NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

trametinib

Trial Indication(s)

solid tumors

Protocol Number

CTMT212X2102

Protocol Title

A Phase I, Open-Label Study to Determine the Effect of Repeat Dosing of Trametinib on the Pharmacokinetics of a Combined Oral Contraceptive (Norethindrone plus Ethinyl Estradiol) in Female Patients with Solid Tumors

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: October 2016 (Actual)
Primary Completion Date: August 2019 (Actual)
Study Completion Date: August 2019 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a Phase I, open-label, single sequence, two-period crossover study to evaluate the effect of trametinib 2 mg once daily on the PK of a daily dose of COC containing 1 mg NE and 0.035 mg EE in female patients with solid tumors. The PK of trametinib and its metabolite M5 were also assessed. The study consisted of a Screening period (within 30 days of Day 1) followed by the PK phase which consisted of Period 1 (5 days, from Day 1 to Day 5) and Period 2 (17 days, from Day 6 to Day 22). Combination oral contraceptive dosing was initiated from Day 1 and trametinib dosing from Day 6. After completing the PK phase of the study, patients were allowed to continue in the post-PK treatment phase of the study and continue to take trametinib if they derived benefit from it, unless they experienced disease progression, intolerance of study drug, withdrawal of consent or lost to follow up as per the Investigator's discretion. Continuation of COC after the PK phase was optional. An End of Treatment visit was conducted within 7 days of the last dose of the study treatment and a final safety follow up 30 days after the last dose of the study treatment.

Centers

5 centers in 5 countries: Netherlands(1), Belgium(1), Spain(1), United States(1), United Kingdom(1)

Objectives:

The primary objective was to evaluate the effect of multiple doses of trametinib (2 mg once daily) on the steady-state pharmacokinetics (PK) of Combination oral contraceptive (COC) consisting of norethindrone (NE) and ethinyl estradiol (EE) in female patients with solid tumors.

The secondary objectives were 1. to characterize the steady-state PK of metabolite M5 when trametinib (2 mg once daily) was administered in combination with COC in female patients with solid tumors, and 2. to evaluate the safety and tolerability of trametinib (2 mg once daily) in female patients with solid tumors.

Test Product (s), Dose(s), and Mode(s) of Administration

For this study, study drug referred to Combination Oral Contraceptive (COC) and trametinib and Study treatment referred to COC or trametinib or the combination of these, i.e., COC and trametinib.

For the study treatment Trametinib, the form was an oral tablet, with a dose of 2 mg.

For the COC, the form was an oral tablet, with a dose of 1 mg norethindrone/0.035 mg ethinyl estradiol.

Statistical Methods

The Full analysis set (FAS) and Safety set included all patients in the study who received at least one dose of any study treatment (i.e., trametinib or COC). The FAS and Safety set in this study were identical.

Two separate Pharmacokinetic analysis sets (PAS) were considered for the evaluation of this study, one for COC (PASOC) and one for trametinib/M5 (PASTMT).

The patients in PASOC were included in the PK data analysis of COC in this study. No formal statistical hypothesis was tested and an estimation approach was adopted. A formal statistical analysis was performed for primary PK parameters (maximum observed drug concentration [Cmax], area under concentration from time zero to the last measurable concentration sampling time [AUClast] and area under concentration calculated to the end of a dosing interval at steady-state [AUCtau]) of COC (NE and EE).

A linear mixed effects model was fitted to the log-transformed primary PK parameters (Cmax, AUClast and AUCtau) of COC (NE and EE) to assess the effect of multiple daily doses of 2 mg trametinib on COC (NE and EE). For this analysis,

co-administration of trametinib (2 mg) and COC (1 mg NE and 0.035 mg EE) on Day 21 was the Test treatment, and COC (1 mg NE and 0.035 mg EE) administration alone on Day 5 was the Reference treatment. The model included treatment (Test or Reference) as a fixed effect and patient as a random effect. Point estimate of the treatment difference (Test-Reference) and the corresponding two-sided 90% confidence interval (CI) was calculated and anti-logged to obtain the point estimate, and 90% CI was for the ratio of geometric means of Test versus Reference treatments on the original scale. The median and range of the differences of time to reach maximum drug concentration (Tmax) values of COC, were calculated between the Test and Reference treatments.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

● Had a histologically or cytologically confirmed diagnosis of a solid tumor malignancy (except for any excluded malignancies listed in the Exclusion Criteria) that was not responsive to standard therapy(ies) or for which there was no approved therapy.

● Met one of the following criteria: was currently on a stable regimen of an oral contraceptive containing 1mg NE and 0.035mg EE, or was willing to switch to a regimen of an oral contraceptive containing 1mg NE and 0.035mg EE from a stable regimen of an alternate OC, or was willing to start a regimen of an oral contraceptive containing 1mg NE and 0.035mg EE.

● Met one of the following criteria: was post-menopausal, or, Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during dosing and for four months after stopping medication.

● Had no prior treatment-related toxicities >Grade 1 (except alopecia) at the time of enrolment.

● Patient had to meet the following laboratory values at the screening visit: Absolute Neutrophil Count ≥1.5 x 109/L. Platelets ≥75 x 109/L. Hemoglobin (Hgb) ≥9 g/dL. Serum creatinine <1.5 mg/dL. Total bilirubin ≤1.5 x upper limit of normal (ULN) (isolated bilirubin >1.5x ULN was acceptable if bilirubin was fractionated and direct bilirubin <35%). Aspartate transaminase (AST) ≤ 3.0 x ULN, except for patients with liver metastasis, who could only be included if AST ≤5.0 x ULN. Alanine transaminase (ALT) ≤ 3.0 x ULN, except for patients with liver metastasis or tumor infiltration, who could only be included if ALT ≤5.0 x ULN. Prothrombin time (PT)/International normalized ratio (INR) and Partial thromboplastin time (PTT) ≤1.5xULN. Note: patients receiving therapeutic anticoagulation agents prior screening were permitted. Albumin 2.5 g/dL.

● Patient had an Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Exclusion Criteria:

● History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as

uncontrolled or significant cardiac disease
● Had had any major surgery, extensive radiotherapy, or anti-cancer therapy (e.g., chemotherapy with delayed toxicity, biologic therapy, or immunotherapy) within 21 days prior to enrolment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrolment. Prolonged immobilization must have resolved prior to enrolment.
● Had a known or suspected carcinoma that was excluded as administration of Oral Contraceptive would be contraindicated.
● Had a history of another malignancy.
● Had a history of interstitial lung disease or pneumonitis.
● Had a history of RVO.
● Had a history of any of conditions that would contraindicate administration of an OC
● Had symptomatic or untreated leptomeningeal, brain metastases, or spinal cord compression.

Participant Flow Table

Baseline

	Oral Contraceptive / Trametinib	Total
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue	

	dosing with trametinib only once daily from Day 22 onwards (post PK Phase).	
Started	19	19
Completed	19	19
Not Completed	0	0

Study phase

	Oral Contraceptive / Trametinib	**Total**
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only	

	once daily from Day 22 onwards (post PK Phase).	
Started	19	19
Completed	0	0
Not Completed	19	19
Progressive disease	9	9
Adverse Event	4	4
Death	1	1
Study Terminated by Sponsor	3	3
Subject/guardian decision/Poor quality of life	1	1
Physician Decision	1	1

Baseline Characteristics

	Oral Contraceptive / Trametinib	**Total**
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily	

	from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).	
Number of Participants [units: participants]	19	19
Age, Customized (units: Participants) Count of Participants (Not Applicable)		
In utero	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0
Newborns (0-27 days)	0	0
Infants and toddlers (28 days-23 months)	0	0
Children (2-11 years)	0	0
Adolescents (12-17 years)	0	0
Adults (18-64 years)	19	19

From 65-84 years	0	0
85 years and over	0	0
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)		
Female	19	19
Male	0	0
Age Continuous (units: years) Mean ± Standard Deviation		
	47.3±7.96	
Race (NIH/OMB) (units: participants) Count of Participants (Not Applicable)		
American Indian or Alaska Native	0	0
Asian	0	0
Native Hawaiian or Other Pacific Islander	0	0
Black or African American	0	0
White	14	14
More than one race	0	0
Unknown or Not Reported	5	5

Primary Outcome Result(s)

Pharmacokinetics parameter: AUCtau of NE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: AUCtau of NE alone and in combination with trametinib (units: pg*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	

Norethindrone (n=16)	107000 (77.6%)
Trametinib + Norethindrone (N=14)	128000 (67.0%)

Pharmacokinetics parameter: AUClast of NE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16

Pharmacokinetics parameter: AUClast of NE alone and in combination with trametinib (units: pg*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	
Norethindrone (n=16)	103000 (86.9%)
Trametinib + Norethindrone (n=14)	123000 (71.3%)

Pharmacokinetics parameter: Cmax of NE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily

	from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: Cmax of NE alone and in combination with trametinib (units: pg/mL) Geometric Mean (Geometric Coefficient of Variation)	
Norethindrone (n=16)	15100 (50.7%)
Trametinib + Norethindrone (N=14)	17000 (36.1%)

Pharmacokinetics parameter: Tmax of NE alone and in combination with trametinib

(Time Frame: Days 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib

	once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: Tmax of NE alone and in combination with trametinib (units: hour (hr)) Median (Full Range)	
Norethindrone (n=16)	1.00 (0.500 to 24.0)
Trametinib + Norethindrone (n=14)	1.02 (0.933 to 2.00)

Pharmacokinetics parameter: AUCtau of EE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase

	started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: AUCtau of EE alone and in combination with trametinib (units: pg*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	
Ethinyl Estradiol (n=16)	1020 (59.5%)
Trametinib + Ethinyl Estradiol (n=14)	1050 (49.2%)

Pharmacokinetics parameter: AUClast of EE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase

	patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: AUClast of EE alone and in combination with trametinib (units: pg*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	
Ethinyl Estradiol (n=16)	983 (70.0%)
Trametinib + Ethinyl Estradiol (n=14)	998 (53.1%)

Pharmacokinetics parameter: Cmax of EE alone and in combination with trametinib

(Time Frame: Day 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16
Pharmacokinetics parameter: Cmax of EE alone and in combination with trametinib (units: pg/mL) Geometric Mean (Geometric Coefficient of Variation)	
Ethinyl Estradiol (n=16)	135 (49.6%)

Trametinib + Ethinyl Estradiol (n=14)	120 (40.0%)

Pharmacokinetics parameter: Tmax of EE alone and in combination with trametinib

(Time Frame: Days 5 and 6 and 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	16

Pharmacokinetics parameter: Tmax of EE alone and in combination with trametinib (units: hour (hr)) Median (Full Range)	
Ethinyl Estradiol (n=16)	0.983 (0.500 to 2.50)
Trametinib + Ethinyl Estradiol (n=14)	1.48 (0.517 to 2.58)

Secondary Outcome Result(s)

Pharmacokinetics parameter: AUClast of M5

(Time Frame: Day 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients

	could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	11
Pharmacokinetics parameter: AUClast of M5 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	
	51.5 (100.7%)

Pharmacokinetics parameter: AUCtau of M5

(Time Frame: Day 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took

	both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	0
Pharmacokinetics parameter: AUCtau of M5 (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)	

Pharmacokinetics parameter: Cmax of M5

(Time Frame: Day 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase patients took the Oral Contraceptive once daily from Days 1-5.

	Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	11
Pharmacokinetics parameter: Cmax of M5 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)	
	3.75 (58.1%)

Pharmacokinetics parameter: Tmax of M5

(Time Frame: Day 21 and 22)

	Oral Contraceptive / Trametinib
Arm/Group Description	In treatment period 1 of the PK Phase

	patients took the Oral Contraceptive once daily from Days 1-5. Period 2 of the PK Phase started on Day 6 when patients took both the Oral Contraceptive and trametinib once daily from Days 6 to 21. Patients could continue dosing with trametinib only once daily from Day 22 onwards (post PK Phase).
Number of Participants Analyzed [units: participants]	11
Pharmacokinetics parameter: Tmax of M5 (units: hour (hr)) Median (Full Range)	
	2.50 (1.55 to 3.00)

Safety Results

All-Cause Mortality

	All subjects N = 19
Arm/Group Description	All subjects
Total participants affected	4 (21.05%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field “number of deaths resulting from adverse events” all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.
Source Vocabulary for Table Default	MedDRA 22.0
Assessment Type for Table Default	Systematic Assessment

	All subjects N = 19
Arm/Group Description	All subjects
Total participants affected	8 (42.11%)

Gastrointestinal disorders	
Ascites	2 (10.53%)
Ileus	1 (5.26%)
Nausea	1 (5.26%)
Infections and infestations	
Pneumonia	1 (5.26%)
Metabolism and nutrition disorders	
Hypoglycaemia	1 (5.26%)
Musculoskeletal and connective tissue disorders	
Myositis	1 (5.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Intestinal metastasis	1 (5.26%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field “number of deaths resulting from adverse events” all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.
Source Vocabulary for Table Default	MedDRA 22.0

Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	All subjects N = 19
Arm/Group Description	All subjects
Total participants affected	18 (94.74%)
Blood and lymphatic system disorders	
Anaemia	4 (21.05%)
Neutropenia	2 (10.53%)
Cardiac disorders	
Tachycardia	1 (5.26%)
Gastrointestinal disorders	
Abdominal pain	2 (10.53%)
Anal haemorrhage	1 (5.26%)
Ascites	1 (5.26%)
Constipation	1 (5.26%)
Diarrhoea	6 (31.58%)
Dry mouth	1 (5.26%)
Gastrooesophageal reflux disease	1 (5.26%)
Intestinal obstruction	1 (5.26%)
Nausea	7 (36.84%)

Stomatitis	4 (21.05%)
Vomiting	5 (26.32%)
General disorders and administration site conditions	
Asthenia	2 (10.53%)
Fatigue	3 (15.79%)
Oedema peripheral	2 (10.53%)
Pyrexia	1 (5.26%)
Hepatobiliary disorders	
Hepatic failure	1 (5.26%)
Infections and infestations	
Gastroenteritis viral	1 (5.26%)
Nasopharyngitis	1 (5.26%)
Oral candidiasis	1 (5.26%)
Pneumonia	1 (5.26%)
Vulvovaginal candidiasis	1 (5.26%)
Injury, poisoning and procedural complications	
Wound complication	1 (5.26%)
Investigations	
Alanine aminotransferase increased	1 (5.26%)
Amylase increased	1 (5.26%)

Aspartate aminotransferase increased	2 (10.53%)
Blood alkaline phosphatase increased	4 (21.05%)
Blood bilirubin increased	3 (15.79%)
Blood pressure increased	1 (5.26%)
C-reactive protein increased	1 (5.26%)
Ejection fraction decreased	1 (5.26%)
Gamma-glutamyltransferase increased	1 (5.26%)
Lipase increased	1 (5.26%)
Waist circumference increased	1 (5.26%)
Weight decreased	1 (5.26%)
Metabolism and nutrition disorders	
Decreased appetite	1 (5.26%)
Hypertriglyceridaemia	1 (5.26%)
Hypoalbuminaemia	1 (5.26%)
Hypocalcaemia	1 (5.26%)
Hypoglycaemia	1 (5.26%)
Hypokalaemia	1 (5.26%)
Hypomagnesaemia	2 (10.53%)
Hyponatraemia	2 (10.53%)

Hypophosphataemia	2 (10.53%)
Musculoskeletal and connective tissue disorders	
Arthralgia	1 (5.26%)
Flank pain	1 (5.26%)
Musculoskeletal chest pain	1 (5.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Tumour obstruction	1 (5.26%)
Nervous system disorders	
Apraxia	1 (5.26%)
Dizziness	1 (5.26%)
Dysgeusia	1 (5.26%)
Lethargy	1 (5.26%)
Somnolence	1 (5.26%)
Psychiatric disorders	
Depression	1 (5.26%)
Renal and urinary disorders	
Acute kidney injury	1 (5.26%)
Faecaluria	1 (5.26%)
Reproductive system and breast disorders	

Vaginal haemorrhage	1 (5.26%)
Respiratory, thoracic and mediastinal disorders	
Acute respiratory failure	1 (5.26%)
Dyspnoea exertional	1 (5.26%)
Epistaxis	1 (5.26%)
Respiratory distress	1 (5.26%)
Skin and subcutaneous tissue disorders	
Dermatitis acneiform	1 (5.26%)
Dry skin	3 (15.79%)
Hypertrichosis	1 (5.26%)
Pruritus	2 (10.53%)
Rash	10 (52.63%)
Skin disorder	1 (5.26%)
Skin ulcer	1 (5.26%)
Vascular disorders	
Hot flush	2 (10.53%)
Hypertension	2 (10.53%)
Plethoric face	1 (5.26%)

Conclusion:

Based on the study data, when co-administered with trametinib, norethindrone (NE) showed 20% increase in the exposure that is clinically non-significant and ethinyl estradiol (EE) exposure remained unchanged. Thus, there is no

expected loss of efficacy of the Combination Oral Contraceptive (COC). Based on the limited data generated in this heterogeneous population, the safety profile is consistent with previous safety data of trametinib. The study results support the use of COC in solid tumor patients treated with trametinib.

Date of Clinical Trial Report

18 May 2020