Study protocol No: 5592-17-02-23

CASE REPORT FORM

STUDY OF EFFICACY OF CURCUMIN IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH ADVANCED BREAST CANCER: RANDOMIZED, DOULBE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL

SHORT TITLE: "CURCUMIN" IN COMBINATION WITH CHEMOTHERAPY

Principal Investigator: Tatul Saghatelyan, MD, PhD
Sponsor:BRIU GmbH Konigstein, Hessen, Germany
ClinicalTrials.gov Identifier: NCT03072992
Name of site*: National Center of Oncology (NCO), Yerevan, Armenia*
CRF Version Number:1.0, 25/09/2016, Final.

Patient's name and surname:			
Patient's entry Number ☐☐☐			TREATMENT CODE ☐☐☐
Sex	☐ Male ☒ Female	**Screening date:** ☐☐ ☐☐ ☐☐☐☐	
Age (years) ☐☐		**Accrual date:** ☐☐ ☐☐ ☐☐☐☐	
Height (cm) ☐☐☐		Date: _____ Investigators' signature:_____	
Weight (kg) ☐☐☐		Date: _____ Monitor's signature:_____	

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Completed by: _____
Name Signature Date

CRF COMPLETION INSTRUCTIONS

General

Complete the CRF using a **black or blue ballpoint pen** and ensure thatall entries are complete and legible.

Avoid the use of abbreviations and acronyms.

The CRF should be completed as soon as possible after the scheduled visit.

Each CRF page should be signed and dated by the person completing the form.
The 'completed by' Name in the footer of each page must be legible and **CRFs should only be completed by individuals delegated to complete CRFs on the Site Delegation log (and signed by the PI).**

Ensure that all fields are completed on each page:

- If a test was Not Done record **ND** in the relevant box(es)
- Where information is Not Known write **NK** in relevant box(es)
- Where information is not applicable write **NA** in the relevant box(es)

Corrections to entries

If an error is made, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data point on the CRF and initial and date the change.

Do NOT

- Obscure the original entry by scribbling it out
- Try to correct/ modify the original entry
- Use Tippex or correction fluid

Medications taken by the subject during the trial should be recorded on the "Concomitant Medications Log" using the generic name whenever possible, except combination products which will be recorded using the established trade name. All non-IMPs mentioned in the protocol should also be recorded on the "Concomitant medication Log" for the duration of the trial.

Verbatim Adverse Event terms (initial medical term) should be recorded as the final diagnosis whenever possible.

Complete all **dates** as day, month, year i.e. 27/07/1975. Partial dates should be recorded as NK/MM/2008.

All **times** are to be recorded in 24 hour format without punctuation and always use 4-digits; i.e. 0200 or 2130. Midnight is recorded as 0000.

Weights should be recorded to the nearest 0.1 kg.

Source documents such as lab reports, ECG reports etc. should be filed separately from the CRF (if not in the medical notes) for each subject and be signed and dated by a delegated Investigator as proof of review of the assessment during the trial. Questionnaire should be considered as the CRF appendices (except standard approved questionnaire e.g. EQ-5D)

If a subject prematurely withdraws from the trial a single line must be drawn across each uncompleted page to correspond with the last visit of the subject as mentioned on the "Trial Completion" page.

The protocol deviation/violation/serious breach log should be used to record comments relating to each CRF visit that cannot be captured on the page itself. This includes reason for delayed or missed protocol visits or trial assessments, unscheduled visits etc.

The Chief Investigator (for lead site)/Principal Investigator is responsible for the accuracy of the data reported on the CRF. The CI/PI must sign and date the Principal Investigator's Sign Off page to certify accuracy, completeness and legibility of the data reported in the CRF.

Serious Adverse Events (SAEs)

SAEs should be faxed **within 24 hours** of the site being aware of the event using the trial specific SAE report form to _____**(phone, email.)**

Storage

CRF documents should be stored in a locked, secure area when not in use where confidentiality can be maintained. Ensure that they are stored separately to any other documents that might reveal the identity of the subject

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) DEMOGRAPHIC DATA, MED. HISTORY

Date of Assessment:__ __ / __ __ / __ __ __ __

(DD / MMM / YYYY)

Demographic Data:	
Date of Birth:	__ __ / __ __ / __ __ __ __ (DD / MMM / YYYY)
Sex:	☐ Male ☐ Female

Informed Consent:	
Date participant/relative **signed written consent form:** __ __ / __ __ / __ __ __ __ (DD / MMM / YYYY)	**Date of first trial-related procedure:** __ __ / __ __ / __ __ __ __ (DD / MMM / YYYY)
Name of person taking informed consent: _____	

Has the patient had any relevant medical history?	☐ **No** ☐ **Yes,** Complete below		
Condition / illness /surgical procedure	**Start date** (DD/MMM/YYYY)	**Stop date** (DD/MMM/YYYY)	**Or tick if ongoing at Screening Visit?**
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐
	____/____/____	____/____/____	☐

Completed by: _____

Name Signature Date

VISIT 1 (SCREENING)**CLINICAL EXAM**

Date of Assessment: __ __ / __ __ / __ __ __ __

(DD /MM / YYYY)

Was Physical Examination performed? ☐**No** ☐**Yes, Complete below**				
System	***Abnormal**	**Normal**	**Not done**	***If noted ABNORMAL, please provide brief description and comment if clinically significant or not (CS/NCS)**
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Breast/chestwall	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Patient's performance status	
Karnofsky performance score (KPS), %	
ECOG score	

Completed by: _____

Name Signature Date

VISIT 1 (SCREENING) **VITAL SIGNS & ECG**

Were Vital Signs performed?	☐**No (comment below)** ☐**Yes,** Complete below Comment*: _____
Date of Vital Signs:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)
Time of Vital Signs:	_____:_____ **HH:MM**
Blood Pressure: ___ ___ ___ / ___ ___ ___ mmHg	
Pulse: ____ ___ ___ beats/min	
Weight: ___ ___ ___ . ___ kg	**Height:** ___ . ___ ___ m
Temperature: ___ ___ . ___ **°C**	

Was an ECG performed?	☐**No (comment below)** ☐**Yes,** Complete below Comment*: _____
Date& Time of ECG:	__ __ / __ __ __ / __ __ __ _____:_____ (DD / MMM / YYYY)**HH:MM**
The ECG is:	☐**Within normal limits** ☐**Abnormal, NOT clinically significant** ☐**Abnormal, clinically significant, please specify:** _____

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) **HAEMATOLOGY**

Clinical Haematology Laboratory tests performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment:** _____
Date of Sample:	__ __ / __ __ __ / __ __ __ __ **(DD / MMM / YYYY)**

HAEMATOLOGY Laboratory Parameter	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant:
WBC			☐No ☐Yes
RBC			☐No ☐Yes
Hb			☐No ☐Yes
HCT			☐No ☐Yes
MCV			☐No ☐Yes
MCH			☐No ☐Yes
PLT			☐No ☐Yes
NEUTROPHILS			☐No ☐Yes
LYMPHOCYTES			☐No ☐Yes
MONOCYTES			☐No ☐Yes
EOSINOPHILS			☐No ☐Yes
BASOPHILS			☐No ☐Yes
RETICULOCYTES			☐No ☐Yes
ESR		**mm/h**	☐No ☐Yes

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) **BIOCHEMISTRY**

Clinical Biochemistry Laboratory tests performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment:** _____
Date of Sample:	__ __/ __ __/ __ __ __ __ **(DD /MM / YYYY)**

BIOCHEMISTRY **Laboratory Parameter**	**Value**	**Unit**	**If parameter indicated as out of normal range on report, please check if clinically significant:**
GLUCOSE			☐**No** ☐**Yes**
UREA			☐**No** ☐**Yes**
CREATININE			☐**No** ☐**Yes**
TOTAL PROTEIN			☐**No** ☐**Yes**
TOTAL BILIRUBIN			☐**No** ☐**Yes**
ALK PHOS			☐**No** ☐**Yes**
ALT			☐**No** ☐**Yes**
AST			☐**No** ☐**Yes**
GGT			☐**No** ☐**Yes**
LDH			☐**No** ☐**Yes**
CALCIUM			☐**No** ☐**Yes**
PROTROMBINE			☐**No** ☐**Yes**
FIBRINOGEN			☐**No** ☐**Yes**
			☐**No** ☐**Yes**
			☐**No** ☐**Yes**
			☐**No** ☐**Yes**

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) **TUMOR MARKERS**

Tumour Markers Laboratory tests performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment *:** _____
Date of Sample:	__ __ / __ __ __ / __ __ __ __ **(DD / MMM / YYYY)**

TUMOR MARKERS **Laboratory Parameter**	**Value**	**Unit (site to pre-complete prior to the finalization of the template)**	**If parameter indicated as out of normal range on report, please check if clinically significant:**
CEA			☐**No** ☐**Yes**
CA15-3			☐**No** ☐**Yes**

VISIT 1 (SCREENING) **URINALYSIS**

Urinalysis performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment:** _____
Date of Sample:	__ __ / __ __ / __ __ __ __ **(DD / MM / YYYY)**

Urinalysis **Laboratory Parameter**	**Value**	**Unit**	**If parameter indicated as out of normal range on report, please check if clinically significant:**
SG			☐**No** ☐**Yes**
PROTEINS			☐**No** ☐**Yes**
RBC			☐**No** ☐**Yes**
LEUCOCYTES			☐**No** ☐**Yes**
EPITHELIUM			☐**No** ☐**Yes**
YEASTS			☐**No** ☐**Yes**
BACTERIA			☐**No** ☐**Yes**
			☐**No** ☐**Yes**

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

VISIT 1 (SCREENING) CONCOMITANT MEDICATIONS

Date of Assessment: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Is the participant taken any concomitant medications at screening or <insert time frame as specified in protocol>	☐**No** ☐**Yes,** Complete below						
Medication (Record Generic or trade name)	**Reason for use** (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose and units	**Freque -ncy**	**Route**	**Start Date** (DD/MMM/YYYY)	**Stop Date** (DD//MMM/YYY)	**Or tick if ongoing at Screening Visit**
1.					____/_____/_____	____/_____/_____	☐
2.					____/_____/_____	____/_____/_____	☐
3.					____/_____/_____	____/_____/_____	☐
4.					____/_____/_____	____/_____/_____	☐
5.					____/_____/_____	____/_____/_____	☐
6.					____/_____/_____	____/_____/_____	☐
7.					____/_____/_____	____/_____/_____	☐
8.					____/_____/_____	____/_____/_____	☐
9.					____/_____/_____	____/_____/_____	☐
10.					____/_____/_____	____/_____/_____	☐

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

VISIT 1 (SCREENING)**X-RAY**

X-ray performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment *:** _____
Date of Sample:	__ __ / __ __ / __ __ __ __**(DD / MM / YYYY)**

Does the X-ray reveal bidimentionally measurable disease?	**Yes**	**No**
	☐	☐

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) **CT**

CT performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment *:** _____
Date of Study:	__ __ / __ __ / __ __ __ __ **(DD / MM / YYYY)**

Does the CT reveal bidimentionally measurable disease?	**Yes**	**No**
	☐	☐

Completed by: _____
Name Signature Date

VISIT 1 (SCREENING) **MRI**

MRI performed?	☐**No (comment below)** ☐**Yes,** Complete below **Comment *:** _____
Date of Sample:	__ __ / __ __ / __ __ __ __ **(DD / MM / YYYY)**

Does the MRI reveal bidimentionally measurable disease?	**Yes**	**No**
	☐	☐

Completed by: _____

Name Signature Date

VISIT 1 (SCREENING) **INCLUSION CRITERIA**

Date of Assessment: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

The following criteria MUST be answered YES for participant to be included in the trial (except where NA is appropriate):		**Yes**	**No**	**N/A**
1.	*Patient is able to give fully informed written consent according to International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines and to comply with the instructions in the protocol*	☐	☐	☐
2.	*Patients is diagnosed with histologically-proven breast carcinoma (adenocarcinoma), 2016 ICD-10-CM Diagnosis Code C.50-, http://www.icd10data.com/ICD10CM/Codes/C00-D49/C50-C50/C50-*	☐	☐	☐
3.	*Patient's age is 18 to 75 years*	☐	☐	☐
4.	*Patient has radiographic/clinical evidence of measurable disease with CT, X-ray, MRI performed within 8 weeks prior to randomization*	☐	☐	☐
5.	*Patient has bidimensionally measurable manifestations of progressive advanced disease after one prior chemotherapy regimen, or has locally advanced or MBC that progressed during or within 12 months of completing an adjuvant or neoadjuvant chemotherapy regimen or other cases of breast cancer in which weekly paclitaxel treatment is considered an adequate approach.*	☐	☐	☐
6.	*No Herceptin and.or other chemotherapy and/or bisphosphonate therapy 4 weeks before random assignment and during the study*	☐	☐	☐
7.	*Patient uses effective contraception (For women of child-bearing age)*	☐	☐	☐
8.	*Life expectancy 3 month or greater*	☐	☐	☐
9.	*Karnofsky performance score (KPS) ≥60, ECOG≤2*	☐	☐	☐
10.	*Sufficient hematological status. Adequate bone marrow function defined as:* ○ *WBC greater than 4.0 x 10^9/L* ○ *Granulocyte count greater than 1.5 x 10^9/L* ○ *Platelet count greater than 100 x 10^9/L* ○ *Haemoglobin greater than 10 g/dl*	☐	☐	☐
11.	*Adequate renal function: calculated creatinine clearance (Cockcroft-Gault formula) greater than 45 ml/min*	☐	☐	☐
12	*Adequate hepatic function defined as a total bilirubin less than Upper Limit of Normal (ULN), Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) less than 2.5 x ULN, or 1.5 x ULN if Alkaline Phosphatase (Alk Phos) less than 2.5 x ULN. Alk Phos less than 5 x ULN unless patient has bone metastases*	☐	☐	☐
If any of the above criteria is answered NO, the participant is NOT eligible for the trial and must not be included in the study. Please list reason(s) for ineligibility for screen failure on Participant Eligibility Review page.				

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

VISIT 1 (SCREENING) **EXCLUSION CRITERIA**

Date of Assessment: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

The following criteria MUST be answered NO for the participant to be included in the trial:		**Yes**	**No**
1.	*Karnofsky performance score (KPS) <60, ECOG>2*	☐	☐
2.	*Life expectancy less than 3 months*	☐	☐
3.	*inadequate haematological status*	☐	☐
4.	*inadequate renal and hepatic functions*	☐	☐
5.	*uncontrolled central nervous system metastases,*	☐	☐
6.	*severe cardiovascular disorders,*	☐	☐
7.	*active infection*	☐	☐
8.	*Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements*	☐	☐
9.	*Other non-malignant systemic and/or other disease,that would preclude the patient from receiving study treatment or would prevent required follow-up (at the discretion of the principal investigator),*	☐	☐
10.	*Known hypersensitivity to any of the study drugs or excipients.*	☐	☐
11.	*Pregnancy or lactation*	☐	☐
12.	*Second primary malignancy diagnosed within the last 5 years (except for adequately treated non-melanomaskin cancers and in-situ cervical **c**arcinoma adequately treated by cone ex**c**ision)*	☐	☐
13	*Herceptin and/or chemotherapy and/or bisphosphonate therapy less than 4 weeks before the randomisation*	☐	☐
If any of the above criteria is answered YES, the participant is NOT eligible for the trial and must not be included in the study. Please list reason(s) for ineligibility for screen failure on Participant Eligibility Review page.			

Completed by: _____

Name Signature Date

VISIT 1 (SCREENING) PARTICIPANT ELIGIBILITY REVIEW

End of Screening Visit Checklist:			
		Yes	**No**
1.	**Does the participant satisfy the inclusion and exclusion criteria to date?**	☐	☐
2.	**Have all Screening Visit procedures been completed?**	☐	☐
3.	**Have the Medical History and Concomitant Medication pages been completed?**	☐	☐
4.	**Is the participant still willing to proceed in the trial?**	☐	☐

Participant's eligibility Investigator Sign-Off:	
Is the participant eligible to take part in the Clinical Trial? **Investigator's Signature**: _____ **Date** :__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY) **Investigator's Name:** _____	☐ Yes ☐ No, Please give reason for screen failure below
Reason(s) for screen failure:	
1.	
2.	
3.	

VISIT 1 RANDOMISATION / ENROLMENT

Participant Randomisation/Enrolment	
Participant study Number allocated:	____ ____ ____
Date of Randomisation/Enrolment:	__ __/ __ __/ __ __ __ __ **(DD / MM / YYYY)**

PI's signature_____

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

VISIT 2-13(TREATMENT)**CHECKLIST**

Date of Visit: __ __ / __ __ __ / __ __ __ __

(DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Eventspage)	☐	☐
2.	**Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log)	☐	☐
3.		☐	☐
4.		☐	☐

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

VISIT 2-13 (TREATMENT) **CLINICAL EXAM**

Date of Assessment: __ __ / __ __ / __ __ __ __

(DD / MM / YYYY)

Was Physical Examination performed? ☐No ☐Yes, Complete below				
System	***Abnormal**	**Normal**	**Not done**	***If noted ABNORMAL, please provide brief description and comment if clinically significant or not (CS/NCS)**
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Breast/chestwall	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Patient's performance status	
Karnofsky performance score (KPS), %	
ECOG score	

Completed by: _____

Name Signature Date

VISIT 2-13(TREATMENT) **VITAL SIGNS**

Were Vital Signs performed?	☐**No (Comment Below)** ☐**Yes,** Complete below Comment* _____
Date& Time of Vital Signs:	__ __ / __ __ __ / __ __ __ __ : ____ (DD / MMM / YYYY) HH:MM
Blood Pressure : ___ ___ / ___ ___ mmHg	**Pulse:** ___ ___ ___ beats/min
Weight: ___ ___ ___ . ___ kg	**Height:** ___ . ___ ___ m
Temperature: ___ ___ . ___ **°C**	

SIT E>**HAEMATOLOGY**

VISIT 2-13(TREATMENT) **HAEMATOLOGY**

Clinical Haematology Laboratory tests performed?			☐**No (Comment Below)** ☐**Yes, Complete below** **Comment*:**_____
Date & Time of Sample:			__ __ / __ __ / __ __ __ __ (DD / MM / YYYY)
HAEMATOLOGY **Laboratory Parameter**	**Value**	**Unit**	**If parameter indicated as out of normal range on report, please check if clinically significant). IF CS consider if it is an AE and add to log (if appropriate):**
WBC			☐**No** ☐**Yes**
RBC			☐**No** ☐**Yes**
Hb			☐**No** ☐**Yes**
HCT			☐**No** ☐**Yes**
PLT			☐**No** ☐**Yes**
NEUTROPHILS			☐**No** ☐**Yes**
LYMPHOCYTES			☐**No** ☐**Yes**
MONOCYTES			☐**No** ☐**Yes**
EOSINOPHILS			☐**No** ☐**Yes**
BASOPHILS			☐**No** ☐**Yes**
RETICULOCYTES			☐**No** ☐**Yes**
ESR		**mm/h**	☐**No** ☐**Yes**

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

VISIT 2-13(TREATMENT)**BIOCHEMISTRY**

Clinical Biochemistry Laboratory tests performed? ☐**No (comment below)** ☐**Yes,** Complete below

Comment: _____

Date of Sample: __ __ / __ __ / __ __ __ __

(DD / MM / YYYY)

BIOCHEMISTRY **Laboratory Parameter**	**Value**	**Unit**	**If parameter indicated as out of normal range on report, please check if clinically significant:**
GLUCOSE			☐**No** ☐**Yes**
UREA			☐**No** ☐**Yes**
CREATININE			☐**No** ☐**Yes**
TOTAL PROTEIN			☐**No** ☐**Yes**
TOTAL BILIRUBIN			☐**No** ☐**Yes**
ALK PHOS			☐**No** ☐**Yes**
ALT			☐**No** ☐**Yes**
AST			☐**No** ☐**Yes**
GGT			☐**No** ☐**Yes**
LDH			☐**No** ☐**Yes**
CALCIUM			☐**No** ☐**Yes**
PROTROMBINE			☐**No** ☐**Yes**
FIBRINOGEN			☐**No** ☐**Yes**
			☐**No** ☐**Yes**
			☐**No** ☐**Yes**
			☐**No** ☐**Yes**
			☐**No** ☐**Yes**

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

VISIT 2-13(TREATMENT)OTHER TESTS

Date & Time of Sample:	__ __ / __ __ __ / __ __ __ _____:_____ **(DD / MMM / YYYY) HH:MM**

<INSERT ASSESSMENT>	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant IF CS consider if it is an AE and add to log (if appropriate)::
			☐No ☐Yes
			☐No ☐Yes
			☐No ☐Yes
			☐No ☐Yes

VISIT 2-13OTHER TESTS

Completed by: _____

Name Signature Date

VISIT 2-13(TREATMENT)TRIAL MEDICATION ADIMINSTRATION

Paclitaxel and Curcumin/Placebo Administration

No.	Medication	Date of infusion (DD/MM/YYYY)	Time of Dosing (24 hr)	Dose (including units)	Comment ONLY if dose delayed, interrupted, reduced or altered
1.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
2.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
3.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
4.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
5.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
6.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
7.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
8.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
9.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
10.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
11.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		
12.	**Curcumin/Placebo**	____/_____/_____	____:____		
	Paclitaxel	____/_____/_____	____:____		

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

ADMINISTRATION OF MEDICATION AND RETURN QUANTITY

DISPENCING

Medication	**Date of Dispensing** (DD/MM/YYYY)	**Quantity Dispensed**	**Weekly Dose** (including units)	**Comment ONLY if dose delayed, reduced or altered**
Paclitaxel	____/_____/_____			
Curcumin/placebo (IMP pack)	___/_____/_____			

ADMINISTRATION AND RETURN QUANTITY

Medication	**Date**	**Injections made**	**Injections left (counted)**
Paclitaxel	____/_____/_____		
Curcumin/placebo (IMP pack)	___/_____/_____		

Quantiry returned: 1. Paclitaxel

2. Curcumin/Placebo

Return date: ___/___/___ Doctor's signature_____

Date: _____Investigators' sign:_____

Date: _____Monitor's sign:_____

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

VISIT 14 (FOLLOW-UP) CLINICAL EXAMINATION

Date of Assessment: __ __ / __ __ / __ __ __ __

(DD / MM / YYYY)

Was Physical Examination performed? ☐No ☐Yes, Complete below

System	*Abnormal	Normal	Not done	*If noted ABNORMAL, please provide brief description and comment if clinically significant or not (CS/NCS)
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Breast/chestwall	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Patient's performance status	
Karnofsky performance score (KPS), %	
ECOG score	

Completed by: _____

Name Signature Date

VISIT 14 (FOLLOW-UP) VITAL SIGNS

Were Vital Signs performed?	☐**No (Comment Below)** ☐**Yes,** Complete below Comment* _____
Date & Time of Vital Signs:	__ __ / __ __ __ / __ __ __ __ : _____ (DD / MMM / YYYY) HH:MM
Blood Pressure : ___ ___ / ___ ___ mmHg	**Pulse:** ___ ___ ___ beats/min
Weight: ___ ___ ___ . ___ kg	**Height:** ___ . ___ ___ m
Temperature: ___ ___ . ___ **°C**	

SIT E>**HAEMATOLOGY**

VISIT 14 (FOLLOW-UP) HAEMATOLOGY

Clinical Haematology Laboratory tests performed?	☐**No (Comment Below)** ☐**Yes, Complete below** **Comment*:**_____
Date & Time of Sample:	__ __ / __ __ / __ __ __ __ (DD / MM / YYYY)

HAEMATOLOGY **Laboratory Parameter**	**Value**	**Unit**	**If parameter indicated as out of normal range on report, please check if clinically significant). IF CS consider if it is an AE and add to log (if appropriate):**
WBC			☐**No** ☐**Yes**
RBC			☐**No** ☐**Yes**
Hb			☐**No** ☐**Yes**
HCT			☐**No** ☐**Yes**
PLT			☐**No** ☐**Yes**
NEUTROPHILS			☐**No** ☐**Yes**
LYMPHOCYTES			☐**No** ☐**Yes**
MONOCYTES			☐**No** ☐**Yes**
EOSINOPHILS			☐**No** ☐**Yes**
BASOPHILS			☐**No** ☐**Yes**
RETICULOCYTES			☐**No** ☐**Yes**
ESR		**mm/h**	☐**No** ☐**Yes**

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

VISIT 14 (FOLLOW-UP)BIOCHEMISTRY

Clinical Biochemistry Laboratory tests performed? ☐**No (comment below)** ☐**Yes,** Complete below

Comment: _____

Date of Sample: __ __ / __ __ / __ __ __ __

(DD / MM / YYYY)

BIOCHEMISTRY Laboratory Parameter	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant:
GLUCOSE			☐No ☐Yes
UREA			☐No ☐Yes
CREATININE			☐No ☐Yes
TOTAL PROTEIN			☐No ☐Yes
TOTAL BILIRUBIN			☐No ☐Yes
ALK PHOS			☐No ☐Yes
ALT			☐No ☐Yes
AST			☐No ☐Yes
GGT			☐No ☐Yes
LDH			☐No ☐Yes
CALCIUM			☐No ☐Yes
PROTROMBINE			☐No ☐Yes
FIBRINOGEN			☐No ☐Yes
			☐No ☐Yes
			☐No ☐Yes
			☐No ☐Yes
			☐No ☐Yes

Completed by: _____

Name Signature Date

VISIT 14 (FOLLOW-UP)RECIST TESTS

X-ray:

CT:

MRI:

Completed by: _____

Name Signature Date

VISIT 15 (FOLLOW-UP)CLINICAL EXAMINATION

Date of Assessment: __ __ / __ __ / __ __ __ __

(DD / MM / YYYY)

Was Physical Examination performed? ☐No ☐Yes, Complete below

System	*Abnormal	Normal	Not done	*If noted ABNORMAL, please provide brief description and comment if clinically significant or not (CS/NCS)
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Breast/chestwall	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Patient's performance status	
Karnofsky performance score (KPS), %	
ECOG score	

Completed by: _____

Name Signature Date

VISIT 15 (FOLLOW-UP) VITAL SIGNS

Were Vital Signs performed?	☐**No (Comment Below)** ☐**Yes,** Complete below Comment* _____
Date & Time of Vital Signs:	__ __ / __ __ __ / __ __ __ __ : ____ (DD / MMM / YYYY) HH:MM
Blood Pressure : ___ ___ / ___ ___ mmHg	**Pulse:** ___ ___ ___ beats/min
Weight: ___ ___ ___ . ___ kg	**Height:** ___ . ___ ___ m
Temperature: ___ ___ . ___ **°C**	

VISIT 15 (FOLLOW-UP) OTHER ASSESMENTS

Other tests (on discretion of investigators):

Completed by: _____

Name Signature Date

VISIT 15 (FOLLOW-UP) PRIMARY OUTCOMES

1. RECIST Assessments

Examination	Visit 1 (baseline)	Visit 14	Visit 15
Clinical			
X-ray			
CT			
MRI			

2. Tumour markers

Marker	Visit 1 (baseline)	Visit 13 (14)	Visit 15
CEA			
CA15-3			

RESIST Outcome (change from baseline)

Outcome	Visit 14	Visit 15	Comments /date of event observed
Progressive Disease (PD)			
Stable Disease (SD)			
Partial Response (PR)			
Complete response (CR)			

Completed by: _____

Name Signature Date

VISIT 15 (FOLLOW-UP) SECONDARY OUTCOMES

1. Adverse Events (to be filled in according the Adverse Event Page)

2. Quality of Life (EORTC QLQ-C30, Global Health Status/QoL scales)

Scale	Visit 2 (baseline)	Visit 13 (end of treatment)	Visit 14	Visit 15
Overall physical condition				
Overall quality of life				

3. Response duration

Event (specify)_____

Date of event: __ __ / __ __ / __ __ __ __
(DD / MM / YYYY)

Measurement	Duration (weeks)	Comments
Progression free survival (PFS)		
Time to Treatment Failure (TTTF)		
Time to Tumour Progression (TTP)		

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. | | | |

TRIAL COMPLETION

Did participant complete the trial?	☐ **Yes,** Please provide **date of last visit**: __ __ / __ __ / 2 0 __ __ (DD / MM / YYYY) ☐ **No,** Please provide **date of withdrawal** and complete below: __ __ / __ __ / 2 0 __ __ (DD / MM / YYYY)

Early Withdrawal: please tick most appropriate reason for participant not completing the trial:

☐ **Adverse Eventsrelated:** please state related AE: _____ (add details to AE page)

☐ **Participant's decision, specify: _____,** date __ __/__ __/__ __ __ __

☐ **Investigator's decision, specify: _____,** date __ __/__ __/__ __ __ __

☐ **Sponsor's decision**

☐ **Lost to follow up**_____, date __ __/__ __/__ __ __ __

☐ **Patient deceased**_____, date __ __/__ __/__ __ __ __

☐ **Other, specify:** _____

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

ADVERSE EVENTS PAGE

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please complete a JRO SAE form	Con-comitant Medication given	Severity 0 - Mild 1- Mode-rate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequelea 2 - Not resolved	Relationship to Study Drug 0 - Definitely 1 - Probably 2 - Possibly 3 - Unlikely 4 - Not related 5 - Not assessable
1		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
2		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
3		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
4		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
5		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
6		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant

PI signature _____ _____ **Date:**_____ ☐ **Please check box if this is the last page used**

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

ADVERSE EVENTS PAGE (CONTINUATION PAGE)

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please complete a JRO SAE form	Concomitant Medication given	Severity 0 - Mild 1- Mode-rate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequelea 2 - Not resolved	Relationship to Study Drug 0 - Definitely 1 - Probably 2 - Possibly 3 - Unlikely 4 - Not related 5 - Not assessable
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				
__		____/____/____	____/____/____	☐No ☐Yes	☐No ☐Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant

PI signature_____ **Date:**_____ ☐ **Please check box if this is the last page used**

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

CONCOMITANT MEDICATIONS LOG

Has the participant used any Concomitant Medications? ☐**No** ☐**Yes,**Complete below

CM No.	**Medication name** (Record <specify Generic or Brand> name)	**Start date** (DD/MMM/YYYY)	**Stop date** (DD/MMM/YYYY)	**Or tick if ongoing at end of study?**	**Reason for use** (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	**Dose** (Units)	**Route**	**Frequency**
1.		____/_____/_____	____/_____/_____	☐				
2.		____/_____/_____	____/_____/_____	☐				
3.		____/_____/_____	____/_____/_____	☐				
4.		____/_____/_____	____/_____/_____	☐				
5.		____/_____/_____	____/_____/_____	☐				
6.		____/_____/_____	____/_____/_____	☐				
7.		____/_____/_____	____/_____/_____	☐				

☐ **Please check box if this is the last page used**

Note: Use the Concomittent log to record Non-IMPs

Completed by: _____

Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No. ☐☐☐

CONCOMITANT MEDICATIONS LOG (CONTINUATION PAGE)

CM No.	Medication name (Record Generic name)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing at end of study?	Reason for use (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	Dose (Units)	Route	Frequency
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				
__.		____/_____/_____	____/_____/_____	☐				

☐ **Please check box if this is the last page used**

Completed by: _____

Name Signature Date

PRINICIPAL INVESTIGATOR'S SIGN OFF

Principal Investigator's Signature Statement:	
I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by me or by a person under my supervision who has signed the Delegation and Signature Log.	
Principal Investigator's Signature: _____ **Principal Investigator's Name:** _____ _____	**Date of Signature:** __ __/ __ __/ __ __ __ __ (DD / MM / YYYY)
Monitor's Signature: _____ **Monitor's Name:** _____	**Date of Signature:** __ __/ __ __/ __ __ __ __ (DD / MM / YYYY)

ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM.

Completed by: _____
Name Signature Date

QOL ASSESSMENTS (EORTC QLQ-C30, GLOBAL HEALTH STATUS/QOL SCALES)

1. Visit 2 (baseline)

How would you rate your overall **physical condition** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient's signature_____ date ___/____/____

2. Visit 13 (End of Treatment)

How would you rate your overall **physical condition** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient's signature_____ date ___/____/____

3. Visit 14

How would you rate your overall **physical condition** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient's signature_____ date ___/____/____

4. Visit 15

How would you rate your overall **physical condition** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient's signature_____ date ___/____/____

Completed by: _____
Name Signature Date

Site NCO, Yerevan, Armenia

Patient: Name, Surname

Patient's entry No.

PATIENT INFORMATION LEAFLET

Completed by: _____

Name Signature Date

INFORMED CONSENT FORM

This Informed Consent Form should not be signed until you have been described and received written detailed information about the Study, the Study Drug and the Study Conditions.

Informed Consent Form for Clinical Study of
"CURCUMIN" IN COMBINATION WITH CHEMOTHERAPY IN ADVANCED BREAST CANCER"

I _____ confirm that:
Print name

- I have been described and provided with a written detailed explanation of the study objectives, procedure, expected effects, possible inconveniencies and benefits, and an explanation regarding the confidentiality of the data collected during the Study.
- I have reviewed and have fully understood the content of the above mentioned informative sheet. All my questions regarding this study have been explained in detail. I have been provided with the copies of the "Informative Sheet for the Study Subjects" and the "Informed Consent Form".
- I have had enough time to make a positive or negative decision on my participation in this study.
- I agree that the representatives of the BRIU GmbH, Principal Investigator and Ethic Committee may receive medical data concerning this Study, with my participation, on condition that the information will be kept in strictest confidence.
- It is my obligation to inform the Doctor/Principal Investigator about any, and every, adverse event, and strictly follow his instructions and advice.
- I voluntarily agree to participate in this study, knowing that I can withdraw from participation at any time, without explanation and this will not affect the following medical care by the physician.
- I understand and agree that if I have given any incorrect, misinformation, or misled the Study Organizers in any way, all of my legal rights, redress, benefits, both cash or otherwise, are null and void and I cannot and will not hold the Study Organizers responsible for any current or future adverse effects due to my participation in this Study.
- I voluntarily agree to participate in the current study. I know that I have the right to withdraw from participation at any time, without explanation.

Patient's Full Name _____ **Passport N** _____

Date _____ **Signature**_____

Medical Investigator's Full Name_____

Date _____ **Signature**_____

Completed by: _____
Name Signature Date