD	20.89	20.89
Median	10.0	10.0
Min	4.4	4.4
Max	62.0	62.0
Time from initial diagnosis to most recent recurrence/ relapse (months)		
N	11	11
Mean	47.2	47.2
SD	31.50	31.50
Median	39.1	39.1
Min	10.4	10.4
Max	124.0	124.0

Disease history	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Time since most recent recurrence/relapse (months)		
N	11	11
Mean	1.5	1.5
SD	0.57	0.57
Median	1.3	1.3
Min	0.9	0.9
Max	2.8	2.8
Types of lesions at baseline		
Target only	1 (9.1)	1 (9.1)
Both target and non-target	10 (90.9)	10 (90.9)
HER2 status (1)		
HER2-	1 (9.1)	1 (9.1)
ER status (1)		
ER+	1 (9.1)	1 (9.1)
PR status (1)		
PR+	1 (9.1)	1(9.1)
HER2 status and ER status(1)		
HER2- ER+	1 (9.1)	1 (9.1)

(1) For breast cancer patients only.
ER/PR: Estrogen receptor/Progesterone receptor
HER2: Human epidermal growth factor receptor 2
+/-: Positive/Negative

BEZ235 SDS in combination with trastuzumab

Demographics summary, by dose cohort, SDS + Trastuzumab- FAS

Demographic Variable	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=10 n (%)	All SDS + T N=30 n (%)
Age (Years)				
N	3	17	10	30
Mean	44.3	48.4	52.3	49.3
SD	15.31	10.20	10.18	10.58
Median	36.0	47.0	51.0	49.0
Min	35.0	30.0	38.0	30.0
Max	62.0	71.0	69.0	71.0

Demographic Variable	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=10 n (%)	All SDS + T N=30 n (%)
Age category (Years)				
<65	3 (100.0)	16 (94.1)	8 (80.0)	27 (90.0)
≥ 65	0	1 (5.9)	2 (20.0)	3 (10.0)
Sex				
Female	3(100.0)	17(100.0)	10(100.0)	30(100.0)
Race				
Caucasian	3 (100.0)	16 (94.1)	8 (80.0)	27 (90.0)
Asian	0	1 (5.9)	2 (20.0)	3 (10.0)
Ethnicity				
Hispanic/Latino	0	11 (64.7)	0	11 (36.7)
Indian (Indian subcontinent)	0	0	1 (10.0)	1 (3.3)
Japanese	0	0	1 (10.0)	1 (3.3)
Other	3 (100.0)	6 (35.3)	8 (80.0)	17 (56.7)
Weight (kg)				
N	3	17	10	30
Mean	56.3	72.7	57.1	65.9
SD	5.86	13.74	12.64	14.80
Median	54.0	67.8	58.0	64.6
Min	52.0	58.7	38.6	38.6
Max	63.0	107.4	77.0	107.4
Height (cm)				
N	3	17	10	30
Mean	159.7	161.8	160.3	161.1
SD	3.21	8.32	6.43	7.24
Median	161.0	162.0	161.5	161.5
Min	156.0	142.0	149.0	142.0
Max	162.0	175.0	168.0	175.0
WHO performance status				
0	2 (66.7)	9 (52.9)	6 (60.0)	17 (56.7)
1	1 (33.3)	8 (47.1)	4 (40.0)	13 (43.3)
Presence of a Cowden syndrome				
No	3 (100.0)	17 (100.0)	10 (100.0)	30 (100.0)

Outcome measures

Primary Outcome Results

MTD Assessment

The dose determining set for BEZ235 HGC under fasted condition consisted of 38 patients (60.3%), in seven cohorts over 7 BEZ235 dose levels. The MTD was not reached and the dose escalation was stopped.

The dose determining set for BEZ235 HGC under fed condition consisted of 16 patients (80%), in five cohorts over four BEZ235 dose levels. The MTD was not reached and the dose escalation was stopped.

The dose determining set for BEZ235 SDS Capsule A formulation consisted of 20 patients (74.1%), in five cohorts over three BEZ235 dose levels. A total of three patients experienced DLTs. In the 800 mg/day dose cohort, one patient experienced fatigue (grade 3), in the 1000 mg/day dose cohort, two patients experienced DLTs, macular papular skin rash (grade 3) and fatigue (grade 3). The MTD was declared at 1000 mg/day.

The dose determining set for BEZ235 SDS Sachet formulation consisted of 50 patients (63.3%) in nine cohorts over five BEZ235 dose levels. A total of 10 patients experienced DLTs in the SDS Sachet group. In the 1000 mg/day dose cohort, one patient experienced thrombocytopenia (grade 3). In the 1200 mg/day dose cohort, two patients experienced DLTs, vomiting (grade 3) and nausea (grade 2). In the 1400 mg/day dose cohort, six patients experienced DLTs; asthenia (grade 3), fatigue (grade 3), hyperglycemia, diarrhea (grade 3), mucositis and fatigue (each grade 3). In the 1600 mg/day dose cohort, one patient experienced thrombocytopenia (grade 3). The MTD was declared at 1200 mg/day.

The dose determining set for BEZ235 SDS Capsule B formulation consisted of nine patients (60%) in two cohorts at the 800 mg/day BEZ235 dose level. One patient experienced DLT, uveitis (grade 2). The inter-subject variability in exposure to BEZ235 was not improved with SDS Capsule B compared to SDS Capsule A, and no advantage in efficacy or safety was observed and it was concluded that the SDS Capsule B formulation did not bring additional value. Therefore only the 800 mg dose level was tested and this formulation was not investigated further. No MTD was determined for the SDS Capsule B formulation.

The dose determining set for BEZ235 SDS + trastuzumab consisted of 25 patients (73.5%), in five cohorts over three BEZ235 dose levels. A total of four patients experienced DLTs in the group. In the 600 mg/day dose cohort, one patient experienced nausea (grade 3). In the 800 mg/day dose cohort, three patients experienced DLTs; rash, nausea and fatigue (grade 3). The MTD was declared at 600 mg/day for BEZ235 SDS sachet + trastuzumab 2 mg/kg/week.

BEZ235 HGC group

Summary of posterior distribution of DLT rates at end of HGC patients recruitment – Dose determining set-HGC Fast

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
10	1.000	0.000	0.000	0.001	0.004	0	0	0.012
25	1.000	0.000	0.000	0.003	0.005	0	0.001	0.018
50	1.000	0.000	0.000	0.004	0.007	0	0.001	0.025
100	1.000	0.000	0.000	0.007	0.010	0	0.003	0.037
200	1.000	0.000	0.000	0.014	0.016	0	0.009	0.06
300	0.998	0.002	0.000	0.023	0.024	0.001	0.015	0.088
400	0.989	0.010	0.000	0.034	0.034	0.002	0.024	0.128
700	0.860	0.111	0.029	0.083	0.093	0.005	0.052	0.35
800	0.806	0.140	0.054	0.103	0.117	0.005	0.062	0.447
1000	0.711	0.176	0.113	0.142	0.161	0.006	0.082	0.627
1100	0.673	0.185	0.142	0.161	0.180	0.007	0.093	0.701

Summary of posterior distribution of DLT rates at end of HGC patients recruitment – Dose determining set-HGC Fed

	Posterior probabilities that Pr (DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
10	1.000	0.000	0.000	0.001	0.003	0	0	0.008
25	1.000	0.000	0.000	0.002	0.005	0	0	0.012
50	1.000	0.000	0.000	0.002	0.006	0	0	0.018
100	1.000	0.000	0.000	0.004	0.008	0	0.001	0.026
200	1.000	0.000	0.000	0.007	0.013	0	0.003	0.042
300	0.999	0.001	0.000	0.011	0.017	0	0.005	0.059
400	0.998	0.002	0.000	0.016	0.022	0	0.008	0.077
700	0.976	0.023	0.001	0.035	0.043	0.001	0.019	0.158
800	0.955	0.042	0.003	0.044	0.054	0.001	0.024	0.198
1000	0.898	0.084	0.018	0.063	0.081	0.001	0.033	0.299
1100	0.867	0.102	0.031	0.074	0.096	0.001	0.038	0.356

BEZ235 SDS single agent group

Summary of posterior distribution of DLT rates at time of MTD, Dose determining set, posterior probabilities of DLT at selected doses - MTD declaration- SDS Caps A

	Posterior probabilities that Pr (DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.000	0.000	0	0	0
200	0.998	0.002	0.000	0.022	0.023	0.001	0.014	0.086
400	0.984	0.016	0.000	0.054	0.035	0.012	0.046	0.146
600	0.871	0.128	0.002	0.102	0.051	0.03	0.093	0.225
800	0.550	0.413	0.037	0.163	0.080	0.045	0.15	0.348
1000	0.331	0.481	0.188	0.228	0.118	0.058	0.209	0.504
1200	0.217	0.425	0.358	0.293	0.155	0.069	0.265	0.649
1400	0.157	0.362	0.480	0.351	0.185	0.079	0.32	0.755
1600	0.121	0.308	0.571	0.402	0.208	0.087	0.372	0.831

Summary of posterior distribution of DLT rates at the end of study, Dose determining set, posterior probabilities of DLT at selected doses - End of Study- SDS Caps A

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.000	0.000	0	0	0
200	1.000	0.000	0.000	0.017	0.016	0.002	0.012	0.061
400	0.999	0.001	0.000	0.042	0.024	0.011	0.037	0.103
600	0.985	0.015	0.000	0.076	0.030	0.031	0.071	0.149
800	0.856	0.144	0.000	0.118	0.040	0.054	0.112	0.211
1000	0.521	0.472	0.008	0.164	0.056	0.074	0.157	0.294
1200	0.265	0.657	0.078	0.214	0.077	0.091	0.204	0.388
1400	0.147	0.614	0.239	0.263	0.099	0.106	0.251	0.482
1600	0.092	0.512	0.396	0.310	0.120	0.12	0.296	0.572

Summary of posterior distribution of DLT rates at time of MTD, Dose determining analysis set, Posterior probabilities of DLT at selected doses - MTD declaration- SDS Sachet

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.000	0.000	0	0	0
200	0.994	0.006	0.000	0.027	0.030	0.002	0.017	0.112
400	0.967	0.033	0.000	0.063	0.041	0.012	0.053	0.17
600	0.864	0.136	0.000	0.107	0.048	0.038	0.099	0.222
800	0.562	0.435	0.003	0.158	0.051	0.075	0.152	0.274
1000	0.177	0.795	0.028	0.213	0.056	0.115	0.208	0.333
1200	0.036	0.790	0.174	0.269	0.066	0.152	0.265	0.406
1400	0.009	0.542	0.449	0.323	0.078	0.182	0.319	0.486
1600	0.003	0.330	0.666	0.374	0.093	0.207	0.371	0.562

Summary of posterior distribution of DLT rates at the end of study Dose determining analysis set, Posterior probabilities of DLT at selected doses - End of study-SDS Sachet.

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.000	0.000	0	0	0
200	0.999	0.001	0.000	0.018	0.020	0.001	0.011	0.077
400	0.996	0.004	0.000	0.043	0.029	0.008	0.036	0.119
600	0.978	0.022	0.000	0.075	0.034	0.026	0.069	0.157
800	0.891	0.109	0.000	0.113	0.037	0.054	0.109	0.197
1000	0.571	0.429	0.000	0.156	0.041	0.086	0.153	0.246
1200	0.210	0.778	0.012	0.202	0.050	0.114	0.198	0.311
1400	0.069	0.824	0.107	0.249	0.064	0.137	0.244	0.385
1600	0.029	0.657	0.315	0.295	0.080	0.156	0.289	0.463

BEZ235 SDS in combination with trastuzumab group

Summary of posterior distribution of DLT rates at time of MTD, Dose determining set, Posterior probabilities of DLT at selected doses - MTD declaration-SDS sachet+Trastuzumab

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.051	0.010	0.034	0.05	0.073
200	0.780	0.214	0.006	0.121	0.061	0.036	0.11	0.27
400	0.522	0.443	0.035	0.168	0.076	0.053	0.156	0.349
600	0.261	0.609	0.130	0.224	0.091	0.079	0.214	0.43
800	0.106	0.573	0.322	0.287	0.105	0.109	0.278	0.514
1000	0.044	0.414	0.543	0.350	0.118	0.141	0.343	0.599
1200	0.019	0.270	0.711	0.410	0.131	0.169	0.405	0.675
1400	0.010	0.175	0.814	0.464	0.143	0.196	0.463	0.742

Summary of posterior distribution of DLT rates at the end of study Dose determining set, posterior probabilities of DLT at selected doses, End of study-SDS sachet+Trastuzumab

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
Dose (mg)	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
0	1.000	0.000	0.000	0.051	0.010	0.034	0.05	0.071
200	0.949	0.050	0.000	0.085	0.040	0.027	0.078	0.181
400	0.841	0.158	0.001	0.112	0.050	0.038	0.104	0.229
600	0.630	0.362	0.007	0.147	0.061	0.052	0.14	0.288
800	0.384	0.572	0.044	0.190	0.074	0.071	0.181	0.355
1000	0.206	0.642	0.152	0.236	0.089	0.09	0.227	0.433
1200	0.111	0.578	0.310	0.284	0.105	0.108	0.274	0.515
1400	0.066	0.464	0.470	0.331	0.122	0.125	0.32	0.593
1600	0.042	0.361	0.597	0.376	0.137	0.14	0.365	0.664

Secondary Outcome Result

Efficacy evaluation

Best overall response as per Investigator assessment, per dose cohort- HCG Fast-(FAS)

	Fast 10 mg/day (N=3) n (%)	Fast 25 mg/day (N=6) n (%)	Fast 50 mg/day (N=4) n (%)	Fast 100 mg/day (N=6) n (%)	Fast 200 mg/day (N=5) n (%)	Fast 300 mg/day (N=6) n (%)	Fast 400 mg/day (N=11) n (%)	All HGC Fast (N=41) n (%)

	Fast 10 mg/day (N=3) n (%)	Fast 25 mg/day (N=6) n (%)	Fast 50 mg/day (N=4) n (%)	Fast 100 mg/day (N=6) n (%)	Fast 200 mg/day (N=5) n (%)	Fast 300 mg/day (N=6) n (%)	Fast 400 mg/day (N=11) n (%)	All HGC Fast (N=41) n (%)
Best overall response								
Complete Response (CR)	0	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0	0	0	0
Stable Disease (SD)	0	3 (50.0)	3 (75.0)	1 (16.7)	1 (20.0)	1 (16.7)	6 (54.5)	15 (36.6)
Progressive Disease (PD)	3 (100.0)	3 (50.0)	1 (25.0)	4 (66.7)	3 (60.0)	3 (50.0)	3 (27.3)	20 (48.8)
Unknown	0	0	0	1 (16.7)	1 (20.0)	2 (33.3)	2 (18.2)	6 (14.6)
Objective Response Rate ORR (CR or PR)	0	0	0	0	0	0	0	0
90% CI for ORR	[0.0; 63.2]	[0.0; 39.3]	[0.0; 52.7]	[0.0; 39.3]	[0.0; 45.1]	[0.0; 39.3]	[0.0; 23.8]	[0.0; 7.0]
Disease control rate (CR or PR or SD)	0	3 (50.0)	3 (75.0)	1 (16.7)	1 (20.0)	1 (16.7)	6 (54.5)	15 (36.6)
90% CI for DCR	[0.0; 63.2]	[15.3; 84.7]	[24.9; 98.7]	[0.9; 58.2]	[1.0; 65.7]	[0.9; 58.2]	[27.1; 80.0]	[24.1; 50.6]

Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test

Best overall response as per Investigator assessment, per dose cohort- HCG Fed-(FAS)

	Fed 300 mg/day (N=6) n (%)	Fed 400 mg/day (N=3) n (%)	Fed 700 mg/day (N=5) n (%)	Fed 1100 mg/day (N=4) n (%)	All HGC Fed (N=18) n (%)
Best overall response					
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0
Stable Disease (SD)	4 (66.7)	2 (66.7)	3 (60.0)	1 (25.0)	10 (55.6)
Progressive Disease (PD)	2 (33.3)	0	2 (40.0)	2 (50.0)	6 (33.3)
Unknown	0	1 (33.3)	0	1 (25.0)	2 (11.1)
Objective Response Rate ORR (CR or PR)	0	0	0	0	0
90% CI for ORR	[0.0; 39.3]	[0.0; 63.2]	[0.0; 45.1]	[0.0; 52.7]	[0.0; 15.3]
Disease control rate (CR or PR or SD)	4 (66.7)	2 (66.7)	3 (60.0)	1 (25.0)	10 (55.6)
90% CI for DCR	[27.1; 93.7]	[13.5; 98.3]	[18.9; 92.4]	[1.3; 75.1]	[34.1; 75.6]

	Fed 300 mg/day (N=6) n (%)	Fed 400 mg/day (N=3) n (%)	Fed 700 mg/day (N=5) n (%)	Fed 1100 mg/day (N=4) n (%)	All HGC Fed (N=18) n (%)
Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test					

BEZ235 SDS single agent group

Best overall response as per Investigator assessment, per dose cohort SDS Caps A-FAS

	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All Caps A N=22 n (%)
Best overall response				
Complete Response (CR)	0	0	0	0
Partial Response (PR)	0	1 (16.7)	0	1 (4.5)
Stable Disease (SD)	0	1 (16.7)	2 (18.2)	3 (13.6)
Progressive Disease (PD)	2 (40.0)	3 (50.0)	7 (63.6)	12 (54.5)
Unknown	3 (60.0)	1 (16.7)	2 (18.2)	6 (27.3)
Objective Response Rate ORR (CR or PR)	0	1 (16.7)	0	1 (4.5)
90 % CI for ORR	[0.0; 45.1]	[0.9; 58.2]	[0.0; 23.8]	[0.2; 19.8]
Disease control rate (CR or PR or SD)	0	2 (33.3)	2 (18.2)	4 (18.2)
90 % CI for DCR	[0.0; 45.1]	[6.3; 72.9]	[3.3; 47.0]	[6.5; 36.9]
Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test				

Best overall response as per Investigator assessment, per dose cohort SDS Sachet-FAS

	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Best overall response						
Complete Response (CR)	0	0	0	0	0	0
Partial Response (PR)	0	0	0	0	0	0
Stable Disease (SD)	0	2 (20.0)	10 (41.7)	4 (28.6)	3 (42.9)	19 (31.1)
Progressive Disease (PD)	4 (66.7)	4 (40.0)	13 (54.2)	3 (21.4)	3 (42.9)	27 (44.3)

	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Unknown	2 (33.3)	4 (40.0)	1 (4.2)	7 (50.0)	1 (14.3)	15 (24.6)
Objective Response Rate ORR (CR or PR)	0	0	0	0	0	0
90 % CI for ORR	[0.0; 39.3]	[0.0; 25.9]	[0.0; 11.7]	[0.0; 19.3]	[0.0; 34.8]	[0.0; 4.8]
Disease control rate (CR or PR or SD)	0	2 (20.0)	10 (41.7)	4 (28.6)	3 (42.9)	19 (31.1)
90 % CI for DCR	[0.0; 39.3]	[3.7;50.7]	[24.6; 60.3]	[10.4; 54.0]	[12.9; 77.5]	[21.5; 42.3]

Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test

Best overall response as per Investigator assessment, per dose cohort SDS Caps B-FAS

	SDS caps B 800 mg/day N=11 n (%)
Best overall response	
Complete Response (CR)	0
Partial Response (PR)	0
Stable Disease (SD)	3 (27.3)
Progressive Disease (PD)	5 (45.5)
Unknown	3 (27.3)
Objective Response Rate ORR (CR or PR)	0
90 % CI for ORR	[0.0; 23.8]
Disease control rate (CR or PR or SD)	3 (27.3)
90 % CI for DCR	[7.9; 56.4]

Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test

BEZ235 SDS in combination with trastuzumab group

Best overall response as per Investigator assessment, per dose cohort, SDS + Trastuzumab-FAS

	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=10 n (%)	All SDS + T N=30 n (%)
Best overall response				
Complete Response (CR)	0	0	0	0
Partial Response (PR)	1 (33.3)	2 (11.8)	1 (10.0)	4 (13.3)
Stable Disease (SD)	2 (66.7)	6 (35.3)	4 (40.0)	12 (40.0)
Progressive Disease (PD)	0	5 (29.4)	1 (10.0)	6 (20.0)
Unknown	0	4 (23.5)	4 (40.0)	8 (26.7)
Objective Response Rate ORR (CR or PR)	1 (33.3)	2 (11.8)	1 (10.0)	4 (13.3)
90 % CI for ORR	[1.7; 86.5]	[2.1; 32.6]	[0.5; 39.4]	[4.7; 28.0]
Disease control rate (CR or PR or SD)	3 (100.0)	8 (47.1)	5 (50.0)	16 (53.3)
90 % CI for DCR	[36.8; 100.0]	[26.0; 68.9]	[22.2; 77.8]	[37.0; 69.2]

Estimates (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval test

Pharmacokinetics results - BEZ235 HGC group

Summary of primary PK parameters for BEZ235, HGC Fast-FAS

Cycle and day of sampling	Treatment	AUC 0-24h (h.ng/mL)	AUC inf (h.ng/mL)	AUC (0-tlast) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
Cycle 1 Day 1	Fast 10 mg/day (N= 3)	21.71[17.3;26.1](2)	23.26[19.9;26.6](2)	16.39 [9.5;23.4](3)	13.30 [4.7;14.1](3)	2.00 [0.5;3.0](3)
	Fast 25 mg/day (N= 6)	20.98[3.7;390.8](6)	40.32[17.0;368.3](4)	19.71 [2.9;360.9](6)	12.15[2.3;126.0](6)	1.00 [0.8;2.0](6)
	Fast 50 mg/day (N= 4)	70.75[21.4;136.0](4)	65.39[21.4;127.7](4)	59.58 [20.3;123.1](4)	16.35 [8.2;37.3](4)	2.29 [1.2;3.0](4)
	Fast 100 mg/day (N= 6)	54.94[41.8;476.1](5)	160.55[49.0;491.5](4)	47.91 [33.0;475.7](6)	14.10 [6.2;90.9](6)	2.54 [1.5;6.1](6)
	Fast 200 mg/day (N= 5)	534.17[46.0;961.2](5)	552.87[39.7;1126.4](5)	524.21 [34.4;961.0](5)	71.50[11.3;246.0](5)	2.00 [1.1;4.1](5)
	Fast 300 mg/day (N= 6)	213.92[84.8;981.4](5)	228.42[154.5;320.5](3)	170.76 [4.3;913.5](6)	15.80 [2.2;105.0](6)	3.02[2.0;4.1](6)
	Fast 400 mg/day (N= 11)	260.43[52.8;1790.5](10)	495.27[67.0;1825.7](4)	194.14 [10.4;1802.2](11)	32.50 2.3;144.0](11)	2.97 [1.1;8.0](11)
Cycle 1 Day 8	Fast 10 mg/day (N= 3)	33.13[31.2;43.1](3)	43.37[43.4;43.4](1)	34.17 [28.8;41.7](3)	9.29 [5.6;17.7](3)	3.00 [2.9;4.1](3)

Cycle and day of sampling	Treatment	AUC 0-24h (h.ng/mL)	AUC inf (h.ng/mL)	AUC (0-tlast) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
	Fast 25 mg/day (N= 6)	24.71[8.5;50.0](6)	34.48[20.1;50.1](4)	23.37[7.5;46.5](6)	10.54 [4.1;14.3](6)	1.30 [1.0;3.0](6)
	Fast 50 mg/day (N= 4)	80.82[22.5;494.4](4)	72.40[25.9;504.3](4)	66.53[21.4;493.4](4)	21.05[7.4;42.4](4)	2.31[1.0;8.0](4)
	Fast 100 mg/day (N= 6)	149.85[25.2;475.4](6)	221.58[116.4;426.8](4)	135.78[16.0;412.2](6)	37.80[2.8;127.0](6)	2.49[1.0;4.1](6)
	Fast 200 mg/day (N= 5)	209.76[19.9;816.1](5)	526.15[214.2;838.1](2)	203.66[21.4;816.9](5)	51.20[3.2;242.0](5)	2.00[2.0;3.2](5)
	Fast 300 mg/day (N= 6)	536.27[52.7;1311.0](6)	375.27[44.3;1343.3](4)	544.52[40.5;1311.0](6)	66.95[9.7;252.0](6)	3.50[2.0;8.1](6)
	Fast 400 mg/day (N= 11)	202.14[20.0;7346.2](9)	1172.53[21.6;7648.6](8)	189.14[17.9;7346.2](10)	42.60[6.8;820.0](10)	2.58[0.5;8.3](10)
Cycle 1 Day 28	Fast 10 mg/day (N= 3)	26.51[19.5;55.2](3)	20.93[20.2;21.7](2)	18.31[18.2;66.9](3)	5.27[3.8;6.3](3)	4.00[3.0;4.0](3)
	Fast 25 mg/day (N= 6)	18.92[4.6;466.8](6)	21.51[17.5;516.7](5)	17.56[3.2;468.6](6)	12.13[2.5;108.0](6)	1.25[0.7;3.0](6)
	Fast 50 mg/day (N= 4)	63.40[23.0;285.0](4)	88.08[24.5;284.8](3)	49.37[21.8;240.5](4)	15.81[6.3;50.6](4)	1.55[1.0;3.1](4)
	Fast 100 mg/day (N= 6)	125.06[28.6;492.7](5)	140.16[98.5;561.3](4)	101.35[2.2;492.1](6)	28.15[3.3;82.0](6)	1.34[1.0;8.0](6)

Cycle and day of sampling	Treatment	AUC 0-24h (h.ng/mL)	AUC inf (h.ng/mL)	AUC (0-tlast) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
	Fast 200 mg/day (N= 5)	379.96[57.5;522.8](4)	415.82[409.9;421.7](2)	374.37[59.4;531.2](4)	43.40[6.9;104.0](4)	3.61[1.6;24.2](4)
	Fast 300 mg/day (N= 6)	437.47[89.6;3638.0](4)	757.19[154.2;3712.3](3)	739.14[89.6;5445.4](5)	144.00[13.0;440.0](5)	3.77[1.5;8.0](5)
	Fast 400 mg/day (N= 11)	1201.96[67.7;8744.6](8)	590.73[82.5;5760.8](7)	1033.49[67.3;8754.9](8)	183.15[5.4;692.0](8)	5.00[0.9;8.1](8)

Values are Median [Min ; Max] (n)

Summary of primary PK parameters for BEZ235, HGC Fed

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	AUC(0-inf) (h.ng/mL)	AUC(0-tlast) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
Cycle 1 Day 1	Fed 300 mg/day (N= 6)	680.39[257.5;4270.8](6)	696.53[275.1;1565.9](4)	680.37[257.5;4283.6](6)	120.50[40.9;318.0](6)	3.98[1.5;8.0](6)
	Fed 400 mg/day (N= 3)	544.65[318.9;8652.3](3)	610.63[338.1;8724.6](3)	542.43[318.1;8667.1](3)	94.70[27.9;629.0](3)	4.50[4.3;8.0](3)
	Fed 700 mg/day (N= 5)	1253.47[256.0;10868.6](4)	246.07[246.1;246.1](1)	2129.78[209.7;10789.6](5)	116.00[43.8;844.0](5)	4.02[2.1;24.0](5)
	Fed 1100 mg/day (N= 4)	280.92[264.8;11967.3](3)	293.30[285.0;13732.6](3)	4473.63[264.8;12056.9](4)	275.90[25.8;852.0](4)	7.22[4.0;8.0](4)
Cycle 1 Day 8	Fed 300 mg/day (N= 6)	3208.65[249.4;11077.7](6)	3308.50[352.6;11139.7](4)	3210.40[250.9;11095.6](6)	418.00[30.5;1220.0](6)	3.95[2.0;8.0](6)
	Fed 400 mg/day (N= 3)	1766.88[337.3;3196.4](2)	1795.66[351.4;3240.0](2)	405.27[335.0;3205.8](3)	50.10[28.8;329.0](3)	3.00[2.0;8.1](3)
	Fed 700 mg/day (N= 5)	11380.24[83.7;27287.8](4)	7567.41[74.2;15060.6](2)	12628.66[70.3;27396.5](5)	926.00[25.4;1970.0](5)	4.17[1.6;8.0](5)

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	AUC(0-inf) (h.ng/mL)	AUC(0-tlast) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)
Cycle 1 Day 28	Fed 1100 mg/day (N= 4)	931.22[480.7;12514.9](4)	970.76[542.2;13159.7](4)	933.17[479.7;12655.8](4)	100.35[33.8;1120.0](4)	4.50[0.5;6.5](4)
	Fed 300 mg/day (N= 6)	5781.64[427.2;15279.4](4)	7186.90[442.5;15936.3](3)	5322.22[433.2;15287.1](5)	301.00[27.1;1340.0](5)	6.00[1.8;24.2](5)
	Fed 400 mg/day (N= 3)	406.71[211.6;1045.4](3)	431.15[256.1;1144.2](3)	417.97[211.6;1075.0](3)	40.80[31.2;125.0](3)	2.08[2.0;8.0](3)
	Fed 700 mg/day (N= 5)	4385.64[204.4;52940.0](4)	4484.06[212.1;65661.0](4)	4385.79[203.2;52940.0](4)	421.75[28.9;3840.0](4)	4.63[3.0;6.0](4)
	Fed 1100 mg/day (N= 4)	604.35[604.4;604.4](1)		612.82[612.8;612.8](1)	46.10[46.1;46.1](1)	4.00[4.0;4.0](1)

Values are Median [Min ; Max] (n)

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Day comparisons –HGC Fast patients (FAS)

			Day Comparison	
			____90% CI____	
PK Parameter (unit)	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	D8:D1	1.41	1.02	1.95
	D28:D8	1.23	0.88	1.7
C_{max} (ng/mL)	D8:D1	1.4	1.05	1.88
	D28:D8	1.07	0.79	1.46

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Day comparisons –HGC Fed patients (FAS)

			Day Comparison	
			____90% CI____	
PK Parameter (unit)	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	D8:D1	1.8	0.96	3.37
	D28:D8	1.03	0.5	2.13
C_{max} (ng/mL)	D8:D1	1.63	0.99	2.7
	D28:D8	0.83	0.47	1.47

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Estimation of the effects of food intake– Day 1 All HGC patients (FAS)

					Food Effect Comparison		
						____90% CI____	
PK Parameter (unit)	**Category***	**n****	**Adjusted Geo-mean**	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0\text{-}24h)}$ (ng.h/mL)	300mg HGC Fed	6	816.91	Fast:Fed	0.26	0.1	0.63
	300mg HGC Fast	5	210.06				
	400mg HGC Fed	3	963.52				
	400mg HGC Fast	10	247.76				
C_{max} (ng/mL)	300mg HGC Fed	6	104.38	Fast:Fed	0.19	0.08	0.43
	300mg HGC Fast	6	19.76				
	400mg HGC Fed	3	135.43				
	400mg HGC Fast	11	25.63				

- Category* : classification according to Dose x food intake status
- n** = number of subjects with non-missing values

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Estimation of the effect of food intake– Day 8 All HGC patients (FAS)

					Food Effect Comparison		
						90% CI	
PK Parameter (unit)	**Category***	**N****	**Adjusted Geo-mean**	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0-24h)}$ (ng.h/mL)	300mg HGC Fed	6	1675.34	Fast:Fed	0.25	0.06	1.07
	300mg HGC Fast	6	425.07				
	400mg HGC Fed	2	1697.57				
	400mg HGC Fast	9	430.71				
C_{max} (ng/mL)	300mg HGC Fed	6	174.4	Fast:Fed	0.39	0.13	1.2
	300mg HGC Fast	6	67.89				
	400mg HGC Fed	3	147.77				
	400mg HGC Fast	10	57.53				

- Category* : classification according to Dose x food intake status
- n** = number of subjects with non-missing values

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Estimation of the effects of food intake– Day 28 All HGC patients (FAS)

					Food Effect Comparison		
						90% CI	
PK Parameter (unit)	**Category***	**n****	**Adjusted Geo-mean**	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**
$AUC_{(0-24h)}$ (ng.h/mL)	300mg HGC Fed	4	1841.75	Fast:Fed	0.48	0.1	2.22
	300mg HGC Fast	4	886.06				
	400mg HGC Fed	3	1191.65				
	400mg HGC Fast	8	573.3				
C_{max} (ng/mL)	300mg HGC Fed	5	179.84	Fast:Fed	0.74	0.2	2.7
	300mg HGC Fast	5	133.09				
	400mg HGC Fed	3	104				

					Food Effect Comparison		
						90% CI	
PK Parameter (unit)	Category*	n**	Adjusted Geo-mean	Comparison(s)	Adjusted Geo-mean Ratio	Lower	Upper
	400mg HGC Fast	8	76.96				

- Category* : classification according to Dose x food intake status
- n** = number of subjects with non-missing values

BEZ235 SDS single agent group

Summary of primary PK parameters for BEZ235, SDS Caps A-FAS

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
Cycle 1 Day 1	SDS caps A 400 mg/day (N= 5)	2247.84 [968.9;3526.8](2)	131.00 [53.8;405.0](5)	4.00 [2.0;8.0](5)	3.72 [3.7;3.8](2)	
	SDS caps A 800 mg/day (N= 6)	2543.62 [704.9;15862.0](3)	164.00 [36.5;1290.0](6)	6.00 [4.0;8.0](6)	21.20 [21.2;21.2](1)	
	SDS caps A 1000 mg/day (N= 11)	2906.34 [197.3;12233.2](9)	309.00 [25.2;771.0](11)	6.00 [2.0;8.0](11)	4.02 [1.6;8.2](6)	
Cycle 1 Day 8	SDS caps A 400 mg/day (N= 5)	10201.24 [1102.6;13949.2](4)	982.00 [107.0;1450.0](5)	4.00 [2.0;6.0](5)	4.20 [3.8;8.3](4)	11.31 [11.3;11.3](1)
	SDS caps A 800 mg/day (N= 6)	19769.65 [4791.8;50114.5](4)	1000.00 [362.0;3960.0](5)	6.00 [4.0;8.0](5)	11.87 [10.5;13.3](2)	13.22 [11.4;15.1](2)
	SDS caps A 1000 mg/day (N= 11)	11725.47 [1100.4;46817.5](8)	929.50 [142.0;3230.0](10)	6.00 [2.0;22.0](10)	5.10 [4.7;5.5](2)	3.53 [0.3;21.8](6)
Cycle 1 Day 28	SDS caps A 400 mg/day (N= 5)	19555.36 [6309.1;32801.6](2)	826.00 [192.0;1820.0](4)	5.00 [2.0;8.0](4)	2.61 [1.4;3.8](2)	9.30 [9.3;9.3](1)
	SDS caps A 800 mg/day (N= 6)	25404.92 [3558.4;47251.5](2)	1940.00 [307.0;3890.0](4)	4.00 [2.0;8.1](4)	4.11 [4.1;4.1](1)	

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
	SDS caps A 1000 mg/day (N= 11)	14087.89 [6134.8;73801.2](4)	701.00 [76.4;4100.0](6)	4.00 [4.0;8.0](6)	4.10 [3.2;5.0](2)	4.78 [1.5;8.0](2)

Values are Median [Min ; Max] (n)

- Patients with at least six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D28 and no vomiting within the 4 hours post-dose on the day of PK sampling were included in the analysis.

Summary of primary PK parameters for BEZ235, SDS Sachet-FAS

Cycle and day of sampling	SDS sachet (mg/day)	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
Cycle 1 Day 1	800 (N= 6)	982.4 [492.7;10545.0] (6)	191.00 [38.2;656.0] (6)	1.53 [1.0;24.3] (6)	6.72 [3.1;19.2] (5)	
	1000 (N= 10)	5685.26 [1318.7;17533.5] (10)	489.50 [120.0;1090.0] (10)	5.04 [1.1;8.0] (10)	5.01 [2.8;7.8] (5)	
	1200 (N= 24)	1895.69 [499.4;15868.1] (17)	194.50 [25.8;882.0] (20)	4.01 [1.0;23.5] (20)	5.33 [1.9;8.5] (13)	
	1400 (N= 14)	5291.62 [1366.4;28890.4] (9)	441.00 [125.0;2720.0] (13)	7.98 [1.0;24.1] (13)	4.97 [1.7;7.2] (6)	
	1600 (N= 7)	2563.78 [1331.6;6849.6] (7)	251.00 [163.0;599.0] (7)	6.00 [1.0;8.0] (7)	4.29 [3.8;6.1] (4)	
Cycle 1 Day 8	800 (N= 6)	6959.56 [767.2;13434.4] (3)	814.00 [116.0;1060.0] (3)	4.00 [1.0;6.0] (3)	6.67 [4.1;9.2] (2)	8.83 [1.6;17.4] (3)
	1000 (N= 10)	19423.08 [4499.0;39154.2] (8)	1280.00 [353.0;3070.0] (9)	4.07 [2.0;8.2] (9)	9.68 [4.0;14.1] (5)	2.89 [1.3;11.4] (8)
	1200 (N= 24)	13113.03 [538.5;53654.9] (18)	1195.00 [134.0;3760.0] (20)	4.00 [1.0;9.4] (20)	6.42 [4.0;26.5] (12)	9.05 [2.7;35.5] (15)
	1400 (N= 14)	7622.28 [1613.5;56383.2](5)	1180.50 [244.0;3220.0](6)	5.01[1.0;8.0](6)	5.69[2.1;40.1](3)	2.02[1.2;2.9](2)
	1600 (N= 7)	23828.46 [16284.5;38008.1](6)	1900.00 [434.0;2760.0](7)	5.93[2.0;8.0](7)	3.81[3.5;6.3](3)	6.85[2.4;13.7](6)
Cycle 1 Day 28	800 (N= 6)	5888.51 [2981.8;13649.0](3)	668.00 [410.0;705.0](3)	2.03[1.0;4.0](3)	4.67[3.6;53.3](3)	3.78[1.3;17.6](3)

Cycle and day of sampling	SDS sachet (mg/day)	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
	1000 (N= 10)	13571.59 [5246.6;34226.5](5)	1280.00 [475.0;2200.0](5)	4.00[4.0;4.0](5)	5.89[3.7;13.8](5)	7.29[2.0;11.6](5)
	1200 (N= 24)	17996.82 [2618.8;53308.0](15)	1335.00 [273.0;3680.0](16)	3.04[1.0;8.0](16)	6.03[3.2;21.6](12)	5.68[1.4;27.5](12)
	1400 (N= 14)	18043.24 [1632.6;45678.1](5)	1010.00 [367.0;2590.0](5)	4.00[1.2;8.0](5)	11.03[3.6;37.1](4)	2.98[2.5;3.5](2)
	1600 (N= 7)	13729.30 [7253.7;26611.1](4)	977.00 [394.0;2080.0](5)	4.00[2.0;6.0](5)	3.85[3.2;3.9](3)	4.27[1.1;13.8](4)

Values are Median [Min ; Max] (n)

- Patients with at least six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D28 and no vomiting within the 4 hours post-dose on the day of PK sampling were included in the analysis.

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Day 1 / Day 8 comparison, SDS Sachet-FAS

					Profile Day Comparison		
						90% CI	
PK Parameter (unit)	Dose x Day	n*	Adjusted Geo-mean	Comparison(s)	Adjusted Geo-mean Ratio	Lower	Upper
AUC(0-24) (ng.h/mL)	800mg D1	6	1496.64	D8:D1	4.93	3.91	6.21
	800mg D8	3	7371.96				
	1000mg D1	10	4180.6				
	1000mg D8	8	20592.26				
	1200mg D1	17	2774.59				
	1200mg D8	18	13666.72				
	1400mg D1	9	3642.37				
	1400mg D8	5	17941.11				
	1600mg D1	7	3470.45				
	1600mg D8	6	17094.27				
Cmax (ng/mL)	800mg D1	6	163.05	D8:D1	4.36	3.59	5.31
	800mg D8	3	711.5				
	1000mg D1	10	354.2				
	1000mg D8	9	1545.66				
	1200mg D1	20	254.59				
	1200mg D8	20	1110.98				
	1400mg D1	13	377.17				
	1400mg D8	6	1645.87				
	1600mg D1	7	296.46				
	1600mg D8	7	1293.68				

					Profile Day Comparison		
						90% CI	
PK Parameter (unit)	**Dose x Day**	**n***	**Adjusted Geo-mean**	**Comparison(s)**	**Adjusted Geo-mean Ratio**	**Lower**	**Upper**

Note: - n* = number of subjects with non-missing values

- Results are based on the following Model:

ln(parameter) = a + Dose + Day + Patient + error

Patient effect is random. Other effects are fixed. Dose is treated as categorical data.

- Data for patients with less than six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the cycle day and vomiting within the 4 hours post-dose on the day of PK sampling were excluded from the analysis.

Summary of statistical analysis of primary PK parameters for plasma BEZ235 – Day 8 / Day 28 comparison, SDS Sachet-FAS

					Profile Day Comparison		
						90% CI	
PK Parameter (unit)	Dose x Day	n*	Adjusted Geo-mean	Comparison(s)	Adjusted Geo-mean Ratio	Lower	Upper
AUC(0-24) (ng.h/mL)	800mg D8	3	7371.96	D28:D8	0.89	0.69	1.15
	800mg D28	3	6590.5				
	1000mg D8	8	20592.26				
	1000mg D28	5	18409.38				
	1200mg D8	18	13666.72				
	1200mg D28	15	12217.98				
	1400mg D8	5	17941.11				
	1400mg D28	5	16039.27				
	1600mg D8	6	17094.27				
	1600mg D28	4	15282.2				
Cmax (ng/mL)	800mg D8	3	711.5	D28:D8	0.91	0.73	1.14
	800mg D28	3	649.6				
	1000mg D8	9	1545.66				
	1000mg D28	5	1411.18				
	1200mg D8	20	1110.98				
	1200mg D28	16	1014.32				
	1400mg D8	6	1645.87				
	1400mg D28	5	1502.67				
	1600mg D8	7	1293.68				
	1600mg D28	5	1181.12				

Note: - n* = number of subjects with non-missing values
- Results are based on the following Model:
ln(parameter) = a + Dose + Day + Patient + error
Patient effect is random. Other effects are fixed. Dose is treated as categorical data.
- Data for patients with less than six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the cycle day and vomiting within the 4 hours post-dose on the day of PK sampling were excluded from the analysis.

Summary of primary PK parameters for BEZ235, SDS Caps B-FAS

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
Cycle 1 Day 1	SDS caps B 800 mg/day (N= 11)	1855.39 [465.3;13146.5](10)	243.00 [21.3;1080.0](11)	4.00 [1.1;24.0](11)	4.85 [3.7;12.3](6)	
Cycle 1 Day 8	SDS caps B 800 mg/day (N= 11)	2960.60 [1028.0;33766.4](10)	298.00 [104.0;2130.0](10)	5.00 [2.0;8.1](10)	5.53 [4.8;11.5](7)	2.36 [0.3;11.1](9)
Cycle 1 Day 28	SDS caps B 800 mg/day (N= 11)	4506.66 [1790.9;51961.1](8)	446.50 [203.0;3210.0](8)	4.00 [2.0;8.0](8)	7.08 [3.7;8.6](5)	2.02 [0.3;17.1](7)

- Patients with at least six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D28 and no vomiting within the 4 hours post-dose on the day of PK sampling were included in the analysis.

BEZ235 SDS in combination with trastuzumab

Summary of primary PK parameters for BEZ235, SDS + Trastuzumab -FAS

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
Cycle 1 Day 1	Caps A 400 mg/day + T (N= 3)	5515.94 [5515.9;5515.9](1)	352.00 [324.0;699.0](3)	6.05 [6.0;8.0](3)		
	Sachet 600 mg/day + T (N= 17)	4331.95 [754.0;22385.2](15)	346.00 [53.6;2080.0](16)	4.23 [1.8;24.0](16)	5.12 [1.6;14.6](10)	
	Sachet 800 mg/day + T (N= 10)	6830.65 [593.3;12629.5](8)	606.00 [74.8;1210.0](10)	6.96 [2.0;24.3](10)	5.31 [4.0;12.9](3)	
Cycle 1 Day 8	Caps A 400 mg/day + T (N= 3)	29681.34 [16991.6;68871.2](3)	1630.00 [1340.0;4050.0](3)	6.00 [4.0;8.0](3)	12.64[7.4;18.5](3)	5.38 [5.4;5.4](1)
	Sachet 600 mg/day + T (N= 17)	13419.26 [238.8;29301.9](15)	998.00 [32.6;2320.0](15)	4.07 [0.0;8.0](15)	5.89 [4.5;17.2](9)	4.15 [0.9;11.6](14)
	Sachet 800 mg/day + T (N= 10)	18805.82 [7714.5;26052.0](6)	1185.00 [636.0;2170.0](6)	4.04 [2.0;8.0](6)	8.00 [5.3;9.5](4)	2.13 [1.1;37.9](5)
Cycle 1 Day 28	Caps A 400 mg/day + T (N= 3)	8604.48 [1251.3;15957.7](2)	1350.00 [170.0;1700.0](3)	4.00 [4.0;4.0](3)	6.48 [6.0;7.0](2)	0.23 [0.2;0.2](1)
	Sachet 600 mg/day + T (N= 17)	7756.11 [2375.3;43839.3](14)	625.00 [293.0;2730.0](15)	4.00 [1.0;23.9](15)	5.73 [3.6;12.8](11)	1.96 [0.2;16.3](13)

Cycle and day of sampling	Treatment	AUC(0-24h) (h.ng/mL)	Cmax (ng/mL)	Tmax (h)	T(1/2) (h)	Racc (h)
	Sachet 800 mg/day + T (N= 10)	13197.57 [9008.0;22497.1](3)	1130.00 [776.0;2170.0](3)	4.00 [4.0;4.0](3)	6.77 [6.0;7.1](3)	1.04 [1.0;1.0](2)

Values are Median [Min ; Max] (n)

- Patients with at least six continuous days of daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D28 and no vomiting within the 4 hours post-dose on the day of PK sampling were included in the analysis.

Safety Results

Adverse Events by System Organ Class

BEZ235 HGC group

Frequent AEs (more than or equal to 5 percent), regardless of study drug relationship, by system organ class – HGC Fast (Safety set)

	Fast 10 mg/day	Fast 25 mg/day	Fast 50 mg/day	Fast 100 mg/day	Fast 200 mg/day	Fast 300 mg/day	Fast 400 mg/day	All HGC Fast
	N=3	N=6	N=4	N=6	N=5	N=6	N=11	N=41
System Organ Class	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-**Total**	3 (100.0)	6 (100.0)	3 (75.0)	6 (100.0)	5 (100.0)	5 (83.3)	11 (100.0)	39 (95.1)
Gastrointestinal disorders	2 (66.7)	2 (33.3)	2 (50.0)	5 (83.3)	4 (80.0)	5 (83.3)	7 (63.6)	27 (65.9)
General disorders and administration site conditions	2 (66.7)	5 (83.3)	1 (25.0)	3 (50.0)	5 (100.0)	3 (50.0)	7 (63.6)	26 (63.4)
Blood and lymphatic system disorders	2 (66.7)	3 (50.0)	0	3 (50.0)	3 (60.0)	1 (16.7)	3 (27.3)	15 (36.6)
Investigations	1 (33.3)	1 (16.7)	2 (50.0)	2 (33.3)	2 (40.0)	2 (33.3)	5 (45.5)	15 (36.6)
Musculoskeletal and connective tissue disorders	2 (66.7)	2 (33.3)	2 (50.0)	1 (16.7)	2 (40.0)	2 (33.3)	4 (36.4)	15 (36.6)
Metabolism and nutrition disorders	0	2 (33.3)	2 (50.0)	0	1 (20.0)	2 (33.3)	7 (63.6)	14 (34.1)
Respiratory, thoracic and mediastinal disorders	3 (100.0)	1 (16.7)	2 (50.0)	2 (33.3)	3 (60.0)	0	3 (27.3)	14 (34.1)
Eye disorders	0	1 (16.7)	2 (50.0)	1 (16.7)	3 (60.0)	1 (16.7)	3 (27.3)	11 (26.8)
Nervous system disorders	1 (33.3)	2 (33.3)	2 (50.0)	1 (16.7)	0	2 (33.3)	3 (27.3)	11 (26.8)
Skin and subcutaneous tissue disorders	0	2 (33.3)	2 (50.0)	2 (33.3)	3 (60.0)	1 (16.7)	0	10 (24.4)
Infections and infestations	1 (33.3)	1 (16.7)	2 (50.0)	2 (33.3)	0	2 (33.3)	1 (9.1)	9 (22.0)
Psychiatric disorders	0	1 (16.7)	1 (25.0)	1 (16.7)	0	1 (16.7)	3 (27.3)	7 (17.1)
Hepatobiliary disorders	0	0	0	2 (33.3)	1 (20.0)	1 (16.7)	0	4 (9.8)
Injury, poisoning and procedural complications	0	0	1 (25.0)	1 (16.7)	0	0	2 (18.2)	4 (9.8)
Vascular disorders	0	0	1 (25.0)	1 (16.7)	1 (20.0)	0	1 (9.1)	4 (9.8)
Neoplasms benign, malignant and unspecified (incl cysts and plyps)	1 (33.3)	0	1 (25.0)	0	0	1 (16.7)	0	3 (7.3)

System Organ Class	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment								

Frequent AEs (more than or equal to 5 percent), regardless of study drug relationship, by system organ class (SOC) – HGC Fed (Safety set)

System Organ Class	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
-Total	5 (83.3)	3 (100.0)	5 (100.0)	4 (100.0)	17 (94.4)
Gastrointestinal disorders	4 (66.7)	3 (100.0)	5 (100.0)	4 (100.0)	16 (88.9)
General disorders and administration site conditions	5 (83.3)	3 (100.0)	3 (60.0)	1 (25.0)	12 (66.7)
Investigations	4 (66.7)	2 (66.7)	3 (60.0)	0	9 (50.0)
Musculoskeletal and connective tissue disorders	4 (66.7)	3 (100.0)	1 (20.0)	1 (25.0)	9 (50.0)
Metabolism and nutrition disorders	3 (50.0)	2 (66.7)	1 (20.0)	2 (50.0)	8 (44.4)
Nervous system disorders	4 (66.7)	2 (66.7)	2 (40.0)	0	8 (44.4)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	2 (66.7)	2 (40.0)	2 (50.0)	8 (44.4)
Infections and infestations	3 (50.0)	2 (66.7)	0	1 (25.0)	6 (33.3)
Skin and subcutaneous tissue disorders	1 (16.7)	1 (33.3)	2 (40.0)	1 (25.0)	5 (27.8)
Blood and lymphatic system disorders	1 (16.7)	1 (33.3)	1 (20.0)	1 (25.0)	4 (22.2)
Eye disorders	2 (33.3)	1 (33.3)	0	1 (25.0)	4 (22.2)
Psychiatric disorders	0	2 (66.7)	1 (20.0)	0	3 (16.7)
Renal and urinary disorders	2 (33.3)	0	0	1 (25.0)	3 (16.7)
Vascular disorders	1 (16.7)	1 (33.3)	1 (20.0)	0	3 (16.7)
Hepatobiliary disorders	0	0	0	2 (50.0)	2 (11.1)
Injury, poisoning and procedural complications	1 (16.7)	1 (33.3)	0	0	2 (11.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (33.3)	0	0	1 (5.6)
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment					

BEZ235 SDS single agent group

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by system organ class SDS Caps A-Safety analysis set

System Organ Class	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
-**Total**	5 (100.0)	6 (100.0)	11 (100.0)	22 (100.0)
Gastrointestinal disorders	5 (100.0)	6 (100.0)	11 (100.0)	22 (100.0)
General disorders and administration site conditions	3 (60.0)	6 (100.0)	10 (90.9)	19 (86.4)
Metabolism and nutrition disorders	2 (40.0)	5 (83.3)	7 (63.6)	14 (63.6)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	4 (66.7)	5 (45.5)	10 (45.5)
Investigations	0	2 (33.3)	6 (54.5)	8 (36.4)
Skin and subcutaneous tissue disorders	2 (40.0)	3 (50.0)	3 (27.3)	8 (36.4)
Blood and lymphatic system disorders	1 (20.0)	2 (33.3)	3 (27.3)	6 (27.3)
Eye disorders	1 (20.0)	2 (33.3)	2 (18.2)	5 (22.7)
Musculoskeletal and connective tissue disorders	2 (40.0)	1 (16.7)	2 (18.2)	5 (22.7)
Infections and infestations	1 (20.0)	1 (16.7)	2 (18.2)	4 (18.2)
Renal and urinary disorders	1 (20.0)	1 (16.7)	2 (18.2)	4 (18.2)
Nervous system disorders	1 (20.0)	1 (16.7)	1 (9.1)	3 (13.6)
Hepatobiliary disorders	0	0	2 (18.2)	2 (9.1)
Psychiatric disorders	1 (20.0)	1 (16.7)	0	2 (9.1)

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by system organ class SDS Sachet-Safety analysis set

System Organ Class	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
-Total	6 (100.0)	10 (100.0)	24 (100.0)	14 (100.0)	7 (100.0)	61 (100.0)
Gastrointestinal disorders	5 (83.3)	10 (100.0)	24 (100.0)	13 (92.9)	7 (100.0)	59 (96.7)
General disorders and administration site conditions	6 (100.0)	9 (90.0)	20 (83.3)	10 (71.4)	5 (71.4)	50 (82.0)
Metabolism and nutrition disorders	2 (33.3)	6 (60.0)	19 (79.2)	11 (78.6)	2 (28.6)	40 (65.6)
Investigations	3 (50.0)	6 (60.0)	14 (58.3)	6 (42.9)	3 (42.9)	32 (52.5)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	5 (50.0)	14 (58.3)	5 (35.7)	2 (28.6)	27 (44.3)

System Organ Class	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Blood and lymphatic system disorders	4 (66.7)	4 (40.0)	7 (29.2)	6 (42.9)	5 (71.4)	26 (42.6)
Infections and infestations	2 (33.3)	5 (50.0)	11 (45.8)	5 (35.7)	3 (42.9)	26 (42.6)
Nervous system disorders	2 (33.3)	3 (30.0)	11 (45.8)	6 (42.9)	3 (42.9)	25 (41.0)
Skin and subcutaneous tissue disorders	2 (33.3)	2 (20.0)	8 (33.3)	7 (50.0)	5 (71.4)	24 (39.3)
Musculoskeletal and connective tissue disorders	2 (33.3)	4 (40.0)	9 (37.5)	1 (7.1)	3 (42.9)	19 (31.1)
Psychiatric disorders	1 (16.7)	2 (20.0)	5 (20.8)	3 (21.4)	4 (57.1)	15 (24.6)
Eye disorders	1 (16.7)	2 (20.0)	5 (20.8)	2 (14.3)	4 (57.1)	14 (23.0)
Renal and urinary disorders	0	0	4 (16.7)	2 (14.3)	3 (42.9)	9 (14.8)
Vascular disorders	0	1 (10.0)	4 (16.7)	1 (7.1)	1 (14.3)	7 (11.5)
Hepatobiliary disorders	2 (33.3)	0	4 (16.7)	0	0	6 (9.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	5 (20.8)	1 (7.1)	0	6 (9.8)
Cardiac disorders	1 (16.7)	0	2 (8.3)	1 (7.1)	1 (14.3)	5 (8.2)
Reproductive system and breast disorders	0	0	3 (12.5)	0	1 (14.3)	4 (6.6)

BEZ235 SDS in combination with trastuzumab

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by system organ class, SDS+Trastuzumab-Safety analysis set

System Organ Class	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
-Total	1 (100.0)	3 (100.0)	17 (100.0)	9 (100.0)	30 (100.0)
Gastrointestinal disorders	1 (100.0)	3 (100.0)	17 (100.0)	9 (100.0)	30 (100.0)
General disorders and administration site conditions	1 (100.0)	2 (66.7)	10 (58.8)	7 (77.8)	20 (66.7)
Metabolism and nutrition disorders	1 (100.0)	2 (66.7)	6 (35.3)	7 (77.8)	16 (53.3)
Investigations	0	2 (66.7)	6 (35.3)	6 (66.7)	14 (46.7)
Nervous system disorders	1 (100.0)	3 (100.0)	5 (29.4)	5 (55.6)	14 (46.7)
Skin and subcutaneous tissue disorders	0	3 (100.0)	6 (35.3)	3 (33.3)	12 (40.0)
Infections and infestations	0	2 (66.7)	6 (35.3)	3 (33.3)	11 (36.7)
Blood and lymphatic system disorders	0	1 (33.3)	4 (23.5)	5 (55.6)	10 (33.3)

System Organ Class	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
Musculoskeletal and connective tissue disorders	0	1 (33.3)	6 (35.3)	2 (22.2)	9 (30.0)
Psychiatric disorders	0	2 (66.7)	3 (17.6)	4 (44.4)	9 (30.0)
Eye disorders	0	1 (33.3)	3 (17.6)	2 (22.2)	6 (20.0)
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	4 (23.5)	1 (11.1)	6 (20.0)
Injury, poisoning and procedural complications	0	1 (33.3)	3 (17.6)	0	4 (13.3)
Cardiac disorders	1 (100.0)	0	0	1(11.1)	2 (6.7)
Vascular disorders	0	0	2 (11.8)	0	2 (6.7)

Most Frequently Reported AEs Overall by Preferred Term n (%)

BEZ235 HGC group

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term, HGC Fast – Safety analysis set

	Fast 10 mg/day N=3		Fast 25 mg/day N=6		Fast 50 mg/day N=4		Fast 100 mg/day N=6		Fast 200 mg/day N=5		Fast 300 mg/day N=6		Fast 400 mg/day N=11		All HGC Fast N=41	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	3 (100.0)	1 (33.3)	6 (100.0)	0	3 (75.0)	2 (50.0)	6 (100.0)	2 (33.3)	5 (100.0)	2 (40.0)	5 (83.3)	3 (50.0)	11 (100.0)	4 (36.4)	39 (95.1)	14 (34.1)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0	2 (50.0)	0	2 (33.3)	0	2 (40.0)	0	4 (66.7)	0	3 (27.3)	0	13 (31.7)	0
Diarrhoea	0	0	1 (16.7)	0	2 (50.0)	0	3 (50.0)	0	0	0	4 (66.7)	0	2 (18.2)	0	12 (29.3)	0
Anaemia	2 (66.7)	0	2 (33.3)	0	0	0	2 (33.3)	2 (33.3)	3 (60.0)	1 (20.0)	0	0	1 (9.1)	0	10 (24.4)	3 (7.3)
Asthenia	0	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)	0	3 (60.0)	1 (20.0)	1 (16.7)	1 (16.7)	3 (27.3)	0	10 (24.4)	2 (4.9)
Decreased appetite	0	0	1 (16.7)	0	1 (25.0)	0	0	0	1 (20.0)	0	2 (33.3)	1 (16.7)	5 (45.5)	0	10 (24.4)	1 (2.4)
Vomiting	1 (33.3)	0	1 (16.7)	0	1 (25.0)	0	2 (33.3)	1 (16.7)	1 (20.0)	0	1 (16.7)	0	3 (27.3)	0	10 (24.4)	1 (2.4)
Fatigue	0	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)	0	1 (20.0)	0	2 (33.3)	0	3 (27.3)	3 (27.3)	9 (22.0)	3 (7.3)
Constipation	1 (33.3)	0	0	0	2 (50.0)	0	0	0	1 (20.0)	0	3 (50.0)	0	1 (9.1)	0	8 (19.5)	0

	Fast 10 mg/day N=3		Fast 25 mg/day N=6		Fast 50 mg/day N=4		Fast 100 mg/day N=6		Fast 200 mg/day N=5		Fast 300 mg/day N=6		Fast 400 mg/day N=11		All HGC Fast N=41	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Abdominal pain	1 (33.3)	1 (33.3)	0	0	1 (25.0)	0	3 (50.0)	0	0	0	1 (16.7)	0	1 (9.1)	0	7 (17.1)	1 (2.4)
Dyspnoea	2 (66.7)	1 (33.3)	0	0	1 (25.0)	0	1 (16.7)	0	2 (40.0)	0	0	0	1 (9.1)	0	7 (17.1)	1 (2.4)
Pyrexia	0	0	2 (33.3)	0	0	0	1 (16.7)	0	2 (40.0)	0	1 (16.7)	0	1 (9.1)	0	7 (17.1)	0
Back pain	0	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)	0	0	0	0	0	2 (18.2)	0	5 (12.2)	0
Musculoskeletal pain	1 (33.3)	0	1 (16.7)	0	0	0	0	0	2 (40.0)	0	0	0	1 (9.1)	0	5 (12.2)	0
Alanine aminotransferase increased	1 (33.3)	0	1 (16.7)	0	0	0	0	0	0	0	0	0	2 (18.2)	0	4 (9.8)	0
Aspartate aminotransferase increased	0	0	1 (16.7)	0	0	0	1 (16.7)	0	0	0	0	0	2 (18.2)	1 (9.1)	4 (9.8)	1 (2.4)
Depression	0	0	1 (16.7)	0	0	0	0	0	0	0	1 (16.7)	0	2 (18.2)	0	4 (9.8)	0
Oedema peripheral	1 (33.3)	0	1 (16.7)	0	0	0	0	0	2 (40.0)	1 (20.0)	0	0	0	0	4 (9.8)	1 (2.4)
Oropharyngeal pain	1 (33.3)	0	1 (16.7)	0	0	0	1 (16.7)	0	0	0	0	0	1 (9.1)	0	4 (9.8)	0
Rash	0	0	2 (33.3)	0	1 (25.0)	0	1 (16.7)	0	0	0	0	0	0	0	4 (9.8)	0
Urinary tract infection	0	0	0	0	1 (25.0)	0	2 (33.3)	0	0	0	0	0	1 (9.1)	0	4 (9.8)	0
Abdominal distension	1 (33.3)	0	0	0	0	0	0	0	2 (40.0)	0	0	0	0	0	3 (7.3)	0
Abdominal pain upper	0	0	0	0	1 (25.0)	0	0	0	1 (20.0)	1 (20.0)	0	0	1 (9.1)	0	3 (7.3)	1 (2.4)
Cough	1 (33.3)	0	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (9.1)	0	3 (7.3)	0

	Fast 10 mg/day N=3		Fast 25 mg/day N=6		Fast 50 mg/day N=4		Fast 100 mg/day N=6		Fast 200 mg/day N=5		Fast 300 mg/day N=6		Fast 400 mg/day N=11		All HGC Fast N=41	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Dysphagia	1 (33.3)	1 (33.3)	0	0	0	0	0	0	0	0	0	0	2 (18.2)	0	3 (7.3)	1 (2.4)
Flank pain	1 (33.3)	0	0	0	1 (25.0)	1 (25.0)	0	0	1 (20.0)	0	0	0	0	0	3 (7.3)	1 (2.4)
Gastrooesophageal reflux disease	1 (33.3)	0	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (9.1)	0	3 (7.3)	0
Hyperbilirubinaemia	0	0	0	0	0	0	1 (16.7)	0	1 (20.0)	1 (20.0)	1 (16.7)	0	0	0	3 (7.3)	1 (2.4)
Hypokalaemia	0	0	0	0	1 (25.0)	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (9.1)	0	3 (7.3)	1 (2.4)
Lymphadenopathy	0	0	1 (16.7)	0	0	0	0	0	0	0	0	0	2 (18.2)	0	3 (7.3)	0
Neck pain	1 (33.3)	0	0	0	0	0	1 (16.7)	0	0	0	0	0	1 (9.1)	0	3 (7.3)	0
Pain	0	0	0	0	0	0	0	0	0	0	0	0	3 (27.3)	0	3 (7.3)	0
Pleural effusion	1 (33.3)	0	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (9.1)	1 (9.1)	3 (7.3)	1 (2.4)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term, HGC Fed – Safety analysis set

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	5 (83.3)	0	3 (100.0)	3 (100.0)	5 (100.0)	1 (20.0)	4 (100.0)	3 (75.0)	17 (94.4)	7 (38.9)
Diarrhoea	4 (66.7)	0	1 (33.3)	0	4 (80.0)	1 (20.0)	2 (50.0)	0	11 (61.1)	1 (5.6)
Nausea	1 (16.7)	0	2 (66.7)	0	3 (60.0)	0	1 (25.0)	0	7 (38.9)	0
Vomiting	0	0	2 (66.7)	0	4 (80.0)	0	1 (25.0)	0	7 (38.9)	0
Fatigue	1 (16.7)	0	2 (66.7)	0	2 (40.0)	0	1 (25.0)	0	6 (33.3)	0
Pyrexia	2 (33.3)	0	2 (66.7)	0	0	0	1 (25.0)	0	5 (27.8)	0
Stomatitis	0	0	1 (33.3)	0	3 (60.0)	0	1 (25.0)	0	5 (27.8)	0
Cough	2 (33.3)	0	1 (33.3)	0	0	0	1 (25.0)	0	4 (22.2)	0
Dyspnoea	2 (33.3)	0	2 (66.7)	0	0	0	0	0	4 (22.2)	0
Abdominal pain	2 (33.3)	0	0	0	0	0	1 (25.0)	0	3 (16.7)	0
Abdominal pain upper	1 (16.7)	0	2 (66.7)	0	0	0	0	0	3 (16.7)	0
Alanine aminotransferase increased	2 (33.3)	0	0	0	1 (20.0)	0	0	0	3 (16.7)	0
Anaemia	1 (16.7)	0	1 (33.3)	1 (33.3)	0	0	1 (25.0)	0	3 (16.7)	1 (5.6)
Asthenia	1 (16.7)	0	1 (33.3)	0	1 (20.0)	0	0	0	3 (16.7)	0
Back pain	0	0	1 (33.3)	0	1 (20.0)	0	1 (25.0)	0	3 (16.7)	0
Dizziness	2 (33.3)	0	1 (33.3)	0	0	0	0	0	3 (16.7)	0
Headache	0	0	1 (33.3)	0	2 (40.0)	0	0	0	3 (16.7)	0
Aspartate aminotransferase increased	2 (33.3)	0	0	0	0	0	0	0	2 (11.1)	0

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Cataract	1 (16.7)	0	0	0	0	0	1 (25.0)	0	2 (11.1)	0
Chills	2 (33.3)	0	0	0	0	0	0	0	2 (11.1)	0
Decreased appetite	2 (33.3)	0	0	0	0	0	0	0	2 (11.1)	0
Dehydration	1 (16.7)	0	1 (33.3)	0	0	0	0	0	2 (11.1)	0
Epistaxis	0	0	0	0	2 (40.0)	0	0	0	2 (11.1)	0
Hyperbilirubinaemia	0	0	0	0	0	0	2 (50.0)	1 (25.0)	2 (11.1)	1 (5.6)
Hypokalaemia	0	0	1 (33.3)	0	0	0	1 (25.0)	0	2 (11.1)	0
Insomnia	0	0	1 (33.3)	0	1 (20.0)	0	0	0	2 (11.1)	0
Myalgia	1 (16.7)	0	1 (33.3)	0	0	0	0	0	2 (11.1)	0
Oedema peripheral	1 (16.7)	0	1 (33.3)	0	0	0	0	0	2 (11.1)	0
Oropharyngeal pain	1 (16.7)	0	0	0	1 (20.0)	0	0	0	2 (11.1)	0
Pruritus	0	0	1 (33.3)	0	0	0	1 (25.0)	0	2 (11.1)	0
Rash	0	0	0	0	2 (40.0)	0	0	0	2 (11.1)	0
Weight decreased	1 (16.7)	0	0	0	1 (20.0)	0	0	0	2 (11.1)	0
Abdominal pain lower	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Age-related macular degeneration	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Anterior chamber inflammation	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Arthralgia	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Ascites	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (5.6)	1 (5.6)
Ataxia	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Bile duct obstruction	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (5.6)	1 (5.6)

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Blister	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Blood creatinine increased	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Blood uric acid increased	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Bone pain	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Breath odour	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Catheter site rash	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Chest discomfort	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Conjunctivitis viral	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Constipation	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Contusion	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Corneal opacity	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Dental caries	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Device occlusion	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Dry mouth	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Dysgeusia	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Dyspepsia	1 (16.7)	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Dysphagia	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Dysuria	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Electrocardiogram QT prolonged	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Eye irritation	0	0	0	0	0	0	0	0	1 (5.6)	0
Eyelid oedema	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Face oedema	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Flank pain	0	0	1 (33.3)	0	0	0	1 (25.0)	0	1 (5.6)	0
Flatulence	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Fungal infection	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Glossitis	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Glycosylated haemoglobin increased	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Grand mal convulsion	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (5.6)	1 (5.6)
Haemoptysis	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Hiccups	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Hypercholesterolaemia	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Hyperglycaemia	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Hyperhidrosis	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Hyperlipasaemia	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (5.6)	1 (5.6)
Hypertension	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Hypomagnesaemia	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Hypotension	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Influenza like illness	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Leukaemoid reaction	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Leukocyturia	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Lip blister	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Lip swelling	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Lipase increased	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (5.6)	1 (5.6)
Malaise	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Mental disorder	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Muscle spasms	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Muscular weakness	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Musculoskeletal chest pain	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Musculoskeletal pain	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Nasal congestion	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Neck pain	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Neuropathy peripheral	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Non-cardiac chest pain	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Oral herpes	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Pain	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Pain in extremity	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Pallor	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Pharyngeal inflammation	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Renal failure acute	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Respiratory tract infection	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Skin neoplasm bleeding	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Somnolence	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Subileus	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0

	Fed 300 mg/day N=6		Fed 400 mg/day N=3		Fed 700 mg/day N=5		Fed 1100 mg/day N=4		All HGC Fed N=18	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Thrombocytopenia	0	0	0	0	1 (20.0)	0	0	0	1 (5.6)	0
Transaminases increased	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (5.6)	1 (5.6)
Tumour pain	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (5.6)	1 (5.6)
Upper respiratory tract infection	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Urinary tract infection	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Urinary tract infection fungal	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0
Vision blurred	0	0	0	0	0	0	1 (25.0)	0	1 (5.6)	0
Weight increased	1 (16.7)	0	0	0	0	0	0	0	1 (5.6)	0
Wound secretion	0	0	1 (33.3)	0	0	0	0	0	1 (5.6)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row

BEZ235 SDS single agent group

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term, SDS Caps A-Safety analysis set

	SDS caps A 400 mg/day N=5		SDS caps A 800 mg/day N=6		SDS caps A 1000 mg/day N=11		All SDS caps A N=22	
Preferred Term	All grades n (%)	Grade ¾ n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	5 (100.0)	2 (40.0)	6 (100.0)	4 (66.7)	11 (100.0)	9 (81.8)	22 (100.0)	15 (68.2)
Nausea	3 (60.0)	0 (0)	5 (83.3)	0 (0)	8 (72.7)	0 (0)	16 (72.7)	0 (0)
Diarrhoea	2 (40.0)	0	4 (66.7)	0	8 (72.7)	1 (9.1)	14 (63.6)	1 (4.5)
Vomiting	2 (40.0)	0	5 (83.3)	0	6 (54.5)	0	13 (59.1)	0
Asthenia	2 (40.0)	0	5 (83.3)	0	4 (36.4)	0	11 (50.0)	0
Decreased appetite	1 (20.0)	0	3 (50.0)	0	6 (54.5)	1 (9.1)	10 (45.5)	1 (4.5)
Fatigue	0	0	2 (33.3)	1 (16.7)	5 (45.5)	2 (18.2)	7 (31.8)	3 (13.6)
Constipation	1 (20.0)	0	3 (50.0)	0	1 (9.1)	0	5 (22.7)	0
Abdominal pain	1 (20.0)	0	1 (16.7)	0	2 (18.2)	1 (9.1)	4 (18.2)	1 (4.5)
Abdominal pain upper	0	0	2 (33.3)	0	2 (18.2)	0	4 (18.2)	0
Anaemia	1 (20.0)	1 (20.0)	1 (16.7)	0	2 (18.2)	1 (9.1)	4 (18.2)	2 (9.1)
Oedema peripheral	1 (20.0)	0	1 (16.7)	0	2 (18.2)	0	4 (18.2)	0
Stomatitis	1 (20.0)	0	2 (33.3)	0	1 (9.1)	1 (9.1)	4 (18.2)	1 (4.5)
Blood creatinine increased	0	0	1 (16.7)	0	2 (18.2)	1 (9.1)	3 (13.6)	1 (4.5)
Cough	0	0	1 (16.7)	0	2 (18.2)	0	3 (13.6)	0
Dyspepsia	0	0	2 (33.3)	0	1 (9.1)	0	3 (13.6)	0
Dyspnoea	1 (20.0)	1 (20.0)	1 (16.7)	1 (16.7)	1 (9.1)	0	3 (13.6)	2 (9.1)
Pain	1 (20.0)	0	1 (16.7)	0	1 (9.1)	0	3 (13.6)	0
Rash	1 (20.0)	0	2 (33.3)	0	0	0	3 (13.6)	0
Aspartate aminotransferase increased	0	0	1 (16.7)	1 (16.7)	1 (9.1)	1 (9.1)	2 (9.1)	2 (9.1)
Back pain	1 (20.0)	0	1 (16.7)	0	0	0	2 (9.1)	0
Blood bilirubin increased	0	0	1 (16.7)	0	1 (9.1)	1 (9.1)	2 (9.1)	1 (4.5)
Dry mouth	0	0	1 (16.7)	0	1 (9.1)	0	2 (9.1)	0
Haemoptysis	1 (20.0)	0	0	0	1 (9.1)	0	2 (9.1)	0
Hyperbilirubinaemia	0	0	0	0	2 (18.2)	1 (9.1)	2 (9.1)	1 (4.5)
Hyperhidrosis	1 (20.0)	0	0	0	1 (9.1)	0	2 (9.1)	0
Non-cardiac chest pain	1 (20.0)	0	1 (16.7)	0	0	0	2 (9.1)	0
Pharyngitis	0	0	1 (16.7)	0	1 (9.1)	0	2 (9.1)	0

	SDS caps A 400 mg/day N=5		SDS caps A 800 mg/day N=6		SDS caps A 1000 mg/day N=11		All SDS caps A N=22	
	All grades	Grade ¾	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Small intestinal obstruction	1 (20.0)	1 (20.0)	0	0	1 (9.1)	1 (9.1)	2 (9.1)	2 (9.1)
Transaminases increased	0	0	1 (16.7)	1 (16.7)	1 (9.1)	1 (9.1)	2 (9.1)	2 (9.1)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

- A patient with multiple adverse events is counted only once in the total row

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term, SDS sachet-Safety analysis set

	SDS Sachet 800 mg/day N=6		SDS Sachet 1000 mg/day N=10		SDS Sachet 1200 mg/day N=24		SDS Sachet 1400 mg/day N=14		SDS Sachet 1600 mg/day N=7		All SDS Sachet N=61	
	All grades	Grade 3/4	All grades	Grade ¾	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-**Total**	6 (100.0)	3 (50.0)	10 (100.0)	6 (60.0)	24 (100.0)	18 (75.0)	14 (100.0)	11 (78.6)	7 (100.0)	4 (57.1)	61 (100.0)	42 (68.9)
Nausea	5 (83.3)	0	7 (70.0)	2 (20.0)	20 (83.3)	1 (4.2)	12 (85.7)	1 (7.1)	5 (71.4)	0	49 (80.3)	4 (6.6)
Diarrhoea	2 (33.3)	0	8 (80.0)	0	20 (83.3)	1 (4.2)	11 (78.6)	3 (21.4)	5 (71.4)	0	46 (75.4)	4 (6.6)
Vomiting	2 (33.3)	0	5 (50.0)	1 (10.0)	16 (66.7)	2 (8.3)	10 (71.4)	1 (7.1)	6 (85.7)	0	39 (63.9)	4 (6.6)
Decreased appetite	1 (16.7)	0	4 (40.0)	0	14 (58.3)	1 (4.2)	6 (42.9)	1 (7.1)	2 (28.6)	0	27 (44.3)	2 (3.3)
Fatigue	4 (66.7)	0	3 (30.0)	0	8 (33.3)	3 (12.5)	5 (35.7)	3 (21.4)	3 (42.9)	0	23 (37.7)	6 (9.8)
Stomatitis	2 (33.3)	0	4 (40.0)	0	9 (37.5)	1 (4.2)	4 (28.6)	2 (14.3)	2 (28.6)	0	21 (34.4)	3 (4.9)
Asthenia	1 (16.7)	0	5 (50.0)	1 (10.0)	6 (25.0)	0	5 (35.7)	2 (14.3)	1 (14.3)	0	18 (29.5)	3 (4.9)
Anaemia	3 (50.0)	0	3 (30.0)	1 (10.0)	3 (12.5)	2 (8.3)	4 (28.6)	0	4 (57.1)	0	17 (27.9)	3 (4.9)
Weight decreased	0	0	1 (10.0)	0	10 (41.7)	0	3 (21.4)	0	1 (14.3)	0	15 (24.6)	0
Dehydration	2 (33.3)	0	2 (20.0)	1 (10.0)	4 (16.7)	1 (4.2)	5 (35.7)	1 (7.1)	0	0	13 (21.3)	3 (4.9)
Dyspnoea	1 (16.7)	0	2 (20.0)	1 (10.0)	8 (33.3)	4 (16.7)	1 (7.1)	0	1 (14.3)	0	13 (21.3)	5 (8.2)
Abdominal pain	1 (16.7)	0	0	0	5 (20.8)	0	2 (14.3)	0	4 (57.1)	0	12 (19.7)	0
Cough	0	0	1 (10.0)	0	6 (25.0)	2 (8.3)	4 (28.6)	0	1 (14.3)	0	12 (19.7)	2 (3.3)
Pyrexia	1 (16.7)	0	3 (30.0)	0	5 (20.8)	0	1 (7.1)	0	2 (28.6)	0	12 (19.7)	0
Rash	0	0	2 (20.0)	0	5 (20.8)	2 (8.3)	3 (21.4)	0	2 (28.6)	0	12 (19.7)	2 (3.3)
Blood creatinine increased	0	0	2 (20.0)	0	3 (12.5)	0	5 (35.7)	0	1 (14.3)	0	11 (18.0)	0
Pruritus	0	0	1 (10.0)	0	4 (16.7)	0	2 (14.3)	0	3 (42.9)	0	10 (16.4)	0

	SDS Sachet 800 mg/day N=6		SDS Sachet 1000 mg/day N=10		SDS Sachet 1200 mg/day N=24		SDS Sachet 1400 mg/day N=14		SDS Sachet 1600 mg/day N=7		All SDS Sachet N=61	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade ¾ n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Constipation	2 (33.3)	0	1 (10.0)	0	3 (12.5)	0	2 (14.3)	0	0	0	8 (13.1)	0
Dysgeusia	0	0	1 (10.0)	0	3 (12.5)	0	3 (21.4)	0	1 (14.3)	0	8 (13.1)	0
Dyspepsia	0	0	0	0	3 (12.5)	0	3 (21.4)	0	2 (28.6)	0	8 (13.1)	0
Hyperglycaemia	0	0	1 (10.0)	0	3 (12.5)	1 (4.2)	4 (28.6)	2 (14.3)	0	0	8 (13.1)	3 (4.9)
Thrombocytopenia	1 (16.7)	1 (16.7)	2 (20.0)	1 (10.0)	2 (8.3)	0	2 (14.3)	1 (7.1)	1 (14.3)	1 (14.3)	8 (13.1)	4 (6.6)
Abdominal pain upper	0	0	0	0	6 (25.0)	1 (4.2)	0	0	1 (14.3)	0	7 (11.5)	1 (1.6)
Epistaxis	0	0	1 (10.0)	0	3 (12.5)	0	3 (21.4)	0	0	0	7 (11.5)	0
Insomnia	1 (16.7)	0	2 (20.0)	0	1 (4.2)	0	1 (7.1)	0	2 (28.6)	0	7 (11.5)	0
Oedema peripheral	1 (16.7)	0	1 (10.0)	0	3 (12.5)	0	1 (7.1)	0	1 (14.3)	1 (14.3)	7 (11.5)	1 (1.6)
Oral pain	0	0	0	0	2 (8.3)	0	4 (28.6)	0	1 (14.3)	0	7 (11.5)	0
Aspartate aminotransferase increased	1 (16.7)	1 (16.7)	2 (20.0)	1 (10.0)	1 (4.2)	1 (4.2)	1 (7.1)	0	1 (14.3)	0	6 (9.8)	3 (4.9)
Back pain	0	0	1 (10.0)	0	3 (12.5)	0	0	0	2 (28.6)	0	6 (9.8)	0
Headache	2 (33.3)	0	0	0	1 (4.2)	0	3 (21.4)	0	0	0	6 (9.8)	0
Hypophosphataemia	0	0	0	0	5 (20.8)	3 (12.5)	1 (7.1)	0	0	0	6 (9.8)	3 (4.9)
Abdominal distension	0	0	1 (10.0)	0	2 (8.3)	0	1 (7.1)	0	1 (14.3)	0	5 (8.2)	0
Arthralgia	1 (16.7)	0	1 (10.0)	0	2 (8.3)	1 (4.2)	1 (7.1)	0	0	0	5 (8.2)	1 (1.6)
Dizziness	0	0	1 (10.0)	0	1 (4.2)	0	1 (7.1)	0	2 (28.6)	0	5 (8.2)	0
Hyperbilirubinaemia	2 (33.3)	1 (16.7)	0	0	3 (12.5)	0	0	0	0	0	5 (8.2)	1 (1.6)
Hypokalaemia	0	0	0	0	3 (12.5)	1 (4.2)	2 (14.3)	0	0	0	5 (8.2)	1 (1.6)
Hypomagnesaemia	0	0	0	0	3 (12.5)	0	2 (14.3)	0	0	0	5 (8.2)	0
Pain in extremity	0	0	1 (10.0)	0	2 (8.3)	0	1 (7.1)	0	1 (14.3)	0	5 (8.2)	0

	SDS Sachet 800 mg/day N=6		SDS Sachet 1000 mg/day N=10		SDS Sachet 1200 mg/day N=24		SDS Sachet 1400 mg/day N=14		SDS Sachet 1600 mg/day N=7		All SDS Sachet N=61	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade ¾ n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Urinary tract infection	0	0	1 (10.0)	1 (10.0)	3 (12.5)	0	1 (7.1)	1 (7.1)	0	0	5 (8.2)	2 (3.3)
Alanine aminotransferase increased	1 (16.7)	1 (16.7)	1 (10.0)	1 (10.0)	1 (4.2)	0	0	0	1 (14.3)	0	4 (6.6)	2 (3.3)
Haemorrhoids	0	0	0	0	1 (4.2)	0	3 (21.4)	0	0	0	4 (6.6)	0
Oropharyngeal pain	0	0	0	0	1 (4.2)	0	2 (14.3)	0	1 (14.3)	0	4 (6.6)	0
Pleural effusion	0	0	1 (10.0)	0	3 (12.5)	2 (8.3)	0	0	0	0	4 (6.6)	2 (3.3)
Vision blurred	1 (16.7)	0	1 (10.0)	0	0	0	1 (7.1)	0	1 (14.3)	0	4 (6.6)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term, SDS Caps B-Safety analysis set

	SDS caps B 800 mg/day N=11		All SDS caps B N=11	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	11 (100.0)	4 (36.4)	11 (100.0)	4 (36.4)
Asthenia	7 (63.6)	1 (9.1)	7 (63.6)	1 (9.1)
Diarrhoea	7 (63.6)	1 (9.1)	7 (63.6)	1 (9.1)
Vomiting	7 (63.6)	0 (0.0)	7 (63.6)	0 (0.0)
Decreased appetite	5 (45.5)	0 (0.0)	5 (45.5)	0 (0.0)
Nausea	5 (45.5)	0 (0.0)	5 (45.5)	0 (0.0)
Abdominal pain	3 (27.3)	0 (0.0)	3 (27.3)	0 (0.0)
Anaemia	3 (27.3)	1 (9.1)	3 (27.3)	1 (9.1)
Dyspnoea	3 (27.3)	1 (9.1)	3 (27.3)	1 (9.1)
Fatigue	3 (27.3)	0	3 (27.3)	0
Abdominal pain upper	2 (18.2)	0	2 (18.2)	0
Back pain	2 (18.2)	0	2 (18.2)	0
Constipation	2 (18.2)	0	2 (18.2)	0
Cough	2 (18.2)	0	2 (18.2)	0
Dehydration	2 (18.2)	0	2 (18.2)	0
Dizziness	2 (18.2)	0	2 (18.2)	0
Dyspepsia	2 (18.2)	0	2 (18.2)	0
Erythema	2 (18.2)	0	2 (18.2)	0
Haematuria	2 (18.2)	0	2 (18.2)	0
Hypokalaemia	2 (18.2)	0	2 (18.2)	0
Non-cardiac chest pain	2 (18.2)	0	2 (18.2)	0
Abdominal distension	1 (9.1)	0	1 (9.1)	0
Abdominal pain lower	1 (9.1)	0	1 (9.1)	0
Amylase increased	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)
Arthralgia	1 (9.1)	0	1 (9.1)	0
Aspartate aminotransferase increased	1 (9.1)	0	1 (9.1)	0
Aspiration	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)
Blood albumin decreased	1 (9.1)	0	1 (9.1)	0
Bone lesion	1 (9.1)	0	1 (9.1)	0
Bone pain	1 (9.1)	0	1 (9.1)	0
Cancer pain	1 (9.1)	0	1 (9.1)	0
Cataract	1 (9.1)	0	1 (9.1)	0
Chest discomfort	1 (9.1)	0	1 (9.1)	0
Colitis	1 (9.1)	0	1 (9.1)	0
Confusional state	1 (9.1)	0	1 (9.1)	0

	SDS caps B 800 mg/day N=11		All SDS caps B N=11	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Conjunctivitis	1 (9.1)	0	1 (9.1)	0
Depression	1 (9.1)	0	1 (9.1)	0
Diarrhoea haemorrhagic	1 (9.1)	0	1 (9.1)	0
Dysarthria	1 (9.1)	0	1 (9.1)	0
Dysgeusia	1 (9.1)	0	1 (9.1)	0
Ecchymosis	1 (9.1)	0	1 (9.1)	0
Epistaxis	1 (9.1)	0	1 (9.1)	0
Extraocular muscle paresis	1 (9.1)	0	1 (9.1)	0
Eye irritation	1 (9.1)	0	1 (9.1)	0
Frequent bowel movements	1 (9.1)	0	1 (9.1)	0
Furuncle	1 (9.1)	0	1 (9.1)	0
Gastrointestinal toxicity	1 (9.1)	0	1 (9.1)	0
Gastrooesophageal reflux disease	1 (9.1)	0	1 (9.1)	0
Haematocrit decreased	1 (9.1)	0	1 (9.1)	0
Haemoptysis	1 (9.1)	0	1 (9.1)	0
Haemorrhage intracranial	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)
Herpes simplex	1 (9.1)	0	1 (9.1)	0
Hypocalcaemia	1 (9.1)	0	1 (9.1)	0
Hypomagnesaemia	1 (9.1)	0	1 (9.1)	0
Insomnia	1 (9.1)	0	1 (9.1)	0
Keratitis	1 (9.1)	0	1 (9.1)	0
Leukocytosis	1 (9.1)	0	1 (9.1)	0
Lipase increased	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)
Lipids increased	1 (9.1)	0	1 (9.1)	0
Metabolic acidosis	1 (9.1)	0	1 (9.1)	0
Musculoskeletal chest pain	1 (9.1)	0	1 (9.1)	0
Musculoskeletal pain	1 (9.1)	0	1 (9.1)	0
Neutrophil count increased	1 (9.1)	0	1 (9.1)	0
Night sweats	1 (9.1)	0	1 (9.1)	0
Oedema peripheral	1 (9.1)	0	1 (9.1)	0
Oropharyngeal pain	1 (9.1)	0	1 (9.1)	0
Pericardial effusion	1 (9.1)	0	1 (9.1)	0
Pleural effusion	1 (9.1)	0	1 (9.1)	0
Pollakiuria	1 (9.1)	0	1 (9.1)	0
Protein total decreased	1 (9.1)	0	1 (9.1)	0
Pulmonary embolism	1 (9.1)	0	1 (9.1)	0
Pyrexia	1 (9.1)	0	1 (9.1)	0
Radius fracture	1 (9.1)	0	1 (9.1)	0

	SDS caps B 800 mg/day N=11		All SDS caps B N=11	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Renal failure	1 (9.1)	0	1 (9.1)	0
Retinal exudates	1 (9.1)	0	1 (9.1)	0
Somnolence	1 (9.1)	0	1 (9.1)	0
Stomatitis	1 (9.1)	0	1 (9.1)	0
Upper respiratory tract infection	1 (9.1)	0	1 (9.1)	0
Urinary tract infection	1 (9.1)	0	1 (9.1)	0
Uveitis	1 (9.1)	0	1 (9.1)	0
Vulvovaginal pain	1 (9.1)	0	1 (9.1)	0
Weight decreased	1 (9.1)	0	1 (9.1)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

- A patient with multiple adverse events is counted only once in the total row.

BEZ235 SDS in combination with trastuzumab

Frequent adverse events (more than or equal to 5 percent), regardless of study drug relationship by preferred term SDS + Trastuzumab-Safety set

	SDS Sachet 800 mg/day N=1		Caps A 400 mg/day + T N=3		Sachet 600 mg/day + T N=17		Sachet 800 mg/day + T N=9		All SDS+T N=30	
	All grades	Grade ¾	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
-Total	1 (100.0)	1 (100.0)	3 (100.0)	1 (33.3)	17 (100.0)	10 (58.8)	9 (100.0)	5 (55.6)	30 (100.0)	17 (56.7)
Nausea	1 (100.0)	0	3 (100.0)	0	15 (88.2)	2 (11.8)	9 (100.0)	1 (11.1)	28 (93.3)	3 (10.0)
Diarrhoea	0	0	3 (100.0)	0	12 (70.6)	2 (11.8)	9 (100.0)	2 (22.2)	24 (80.0)	4 (13.3)
Vomiting	1 (100.0)	0	3 (100.0)	0	7 (41.2)	0	8 (88.9)	0	19 (63.3)	0
Stomatitis	0	0	3 (100.0)	0	6 (35.3)	0	5 (55.6)	0	14 (46.7)	0
Decreased appetite	1 (100.0)	0	1 (33.3)	0	4 (23.5)	0	5 (55.6)	0	11 (36.7)	0
Dyspepsia	0	0	2 (66.7)	0	5 (29.4)	0	1 (11.1)	0	8 (26.7)	0
Fatigue	0	0	0	0	3 (17.6)	0	5 (55.6)	1 (11.1)	8 (26.7)	1 (3.3)
Aspartate aminotransferase increased	0	0	1 (33.3)	0	3 (17.6)	2 (11.8)	3 (33.3)	1 (11.1)	7 (23.3)	3 (10.0)
Asthenia	0	0	2 (66.7)	0	4 (23.5)	0	1 (11.1)	1 (11.1)	7 (23.3)	1 (3.3)
Rash	0	0	2 (66.7)	0	3 (17.6)	0	2 (22.2)	1 (11.1)	7 (23.3)	1 (3.3)
Anaemia	0	0	1 (33.3)	0	1 (5.9)	1 (5.9)	4 (44.4)	0	6 (20.0)	1 (3.3)
Constipation	0	0	1 (33.3)	0	3 (17.6)	0	2 (22.2)	0	6 (20.0)	0
Alanine aminotransferase increased	0	0	1 (33.3)	0	3 (17.6)	1 (5.9)	1 (11.1)	1 (11.1)	5 (16.7)	2 (6.7)
Headache	0	0	2 (66.7)	0	1 (5.9)	0	2 (22.2)	0	5 (16.7)	0
Gastrooesophageal reflux disease	0	0	0	0	4 (23.5)	1 (5.9)	0	0	4 (13.3)	1 (3.3)
Hyperglycaemia	0	0	0	0	1 (5.9)	0	3 (33.3)	0	4 (13.3)	0

	SDS Sachet 800 mg/day N=1		Caps A 400 mg/day + T N=3		Sachet 600 mg/day + T N=17		Sachet 800 mg/day + T N=9		All SDS+T N=30	
	All grades	Grade ¾	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Insomnia	0	0	1 (33.3)	0	1 (5.9)	0	2 (22.2)	0	4 (13.3)	0
Paraesthesia	1 (100.0)	0	0	0	3 (17.6)	0	0	0	4 (13.3)	0
Pruritus	0	0	2 (66.7)	0	1 (5.9)	0	1 (11.1)	0	4 (13.3)	0
Pyrexia	0	0	1 (33.3)	0	2 (11.8)	0	1 (11.1)	0	4 (13.3)	0
Amylase increased	0	0	1 (33.3)	1 (33.3)	0	0	2 (22.2)	1 (11.1)	3 (10.0)	2 (6.7)
Anxiety	0	0	0	0	1 (5.9)	0	2 (22.2)	0	3 (10.0)	0
Blood alkaline phosphatase increased	0	0	1 (33.3)	0	1 (5.9)	0	1 (11.1)	1 (11.1)	3 (10.0)	1 (3.3)
Dizziness	0	0	1 (33.3)	0	1 (5.9)	0	1 (11.1)	0	3 (10.0)	0
Dysgeusia	0	0	0	0	1 (5.9)	0	2 (22.2)	0	3 (10.0)	0
Dyspnoea	0	0	0	0	3 (17.6)	2 (11.8)	0	0	3 (10.0)	2 (6.7)
Hypokalaemia	0	0	1 (33.3)	0	1 (5.9)	0	1 (11.1)	0	3 (10.0)	0
Nasopharyngitis	0	0	2 (66.7)	0	0	0	1 (11.1)	0	3 (10.0)	0
Neutropenia	0	0	0	0	2 (11.8)	0	1 (11.1)	0	3 (10.0)	0
Thrombocytopenia	0	0	0	0	1 (5.9)	0	2 (22.2)	0	3 (10.0)	0
Upper respiratory tract infection	0	0	1 (33.3)	0	1 (5.9)	0	1 (11.1)	0	3 (10.0)	0
Abdominal pain	0	0	1 (33.3)	0	0	0	1 (11.1)	0	2 (6.7)	0
Blood bilirubin increased	0	0	0	0	0	0	2 (22.2)	1 (11.1)	2 (6.7)	1 (3.3)
Bone pain	0	0	1 (33.3)	0	1 (5.9)	0	0	0	2 (6.7)	0
Cellulitis	0	0	0	0	2 (11.8)	1 (5.9)	0	0	2 (6.7)	1 (3.3)
Chills	0	0	0	0	1 (5.9)	0	1 (11.1)	0	2 (6.7)	0

	SDS Sachet 800 mg/day N=1		Caps A 400 mg/day + T N=3		Sachet 600 mg/day + T N=17		Sachet 800 mg/day + T N=9		All SDS+T N=30	
	All grades	Grade ¾	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cough	0	0	1 (33.3)	0	0	0	1 (11.1)	0	2 (6.7)	0
Dehydration	0	0	0	0	1 (5.9)	0	1 (11.1)	0	2 (6.7)	0
Dry skin	0	0	1 (33.3)	0	1 (5.9)	0	0	0	2 (6.7)	0
Ejection fraction decreased	0	0	0	0	2 (11.8)	0	0	0	2 (6.7)	0
Gait disturbance	0	0	1 (33.3)	0	1 (5.9)	0	0	0	2 (6.7)	0
Hypercholesterolaemia	0	0	1 (33.3)	0	0	0	1 (11.1)	0	2 (6.7)	0
Hypomagnesaemia	0	0	0	0	2 (11.8)	0	0	0	2 (6.7)	0
Lipase increased	0	0	1 (33.3)	1 (33.3)	0	0	1 (11.1)	0	2 (6.7)	1 (3.3)
Neck pain	0	0	0	0	2 (11.8)	0	0	0	2 (6.7)	0
Nervousness	0	0	1 (33.3)	0	1 (5.9)	0	0	0	2 (6.7)	0
Pain in extremity	0	0	0	0	2 (11.8)	1 (5.9)	0	0	2 (6.7)	1 (3.3)
Palpitations	1 (100.0)	0	0	0	0	0	1 (11.1)	0	2 (6.7)	0
Platelet count decreased	0	0	0	0	0	0	2 (22.2)	0	2 (6.7)	0
Rash macular	0	0	1 (33.3)	0	1 (5.9)	0	0	0	2 (6.7)	0
Somnolence	0	0	2 (66.7)	0	0	0	0	0	2 (6.7)	0
White blood cell count decreased	0	0	0	0	1 (5.9)	0	1 (11.1)	1 (11.1)	2 (6.7)	1 (3.3)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.

Serious Adverse Events and Deaths

BEZ235 HGC group

Summary of deaths and adverse events, HGC Fast-Safety analysis set

	Fast 10mg/day N=3 n (%)	Fast 25mg/day N=6 n (%)	Fast 50mg/day N=4 n (%)	Fast 100mg/day N=6 n (%)	Fast 200mg/day N=5 n (%)	Fast 300mg/day N=6 n (%)	Fast 400mg/day N=11 n (%)	All HGC Fast N=41 n (%)
All deaths	1 (33.3)	0	0	1 (16.7)	2 (40.0)	1 (16.7)	3 (27.3)	8 (19.5)
On-treatment deaths [1]	1 (33.3)	0	0	1 (16.7)	2 (40.0)	1 (16.7)	1 (9.1)	6 (14.6)
Adverse events (AEs)	3 (100.0)	6 (100.0)	3 (75.0)	6 (100.0)	5 (100.0)	5 (83.3)	11 (100.0)	39 (95.1)
AEs suspected to be treatment-related	2 (66.7)	4 (66.7)	2 (50.0)	4 (66.7)	1 (20.0)	3 (50.0)	10 (90.9)	26 (63.4)
Grade 3-4 AEs	1 (33.3)	0	2 (50.0)	2 (33.3)	2 (40.0)	3 (50.0)	4 (36.4)	14 (34.1)
Suspected treatment-related G3-4 AEs	0	0	0	1 (16.7)	0	0	2 (18.2)	3 (7.3)
Serious adverse events (SAEs)	1 (33.3)	0	0	1 (16.7)	1 (20.0)	2 (33.3)	2 (18.2)	7 (17.1)
Suspected treatment-related SAEs	0	0	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0	3 (27.3)	3 (7.3)
Other significant AEs	3 (100.0)	3 (50.0)	2 (50.0)	6 (100.0)	5 (100.0)	5 (83.3)	8 (72.7)	32 (78.0)

	Fast 10mg/day N=3 n (%)	Fast 25mg/day N=6 n (%)	Fast 50mg/day N=4 n (%)	Fast 100mg/day N=6 n (%)	Fast 200mg/day N=5 n (%)	Fast 300mg/day N=6 n (%)	Fast 400mg/day N=11 n (%)	All HGC Fast N=41 n (%)
AEs requiring dose interruption and/or reduction	1 (33.3)	0	2 (50.0)	2 (33.3)	0	1 (16.7)	3 (27.3)	9 (22.0)
AEs requiring additional therapy	3 (100.0)	3 (50.0)	2 (50.0)	6 (100.0)	5 (100.0)	5 (83.3)	8 (72.7)	32 (78.0)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized
Additional therapy includes all non-drug therapy and concomitant medications

Summary of deaths and adverse events - HGC Fed Safety analysis set

	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
All deaths	0	0	0	2 (50.0)	2 (11.1)
On-treatment deaths [1]	0	0	0	2 (50.0)	2 (11.1)
Adverse events (AEs)	5 (83.3)	3 (100.0)	5 (100.0)	4 (100.0)	17 (94.4)
AEs suspected to be treatment-related	5 (83.3)	3 (100.0)	5 (100.0)	3 (75.0)	16 (88.9)
Grade 3-4 AEs	0	3 (100.0)	1 (20.0)	3 (75.0)	7 (38.9)
Suspected treatment-related G3-4 AEs	0	1 (33.3)	1 (20.0)	0	2 (11.1)
Serious adverse events (SAEs)	1 (16.7)	2 (66.7)	0	1 (25.0)	4 (22.2)
Suspected treatment-related SAEs	0	0	0	0	0
AEs leading to discontinuation	0	0	1 (20.0)	1 (25.0)	2 (11.1)
Other significant AEs	5 (83.3)	3 (100.0)	5 (100.0)	4 (100.0)	17 (94.4)
AEs requiring dose interruption and/or reduction	0	0	1 (20.0)	1 (25.0)	2 (11.1)
AEs requiring additional therapy	5 (83.3)	3 (100.0)	5 (100.0)	4 (100.0)	17 (94.4)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Additional therapy includes all non-drug therapy and concomitant medications

BEZ235 SDS single agent group

Summary of deaths and adverse events, SDS Caps A-Safety analysis set

Category	SDS caps A 400 mg/day (N=5) n (%)	SDS caps A 800 mg/day (N=6) n (%)	SDS caps A 1000 mg/day (N=11) n (%)	All SDS caps A (N=22) n (%)
All deaths	1 (20.0)	2 (33.3)	2 (18.2)	5 (22.7)
On-treatment deaths [1]	1 (20.0)	2 (33.3)	1 (9.1)	4 (18.2)
Adverse events (AEs)	5 (100.0)	6 (100.0)	11 (100.0)	22 (100.0)
AEs suspected to be treatment-related	3 (60.0)	6 (100.0)	11 (100.0)	20 (90.9)
Grade 3-4 AEs	2 (40.0)	4 (66.7)	9 (81.8)	15 (68.2)
Suspected treatment-related G3-4 AEs	0	2 (33.3)	5 (45.5)	7 (31.8)
Serious adverse events (SAEs)	1 (20.0)	2 (33.3)	5 (45.5)	8 (36.4)
Suspected treatment-related SAEs	0	0	1 (9.1)	1 (4.5)
AEs leading to discontinuation	0	0	1 (9.1)	1 (4.5)

Category	SDS caps A 400 mg/day (N=5) n (%)	SDS caps A 800 mg/day (N=6) n (%)	SDS caps A 1000 mg/day (N=11) n (%)	All SDS caps A (N=22) n (%)
Other significant AEs	5 (100.0)	6 (100.0)	11 (100.0)	22 (100.0)
AEs requiring dose interruption and/or reduction	2 (40.0)	5 (83.3)	8 (72.7)	15 (68.2)
AEs requiring additional therapy	4 (80.0)	6 (100.0)	11 (100.0)	21 (95.5)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Additional therapy includes all non-drug therapy and concomitant medications

Summary of deaths and adverse events, SDS Sachet-Safety analysis set

Category	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
All deaths	0	2 (20.0)	1 (4.2)	0	0	3 (4.9)
On-treatment deaths [1]	0	2 (20.0)	1 (4.2)	0	0	3 (4.9)
Adverse events (AEs)	6 (100.0)	10 (100.0)	24 (100.0)	14 (100.0)	7 (100.0)	61 (100.0)
AEs suspected to be treatment-related	5 (83.3)	10 (100.0)	23 (95.8)	13 (92.9)	7 (100.0)	58 (95.1)
Grade 3-4 AEs	3 (50.0)	6 (60.0)	18 (75.0)	11 (78.6)	4 (57.1)	42 (68.9)
Suspected treatment-related G3-4 AEs	1 (16.7)	4 (40.0)	11 (45.8)	9 (64.3)	1 (14.3)	26 (42.6)
Serious adverse events (SAEs)	1 (16.7)	6 (60.0)	12 (50.0)	4 (28.6)	1 (14.3)	24 (39.3)
Suspected treatment-related SAEs	1 (16.7)	4 (40.0)	4 (16.7)	0	0	9 (14.8)
AEs leading to discontinuation	0	3 (30.0)	2 (8.3)	6 (42.9)	3 (42.9)	14 (23.0)
Other significant AEs	6 (100.0)	10 (100.0)	24 (100.0)	13 (92.9)	7 (100.0)	60 (98.4)
AEs requiring dose interruption and/or reduction	3 (50.0)	6 (60.0)	17 (70.8)	12 (85.7)	4 (57.1)	42 (68.9)
AEs requiring additional therapy	6 (100.0)	10 (100.0)	24 (100.0)	13 (92.9)	7 (100.0)	60 (98.4)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Additional therapy includes all non-drug therapy and concomitant medications

Summary of deaths and adverse events, SDS Caps B-Safety analysis set

Category	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B (N = 11) N=11 n (%)
All deaths	2 (18.2)	2 (18.2)
On-treatment deaths [1]	1 (9.1)	1 (9.1)
Adverse events (AEs)	11 (100.0)	11 (100.0)
AEs suspected to be treatment-related	10 (90.9)	10 (90.9)
Grade 3-4 AEs	4 (36.4)	4 (36.4)
Suspected treatment-related G3-4 AEs	2 (18.2)	2 (18.2)
Serious adverse events (SAEs)	5 (45.5)	5 (45.5)
Suspected treatment-related SAEs	1 (9.1)	1 (9.1)
AEs leading to discontinuation	4 (36.4)	4 (36.4)
Other significant AEs	10 (90.9)	10 (90.9)
AEs requiring dose interruption and/or reduction	4 (36.4)	4 (36.4)
AEs requiring additional therapy	10 (90.9)	10 (90.9)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Additional therapy includes all non-drug therapy and concomitant medications

BEZ235 SDS in combination with trastuzumab

Summary of deaths and adverse events, SDS+Trastuzumab-FAS

Category	SDS Sachet 800 mg/day (N = 1) n (%)	Caps A 400 mg/day + T (N = 3) n (%)	Sachet 600 mg/day + T (N = 17) n (%)	Sachet 800 mg/day + T (N = 9) n (%)	All SDS + T (N = 30) n (%)
All deaths	0	0	2 (11.8)	1 (11.1)	3 (10.0)
On-treatment deaths [1]	0	0	2 (11.8)	0	2 (6.7)
Adverse events (AEs)	1 (100.0)	3 (100.0)	17 (100.0)	9 (100.0)	30 (100.0)
AEs suspected to be treatment-related	1 (100.0)	3 (100.0)	17 (100.0)	9 (100.0)	30 (100.0)
Grade 3-4 AEs	1 (100.0)	1 (33.3)	10 (58.8)	5 (55.6)	17 (56.7)
Suspected treatment-related G3-4 AEs	1 (100.0)	0	5 (29.4)	5 (55.6)	11 (36.7)
Serious adverse events (SAEs)	1 (100.0)	1 (33.3)	7 (41.2)	0	9 (30.0)
Suspected treatment-related SAEs	1 (100.0)	0	0	0	1 (3.3)
AEs leading to discontinuation	0	0	4 (23.5)	1 (11.1)	5 (16.7)
Other significant AEs	1 (100.0)	3 (100.0)	15 (88.2)	8 (88.9)	27 (90.0)
AEs requiring dose interruption and/or reduction	1 (100.0)	2 (66.7)	8 (47.1)	8 (88.9)	19 (63.3)

Category	SDS Sachet 800 mg/day (N = 1) n (%)	Caps A 400 mg/day + T (N = 3) n (%)	Sachet 600 mg/day + T (N = 17) n (%)	Sachet 800 mg/day + T (N = 9) n (%)	All SDS + T (N = 30) n (%)
AEs requiring additional therapy	1 (100.0)	3 (100.0)	15 (88.2)	8 (88.9)	27 (90.0)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Additional therapy includes all non-drug therapy and concomitant medications.

Other Relevant Findings

BEZ235 HGC group

New or worsened hematology/coagulation abnormalities based on CTC grade by dose cohort, HGC Fast- (Safety set)

Test	Worsening from baseline to	Fast 10 mg/day N=3 (n%)	Fast 25 mg/day N=6 (n%)	Fast 50 mg/day N=4 (n%)	Fast 100 mg/day N=6 (n%)	Fast 200 mg/day N=5 (n%)	Fast 300 mg/day N=6 (n%)	Fast 400 mg/day N=11 (n%)	All HGC Fast N=41 (n%)
Abs. Lymphocytes (hypo)	Grade 1	2 0 0.0	6 2 33.3	2 0 0.0	4 1 25.0	4 0 0.0	2 0 0.0	7 4 57.1	27 7 25.9
	Grade 2	2 1 50.0	6 1 16.7	4 1 25.0	5 0 0.0	4 2 50.0	4 2 50.0	9 1 11.1	34 8 23.5
	Grade 3	2 0 0.0	6 0 0.0	4 0 0.0	6 2 33.3	5 0 0.0	6 1 16.7	10 1 10.0	39 4 10.3
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
Abs. Neutrophils (hypo)	Grade 1	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	5 0 0.0	11 1 9.1	40 1 2.5
	Grade 2	3 0 0.0	6 1 16.7	4 0 0.0	6 1 16.7	5 0 0.0	5 0 0.0	11 2 18.2	40 4 10.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 1 16.7	11 0 0.0	41 1 2.4
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Platelets	Grade 1	3 1 33.3	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	5 1 20.0	11 2 18.2	40 4 10.0
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Hemoglobin	Grade 1	1 1 100	4 2 50.0	3 2 66.7	3 2 66.7	0 0.0.0	3 1 33.3	8 5 62.5	22 13 59.1
	Grade 2	3 2 66.7	6 1 16.7	4 0 0.0	5 0 0.0	3 2 66.7	5 0 0.0	11 2 18.2	37 7 18.9
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 2 33.3	5 1 20.0	6 0 0.0	11 0 0.0	41 3 7.3
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0

Test	Worsening from baseline to	Fast 10 mg/day N=3 (n%)	Fast 25 mg/day N=6 (n%)	Fast 50 mg/day N=4 (n%)	Fast 100 mg/day N=6 (n%)	Fast 200 mg/day N=5 (n%)	Fast 300 mg/day N=6 (n%)	Fast 400 mg/day N=11 (n%)	All HGC Fast N=41 (n%)
White Blood Count	Grade 1	3 0 0.0	5 1 20.0	4 0 0.0	5 1 20.0	5 0 0.0	2 0 0.0	7 1 14.3	31 3 9.7
	Grade 2	3 0 0.0	6 1 16.7	4 0 0.0	6 0 0.0	5 0 0.0	5 2 40.0	11 3 27.3	40 6 15.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 1 16.7	11 0 0.0	41 1 2.4
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0

Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- 'New' means 'grade 0' at baseline and '≥ grade 1' after baseline
- Baseline is defined as the last non-missing value prior to the first dose

New or worsened hematology/coagulation abnormalities based on CTC grade by dose cohort, HGC Fed- (safety set)

Test	Worsening from baseline to	Fed 300 mg/day N=6 (n%)	Fed 400 mg/day N=3 (n%)	Fed 700 mg/day N=5 (n%)	Fed 1100 mg/day N=4 (n%)	All HGC Fed N=18 (n%)
Abs. Lymphocytes (hypo)	Grade 1	4 0 0.0	1 1 100	4 1 25.0	3 0 0.0	12 2 16.7
	Grade 2	6 2 33.3	1 0 0.0	5 1 20.0	3 0 0.0	15 3 20.0
	Grade 3	6 1 16.7	2 0 0.0	5 0 0.0	4 1 25.0	17 2 11.8
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Abs. Neutrophils (hypo)	Grade 1	6 0 0.0	3 0 0.0	5 0 0.0	4 1 25.0	18 1 5.6
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0

Test	Worsening from baseline to	Fed 300 mg/day N=6 (n%)	Fed 400 mg/day N=3 (n%)	Fed 700 mg/day N=5 (n%)	Fed 1100 mg/day N=4 (n%)	All HGC Fed N=18 (n%)
Platelets	Grade 1	6 3 50.0	3 0 0.0	5 3 60.0	4 1 25.0	18 7 38.9
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Hemoglobin	Grade 1	3 3 100	1 0 0.0	3 0 0.0	2 2 100	9 5 55.6
	Grade 2	6 2 33.3	3 0 0.0	5 0 0.0	4 0 0.0	18 2 11.1
	Grade 3	6 0 0.0	3 1 33.3	5 0 0.0	4 0 0.0	18 1 5.6
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
White Blood Count	Grade 1	5 1 20.0	2 0 0.0	5 2 40.0	4 1 25.0	16 4 25.0
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0

Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥grade 1’ after baseline
- Baseline is defined as the last non-missing value prior to the first dose

New or worsened biochemistry abnormalities based on CTC grade by dose cohort HGC-Fast (safety set)

Test	Worsening from baseline to	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
Potassium (Hypo)	Grade 1	3 0 0.0	6 1 16.7	3 1 33.3	5 3 60.0	4 1 25.0	5 2 40.0	10 2 20.0	36 10 27.8
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 1 16.7	11 0 0.0	41 1 2.4
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Potassium (Hyper)	Grade 1	3 0 0.0	6 1 16.7	4 1 25.0	6 0 0.0	5 1 20.0	6 0 0.0	10 2 20.0	40 5 12.5
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 1 20.0	6 0 0.0	11 1 9.1	41 2 4.9
	Grade 3	3 0 0.0	6 1 16.7	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 1 2.4
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Magnesium (hypo)	Grade 1	3 0 0.0	6 3 50.0	4 1 25.0	6 3 50.0	4 2 50.0	6 2 33.3	10 1 10.0	39 12 30.8
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Magnesium (hyper)	Grade 1	3 0 0.0	6 1 16.7	4 2 50.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 3 7.3
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Glucose (Hypo)	Grade 1	3 0 0.0	6 0 0.0	3 1 33.3	6 0 0.0	4 0 0.0	6 0 0.0	11 2 18.2	39 3 7.7
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Glucose (Hyper)	Grade 1	3 0 0.0	6 1 16.7	4 0 0.0	5 2 40.0	5 0 0.0	6 1 16.7	11 4 36.4	40 8 20.0
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Lipase	Grade 1	3 0 0.0	6 1 16.7	3 0 0.0	6 1 16.7	4 0 0.0	6 0 0.0	10 0 0.0	38 2 5.3

Test	Worsening from baseline to	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 2 40.0	6 0 0.0	10 0 0.0	40 2 5.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
Amylase	Grade 1	3 0 0.0	6 0 0.0	3 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 2 20.0	39 2 5.1
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 1 20.0	6 0 0.0	10 0 0.0	40 1 2.5
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
SGOT(AST)	Grade 1	3 2 66.7	6 3 50.0	3 0 0.0	5 1 20.0	4 1 25.0	4 0 0.0	8 2 25.0	33 9 27.3
	Grade 2	3 0 0.0	6 0 0.0	4 1 25.0	6 1 16.7	4 0 0.0	6 1 16.7	10 1 10.0	39 4 10.3
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 1 20.0	6 0 0.0	11 1 9.1	41 2 4.9
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Uric acid	Grade 1	3 0 0.0	6 1 16.7	4 0 0.0	5 2 40.0	5 0 0.0	6 1 16.7	9 1 11.1	38 5 13.2
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 1 16.7	5 0 0.0	6 1 16.7	11 1 9.1	41 3 7.3
Total Cholesterol	Grade 1	3 2 66.7	4 3 75.0	2 0 0.0	4 0 0.0	4 0 0.0	3 1 33.3	6 4 66.7	26 10 38.5
(hyper)	Grade 2	3 0 0.0	6 0 0.0	4 1 25.0	6 0 0.0	5 1 20.0	5 0 0.0	11 2 18.2	40 4 10.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Calcium (Hypo)	Grade 1	3 0 0.0	6 3 50.0	2 0 0.0	6 1 16.7	5 1 20.0	6 2 33.3	9 3 33.3	37 10 27.0
	Grade 2	3 0 0.0	6 0 0.0	3 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	40 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Calcium (Hyper)	Grade 1	3 0 0.0	6 0 0.0	4 0 0.0	6 1 16.7	4 1 25.0	6 0 0.0	10 0 0.0	39 2 5.1
	Grade 2	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	10 0 0.0	40 0 0.0
	Grade 3	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 1 9.1	41 1 2.4

Test	Worsening from baseline to	Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0
Alk. Phosphatase	Grade 1	2 0 0.0	4 0 0.0	2 0 0.0	3 0 0.0	3 2 66.7	4 0 0.0	8 3 37.5	26 5 19.2
	Grade 2	3 1 33.3	6 1 16.7	2 0 0.0	5 1 20.0	3 1 33.3	5 0 0.0	10 0 0.0	34 4 11.8
	Grade 3	3 0 0.0	6 0 0.0	4 1 25.0	6 1 16.7	4 0 0.0	5 0 0.0	11 1 9.1	39 3 7.7
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 1 20.0	6 0 0.0	11 0 0.0	41 1 2.4
SGPT(ALT)	Grade 1	3 0 0.0	6 1 16.7	3 0 0.0	6 0 0.0	4 1 25.0	6 0 0.0	10 1 10.0	38 3 7.9
	Grade 2	3 1 33.3	6 0 0.0	3 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 1 9.1	40 2 5.0
	Grade 3	3 0 0.0	6 0 0.0	4 1 25.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 1 2.4
	Grade 4	3 0 0.0	6 0 0.0	4 0 0.0	6 0 0.0	5 0 0.0	6 0 0.0	11 0 0.0	41 0 0.0

Total = number of patients evaluable post-baseline, who had less than grade x at baseline.

- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥ grade 1’ after baseline
- Baseline is defined as the last non-missing value prior to the first dose

New or worsened biochemistry abnormalities based on CTC grade by dose cohort HGC-Fed (safety set)

Test	Worsening from baseline to	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
Creatinine	Grade 1	5 1 20.0	3 0 0.0	5 0 0.0	4 2 50.0	17 3 17.6
	Grade 2	6 0 0.0	3 0 0.0	5 1 20.0	4 0 0.0	18 1 5.6
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Potassium (Hypo)	Grade 1	6 1 16.7	2 1 50.0	5 2 40.0	4 2 50.0	17 6 35.3
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Potassium (Hyper)	Grade 1	6 1 16.7	3 1 33.3	5 0 0.0	4 2 50.0	18 4 22.2
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Glucose (Hypo)	Grade 1	6 1 16.7	3 1 33.3	5 0 0.0	3 0 0.0	17 2 11.8
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Glucose (Hyper)	Grade 1	6 2 33.3	2 0 0.0	4 2 50.0	4 3 75.0	16 7 43.8
	Grade 2	6 0 0.0	3 0 0.0	5 2 40.0	4 0 0.0	18 2 11.1
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Lipase	Grade 1	6 0 0.0	3 0 0.0	5 0 0.0	4 1 25.0	18 1 5.6
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 1 33.3	5 0 0.0	4 0 0.0	18 1 5.6
	Grade 4	6 0 0.0	3 1 33.3	5 0 0.0	4 0 0.0	18 1 5.6
Amylase	Grade 1	6 0 0.0	3 0 0.0	5 0 0.0	4 1 25.0	18 1 5.6
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
SGOT(AST)	Grade 1	6 3 50.0	2 0 0.0	4 2 50.0	1 1 100	13 6 46.2
	Grade 2	6 0 0.0	2 0 0.0	5 0 0.0	4 0 0.0	17 0 0.0
	Grade 3	6 0 0.0	2 0 0.0	5 0 0.0	4 1 25.0	17 1 5.9
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Total Cholesterol (hyper)	Grade 1	5 2 40.0	3 1 33.3	3 2 66.7	0 0	11 5 45.5
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 1 25.0	18 1 5.6
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Albumin (Hypo)	Grade 1	6 0 0.0	2 1 50.0	5 0 0.0	4 1 25.0	17 2 11.8

Test	Worsening from baseline to	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
	Grade 2	6 0 0.0	2 0 0.0	5 0 0.0	4 2 50.0	17 2 11.8
	Grade 3	6 0 0.0	3 1 33.3	5 0 0.0	4 0 0.0	18 1 5.6
Total Bilirubin	Grade 1	6 1 16.7	2 0 0.0	5 0 0.0	4 1 25.0	17 2 11.8
	Grade 2	6 0 0.0	2 0 0.0	5 0 0.0	4 0 0.0	17 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 1 25.0	18 1 5.6
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
Alk. Phosphatase	Grade 1	5 0 0.0	0 0.0.0	4 2 50.0	1 1 100	10 3 30.0
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	2 0 0.0	16 0 0.0
	Grade 3	6 1 16.7	3 0 0.0	5 0 0.0	4 1 25.0	18 2 11.1
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
SGPT(ALT)	Grade 1	6 2 33.3	2 0 0.0	4 0 0.0	3 1 33.3	15 3 20.0
	Grade 2	6 1 16.7	2 0 0.0	5 2 40.0	4 0 0.0	17 3 17.6
	Grade 3	6 0 0.0	2 0 0.0	5 0 0.0	4 0 0.0	17 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0

Total = number of patients evaluable post-baseline, who had less than grade x at baseline.

- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥ grade 1’ after baseline
- Baseline is defined as the last non-missing value prior to the first dose.

New or worsened elevated fasting plasma glucose abnormalities by dose cohort – ADA grade HGC-Fed (safety set)

Test	Worsening from baseline to	Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
Glucose (Hyper)	Grade 1	6 0 0.0	3 0 0.0	5 1 20.0	4 1 25.0	18 2 11.1
	Grade 2	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 3	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0
	Grade 4	6 0 0.0	3 0 0.0	5 0 0.0	4 0 0.0	18 0 0.0

Glucose non CTCAE grading (American Diabetes Association):

Grade 0: < 140 mg/dL [< 7.8 mmol/L]

Grade 1: 140 - 199 mg/dL [7.8 - 11.1 mmol/L]

Grade 2: 200 - 249 mg/dL [11.2 - 13.8 mmol/L]

Grade 3: 250 - 399 mg/dL [13.9 - 22.2 mmol/L]

Grade 4: ≥ 400 mg/dL [≥ 22.3 mmol/L].

BEZ235 SDS single agent group

New or worsened hematology/coagulation abnormalities based on CTC grade by dose cohort, SDS Caps A-Safety set

Test	Worsening from baseline to	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Abs. Lymphocytes (hypo)	Grade 1	3 0 0.0	3 1 33.3	7 2 28.6	13 3 23.1
	Grade 2	4 1 25.0	3 0 0.0	10 1 10.0	17 2 11.8
	Grade 3	5 0 0.0	6 2 33.3	11 4 36.4	22 6 27.3
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
Abs. Neutrophils (hypo)	Grade 1	5 0 0.0	6 0 0.0	11 1 9.1	22 1 4.5
	Grade 2	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
	Grade 3	5 1 20.0	6 0 0.0	11 0 0.0	22 1 4.5
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
Platelets	Grade 1	5 1 20.0	5 1 20.0	11 2 18.2	21 4 19.0
	Grade 2	5 0 0.0	6 1 16.7	11 1 9.1	22 2 9.1
	Grade 3	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
Hemoglobin	Grade 1	2 2 100	2 1 50.0	1 1 100	5 4 80.0
	Grade 2	4 0 0.0	6 3 50.0	8 3 37.5	18 6 33.3
	Grade 3	5 1 20.0	6 0 0.0	11 1 9.1	22 2 9.1
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
White Blood Count	Grade 1	5 1 20.0	3 1 33.3	8 1 12.5	16 3 18.8
	Grade 2	5 0 0.0	6 3 50.0	11 1 9.1	22 4 18.2
	Grade 3	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0

- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥ grade 1’ after baseline
- Baseline is defined as the last non-missing value prior to the first dose.

New or worsened hematology/coagulation abnormalities based on CTC grade by dose cohort, SDS Sachet-Safety set

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Abs. Lymphocytes (hypo)	Grade 1	5 0 0.0	4 1 25.0	11 3 27.3	13 1 7.7	4 1 25.0	37 6 16.2
	Grade 2	6 1 16.7	6 1 16.7	17 8 47.1	14 1 7.1	6 2 33.3	49 13 26.5
	Grade 3	6 0 0.0	7 3 42.9	23 6 26.1	14 1 7.1	7 1 14.3	57 11 19.3
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Abs Neutrophils . (hypo)	Grade 1	6 0 0.0	10 0 0.0	24 1 4.2	14 2 14.3	7 0 0.0	61 3 4.9
	Grade 2	6 0 0.0	10 0 0.0	24 1 4.2	14 0 0.0	7 0 0.0	61 1 1.6
	Grade 3	6 0 0.0	10 0 0.0	24 2 8.3	14 0 0.0	7 0 0.0	61 2 3.3
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Platelets	Grade 1	5 0 0.0	8 2 25.0	24 4 16.7	13 2 15.4	7 1 14.3	57 9 15.8
	Grade 2	6 0 0.0	10 0 0.0	24 3 12.5	14 1 7.1	7 0 0.0	61 4 6.6
	Grade 3	6 1 16.7	10 1 10.0	24 0 0.0	14 1 7.1	7 1 14.3	61 4 6.6
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Hemoglobin	Grade 1	2 1 50.0	3 1 33.3	9 5 55.6	9 4 44.4	1 0 0.0	24 11 45.8
	Grade 2	4 2 50.0	8 2 25.0	21 9 42.9	11 2 18.2	7 5 71.4	51 20 39.2
	Grade 3	6 0 0.0	10 0 0.0	24 1 4.2	14 0 0.0	7 0 0.0	61 1 1.6
	Grade 4	6 0 0.0	10 1 10.0	24 0 0.0	14 0 0.0	7 0 0.0	61 1 1.6
Fibrinogen	Grade 1	3 0 0.0	9 1 11.1	18 0 0.0	12 0 0.0	7 0 0.0	49 1 2.0
	Grade 2	3 0 0.0	9 0 0.0	18 0 0.0	12 0 0.0	7 0 0.0	49 0 0.0
	Grade 3	3 0 0.0	9 0 0.0	18 0 0.0	12 0 0.0	7 0 0.0	49 0 0.0
	Grade 4	3 0 0.0	9 0 0.0	18 0 0.0	12 0 0.0	7 0 0.0	49 0 0.0
Prothrombin Time INR	Grade 1	3 0 0.0	8 0 0.0	17 0 0.0	9 0 0.0	6 0 0.0	43 0 0.0
	Grade 2	3 0 0.0	8 0 0.0	17 0 0.0	9 0 0.0	6 0 0.0	43 0 0.0
	Grade 3	3 0 0.0	8 0 0.0	17 0 0.0	9 0 0.0	6 0 0.0	43 0 0.0
Partial Thromboplastin Time	Grade 1	3 2 66.7	8 2 25.0	20 5 25.0	13 1 7.7	7 1 14.3	51 11 21.6
	Grade 2	3 0 0.0	9 0 0.0	22 0 0.0	13 0 0.0	7 0 0.0	54 0 0.0
	Grade 3	3 0 0.0	9 0 0.0	22 1 4.5	13 0 0.0	7 0 0.0	54 1 1.9
White Blood Count	Grade 1	4 0 0.0	9 3 33.3	23 7 30.4	14 5 35.7	7 0 0.0	57 15 26.3
	Grade 2	5 0 0.0	10 0 0.0	24 3 12.5	14 0 0.0	7 0 0.0	60 3 5.0
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.							
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.							
- Patients are counted only for the worst grade observed post-baseline.							
- 'New' means 'grade 0' at baseline and '≥ grade 1' after baseline							
- Baseline is defined as the last non-missing value prior to the first dose							

New or worsened biochemistry abnormalities based on CTC grade by dose cohort SDS Sachet-Safety set

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Creatinine	Grade 1	5 0 0.0	10 3 30.0	22 12 54.5	13 3 23.1	6 0 0.0	56 18 32.1
	Grade 2	6 1 16.7	10 1 10.0	24 1 4.2	14 4 28.6	7 1 14.3	61 8 13.1
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Sodium (Hyper)	Grade 1	5 1 20.0	10 2 20.0	24 2 8.3	14 2 14.3	7 0 0.0	60 7 11.7
	Grade 2	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Potassium (Hyper)	Grade 1	6 0 0.0	10 1 10.0	24 2 8.3	14 3 21.4	7 2 28.6	61 8 13.1
	Grade 2	6 0 0.0	10 1 10.0	24 1 4.2	14 0 0.0	7 0 0.0	61 2 3.3
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Calcium (Hypo)	Grade 1	6 0 0.0	8 2 25.0	22 4 18.2	13 2 15.4	6 1 16.7	55 9 16.4
	Grade 2	6 0 0.0	10 0 0.0	24 2 8.3	14 0 0.0	7 0 0.0	61 2 3.3
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Calcium (Hyper)	Grade 1	6 0 0.0	10 0 0.0	23 2 8.7	13 1 7.7	7 1 14.3	59 4 6.8
	Grade 2	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Magnesium (hypo)	Grade 1	6 1 16.7	7 4 57.1	22 7 31.8	13 2 15.4	6 2 33.3	54 16 29.6
	Grade 2	6 0 0.0	10 0 0.0	24 0 0.0	14 1 7.1	7 0 0.0	61 1 1.6

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Magnesium (hyper)	Grade 1	6 0 0.0	10 0 0.0	24 2 8.3	14 5 35.7	7 0 0.0	61 7 11.5
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Glucose (Hypo)	Grade 1	6 1 16.7	10 3 30.0	22 2 9.1	13 3 23.1	5 0 0.0	56 9 16.1
	Grade 2	6 0 0.0	10 0 0.0	22 1 4.5	14 0 0.0	7 0 0.0	59 1 1.7
	Grade 3	6 0 0.0	10 0 0.0	22 0 0.0	14 0 0.0	7 0 0.0	59 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	22 0 0.0	14 0 0.0	7 0 0.0	59 0 0.0
Glucose (Hyper)	Grade 1	5 1 20.0	7 1 14.3	18 8 44.4	12 6 50.0	7 3 42.9	49 19 38.8
	Grade 2	6 0 0.0	10 0 0.0	22 4 18.2	14 3 21.4	7 0 0.0	59 7 11.9
	Grade 3	6 1 16.7	10 1 10.0	22 1 4.5	14 1 7.1	7 0 0.0	59 4 6.8
	Grade 4	6 0 0.0	10 0 0.0	22 0 0.0	14 0 0.0	7 0 0.0	59 0 0.0
Albumin (Hypo)	Grade 1	6 3 50.0	8 1 12.5	22 7 31.8	13 3 23.1	7 1 14.3	56 15 26.8
	Grade 2	6 0 0.0	8 0 0.0	24 3 12.5	14 1 7.1	7 0 0.0	59 4 6.8
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Total Bilirubin	Grade 1	6 0 0.0	10 1 10.0	24 2 8.3	14 1 7.1	7 1 14.3	61 5 8.2
	Grade 2	6 2 33.3	10 0 0.0	24 3 12.5	14 0 0.0	7 0 0.0	61 5 8.2
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
SGOT(AST)	Grade 1	4 2 50.0	8 1 12.5	16 7 43.8	10 4 40.0	6 1 16.7	44 15 34.1
	Grade 2	6 0 0.0	10 1 10.0	23 2 8.7	13 0 0.0	7 0 0.0	59 3 5.1
	Grade 3	6 1 16.7	10 1 10.0	24 1 4.2	14 0 0.0	7 0 0.0	61 3 4.9
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
SGPT(ALT)	Grade 1	6 1 16.7	10 3 30.0	20 9 45.0	13 2 15.4	7 2 28.6	56 17 30.4
	Grade 2	6 0 0.0	10 0 0.0	24 3 12.5	14 0 0.0	7 0 0.0	61 3 4.9
	Grade 3	6 1 16.7	10 1 10.0	24 0 0.0	14 0 0.0	7 0 0.0	61 2 3.3
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Amylase	Grade 1	6 0 0.0	9 1 11.1	24 1 4.2	12 1 8.3	7 0 0.0	58 3 5.2
	Grade 2	6 0 0.0	9 0 0.0	24 0 0.0	13 2 15.4	7 0 0.0	59 2 3.4
	Grade 3	6 0 0.0	9 1 11.1	24 0 0.0	13 0 0.0	7 0 0.0	59 1 1.7
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	13 0 0.0	7 0 0.0	60 0 0.0
Lipase	Grade 1	6 0 0.0	10 0 0.0	24 0 0.0	13 0 0.0	7 1 14.3	60 1 1.7
	Grade 2	6 1 16.7	10 0 0.0	24 1 4.2	13 2 15.4	7 0 0.0	60 4 6.7
	Grade 3	6 0 0.0	10 1 10.0	24 0 0.0	13 0 0.0	7 0 0.0	60 1 1.7
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	13 0 0.0	7 0 0.0	60 0 0.0

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Alk. Phosphatase	Grade 1	3 2 66.7	4 2 50.0	13 4 30.8	10 4 40.0	4 2 50.0	34 14 41.2
	Grade 2	5 1 20.0	9 1 11.1	21 5 23.8	12 1 8.3	6 0 0.0	53 8 15.1
	Grade 3	6 1 16.7	10 0 0.0	23 1 4.3	14 0 0.0	7 1 14.3	60 3 5.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Total Cholesterol (hyper)	Grade 1	6 4 66.7	9 1 11.1	13 4 30.8	7 3 42.9	3 1 33.3	38 13 34.2
	Grade 2	6 0 0.0	10 0 0.0	24 1 4.2	14 0 0.0	7 0 0.0	61 1 1.6
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
Triglycerides (hyper)	Grade 1	6 1 16.7	10 2 20.0	19 6 31.6	12 3 25.0	7 0 0.0	54 12 22.2
	Grade 2	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 3	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0
	Grade 4	6 0 0.0	10 0 0.0	24 0 0.0	14 0 0.0	7 0 0.0	61 0 0.0

- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- 'New' means 'grade 0' at baseline and '≥ grade 1' after baseline
- Baseline is defined as the last non-missing value prior to the first dose

New or worsened cardiac enzymes abnormalities based on CTC grade by dose cohort-SDS Sachet-Safety set

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet% N=61 n (%)
Troponin T	Grade 1	1 0 0.0	7 0 0.0	7 1 14.3	4 0 0.0	5 0 0.0	24 1 4.2
	Grade 4	1 0 0.0	7 0 0.0	7 0 0.0	4 1 25.0	5 0 0.0	24 1 4.2

- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- 'New' means 'grade 0' at baseline and '≥ grade 1' after baseline
- Baseline is defined as the last non-missing value prior to the first dose

New or worsened elevated fasting plasma glucose abnormalities by dose cohort – ADA grade, SDS Caps A-Safety set

Test	Worsening from baseline to	SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS caps A N=22 n (%)
Glucose (Hyper)	Grade 1	5 0 0.0	6 1 16.7	8 0 0.0	19 1 5.3
	Grade 2	5 0 0.0	6 0 0.0	11 1 9.1	22 1 4.5
	Grade 3	5 0 0.0	6 0 0.0	11 1 9.1	22 1 4.5
	Grade 4	5 0 0.0	6 0 0.0	11 0 0.0	22 0 0.0

Glucose non CTCAE grading (American Diabetes Association):
Grade 0: < 140 mg/dL [< 7.8 mmol/L]
Grade 1: 140 - 199 mg/dL [7.8 - 11.1 mmol/L]
Grade 2: 200 - 249 mg/dL [11.2 - 13.8 mmol/L]
Grade 3: 250 - 399 mg/dL [13.9 - 22.2 mmol/L]
Grade 4: ≥ 400 mg/dL [≥ 22.3 mmol/L].

New or worsened elevated fasting plasma glucose abnormalities by dose cohort – ADA grade, SDS Sachet-Safety set

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=6 n (%)	SDS Sachet 1000 mg/day N=10 n (%)	SDS Sachet 1200 mg/day N=24 n (%)	SDS Sachet 1400 mg/day N=14 n (%)	SDS Sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
Glucose (Hyper)	Grade 1	6 0 0.0	10 1 10.0	22 7 31.8	14 2 14.3	7 0 0.0	59 10 16.9
	Grade 2	6 0 0.0	10 0 0.0	22 0 0.0	14 1 7.1	7 0 0.0	59 1 1.7
	Grade 3	6 1 16.7	10 1 10.0	22 1 4.5	14 0 0.0	7 0 0.0	59 3 5.1
	Grade 4	6 0 0.0	10 0 0.0	22 0 0.0	14 1 7.1	7 0 0.0	59 1 1.7

Glucose non CTCAE grading (American Diabetes Association):
Grade 0: < 140 mg/dL [< 7.8 mmol/L]
Grade 1: 140 - 199 mg/dL [7.8 - 11.1 mmol/L]
Grade 2: 200 - 249 mg/dL [11.2 - 13.8 mmol/L]
Grade 3: 250 - 399 mg/dL [13.9 - 22.2 mmol/L]
Grade 4: ≥ 400 mg/dL [≥ 22.3 mmol/L].

New or worsened elevated fasting plasma glucose abnormalities by dose cohort – ADA grade, SDS Caps B-Safety set

Test	Worsening from baseline to	SDS caps B 800 mg/day N=11 n (%)	All SDS caps B N=11 n (%)
Glucose (Hyper)	Grade 1	11 2 18.2	11 2 18.2
	Grade 2	11 0 0.0	11 0 0.0
	Grade 3	11 0 0.0	11 0 0.0
	Grade 4	11 0 0.0	11 0 0.0

Glucose non CTCAE grading (American Diabetes Association):
Grade 0: < 140 mg/dL [< 7.8 mmol/L]
Grade 1: 140 - 199 mg/dL [7.8 - 11.1 mmol/L]
Grade 2: 200 - 249 mg/dL [11.2 - 13.8 mmol/L]
Grade 3: 250 - 399 mg/dL [13.9 - 22.2 mmol/L]
Grade 4: ≥ 400 mg/dL [≥ 22.3 mmol/L]

BEZ235 SDS in combination with trastuzumab group

New or worsened hematology/coagulation abnormalities based on CTC grade by dose cohort, SDS+Trastuzumab

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
White Blood Count	Grade 1	0	2 2 100	14 4 28.6	8 1 12.5	24 7 29.2
	Grade 2	0	3 0 0.0	17 1 5.9	9 3 33.3	29 4 13.8
	Grade 3	0	3 0 0.0	17 0 0.0	9 1 11.1	29 1 3.4
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Abs. Lymphocytes (hypo)	Grade 1	0	1 0 0.0	6 2 33.3	7 0 0.0	14 2 14.3
	Grade 2	0	3 3 100	15 5 33.3	8 1 12.5	26 9 34.6
	Grade 3	0	3 0 0.0	17 2 11.8	8 5 62.5	28 7 25.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 1 11.1	29 1 3.4
Abs. Neutrophils (hypo)	Grade 1	0	3 0 0.0	15 2 13.3	9 2 22.2	27 4 14.8
	Grade 2	0	3 0 0.0	17 1 5.9	9 0 0.0	29 1 3.4
	Grade 3	0	3 0 0.0	17 0 0.0	9 1 11.1	29 1 3.4
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
Platelets	Grade 1	0	2 2 100	17 5 29.4	8 6 75.0	27 13 48.1
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Hemoglobin	Grade 1	0	2 1 50.0	10 6 60.0	5 4 80.0	17 11 64.7
	Grade 2	0	3 1 33.3	15 0 0.0	9 4 44.4	27 5 18.5
	Grade 3	0	3 0 0.0	17 1 5.9	9 0 0.0	29 1 3.4
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Partial Thromboplastin Time	Grade 1	0	3 2 66.7	12 0 0.0	8 1 12.5	23 3 13.0
	Grade 2	0	3 0 0.0	13 2 15.4	8 1 12.5	24 3 12.5
	Grade 3	0	3 1 33.3	13 1 7.7	8 0 0.0	24 2 8.3

- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥ grade 1’ after baseline.
- Baseline is defined as the last non-missing value prior to the first dose.

New or worsened biochemistry abnormalities based on CTC grade by dose cohort, SDS+Trastuzumab-Safety set

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
Creatinine	Grade 1	0	3 0 0.0	17 1 5.9	9 0 0.0	29 1 3.4
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Sodium (Hyper)	Grade 1	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Potassium (Hyper)	Grade 1	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4
	Grade 4	0	3 0 0.0	17 1 5.9	9 0 0.0	29 1 3.4
Calcium (Hypo)	Grade 1	0	2 0 0.0	14 5 35.7	9 2 22.2	25 7 28.0
	Grade 2	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
	Grade 3	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Calcium (Hyper)	Grade 1	0	3 0 0.0	17 2 11.8	9 1 11.1	29 3 10.3
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Magnesium (hypo)	Grade 1	0	3 2 66.7	15 4 26.7	8 1 12.5	26 7 26.9
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Magnesium (hyper)	Grade 1	0	2 0 0.0	16 2 12.5	9 0 0.0	27 2 7.4
	Grade 3	0	2 0 0.0	17 0 0.0	9 0 0.0	28 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Glucose (Hypo)	Grade 1	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 2	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Glucose (Hyper)	Grade 1	0	3 2 66.7	16 7 43.8	9 3 33.3	28 12 42.9
	Grade 2	0	3 0 0.0	17 0 0.0	9 1 11.1	29 1 3.4
Albumin (Hypo)	Grade 1	0	3 1 33.3	14 0 0.0	8 1 12.5	25 2 8.0
	Grade 2	0	3 0 0.0	16 2 12.5	9 0 0.0	28 2 7.1
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Total Bilirubin	Grade 1	0	3 1 33.3	17 2 11.8	9 2 22.2	29 5 17.2
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
SGOT(AST)	Grade 1	0	1 0 0.0	11 1 9.1	9 3 33.3	21 4 19.0
	Grade 2	0	3 0 0.0	16 0 0.0	9 0 0.0	28 0 0.0
	Grade 3	0	3 0 0.0	17 2 11.8	9 1 11.1	29 3 10.3
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
SGPT(ALT)	Grade 1	0	2 1 50.0	14 5 35.7	9 2 22.2	25 8 32.0
	Grade 2	0	3 0 0.0	16 1 6.3	9 0 0.0	28 1 3.6
	Grade 3	0	3 0 0.0	17 1 5.9	9 1 11.1	29 2 6.9
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Amylase	Grade 1	0	3 0 0.0	15 0 0.0	9 3 33.3	27 3 11.1
	Grade 2	0	3 0 0.0	16 0 0.0	9 0 0.0	28 0 0.0
	Grade 3	0	3 1 33.3	16 0 0.0	9 1 11.1	28 2 7.1
	Grade 4	0	3 0 0.0	16 0 0.0	9 0 0.0	28 0 0.0
Lipase	Grade 1	0	3 0 0.0	16 3 18.8	9 0 0.0	28 3 10.7
	Grade 2	0	3 0 0.0	16 0 0.0	9 2 22.2	28 2 7.1
	Grade 3	0	3 1 33.3	16 0 0.0	9 0 0.0	28 1 3.6
	Grade 4	0	3 0 0.0	16 0 0.0	9 0 0.0	28 0 0.0

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
Alk. Phosphatase	Grade 1	0	2 1 50.0	13 3 23.1	8 1 12.5	23 5 21.7
	Grade 2	0	3 0 0.0	15 0 0.0	9 0 0.0	27 0 0.0
	Grade 3	0	3 0 0.0	16 1 6.3	9 1 11.1	28 2 7.1
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Total Cholesterol (hyper)	Grade 1	0	1 1 100	14 5 35.7	6 3 50.0	21 9 42.9
	Grade 2	0	3 1 33.3	17 0 0.0	9 0 0.0	29 1 3.4
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
Triglycerides (hyper)	Grade 1	0	3 0 0.0	16 4 25.0	9 1 11.1	28 5 17.9
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0

- Total = number of patients evaluable post-baseline, who had less than grade x at baseline.
- n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline.
- Patients are counted only for the worst grade observed post-baseline.
- ‘New’ means ‘grade 0’ at baseline and ‘≥ grade 1’ after baseline.
- Baseline is defined as the last non-missing value prior to the first dose.

New or worsened elevated fasting plasma glucose abnormalities by dose cohort – ADA grade, SDS+Trastuzumab

Test	Worsening from baseline to	SDS Sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
Glucose (Hyper)	Grade 1	0	3 0 0.0	17 1 5.9	9 1 11.1	29 2 6.9
	Grade 2	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 3	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0
	Grade 4	0	3 0 0.0	17 0 0.0	9 0 0.0	29 0 0.0

-Glucose non CTCAE grading (American Diabetes Association):

Grade 0: < 140 mg/dL [<7.8 mmol/L]
Grade 1: 140 - 199 mg/dL [7.8 - 11.1 mmol/L]
Grade 2: 200 - 249 mg/dL [11.2 - 13.8 mmol/L]
Grade 3: 250 - 399 mg/dL [13.9 - 22.2 mmol/L]
Grade 4: ≥ 400 mg/dL [≥22.3 mmol/L].

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort HGC-Fast (safety set)

		Fast 10 mg/day	Fast 25 mg/day	Fast 50 mg/day	Fast 100 mg/day	Fast 200 mg/day	Fast 300 mg/day	Fast 400 mg/day	All HGC Fast
		N=3	N=6	N=4	N=6	N=5	N=6	N=11	N=41
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
QTcF (ms)	New > 450	3 0 (0)	6 0 (0)	4 0 (0)	6 2 (33.3)	5 1 (20.0)	6 1 (16.7)	11 2 (18.2)	41 6 (14.6)
	New > 480	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
	New > 500	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
	Increase from baseline >30	3 0 (0)	6 1 (16.7)	4 1 (25.0)	6 3 (50.0)	5 1 (20.0)	6 1 (16.7)	11 2 (18.2)	41 9 (22.0)
	Increase from baseline >60	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
QTcB (ms)	New > 450	3 1 (33.3)	6 1 (16.7)	4 1 (25.0)	6 3 (50.0)	5 2 (40.0)	5 1 (20.0)	10 2 (20.0)	39 11 (28.2)
	New > 480	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 1 (20.0)	6 1 (16.7)	11 2 (18.2)	41 4 (9.8)
	New > 500	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 1 (9.1)	41 1 (2.4)
	Increase from baseline >30	3 1 (33.3)	6 1 (16.7)	4 1 (25.0)	6 3 (50.0)	5 1 (20.0)	6 1 (16.7)	11 5 (45.5)	41 13 (31.7)
	Increase from baseline >60	3 0 (0)	6 0 (0)	4 0 (0)	6 1 (16.7)	5 0 (0)	6 0 (0)	11 1 (9.1)	41 2 (4.9)
QT (ms)	New > 450	3 0 (0)	6 0 (0)	4 1 (25.0)	6 1 (16.7)	5 0 (0)	6 1 (16.7)	11 0 (0)	41 3 (7.3)
	New > 480	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
	New > 500	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
	Increase from baseline >30	3 1 (33.3)	6 2 (33.3)	4 2 (50.0)	6 2 (33.3)	5 1 (20.0)	6 3 (50.0)	11 1 (9.1)	41 12 (29.3)
	Increase from baseline >60	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
VR (bpm)	RR decrease > 25% & to a VR > 100	3 0 (0)	6 0 (0)	4 1 (25.0)	6 0 (0)	5 2 (40.0)	6 0 (0)	11 2 (18.2)	41 5 (12.2)
	RR increase > 25% & to a VR < 50	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)
PR (ms)	Increase > 25% & to a value > 200	3 0 (0)	6 0 (0)	4 0 (0)	6 0 (0)	5 0 (0)	6 0 (0)	11 0 (0)	41 0 (0)

		Fast 10 mg/day N=3 n (%)	Fast 25 mg/day N=6 n (%)	Fast 50 mg/day N=4 n (%)	Fast 100 mg/day N=6 n (%)	Fast 200 mg/day N=5 n (%)	Fast 300 mg/day N=6 n (%)	Fast 400 mg/day N=11 n (%)	All HGC Fast N=41 n (%)
QRS (ms)	Increase > 25% & to a value > 110	3 0 (0)	6 0 (0)	4 0 (0)	6 1 (16.7)	5 0 (0)	6 0 (0)	11 0 (0)	41 1 (2.4)

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- Change from baseline: post baseline - baseline.
- Unscheduled visits are included.

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort HGC-Fed (safety set)

		Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
QTcF (ms)	New >450	5 1 (20.0)	3 1 (33.3)	5 1 (20.0)	4 0 (0)	17 3 (17.6)
	New >480	6 1 (16.7)	3 0 (0)	5 0 (0)	4 0 (0)	18 1 (5.6)
	New >500	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
	Increase from baseline >30	6 1 (16.7)	3 1 (33.3)	5 0 (0)	4 1 (25.0)	18 3 (16.7)
	Increase from baseline >60	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
QTcB (ms)	New >450	5 2 (40.0)	2 1 (50.0)	5 3 (60.0)	4 3 (75.0)	16 9 (56.3)
	New >480	6 1 (16.7)	3 1 (33.3)	5 0 (0)	4 0 (0)	18 2 (11.1)
	New >500	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
	Increase from baseline >30	6 3 (50.0)	3 2 (66.7)	5 1 (20.0)	4 2 (50.0)	18 8 (44.4)
	Increase from baseline >60	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
QT (ms)	New >450	6 1 (16.7)	3 0 (0)	5 2 (40.0)	4 1 (25.0)	18 4 (22.2)
	New >480	6 1 (16.7)	3 0 (0)	5 0 (0)	4 0 (0)	18 1 (5.6)
	New >500	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
	Increase from baseline >30	6 2 (33.3)	3 2 (66.7)	5 1 (20.0)	4 0 (0)	18 5 (27.8)

		Fed 300 mg/day N=6 n (%)	Fed 400 mg/day N=3 n (%)	Fed 700 mg/day N=5 n (%)	Fed 1100 mg/day N=4 n (%)	All HGC Fed N=18 n (%)
	Increase from baseline >60	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
VR (bpm)	RR decrease >25% & to a VR > 100	6 0 (0)	3 0 (0)	5 0 (0)	4 1 (25.0)	18 1 (5.6)
	RR increase >25% & to a VR < 50	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
PR (ms)	Increase >25% & to a value >200	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)
QRS (ms)	Increase >25% & to a value >110	6 0 (0)	3 0 (0)	5 0 (0)	4 0 (0)	18 0 (0)

Total is the number of patients at risk for a specific category. For new abnormality post baseline values, this is the number of patients with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations.

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- Change from baseline: post baseline - baseline.
- Unscheduled visits are included.

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort, SDS Caps A-Safety analysis set

		SDS caps A 400 mg/day N=5 n (%)	SDS caps A 800 mg/day N=6 n (%)	SDS caps A 1000 mg/day N=11 n (%)	All SDS Caps N=22 n (%)
QTcF (ms)	New > 450	5 1 (20.0)	6 1 (16.7)	11 0 (0)	22 2 (9.1)
	New > 480	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
	New > 500	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
	Increase from baseline >30	5 1 (20.0)	6 1 (16.7)	11 0 (0)	22 2 (9.1)
	Increase from baseline >60	5 0 (0)	6 0 (0)	11 0 (0)	22 (0)
QTcB (ms)	New > 450	4 2 (50.0)	6 5 (83.3)	9 1 (11.1)	19 8 (42.1)
	New > 480	5 1 (20.0)	6 1 (16.7)	11 0 (0)	22 2 (9.1)
	New > 500	5 1 (20.0)	6 0 (0)	11 0 (0)	22 1 (4.5)
	Increase from baseline >30	5 1 (20.0)	6 3 (50.0)	11 0 (0)	22 4 (18.2)
	Increase from baseline >60	5 0 (0)	6 1 (16.7)	11 0 (0)	22 1 (4.5)
QT (ms)	New > 450	5 0 (0)	6 1 (16.7)	11 0 (0)	22 1 (4.5)
	New > 480	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
	New > 500	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
	Increase from baseline >30	5 1 (20.0)	6 2 (33.3)	11 2 (18.2)	22 5 (22.7)
	Increase from baseline >60	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
VR (bpm)	RR decrease >25% & to a VR >100	5 1 (20.0)	6 1 (16.7)	11 1 (9.1)	22 3 (13.6)
	RR increase >25% & to a VR<50	5 1 (20.0)	6 0 (0)	11 1 (9.1)	22 2 (9.1)
PR (ms)	Increase >25% & to a value >200	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)
QRS (ms)	Increase >25% & to a value >110	5 0 (0)	6 0 (0)	11 0 (0)	22 0 (0)

Total is the number of patients at risk for a specific category. For new abnormality post baseline values, this is the number of patients with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations.

- n is the number of patients meeting the criteria at least once.
- Baseline is defined as mean of the C1D1-predose.
- Change from baseline: post baseline - baseline.
- Unscheduled visits are included.

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort, SDS Sachet-Safety analysis set

		SDS sachet 800 mg/day N=6 n (%)	SDS sachet 1000 mg/day N=10 n (%)	SDS sachet 1200 mg/day N=24 n (%)	SDS sachet 1400 mg/day N=14 n (%)	SDS sachet 1600 mg/day N=7 n (%)	All SDS Sachet N=61 n (%)
QTcF (ms)	New > 450	6 1(16.7)	10 0(0.0)	24 5(20.8)	14 1(7.1)	7 0(0.0)	61 7 (11.5)
	New > 480	6 0 (0)	10 0 (0)	24 0 (0)	14 0 (0)	7 0 (0)	61 0 (0)
	New > 500	6 0 (0)	10 0 (0)	24 0 (0)	14 0 (0)	7 0 (0)	61 0 (0)
	Increase from baseline >30	6 2 (33.3)	10 2 (20.0)	24 6 (25.0)	14 2 (14.3)	7 1 (14.3)	61 13 (21.3)
	Increase from baseline >60	6 0 (0.0)	10 0 (0)	24 1 (4.2)	14 0 (0)	7 0 (0.0)	61 1 (1.6)
QTcB (ms)	New > 450	6 2 (33.3)	9 3 (33.3)	21 8 (38.1)	13 2 (15.4)	7 4 (57.1)	56 19 (33.9)
	New > 480	6 0 (0)	10 0 (0)	24 2 (8.3)	14 1 (7.1)	7 0 (0)	61 3 (4.9)
	New > 500	6 0 (0.0)	10 0 (0.0)	24 0 (.0)	14 0 (0)	7 0 (0.0)	61 0 (0.0)
	Increase from baseline >30	6 1 (16.7)	10 2 (20.0)	24 9 (37.5)	14 2 (14.3)	7 0 (0.0)	61 14 (23.0)
	Increase from baseline >60	6 0 (0)	10 0 (0)	24 2 (8.3)	14 0 (0)	7 0 (0)	61 2 (3.3)
QT (ms)	New >450	6 1 (16.7)	10 0 (0)	24 3 (12.5)	14 0 (0)	7 1 (14.3)	61 5 (8.2)
	New >480	6 0 (0)	10 0 (0)	24 1 (4.2)	14 0 (0)	7 0 (0)	61 1 (1.6)
	New >500	6 0 (0)	10 0 (0)	24 0 (0)	14 0 (0)	7 0 (0)	61 0 (0)
	Increase from baseline >30	6 1 (16.7)	10 3 (30.0)	24 12 (50.0)	14 2 (14.3)	7 3 (42.9)	61 21 (34.4)
	Increase from baseline >60	6 0 (0)	10 0 (0)	24 1 (4.2)	14 0 (0)	7 0 (0)	61 1 (1.6)
VR (bpm)	RR decrease >25% & to a VR > 100	6 0 (0)	10 0 (0)	24 4 (16.7)	14 1 (7.1)	7 1 (14.3)	61 6 (9.8)
	RR increase >25% & to a VR <50	6 0 (0)	10 0 (0)	24 0 (0)	14 0 (0)	7 1 (14.3)	61 1 (1.6)
PR (ms)	Increase >25% & to a value >200	6 0 (0)	10 0 (0)	24 1 (4.2)	14 0 (0)	7 0 (0)	61 1 (1.6)
QRS (ms)	Increase > 25% & to a value > 110	6 0 (0)	10 0 (0)	24 0 (0)	14 0 (0)	7 0 (0)	61 0 (0)

Total is the number of patients at risk for a specific category. For new abnormality post baseline values, this is the number of patients with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations.

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- Change from baseline: post baseline - baseline.
- Unscheduled visits are included.

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort, SDS Caps B-Safety analysis set

		SDS caps B 800 mg/day N=11 n (%)	All SDS Caps B N=11 n (%)
QTcF (ms)	New > 450	11 3 (27.3)	11 3 (27.3)
	New > 480	11 0 (0)	11 0 (0)
	New > 500	11 0 (0)	11 0 (0)
	Increase from baseline >30	11 2 (18.2)	11 2 (18.2)
	Increase from baseline >60	11 0 (0)	11 0 (0)
QTcB (ms)	New > 450	11 7 (63.6)	11 7 (63.6)
	New > 480	11 1 (9.1)	11 1 (9.1)
	New > 500	11 0 (0)	11 0 (0)
	Increase from baseline >30	11 4 (36.4)	11 4 (36.4)
	Increase from baseline >60	11 0 (0)	11 0 (0)
QT (ms)	New >450	11 1 (9.1)	11 1 (9.1)
	New >480	11 0 (0)	11 0 (0)
	New >500	11 0 (0)	11 0 (0)
	Increase from baseline >30	11 6 (54.5)	11 6 (54.5)
	Increase from baseline >60	11 2 (18.2)	11 2 (18.2)
VR (bpm)	RR decrease >25% & to a VR >100	11 1 (9.1)	11 1 (9.1)
	RR increase >25% & to a VR <50	11 1 (9.1)	11 1 (9.1)
PR (ms)	Increase >25% & to a value >200	11 0 (0)	11 0 (0)
QRS (ms)	Increase >25% & to a value >110	11 0 (0)	11 0 (0)

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- Change from baseline: post baseline - baseline.
- Unscheduled visits are included.

Number (percentage) of all patients with notable QT/QTc interval, by dose cohort, SDS +Trastuzumab-Safety analysis set

		SDS sachet 800 mg/day N=1 n (%)	Caps A 400 mg/day + T N=3 n (%)	Sachet 600 mg/day + T N=17 n (%)	Sachet 800 mg/day + T N=9 n (%)	All SDS + T N=30 n (%)
QTcF (ms)	New >450	1 1 (100.0)	2 0 (0)	17 3 (17.6)	9 1 (11.1)	29 5 (17.2)
	New >480	1 0 (0)	3 1 (33.3)	17 0 (0)	9 0 (0)	30 1 (3.3)
	New >500	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)
	Increase from baseline >30	1 0 (0)	3 0 (0)	17 2 (11.8)	9 2 (22.2)	30 4 (13.3)
	Increase from baseline >60	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)
QTcB (ms)	New >450	1 1 (100.0)	2 0 (0)	17 7 (41.2)	8 2 (25.0)	28 10 (35.7)
	New >480	1 0 (0)	2 0 (0)	17 0 (0)	9 0 (0)	29 0 (0)
	New >500	1 0 (0)	3 1 (33.3)	17 0 (0)	9 0 (0)	30 1 (3.3)
	Increase from baseline >30	1 1 (100.0)	3 1 (33.3)	17 4 (23.5)	9 3 (33.3)	30 9 (30.0)
	Increase from baseline >60	1 0 (0)	3 0 (0)	17 1 (5.9)	9 0 (0)	30 1 (3.3)
QT (ms)	New >450	0	3 1 (33.3)	17 1 (5.9)	9 1 (11.1)	29 3 (10.3)
	New >480	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)
	New >500	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)
	Increase from baseline >30	1 0 (0)	3 2 (66.7)	17 6 (35.3)	9 6 (66.7)	30 14 (46.7)
	Increase from baseline >60	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)
VR (bpm)	RR decrease >25% & to a VR >100	1 0 (0)	3 2 (66.7)	17 2 (11.8)	9 0 (0)	30 4 (13.3)
	RR increase >25% & to a VR <50	1 0 (0)	3 0 (0)	17 0 (0)	9 1 (11.1)	30 1 (3.3)
PR (ms)	Increase >25% & to a value >200	1 0 (0)	3 0 (0)	17 0 (0)	9 2 (22.2)	30 2 (6.7)
QRS (ms)	Increase >25% & to a value > 110	1 0 (0)	3 0 (0)	17 0 (0)	9 0 (0)	30 0 (0)

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Date of Latest Update: