Protocol Number:	BTG-002814-01
Protocol Short Title:	VEROnA: A window of opportunity study of vandetanib-eluting radiopaque beads (BTG-002814) in patients with resectable liver malignancies
Protocol Name:	A pilot, open label, single-arm, phase 0, window of opportunity study of vandetanib-eluting radiopaque embolic beads (BTG002814) in patients with resectable liver malignancies
Global Sponsor:	Biocompatibles UK Ltd, a BTG International group company Lakeview Riverside Way Watchmoor Park Camberley Surrey GU15 3YL, UK
Chief Investigator:	Professor Ricky Sharma Chair of Radiation Oncology University College London Cancer Institute, Paul O'Gorman Building 72 Huntley Street London WC1E 6DD
Protocol Medical Monitor:	Dr Eveline Boucher Biocompatibles UK Ltd, a BTG International group company Lakeview Riverside Way Watchmoor Park Camberley Surrey GU15 3YL, UK
Investigational Product	BTG-002814, vandetanib-eluting radiopaque embolic beads
EudraCT Number	2016-004164-19
Protocol ver.6.0 Approval Date:	03 December 2018

Table 1. Protocol Revision History

VERSION NUMBER	*AMENDMENT APPROVAL DATE*	*BRIEF DESCRIPTION OF CHANGES*
1.0		*Original protocol*
2.0	*24 Nov 2016*	*Correction of Hb value in Inclusion Criterion 5*
3.0	*18 Jan 2017*	*Amendment of serum bilirubin Inclusion Criterion 6* *Specification of laboratory tests in Exclusion Criterion 10* *Defining abstinence in Section 5.3 Reproductive Potential* *Addition of advice to minimize exposure to Ultra Violet light in Section 6.12 Safety Criteria for Adjusting or Stopping Treatment* *Addition of Thyroid Stimulating Hormone (TSH) to Section 7.3.8 Clinical Laboratory Evaluations* *Addition of reference to MHRA guidance for regulatory reporting of Urgent Safety Issues to Section 11.9*
4.0	*03 Mar 2017*	*Schema, schedule of events and section 7.2.5 updated stating all visit 4 assessments to be repeated if surgery is delayed > 7 days* *Biochemistry and Haematology analysis moved V2 to V3.* *Term "blood urea nitrogen" changed to "urea" throughout* *Term "glucose" changed to "random glucose" throughout* *Term "uric acid" changed to "urate" throughout* *"Peak" HR and BP to be collected post treatment at visit 2* *Visit 2 note stating treatment not to take place on Fridays* *7.3.14 Vandetanib plasma analysis changed blood sample volume from 2mL to 4mL* *7.3.8. Biochemistry added calculated GFR* *8.1.3 Recording of "time" for Adverse Events removed from onset and resolution* *8.1.6 BTG responsible for sponsor causality assessment and section re-ordered* *8.1.7 BTG responsible for preparing DSURs and CTC for submitting these to the CA and EC*

5.0	***26 Mar 2018***	***The Study Physician role has been transferred from Dr Nermeen Varawalla (Biocompatibles UK Ltd) to Dr Eveline Boucher (Biocompatibles UK Ltd)).***
		Study Summary – Study Design - Changed "total" to "target" sample size to be consistent with the intention of the sample size, as outlined in Section 9.1 - Study Design and Determination of Sample Size ***5.3 All references to Females Of Child-bearing Potential (FOCP) have now been updated to Women Of Child-bearing Potential (WOCBP) and a definition of WOCBP has been included for clarity).*** ***5.6 Rephrased sentence to better define "Lost-to-Follow Up"*** ***7.3.5 FOCP has been changed to WOCBP for consistency*** ***7.3.8 Removed "Reticulocyte count" as a required investigation for Haematology*** ***7.3.14 Added a window of ± 15 mins for the Vandetanib plasma samples taken at 2 hours and 4 hours, and a window of ± 1 hour for the Vandetanib plasma sample taken at 24 hours post administration of BTG-002814*** ***8.2.7 Extended the window for Visit 6 End of Study assessments to from 30-32 to 28-32 days*** ***10.3 Removed specified timelines for CRF return*** ***11.5 Removed the requirement to collect date of birth for patient registration*** ***11.9.2 Added section to define "Serious Breaches" of ICHGCP*** ***11.14 Added notification that BTG Clinical Quality may audit sites as anytime during the study*** ***Minor formatting updates throughout the document***

6.0	***03 Dec 2018***	***Change on BTG Senior Member of Clinical Development protocol signatory*** ***Change of BTG Biostatistical protocol signatory*** ***4.2.3 & 4.5.3 Additional exploratory Objective/endpoint to explore key immune, inflammatory and drug related mechanism on resected tumour tissue*** ***5.2.1 Amendment of required platelet count Inclusion Criterion 5*** ***7.2.5 Window added for Visit 4*** ***7.2.6 Liver biomarker analysis added to Visit procedures*** ***7.3.16 Clarification of the biomarker analysis on the resected liver tissue***

PROTOCOL APPROVAL & RELEASE SIGNATURE PAGE

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Protocol Name:	A pilot, open label, single-arm, phase 0, window of opportunity study of vandetanibeluting radiopaque embolic beads (BTG-002814) in patients with resectable liver malignancies
Protocol Version:	Version 6.0
Protocol Approval Date:	03 December 2018

The above-referenced protocol was reviewed and approved for release by the following:

Approver	**Signature and Date**
Chief Investigator Prof Ricky Sharma	DocuSigned by: Professor Ricky Sharma Signer Name: Professor Ricky Sharma Signing Reason: I approve this document Signing Time: 12/5/2018 12:49:56 PM GMT D3CDA54DCD614C1B9D2EDC6B1E25387B
Sponsor: Manager, Clinical Development Sarah Cooper	DocuSigned by: Sarah Cooper Signer Name: Sarah Cooper Signing Reason: I approve this document Signing Time: 03/12/2018 21:45:18 GMT 6BA8148EE71A4608B22F8730A4456037

Sponsor: Project Physician Dr Eveline Boucher	DocuSigned by: Eveline Boucher Nom du signataire : Eveline Boucher Motif de la signature : I approve this document Heure de signature : 04/12/2018 06:36:45 GMT 133235BE86BD4F25A5F619651DFB12EC
Sponsor: VP, IO Clinical Development Henk Tissing	DocuSigned by: Henk Tissing Signer Name: Henk Tissing Signing Reason: I approve this document Signing Time: 03/12/2018 23:36:03 GMT 9CED9957ABC240699B0B1CA510313F66
Sponsor: Statistician Sam Ryan	DocuSigned by: Samantha Ryan Signer Name: Samantha Ryan Signing Reason: I approve this document Signing Time: 03/12/2018 18:36:55 GMT E6A0566313D0480095B23A6BB0E12108

INVESTIGATOR PROTOCOL REVIEW STATEMENT

Protocol Number:	BTG-002814-01
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The site Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.
The undersigned confirms that the trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, standards of Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.
By written consent to this protocol, the investigator agrees to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation,

including source data, by authorised individuals representing Biocompatibles UK Ltd, REC and/or by competent authorities.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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Table 2. Terms, acronyms, abbreviations.

The following abbreviations and specialist terms are used in this protocol.

AASLD	American Association of the study of Liver Diseases
AE	Adverse Event
AFP	Alpha Feto Protein
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BP	Blood Pressure
C_{max}	Maximum Concentration
CRC	Colorectal Cancer
CRF	Case Report Form
CT	Computerised Tomography
cTACE	Conventional Transarterial Chemoembolisation
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DEB-TACE	Drug Eluting Bead Transarterial Chemoembolisation
DLT	Dose-Limiting Toxicity
DMP	Data Management Plan
DSUR	Development Safety Update Report
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
EGFR	Endothelial Growth Factor Receptor
FOLFIRI	FOLinic acid, Fluorouracil, Irinotecan

FOLFOX	FOLinic acid, Fluorouracil, OXaliplatin
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

Hb	Haemoglobin
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HGF	Hepatocyte Growth Factor
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	International Normalised Ratio
IP	Investigational Product
kg	Kilogram
LDH	Lactate dehydrogenase
mCRC	Metastatic colorectal cancer
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose

NCI	National Cancer Institute
NSCLC	Non-Small-Cell Lung Cancer
OS	Overall Survival
PDGFR	Platelet-Derived Growth Factor Receptor
PFS	Progression Free Survival
PI	Principal Investigator
Plt	Platelets
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PV	Pharmacovigilance
RBC	Red Blood Cells
REC	Research Ethics Committee
RET	Rearranged during Transfection
RO	Radiopaque
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Safety Committee
SoDA	Summary of Drug Arrangements
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACE	Transarterial chemoembolisation
TDP	Torsades de Pointes
UAE	Unexpected Adverse Event
UCL CTC	University College London Cancer Trials Centre
ULN	Upper Limit of Normal
ver.	Version
VEGF	Vascular Endothelial Growth Factor

VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell
WHO	World Health Organisation
WOCBP	Women Of Child-bearing Potential
YBS	York Bioanalytical Solutions

PROTOCOL SYNOPSIS

Protocol Number	BTG-002814-01
Protocol Short Title	VEROnA: A window of opportunity study of vandetanib-eluting radiopaque beads (BTG-002814) in patients with resectable liver malignancies
Protocol Title	A pilot, open label, single arm, phase 0, window of opportunity study of vandetanib-eluting radiopaque embolic beads (BTG-002814) in patients with resectable liver malignancies
Investigational Product	BTG-002814 (vandetanib-eluting radiopaque embolic beads)
Type of Study	Phase 0, Window of Opportunity

Study Rationale	Transarterial chemoembolisation (TACE) is the current standard of care for patients with intermediate-stage hepatocellular carcinoma (HCC) and is also a treatment option for patients with metastatic colorectal cancer (mCRC). Despite advances and technical refinements of TACE, including the introduction of drug-eluting beads (DEB)-TACE, the long term survival of patients managed with TACE has not been optimised, and tumour recurrence occurs in more than half of patients treated. Improving the DEB-TACE administration technique and investigating the ability to deliver new anti-cancer drugs locally to the tumour via TACE are important research approaches to improve the outlook for patients with primary and secondary liver cancer. The combination of a new radiopaque bead , that can be visualised on CT scans, pre-loaded with vandetanib, a tyrosine kinase inhibitor, that targets both VEGFR and EGFR signaling pathways, is a “dual” innovation that could enhance DEB-TACE significantly compared to current liver-directed therapies. This first-in-human study of this new technology will study safety and tolerability in patients with resectable HCC or mCRC. TACE is currently used in the pre-surgical setting to downstage cancers prior to resection or to stop cancers from growing while patients are on the waiting list for surgery. Studying this new drug for DEB-TACE prior to surgery provides an opportunity to confirm the levels of vandetanib in the cancer and in liver tissue.
Study Objectives	Primary objectives: • To assess the safety and tolerability of treatment with BTG002814 • Measure the plasma and resected liver tissue concentrations of vandetanib and the N-desmethyl metabolite following treatment with BTG-002814 Secondary objectives: • Evaluate the anatomical distribution of BTG-002814 on noncontrast enhanced imaging using 4D CT • Evaluate histopathological features in the surgical specimen following treatment with BTG-002814

	• Assess changes in blood flow on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) following treatment with BTG-002814 Exploratory Objectives: • Study blood biomarkers with the potential to identify patients likely to respond to treatment with BTG-002814 • Study tissue biomarkers to explore key immune, inflammatory and drug related mechanisms • Correlate the distribution of BTG-002814 on imaging with pathology by 3D modelling

Co-Primary Endpoints	• Adverse events (AEs) related to treatment with BTG-002814 using the standardised grading criteria (National Cancer Institute-Common Terminology Criteria for Adverse Events- Version 4.0 (NCI-CTCAE v4.0)) • Concentration of vandetanib and N-desmethyl vandetanib in plasma and in resected liver tissue following treatment with BTG002814.
Secondary Endpoints	• Distribution of BTG-002814 on non-contrast enhanced imaging of tumour vasculature and regions of interest using 4D CT • Evaluation of histopathological features in the surgical specimen (malignant and non-malignant liver tissue): tumour necrosis, viable tumour, vascular changes • Assessment of changes in blood flow on DCE-MRI following treatment with BTG-002814. The following parameters will be derived from DCE-MRI images: K^{trans}, K^{ep} and V^{e}
Exploratory Endpoints	• Study blood biomarkers with the potential to identify patients likely to respond to treatment with BTG-002814 • Study tissue biomarkers to explore key immune, inflammatory and drug related mechanisms • Correlate the distribution of BTG-002814 on imaging with pathology by 3D modelling
Study Duration	The study duration is up to 9 weeks per patient (up to 1 week screening, up to 1 week baseline prior to treatment plus up to 3 weeks for surgery, followed by 4 weeks follow-up) A Baseline period of up to 7 days is followed by treatment with BTG002814 at Visit 2. Surgical resection will occur 7 to 21 days following treatment with BTG-002814. The End of Study visit (Visit 6), will occur 28-32 days after surgery.
Study Design	• Open-label, single arm, multicentre, phase 0, window of opportunity study of BTG-002814 up to 3 weeks prior to surgical resection • Three patients with HCC and/or liver metastases from CRC who are candidates for surgery will initially be enrolled to receive one treatment of BTG-002814

	• An interim analysis conducted by a safety committee (SC) is planned when the first three patients complete the last follow-up visit scheduled at 4 weeks after surgery. • If the SC deems that there is no significant toxicity related to BTG002814, a further 9 patients will be enrolled in order to have a target sample size in the study of 6 patients with liver metastases from CRC and 6 patients with HCC.

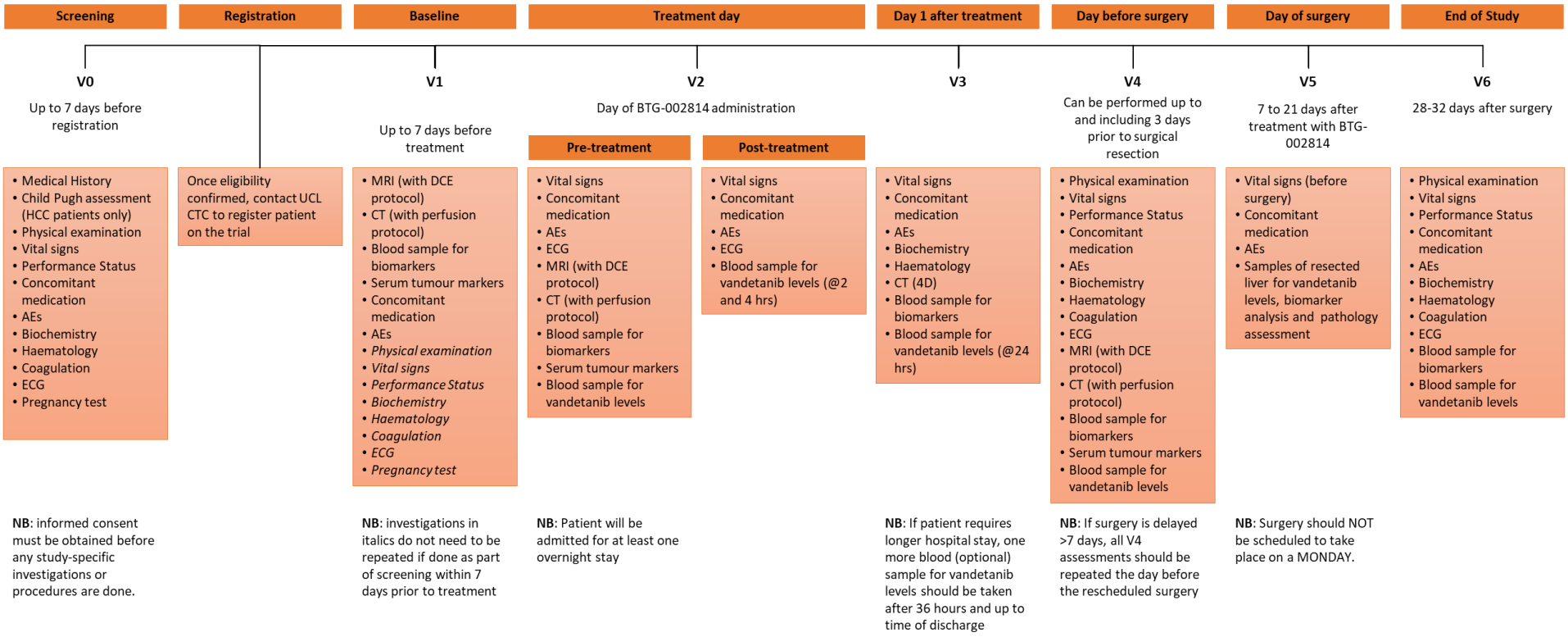
Study Population	Patients with radiologically and/or histologically confirmed diagnosis of HCC or histologically confirmed diagnosis of CRC with liver metastases deemed suitable for liver surgery
Total Number of Patients	12 patients (replacement of up to 2 patients is permitted if patients do not complete the study investigations and follow-up)
Number & Location of Sites	University College London Hospitals NHS Trust and Royal Free London Hospital NHS Trust
Study Treatment	Single treatment arm Patients will receive one treatment of BTG-002814 (1 mL BTG002814 containing 100 mg vandetanib)
Inclusion/Exclusion Criteria	Inclusion Criteria 1. Male or female adults (≥ 18 years old) 2. Patient with resectable HCC (Child Pugh A, INR ≤1.5) or resectable liver metastases from CRC and a candidate for liver surgery 3. Patients with low risk for surgical morbidity and mortality from liver surgery according to the investigators judgement 4. WHO performance status 0, 1 or 2 5. Adequate haematological function with Hb >90 g/L, absolute neutrophil count >1.5 x 10^9/L, Plt >75 x 10^9/L 6. Adequate liver function with serum bilirubin <1.5 x ULN, ALT (or AST if ALT not available) ≤5 x ULN, ALP <5 x ULN 7. Adequate renal function with serum creatinine ≤1.5 x ULN and calculated creatinine clearance (GFR) ≥50 mL/min estimated using a validated creatinine clearance calculation (e.g. Cockroft-Gault or Wright formula). 8. Patient is willing to provide blood samples, and tissue samples at surgical resection, for research purposes 9. Patient is willing and able to provide written informed consent Exclusion Criteria 1. Any systemic chemotherapy within 3 months of the screening visit or any plan to administer systemic chemotherapy prior to surgery 2. Previous treatment with transarterial embolisation (with or without chemotherapy) of the liver, prior radiotherapy or ablation therapy to the liver or prior yttrium-90 microsphere therapy 3. Any contraindication to vandetanib according to its local label including: ○ Hypersensitivity to the active substance

	○ Congenital long QTc syndrome ○ Patients known to have a QTc interval over 480 milliseconds ○ Concomitant use of medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes (see Appendix 1) 4. Any contraindication to hepatic artery catheterisation or hepatic embolisation procedures (e.g. portal venous thrombosis, severely reduced portal venous flow or hepatofugal blood flow, untreated varices at high risk of bleeding) 5. Women of child-bearing potential not using effective contraception or women who are breast feeding 6. Confirmed allergy to iodine-based intravenous contrast media 7. Patients who cannot have CT, MRI or DCE-MRI Imaging (according to site policy) 8. Active uncontrolled cardiovascular disease 9. Any co-morbid disease or condition or event that, in the investigator's judgment, would place the patient at undue risk and would preclude the safe use of BTG-002814 10. Levels of potassium, calcium, magnesium or thyroid stimulating hormone (TSH) outside the normal ranges, and that in the investigator's judgement are clinically significant, or other laboratory findings that in the view of the investigator makes it undesirable for the patient to participate in the study 11. Patients who have participated in another clinical trial with an investigational product within 4 weeks prior to the screening visit
Imaging Requirements	• CT scan chest, abdomen, liver, pelvis, incorporating perfusion CT of liver at baseline, within a day prior to treatment, and the day before surgery. If surgery is delayed more than 7 days, the CT scan should be repeated the day before the re-scheduled surgery. • 4D CT scan of liver on the day after treatment. • Liver MRI, incorporating DCE-MRI at baseline, within a day prior to treatment, and the day before surgery. If surgery is delayed more than 7 days, the MRI scan should be repeated the day before the re-scheduled surgery.
Plasma sampling and analysis - vandetanib and N-desmethyl metabolite	Plasma sampling will be performed in all patients immediately before treatment and at 2 hours (± 15 mins), 4 hours (± 15 mins), and 24 hours (± 1 hour) after treatment. Samples also to be taken within 24 hours prior to surgery and at End of Study visit. If patients require a longer hospital stay, an optional additional sample can be taken after 36 hours and up to the time of discharge.

Liver tissue sampling and analysis - vandetanib and Ndesmethyl metabolite	Samples of liver tissue (both malignant and non-malignant) will be collected for analysis.
Blood and tissue biomarker analysis	Blood biomarkers will be measured to indicate the activity of the investigational treatment on the target cancer, specifically cytokines, chemokines and growth factors relevant to cancer and inflammation. Blood samples will be taken for the measurement of serum alphafetoprotein (AFP) in patients with HCC, and serum CEA, CA19-9 and CA125 in patients with mCRC. Resected liver tumour tissue will be analysed to explore key immune, inflammatory and drug related mechanisms.
Safety Committee	A safety committee (SC) will review study data as detailed in the charter. The SC will review all AEs and SAEs. An Interim analysis is planned when the first three patients complete the last follow-up visit scheduled at 4 weeks after surgery. If the SC deem that there is no significant toxicity related to BTG002814 to prevent additional recruitment, a further 9 patients will be enrolled.
Sample Size Justification	A target sample size of 6 patients with each primary diagnosis is deemed to be sufficient to assess the safety and drug concentrations in plasma and resected specimens following treatment.
Statistical Methods	The number (n) and percentages (%) of patients with adverse events (AEs), and with AEs related to the study treatment, will be summarised overall and by system/organ class and preferred term (MedDRA). AEs will also be tabulated by intensity, treatment, outcome and causality. Deaths, serious adverse events (SAEs), AEs leading to withdrawal and Unexpected Adverse Events (UAE) will be listed separately. For all other endpoints, categorical results will be reported as numbers and percentages, and continuous results will be summarised descriptively with mean, standard deviation, median and range (minimum and maximum).
Procedures in Screening/Baseline Period	See Schedule of Visits
Study Visits and Follow-up	See Schedule of Visits Visits extra to standard care for the clinical study: Screening and Baseline visits, BTG-002814 treatment visit (1 to 2 nights as an inpatient procedure) and end of study visit, 4 weeks post-surgery

The trial will be conducted and documented in accordance with the Declaration of Helsinki, the protocol, standards of Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical trial agreement.

1. SCHEMA



2. SCHEDULE OF VISITS

Study Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4[5]	Visit 5	Visit 6
	Screening	Baseline	Treatment Day				End of Study

Assessment	Up to 7 days before registration	Up to 7 days before treatment and following registration	Pre-treatment	Posttreatment	Day 1 after treatment	Up to 3 days prior to surgical resection	Surgical resection (7 to 21 days after treatment)	28-32 days postsurgery
Informed Consent	X							
Patient Demographics	X							
Medical and Prior Treatment History	X							
Eligibility Assessment (Inclusion/Exclusion Criteria)	X							
Child Pugh Assessment (HCC patients only)	X							
Physical Examination	X	X[2]				X		X
Vital Signs	X	X[2]	X	X	X	X	X	X
WHO Performance Status	X	X[2]				X		X
Concomitant Medications	X	X	X	X	X	X	X	X
Assessment of Adverse Events	X	X	X	X	X	X	X	X
Biochemistry	X	X[2]			X	X		X
Haematology	X	X[2]			X	X		X
Coagulation Tests	X	X[2]				X		X
12-Lead ECG	X	X[2]	X	X		X		X
Serum Pregnancy Test[1]	X	X[2]						
Liver MRI, Incorporating DCE-MRI		X	X[3]			X		
CT scan chest, abdomen, liver, pelvis, incorporating perfusion CT of liver		X	X[3]			X		
4D CT scan liver					X			
Blood Biomarker Analysis		X	X		X	X		X
Serum Tumour Markers (AFP for HCC patients; CEA, CA19-9, CA125 for mCRC patients)		X	X			X		

Study Visit	**Visit 0**	**Visit 1**	**Visit 2**		**Visit 3**	**Visit 4[5]**	**Visit 5**	**Visit 6**
	Screening	**Baseline**	**Treatment Day**					**End of Study**
Assessment	Up to 7 days before registration	Up to 7 days before treatment and following registration	Pre-treatment	Posttreatment	Day 1 after treatment	Up to 3 days prior to surgical resection	Surgical resection (7 to 21 days after treatment)	28-32 days postsurgery
Vandetanib and N-desmethyl metabolite plasma sampling (0 min, 2hr (± 15 mins), 4hr (± 15 mins), 24h (± 1 hour), and up to hospital discharge[4]) in addition to Visits 4 and 6			X	X	X	X		X
Vandetanib and N-desmethyl metabolite tissue sampling, histopathological and biomarker analysis							X	

1. For women of child-bearing potential. A negative pregnancy test must be obtained prior to treatment
2. Do not need to be repeated if screening assessments performed within 7 days prior to treatment
3. May be performed the day before treatment
4. Optional one additional plasma sample can be taken after 36 hours and up to time of hospital discharge
5. If surgery is delayed > 7 days, then all visit 4 assessments should be repeated the day before the rescheduled surgery

3. BACKGROUND

3.1. Disease background

Treatment of primary and secondary liver cancer

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second most common cause of cancer-related death, estimated to have been responsible for nearly 746 000 deaths in 2012 (World Health Organisation, 2012). The incidence varies from 3 out of 100 000 in Western countries to more than 15 out of 100 000 in certain areas of the world, mapping the geographical distribution of viral hepatitis B and hepatitis C which are the most important causes of chronic liver disease and HCC (Parkin, Bray, Ferlay & Pisani, 2005). In developed countries, increasing prevalence of obesity in the general population and alcoholic liver disease account for the rising incidence of HCC.

The prognosis of HCC remains poor because of the high recurrence rate (Lencioni, Petruzzi & Crocetti, 2013). Treatment options such as surgical resection, liver transplantation, and ablative therapies can provide a chance of cure; however, these modalities are limited and often not feasible because HCC is usually diagnosed at an advanced stage. Palliative therapies such as transcatheter arterial embolic therapies, radiation therapy, and systemic therapies provide potential therapeutic solutions for patients not suitable for surgery or ablation.

Secondary liver tumours (i.e., metastatic to the liver from a primary site outside the liver) are the most common form of hepatic malignancy and are even more common than HCC (Lewandowski et al., 2005). The most common sites of primary tumours which spread to the liver are colorectal cancer (CRC), breast cancer and lung cancer. In patients with metastatic colorectal cancer (mCRC), the liver is the most common site of metastatic disease. Approximately 50% of CRC patients will develop liver metastases during the course of the disease (Adam et al., 2012). Progressive hepatic metastases cause liver failure, especially once all chemotherapeutic and/or surgical options have been exhausted. Although surgical resection of liver metastases for curative intent is the treatment of choice, most patients present with unresectable liver-predominant mCRC and are therefore not suitable for surgery. In these cases, locoregional therapies including transarterial chemoembolisation (TACE) are treatment options, either alone or in combination with systemic chemotherapy (De Groote & Prenen, 2015).

Conventional TACE (cTACE) involves the administration of an anticancer agent followed by an embolic agent into the tumour feeding arteries to block its major nutrient source resulting in ischemic necrosis of the targeted tumour. The most common anticancer cytotoxic drugs for local delivery via TACE are doxorubicin, cisplatin, epirubicin, mitoxantrone and mitomycin C. However, the systemic release of chemotherapy agents following cTACE is high and many patients suffer from systemic side effects. These factors led to innovative research to develop a different method of local drug delivery with less of the systemic toxicity associated with cTACE. One of these methods is the use of drug-eluting microspheres for TACE, henceforth referred to as drug-eluting bead TACE (DEB-TACE) (Lewis et al., 2006; Poon et al., 2007; Varela et al., 2007).

DEB-TACE ensures slow and sustained release of the drug locally ensuring high intra-tumoural drug concentrations in addition to the ischaemic effects of the embolic agent. In vitro data have confirmed the slow, sustained release of the drug (Lewis et al., 2006) and it has been shown in HCC patients that TACE with drug-eluting microspheres (DC Bead™) achieves higher intratumoural concentrations and lower systemic concentrations of cytotoxic agent than cTACE, thereby reducing the potential liver toxicity of treatment (Poon et al., 2007; Varela et al., 2007).

TACE using drug-eluting beads loaded with doxorubicin (DEBDOX) has been widely performed in patients with HCC and has become the standard therapy for patients not suitable for surgical resection or transplantation (Lencioni, Petruzzi & Crocetti, 2013). Current international guidelines from the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) recommend TACE as first-line, non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (Bruix, Sherman & American Association for the Study of Liver, 2011; EASL & EORTC, 2012).

Based on extensive experience with TACE in patients with HCC, this treatment has also been developed for patients with liver-dominant metastatic disease, particularly CRC metastases within the liver. It has been shown to be effective in the treatment of patients with mCRC using drugeluting beads loaded with irinotecan (DEBIRI) (Wang, De Baere, Idee & Ballet, 2015). This treatment has been shown to be safe and well tolerated, offering patients with mCRC a potential improvement in quality of life and potentially in overall survival (Fiorentini et al., 2007; Narayanan, Barbery, Suthar, Guerrero & Arora, 2013). According to the recent European ESMO consensus guideline for the management of patients with mCRC, TACE is considered as a treatment that could be offered along with other local ablation therapies to mCRC patients with a limited number of lesions and involved sites (i.e., termed “oligometastatic disease”) (Van Cutsem et al., 2016).

TACE is a treatment that can be repeated several times, but primary and secondary liver cancer can become resistant to the treatment. The mechanisms of post-TACE and DEB-TACE tumour recurrence have not been elucidated. Improving the DEB-TACE administration technique and investigating the ability to deliver new anticancer drugs locally to the tumour via the beads are important research approaches to potentially improving the efficacy of TACE for patients with cancer.

In addition to the use of conventional chemotherapy regimens, biological agents including bevacizumab, a humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF), a central regulator of angiogenesis, and cetuximab/panitumumab, monoclonal antibodies directed against endothelial growth factor receptors (EGFR) have contributed to the improvement of survival for patients with mCRC. Unlike mCRC, HCC is highly refractory to conventional cytotoxic chemotherapy. In the last decade, no effective conventional systemic cytotoxic therapy has been available and no single regimen has emerged as superior to any other (Lopez, Villanueva & Llovet, 2006). Systemic chemotherapy with doxorubicin or cisplatin yields low objective response rates (<10%). To date, only sorafenib, an oral multi-kinase inhibitor and anti-angiogenic agent has been approved in patients with advanced HCC. Sorafenib inhibits abnormal growth of multiple cell surfaces and intra-cellular kinases which are involved in angiogenesis, cell proliferations and cellular differentiation. The different kinases include various VEGF receptors (VEGFR-1,2,3), platelet-derived growth factor receptor (PDGFR-B), c-KIT and RET (Wilhelm S et al, 2006). Sorafenib also inhibits the RAF/MEK/ERK pathway that is important in tumour cell proliferation and survival (Liu et al., 2006).

In order to improve treatment for HCC, new agents targeting the genetic alterations and/or signaling pathways involved in hepatocarcinogenesis are being investigated. These pathways include various growth factors such as EGF, VEGF, hepatocyte growth factor (HGF), insulin-like growth factor and regulating specific intracellular pathways such as RAF/MEK/ERK and P13K/PTEN/Akt/mTOR and Wnt/B-catenin pathways (Kudo, 2012; Raza & Sood, 2014).

3.2. General Description of Investigative Agent(s)/Device

Radiopaque Beads

A current limitation in improving the accuracy of embolic administration during TACE and in understanding how well the treatment is reaching its target is the inability to visualise the beads used to deliver the drug locally within the liver. BTG has recently developed a radiopaque (RO) bead that can be visualised with CT or fluoroscopic imaging and have the advantage of providing intra and post-procedural visible confirmation of bead location during the embolisation procedure, enabling real-time adjustments to optimise patient treatment (Johnson et al., 2016). The radiopaque bead builds on existing DC Bead™ technology used to embolise the blood vessels and deliver drugs at high concentrations to tumours. The lasting radio-opacity of RO beads means that they are visible on X-ray based follow-up scans, allowing precise evaluation of the completeness of tumour treatment.

RO beads are commercially available in the US (as LC Bead LUMI™) for the treatment of hypervascularised tumours and arteriovenous malformations. In Canada, DC Bead LUMI™ is approved for the treatment of HCC in combination with doxorubicin and for the treatment of mCRC in combination with irinotecan. BTG-002814 is an imageable product based on the BTG RO bead platform. It is a pre-loaded, RO bead with a size range of 60–160 µm and is provided in a 20 mL glass vial. In addition, the 60-160 µm size range in the BTG-002814 formulation was chosen to ensure tumour penetration by the embolic agent and to maximise drug exposure to the tumour tissue.

Vandetanib

Vandetanib is a potent inhibitor of the tyrosine kinase activity of VEGFR-2, an endothelial cell receptor for vascular endothelial growth factor (VEGF). It also possesses activity against EGFR and REarranged during Transfection (RET) tyrosine kinases. VEGF is a potent stimulator of new blood vessel growth (angiogenesis) and plays an essential role in the formation and maintenance of the vasculature by activating protease expression, endothelial cell proliferation and migration, and capillary vessel formation. Pathological angiogenesis is necessary for the progression of solid, malignant tumours and inhibition of VEGF-dependent signaling has been identified as a key anti-angiogenic strategy (Ferrara, 2004).

EGFR-dependent signaling is an important pathway contributing to the growth and metastasis of tumour cells, and aberrant EGFR tyrosine kinase activity has been reported in a number of human solid tumours. EGFR tyrosine kinase activity plays a key role in numerous processes that affect tumour growth and progression, including proliferation, dedifferentiation, inhibition of apoptosis, metastasis and angiogenesis (Vlahovic & Crawford, 2003).

By targeting both angiogenesis and EGFR- and RET-dependent tumour cell growth, it is hypothesised that the growth of tumours will be controlled, with relative sparing of normal tissues. The oral version of vandetanib, branded as Caprelsa®, is approved for the treatment of patients with advanced medullary thyroid cancer.

Phase 1 dose-escalation studies performed in Western and Japanese patients, with solid tumours refractory to standard therapy, showed that vandetanib was generally well tolerated at daily doses up to 300 mg (Holden et al., 2005; Tamura et al., 2006). Vandetanib can significantly prolong progression-free survival (PFS) of patients with advanced medullary thyroid cancer (Wells et al., 2010) and is not inferior to erlotinib as a second-line therapy for patients with advanced non-smallcell lung cancer (NSCLC) (Natale et al., 2011). Vandetanib plus docetaxel can significantly

prolong PFS, compared with docetaxel alone, in patients with advanced NSCLC after progression following first-line chemotherapy (Herbst et al., 2010).

Systemic therapy with oral vandetanib has been investigated in a clinical setting in a broad range of human malignancies, including HCC and mCRC. Some of these clinical studies are reviewed below.

Systemic vandetanib treatment of HCC

Sixty-seven HCC patients were randomised to oral vandetanib 300 mg (n=19), oral vandetanib 100 mg (n=25) or placebo (n=23). Twenty nine patients subsequently entered open-label treatment. Vandetanib induced a significant increase in circulating VEGF and decrease in circulating VEGFR levels. In both vandetanib arms, tumour stabilisation rate was not significantly different from placebo. Although trends towards improved PFS and Overall Survival (OS) after vandetanib treatment were found, they were not statistically significant. The most common adverse events were diarrhoea and rash in both treatment groups (Hsu et al., 2012).

Systemic vandetanib treatment of colorectal cancer

A number of phase 1 dose escalation studies were conducted to determine the maximum tolerated dose (MTD) of vandetanib in combination with different therapeutic agents and regimens, predominantly in mCRC patients. In a study of 21 patients with vandetanib 100 mg (n=11) and vandetanib 300 mg (n=10) combined with standard 14-day treatment cycles of FOLFIRI, the most commonly reported AEs were diarrhoea, fatigue and nausea. In one study of vandetanib combined with cetuximab and irinotecan, 27 patients were enrolled at 4 dose levels. Two dose-limiting toxicities (DLTs) (grade 3 QTc prolongation and diarrhoea) were detected at 300 mg vandetanib with cetuximab and irinotecan resulting in 200 mg being the MTD (Meyerhardt et al., 2012). In another study, 13 patients received vandetanib at doses of 100 mg and 300 mg daily in combination with capecitabine and oxaliplatin, which was well tolerated. However, the addition of bevacizumab resulted in severe diarrhoea in three out of four patients. Bevacizumab was not well tolerated with vandetanib and XELOX in combination (Cabebe, Fisher & Sikic, 2012). In 17 patients with advanced mCRC, vandetanib 100 mg (n=9) or 300 mg (n=8) was combined with mFOLFOX6 chemotherapy. The most commonly reported AEs were diarrhoea, lethargy and nausea. The CTCAE Grade 3/4 events that were considered to be related to vandetanib was Grade 3 diarrhoea in 3 patients (1 patient in the 100 mg cohort and 2 patients in the 300 mg cohort) and Grade 3 thrombocytopenia in 1 patients (300 mg cohort) (Michael, Gibbs, Smith, Godwood, Oliver & Tebbutt, 2009). In another study to assess the effect of vandetanib on vascular permeability in patients with advanced CRC and liver metastases, 22 patients received the study drug; 10 received 100 mg and 12 received 300 mg. The most commonly reported AEs were diarrhoea, dry mouth, fatigue and nausea (Mross et al., 2009).

Two phase II, double-blind, placebo-controlled, randomised studies were conducted to assess the efficacy and safety of 2 doses of vandetanib (100 mg and 300 mg) in combination with FOLFOX or FOLFIRI in patients who had failed with FOLFIRI (109 patients) or FOLFOX (121 patients) regimens respectively. The addition of vandetanib to FOLFOX regimen did not show any additional benefit in terms of number of patients with disease progression and the time to progression. A lower risk of disease progression was reported with 100 mg vandetanib combined with FOLFIRI regimen compared to the FOLFIRI regimen with placebo (57% vs 69%). The percentages of patients who had a disease progression event in the vandetanib 300 mg group and placebo group were similar (67% vs 69%). The estimated median times to progression were 114 days for the vandetanib 100 mg group, 151 days for the vandetanib 300 mg group, and 103 days for the placebo group. The safety profile of vandetanib (100 mg and 300 mg) in combination

with both regimens, FOLFOX and FOLFIRI, was acceptable. The most commonly reported AEs were diarrhoea and nausea; thrombocytopenia was reported with FOLFOX-vandetanib and neutropenia with FOLFIRI-vandetanib.

3.3. Pre-Clinical Background of Investigative Agent(s)/Device

In vitro pharmacology

Vandetanib is a potent inhibitor of VEGFR-2 tyrosine kinase activity with an IC_{50} value of 40 nM. In isolated enzyme assays, vandetanib was also found to be a sub-micromolar inhibitor of fmslike tyrosine kinase (Flt)-4 (VEGFR-3, the VEGF-C and –D receptor: IC_{50} =110 nM) and EGFR tyrosine kinases (IC_{50} = 500 nM). Additional vandetanib activity has been demonstrated against oncogenic RET kinase (IC_{50} = 100 nM) which is activated in certain thyroid carcinomas.

Further details are provided in the BTG-002814 Investigator Brochure.

In vivo pharmacology

Vandetanib has demonstrated broad spectrum anti-tumour angiogenesis activity in several histologically diverse tumour xenograft models (lungs, prostate, breast, ovarian, colon). Chronic once daily oral administration (12.5-100 mg/kg/day) produced significant dose dependent inhibition of tumour growth. Vandetanib has also been shown to inhibit growth of tumours implanted orthotopically e.g. orthotopic models of gastric and pancreatic cancer. In mouse models of human prostate and colon cancer, DCE-MRI analysis showed a dose dependent reduction in contrast agent uptake by tumour 24 hours after initiating therapy with vandetanib, consistent with vandetanib inhibition of VEGF induced permeability in tumour vasculature (Ryan & Wedge, 2005). Vandetanib inhibited tumour growth of hepatoma cells in subcutaneous mouse tumour model. In addition, vandetanib suppressed phosphorylation of VEGFR-2 and EGFR in tumour tissues, significantly reduced tumour vessel density, enhanced tumour cell apoptosis, improved survival, reduced number of intra-hepatic metastases and upregulated VEGF, TGF-α and EGF in tumour tissues (Inoue et al., 2012).

Further details are provided in the BTG-002814 Investigator Brochure.

Pre-clinical background of BTG-002814

The safety of the vandetanib-eluting bead has been evaluated in a GLP swine liver embolisation model. In this model, vandetanib-loaded RO beads (100 mg vandetanib per 1 mL bead) were delivered to healthy liver by hepatic intra-arterial administration. Up to 1 mL of vandetanib-loaded bead was administered, which equates to delivery of 100 mg vandetanib to the targeted liver lobe. The animals were maintained for either 30 or 90 days. There were no treatment-related effects evident in parameters evaluated, namely, clinical observations, body weight, ophthalmoscopy, ECG, and organ weights. Transient changes in coagulation and clinical chemistry parameters were observed, likely to be related to the hepatic embolisation procedure.

There were expected microscopic findings associated with hepatic embolisation following intrahepatic administration of vandetanib-loaded bead. The study indicated that intrahepatic administration of up to 1 mL vandetanib-loaded RO bead containing 100 mg of vandetanib was well tolerated, did not produce any obvious systemic toxicity and resulted in nothing more than expected microscopic findings associated with hepatic embolisation and subsequent healing.

In an efficacy study conducted in a rabbit model, VX-2 carcinoma tumours were implanted in the liver, followed by hepatic intra-arterial administration of DC Bead loaded with vandetanib up to 135 mg/mL (DCV). DCV showed equivalent anti-tumoural activity to doxorubicin-loaded bead and superior anti-tumoural activity compared to bland (unloaded) bead. Single hepatic administration of DCV showed equivalent anti-tumoural efficacy to repeat dose of oral vandetanib, at the doses administered (~5.4 mg per animal with DCV vs 1470 mg oral vandetanib, respectively). Compared to oral dosing, it is notable that DCV showed a lower plasma concentration and a higher tumour concentration of vandetanib relative to the total dose administered.

4. STUDY RATIONALE, OBJECTIVES and DESIGN

4.1. Study Rationale

TACE is the current standard of care for patients with intermediate-stage HCC and is also a treatment option for patients with mCRC. Despite advances and technical refinements of TACE, including the introduction of drug-eluting beads (DEB)-TACE, the long term survival of patients managed with TACE is generally poor, mainly as a result of the high rates of tumour recurrence. Improving the technique used for DEB-TACE, by being able to visualise the beads on CT scans, and by developing the ability to load new anti-cancer molecularly targeted drugs on to the beads, specifically vandetanib, are two important approaches to potentially improving the efficacy of TACE for patients with HCC or mCRC.

This clinical trial will study the feasibility of administering radiopaque beads loaded with vandetanib, a tyrosine kinase inhibitor that targets both VEGFR and EGFR signaling pathways, as two novel approaches combined in to one new therapy, BTG-002814, to enhance anti-tumour efficacy compared to current liver-directed therapies. It will be the first time that BTG-002814 has been administered to humans. Since cTACE can be safely used in the pre-operative setting to treat cancers prior to liver surgery, this study will be performed in resectable patients with HCC and mCRC, therefore providing a 'window of opportunity" to measure the levels of vandetanib in the resected liver sample, as well as assessing the safety and tolerability of BTG-002814 in patients with cancer. Tumour recurrence rates for HCC and mCRC after liver surgery are currently up to 50% of patients, so the development of any pre-operative therapy with the potential to improve the chances of long-term disease control following surgery is an important research goal.

4.2. Study Objectives

4.2.1. Primary Objectives

- To assess the safety and tolerability of treatment with BTG-002814
- Measure the plasma and resected liver tissue concentrations of vandetanib and the Ndesmethyl metabolite following treatment with BTG-002814

4.2.2. Secondary Objectives

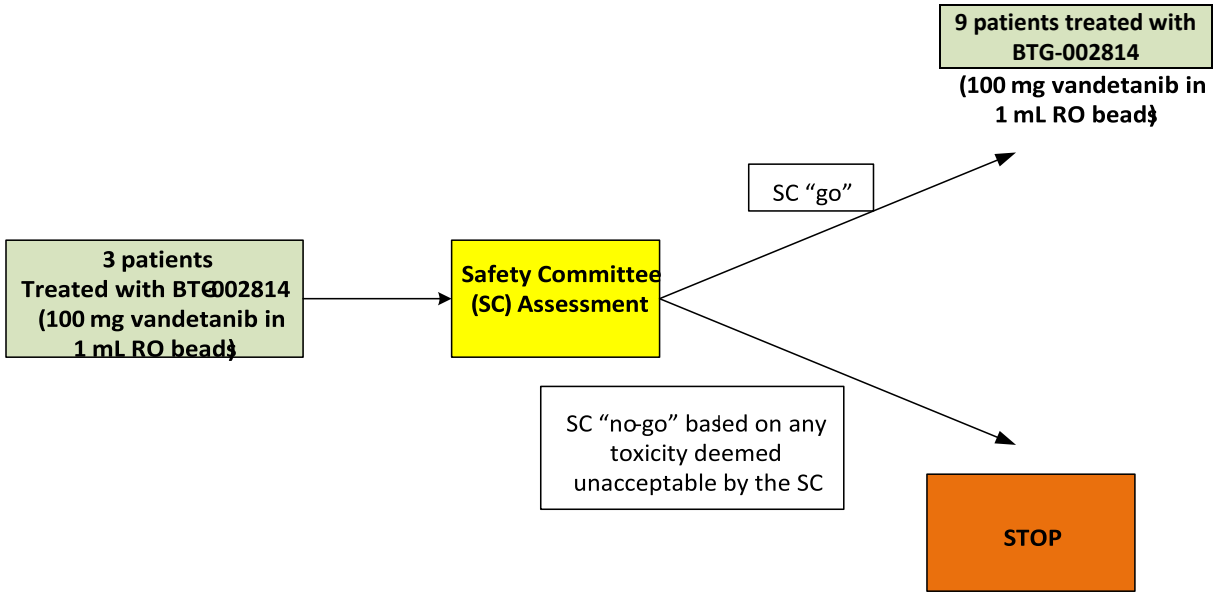
- Evaluate the anatomical distribution of BTG-002814 on non-contrast enhanced imaging using 4D CT
- Evaluate histopathological features in the surgical specimen following treatment with BTG002814
- Assess changes in blood flow on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) following treatment with BTG-002814

4.2.3. Exploratory Objective

- Study blood biomarkers with the potential to identify patients likely to respond to treatment with BTG-002814
- Study tissue biomarkers to explore key immune, inflammatory and drug related mechanisms
- Correlate the distribution of BTG-002814 on imaging with pathology by 3D modelling

4.3. Study Design

4.3.1. Study Design Flow Chart



4.3.2. Summary of Study Design

A pilot, open-label, single arm, multicentre, phase 0, window of opportunity study with DEB-TACE treatment with BTG-002814 given between 1 and 3 weeks prior to surgery in up to 12 patients with resectable HCC or mCRC.

Three patients who have either HCC or liver metastases from CRC and who are candidates to receive surgery will initially be enrolled.

An interim analysis conducted by a Safety Committee (SC) is planned when the first three patients complete the last follow-up visit scheduled at 4 weeks after surgery.

If the SC deems that there is no significant toxicity related to BTG-002814, a further 9 patients will be enrolled in order to have a target sample size of 6 patients with HCC and 6 patients with liver metastases from CRC.

A final analysis will be performed when 12 patients complete the last follow-up visit, or once 14 patients have been enrolled and are no longer on study All patients will receive one treatment of BTG-002814.

4.4. Randomisation

This is a single arm study; so randomisation is not applicable.

4.5. Study Endpoints

4.5.1. Co-Primary Endpoints

- Adverse events (AEs) related to treatment with BTG-002814 using the standardised grading criteria (National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0))
- Concentration of vandetanib and N-desmethyl vandetanib in plasma and in resected liver tissue following treatment with BTG-002814.

4.5.2. Secondary Endpoints

- Distribution of BTG-002814 on non-contrast enhanced imaging of tumour vasculature and regions of interest using 4D CT
- Evaluation of histopathological features in the surgical specimen (malignant and nonmalignant liver tissue): tumour necrosis, viable tumour, vascular changes
- Assessment of changes in blood flow on DCE-MRI following treatment with BTG-002814. The following parameters will be derived from DCE-MRI images: Ktrans, Kep and Ve

4.5.3. Exploratory Endpoints

- Study blood biomarkers with the potential to identify patients likely to respond to treatment with BTG-002814
- Study tissue biomarkers to explore key immune, inflammatory and drug related mechanisms
- Correlate the distribution of BTG-002814 on imaging and pathology by 3D modelling

5. PATIENT SELECTION

5.1. Patient Population

The study population will consist of patients with HCC or liver metastases from CRC who are deemed suitable for liver surgery.

5.2. Subject Selection

5.2.1. Inclusion Criteria

1. Male or female adults (≥ 18 years old)
2. Patient with resectable HCC (Child Pugh A, INR ≤1.5) or resectable liver metastases from CRC and a candidate for liver surgery
3. Patients with low risk for surgical morbidity and mortality from liver surgery according to the investigator's judgement
4. WHO performance status 0, 1 or 2
5. Adequate haematological function with Hb >90 g/L, absolute neutrophil count >1.5 x 10^9/L, Plt >75 x 10^9/L
6. Adequate liver function with serum bilirubin <1.5 x ULN, ALT (or AST if ALT not available) ≤5 x ULN, ALP <5 x ULN
7. Adequate renal function with serum creatinine ≤1.5 x ULN and calculated creatinine clearance (GFR) ≥50 mL/min estimated using a validated creatinine clearance calculation (e.g. Cockroft-Gault or Wright formula).
8. Patient is willing to provide blood samples, and tissue samples at surgical resection, for research purposes
9. Patient is willing and able to provide written informed consent

5.2.2. Exclusion Criteria

1. Any systemic chemotherapy within 3 months of the screening visit or any plan to administer systemic chemotherapy prior to surgery
2. Previous treatment with transarterial embolisation (with or without chemotherapy) of the liver, prior radiotherapy or ablation therapy to the liver or prior yttrium-90 microsphere therapy
3. Any contraindication to vandetanib according to its local label including:
   - Hypersensitivity to the active substance
   - Congenital long QTc syndrome
   - Patients known to have a QTc interval over 480 milliseconds
   - Concomitant use of medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes (see Appendix 1)
4. Any contraindication to hepatic artery catheterisation or hepatic embolisation procedures (e.g. portal venous thrombosis, severely reduced portal venous flow or hepatofugal blood flow, untreated varices at high risk of bleeding)
5. Women of child-bearing potential not using effective contraception or women who are breast feeding
6. Confirmed allergy to iodine-based intravenous contrast media
7. Patients who cannot have CT, MRI or DCE-MRI Imaging (according to site policy)
8. Active uncontrolled cardiovascular disease

9. Any co-morbid disease or condition or event that, in the investigator's judgement, would place the patient at undue risk and would preclude the safe use of DEB-TACE with BTG002814
10. Levels of potassium, calcium, magnesium or thyroid stimulating hormone (TSH) outside of the normal ranges, and that in the investigator's judgment are clinically significant, or other laboratory findings that in the view of the investigator makes it undesirable for the patient to participate in the study
11. Patients who have received treatment in another clinical trial with an investigational medicinal product within 4 weeks prior to the screening visit

5.3. Reproductive Potential

All women of child-bearing potential (WOCBP) enrolled into this study will have a serum pregnancy test at Screening (Visit 0) to assess their suitability for entry into the study. Women who are pregnant or who are breast feeding are excluded from this study.

Definition of WOCBP

A WOCBP is a sexually mature woman (i.e. any woman who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- had premature ovarian failure confirmed by a specialist gynaecologist
- XY genotype, Turner syndrome, uterine agenesis

WOCBP, or any male patient enrolled in the study who has a WOCBP partner, must use effective contraception during the study and for four months after treatment.

Acceptable methods of contraception include established use of oral, injected or implanted hormonal birth control, intrauterine device, or barrier method in conjunction with spermicidal foam/cream/jelly/suppository, female/male sterilisation or abstinence where this is the patient's preferred and usual lifestyle.

5.4. Patient Completion

Patient enrolment is planned to continue until the target number of 12 patients have been included.

Patients will complete the study 28-32 days following the surgical resection.

5.5. Patient Withdrawal

Patients may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the patient at any time (e.g., in the interest of patient safety). The withdrawal of a patient from the study by the Investigator should be discussed where possible with UCL CTC and the Sponsor.

For patients who withdraw before the end of the study, all Visit 6 (End of Study) assessments should be completed, if possible, prior to withdrawal. All AEs must be documented in the patient medical notes and case report forms (CRF).

If a patient withdraws from the study for any reason, all efforts should be made to follow AEs as described in section 8, unless the patient withdraws consent.

A maximum of 2 patients who withdraw from the study early will be replaced.

5.6. Patients “Lost to Follow-up” Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any patients Lost to Follow-up at any time point prior to the last scheduled visit.

6. TREATMENT OF PATIENTS

6.1. Vandetanib-eluting radiopaque bead (BTG-002814)

6.1.1. Dosage & Administration

All patients will receive one treatment of BTG-002814. One vial of BTG-002814 will be used for each patient.

To hydrate BTG-002814, 1 mL of Water For Injection followed by 9 mL of Omnipaque 350 contrast agent will be added to the vial. The full contents of the vial will be delivered slowly (approximately 1 min per mL) under fluoroscopic visualisation while observing the contrast flow rate, through an intra-arterially placed microcatheter and must be used within 4 hours of reconstitution. Full instructions for use will be provided in the Summary of Drug Arrangements (SoDA).

Embolisation procedure

Using a unilateral femoral approach, selective catheterisation of the hepatic artery will be performed. Diagnostic visceral arteriography will be performed to delineate the arterial supply to the tumour, determine the presence of variant arterial anatomy and to confirm patency of the portal vein. Once the patient's arterial anatomy is understood, a catheter is advanced into the right or left hepatic artery distal to the cystic artery (if visualised). The treatment plan is based on the fluoroscopic appearances during arteriography. For the purposes of this clinical trial, since all eligible patients have resectable disease, it is not a requirement of the protocol that all lesions visible on CT are treated with BTG-002814. This decision will be at the discretion of the treating investigator. For example, if a right hemihepatectomy is the operation planned, it is not necessary to treat all the lesions in the anterior and posterior sector; the lesions to be treated may be those deemed to be at highest risk of a positive surgical resection margin and therefore at highest risk of tumour recurrence following surgery. It is important to confirm the location of delivered beads on 4D CT at the end of the procedure relative to the treatment plan based on fluoroscopic appearances.

Once the catheter is in place within the artery feeding the tumour, the re-constituted BTG-002814 suspension will be slowly infused into the artery (approximately 1 mL per minute). Catheter selection will be by operator preference. There will not be any issues with a 4- or 5-Fr catheter, but the choice of a microcatheter, in case of tortuous, narrow or spastic vessels must be consistent with the size of embolic agent used (see IFU). The end point of the procedure is either full delivery of the reconstituted bead volume (i.e. 1 mL beads + vandetanib + contrast) or stasis in the tumoural vessel over 2-5 cardiac cycles. Undelivered volume of reconstituted embolic solution must be recorded.

For HCC patients, a super selective (segmental/subsegmental) approach should be taken with the catheter placed as selectively as possible whilst maintaining sufficient flow to the tumour. For mCRC patients, it is generally a lobar approach, by placing the catheter tip beyond the origin of the cystic artery (or any other arteries supplying extrahepatic organs) and maintaining forward flow.

The catheter will then be removed and haemostasis achieved by manual compression or with a percutaneous closure device. Each patient will be admitted for overnight care.

The amount of contrast agent delivered to the patient during the procedure and skin dose of xrays from fluoroscopy will be recorded as well as the time exposed to fluoroscopic imaging. The vessels embolised will be noted and the amount of embolic agent used will be recorded. All medications used during the procedure will be recorded, including pain management regime.

6.1.2. Safety Criteria for Adjusting or Stopping Treatment

Hypersensitivity reactions may occur to the active substance of vandetanib. Such hypersensitivity is a contraindication for BTG-002814 administration and is covered by this protocol's exclusion criterion 3.

Allergy to contrast media that cannot be managed with standard care may also cause hypersensitivity reactions. Such hypersensitivity is a contraindication for treatment with BTG002814 and is covered by this protocol's exclusion criterion 6.

Should any previously unknown hypersensitivity become apparent at any stage during treatment, administration of BTG-002814 will stop immediately and standard care indicated for hypersensitivity reactions will be initiated and completed.

Rash and other skin reactions including photosensitivity reactions and palmar-plantar erythrodysaesthesia syndrome have been observed in patients who have received vandetanib. Patients will be advised to minimise exposure to the sun by wearing protective clothing and/or sunscreen due to the potential risk of phototoxicity reactions associated with vandetanib for UV light for at least four weeks following treatment (visit 2).

6.1.3. Post-study Management

Management of patients after they have completed or been withdrawn from the study should be as per the investigational site's standard procedures

6.1.4. Duration of Treatment and Follow up

All patients will receive one treatment of BTG-002814 between 7 and 21 days prior to surgery. All patients will be followed up for 28-32 days following surgery.

6.1.5. Concomitant Medications

Concomitant medications are defined as those taken from the date of Informed Consent to the date of the final visit (Visit 6, End of Study).

Patients previously treated with other loco-regional therapies including transarterial embolisation (with or without chemotherapy), prior external beam radiation or prior yttrium-90 microsphere therapy are excluded from this study (see exclusion criterion 2).

Medicinal products known to also prolong the QTc interval and/or induce Torsades de pointes should not be used in combination with BTG-002814, and should not be administered during the study (see exclusion criterion 3). Refer to Appendix 1.

With the exception of the above, there are no concomitant medications specifically prohibited during the study, however, there are multiple known drug interactions that are relevant for the vandetanib active drug, including:

- Strong CYP3A4 inducers (e.g., rifampicin, rifabutin, St John's Wort, carbamazepine, phenytoin, barbiturates)

- Vandetanib can increase the Cmax of metformin, therefore metformin dosage monitoring is recommended.
- Vandetanib can increase the Cmax of P-gp substrates such as digoxin, therefore digoxin dosage monitoring is recommended.
- If the patient's concomitant medication includes vitamin K antagonists (e.g., warfarin, phenindione, acenocoumarol), increased frequency of INR monitoring is recommended.

Documentation of all concomitant medication, including any sedative medication used during treatment and surgery, and any over the counter medications, should continue until the final visit and must be recorded in the patient's medical notes and CRFs.

6.2. Investigational Product/Labeling/Packaging/Storage/ Handling

6.2.1. Investigational Product

BTG-002814 is a radiopaque embolic bead pre-loaded with vandetanib. It is light brown/golden in colour and is provided lyophilized, in glass vials.

Each vial contains 1 mL of BTG-002814 containing 100 mg vandetanib when hydrated as per protocol.

BTG-002814 will be provided free of charge to the site by BTG and must not be used outside the context of this study.

6.2.2. Labeling and Packaging

BTG-002814 will be labelled and packaged by BTG International Germany GmbH.

BTG-002814 vials will be sealed in an aluminium foil pouch and placed within a carton. The vial, pouch and carton will be labelled with a single panel, local language label, in accordance with good manufacturing practice (GMP) and in compliance with local law(s) and legislation. Supplies will be labelled in accordance with Annex 13 guidelines on labelling of Investigational Medicinal Products and in line with local legislation. They will contain the following at a minimum; protocol identifier, contents, directions for use, expiry date, storage, batch number, unique medication identification number i.e., vial number.

6.2.3. Storage and Handling

Prior to use, BTG-002814 must be stored in a secured access, locked area, accessible only to authorised site personnel.

BTG-002814 should be stored above 8ºC and must not be refrigerated or frozen.

In the event of a product complaint, the Sponsor and UCL CTC must be informed within 24 hours, including a brief description of the incident seen. The Sponsor will then investigate and inform the site on any actions that need to be taken. Refer to the SoDA for reporting instructions.

6.2.4. Accountability

Ordering and Receipt of Investigational Product

Procedures for ordering and receipt of BTG-002814 will be provided in the SoDA.

Compliance and Accountability Procedures

Biocompatibles UK Ltd will supply BTG-002814 for use within this study only to approved investigational sites with an authorised investigational pharmacist as designated by the Investigator. The investigational pharmacist is responsible for accurate documentation of receipt, inventory, storage, preparation, and dispensing of BTG-002814.

Additional instructions on BTG-002814 accountability will be provided in the SoDA.

Unused Supplies

At the end of the study, or as instructed by the Sponsor or designee, all unused BTG-002814 provided for use in this study must be returned to Biocompatibles UK Ltd/designee or destroyed according to instruction detailed within the SoDA once full accountability has been completed. Destruction must not occur at site without prior approval from the Sponsor.

7. STUDY PROCEDURES

7.1. Study Schedule

See Section 2, Schedule of Visits for the study schedule and the sequence of study procedures.

7.2. Schedule of Visits, Procedures, and Evaluations

7.2.1. Visit 0: Screening (up to 7 days before registration)

The following assessments and procedures are required to evaluate the eligibility of patients prior to entry. Results from assessments or procedures carried out as part of routine practice may be used to assess eligibility, as long as they were carried out according to the timeframe and specification in the protocol. Patients must give written informed consent before any trial specific screening investigations may be carried out.

- Written Informed consent will be obtained, as described in section 7.3.1
- All patients who have signed the Informed Consent form will be included on the Screening and Enrolment Log. If the patient fails to fulfil the eligibility criteria, the Screening and Enrolment Log must be completed with the reason for the failure.
- Patient demographic information will be collected, as described in section 7.3.2
- Eligibility to participate in the study will be assessed, as described in section 7.3.17
- Child Pugh assessment (HCC patients only), as described in section 7.3.17
- Medical history information will be collected, as described in section 7.3.3
- Physical examination will be conducted, as described in section 7.3.4
- Vital signs will be taken, as described in section 7.3.5
- Performance status will be assessed, as described in section 7.3.6
- Medications and prior treatments will be recorded, as described in section 7.3.7
- Adverse events will be recorded and assessed as described in section 7.3.21
- Blood samples for biochemistry, haematology and coagulation, as described in section 7.3.8
- A 12-lead ECG will be taken as described in section 7.3.12
- Blood sample for serum pregnancy test for all patients of child-bearing potential, as described in section 7.3.9

7.2.2. Visit 1: Baseline Visit (up to 7 days before treatment)

Following fulfilment of the inclusion and exclusion criteria and registration of the patient, the following assessments and procedures are required to be done within 7 days prior to treatment with BTG-002814:

- Liver MRI, incorporating Dynamic Contrast Enhanced MRI (DCE-MRI), as described in section 7.3.11
- CT scan of chest, abdomen & pelvis, incorporating perfusion CT of liver, as described in section 7.3.11
- Blood sample for biomarkers, as described in section 7.3.13
- Blood sample for serum tumour markers, as described in section 7.3.10
- Record any concomitant medications, as described in section 7.3.20
- Adverse events will be recorded and assessed as described in section 7.3.21

The following tests and procedures do not need to be repeated if carried out within 7 days prior to treatment with BTG-002814 as part of screening work up:

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Physical examination will be conducted, as described in section 7.3.4
Vital signs will be taken, as described in section 7.3.5

- Performance status will be assessed, as described in section 7.3.6
- Blood samples for biochemistry, haematology and coagulation, as described in section 7.3.8
- A 12-lead ECG will be done as described in section 7.3.12
- Blood sample for serum pregnancy test for all patients of child-bearing potential, as described in section 7.3.9

7.2.3. Visit 2: Treatment Day

NB: Treatment should NOT be scheduled to take place on a Friday, due to the assessments required to be performed the day after treatment (Visit 3).

Pre-treatment Assessments

The following scans will be performed within a day prior to administration of BTG-002814:

- Liver MRI, incorporating DCE-MRI, as described in section 7.3.11
- CT scan of chest, abdomen & pelvis, incorporating perfusion CT of liver, as described in section 7.3.11

The following assessments and procedures will be performed on the day of treatment prior to administration of BTG-002814:

- Vital signs will be taken, as described in section 7.3.5
- Record any concomitant medications, as described in section 7.3.20
- Record any adverse events, as described in section 7.3.21
- A 12-lead ECG will be taken, as described in section 7.3.12
- Blood sample for biomarkers, as described in section 7.3.13
- Blood sample for serum tumour markers, as described in section 7.3.10
- Blood sample for vandetanib and metabolite analysis, as described in section 7.3.14

Post-treatment Assessments

The following assessments and procedures will be performed on the day of treatment after administration of BTG-002814:

- Vital signs will be taken, as described in section 7.3.5. Peak heart rate (HR) and peak blood pressure (BP) should be recorded in the CRF
- Record any concomitant medications, as described in section 7.3.20
- Record any adverse events, as described in section 7.3.21
- A 12-lead ECG will be taken, as described in section 7.3.12
- Blood samples for vandetanib and metabolite analysis at 2 and 4 hours after treatment, as described in section 7.3.14

7.2.4. Visit 3 (Day 1 after treatment)

The following assessments and procedures will be performed:

- Vital signs will be taken, as described in section 7.3.5
- Record any concomitant medications, as described in section 7.3.20
- Record any adverse events, as described in section 7.3.21

- Blood samples for biochemistry and haematology, as described in section 7.3.8
- 4D CT scan of liver will be performed, as described in section 7.3.11
  Blood sample for biomarkers, as described in section 7.3.13
  Blood sample for vandetanib and metabolite analysis, as described in section 7.3.14

7.2.5. Visit 4 (Up to and including 3 days prior to surgical resection)

The following assessments and procedures will be performed:

NB: if surgery is delayed by > 7 days, all visit 4 assessments should be repeated up to and including 3 days before the rescheduled surgery.

- Physical examination will be conducted, as described in section 7.3.4
- Vital signs will be taken, as described in section 7.3.5
- Performance status will be assessed, as described in section 7.3.6
- Record any concomitant medications, as described in section 7.3.20
- Record any adverse events, as described in section 7.3.21
- Blood samples for biochemistry, haematology and coagulation, as described in section 7.3.8
- A 12-lead ECG will be taken, as described in section 7.3.12
- Liver MRI, incorporating DCE-MRI, as described in section 7.3.11
- CT scan of chest, abdomen & pelvis, incorporating perfusion CT of liver, as described in section 7.3.11.
- Blood sample for biomarkers, as described in section 7.3.13
- Blood sample for serum tumour markers, as described in section 7.3.10
- Blood sample for vandetanib and metabolite analysis, as described in section 7.3.14

7.2.6. Visit 5 Surgical Resection (7 to 21 days following treatment with BTG-002814)

The following assessments and procedures will be performed:

- Vital signs will be taken before surgery, as described in section 7.3.5
- Record any concomitant medications, as described in section 7.3.20
- Record any adverse events, as described in section 7.3.21
- Samples of resected liver will be taken for vandetanib and metabolite analysis, as described in section 7.3.15 and for histopathological and biomarker analysis as described in section 7.3.16

7.2.7. Visit 6 End of Study/Early Withdrawal (28-32 days postsurgery)

Patients complete the study 28-32 days following the day of surgical resection. The following assessments and procedures will be performed for those patients who complete the study or those who withdraw early.

- Physical examination will be conducted, as described in section 7.3.4
- Vital signs will be taken, as described in section 7.3.5
- Performance status will be assessed, as described in section 7.3.6
- Record any concomitant medications, as described in section 7.3.20

- Record any adverse events, as described in section 7.3.21. Any AEs related to BTG-002814 continuing at this visit should be recorded as 'ongoing' in the patient's medical notes and CRFs.
- Blood samples for biochemistry, haematology and coagulation, as described in section 7.3.8
  A 12-lead ECG will be taken, as described in section 7.3.12
  Blood sample for biomarkers, as described in section 7.3.13
  Blood sample for vandetanib and metabolite analysis, as described in section 7.3.14
- As appropriate, record the date and reason for study completion as listed in section 5.4
  As appropriate, record the date and reason for study withdrawal as listed in section 5.5

7.3. Study Evaluations and Procedures

7.3.1. Informed Consent Process

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the study.

Patients with the potential to meet eligibility criteria may be offered the opportunity to be evaluated for participation in this clinical study. All such patients must sign the current REC approved informed consent form (ICF) before any study-related evaluations can be performed.

The Investigator or delegate will review the study and the treatment plan with the patients and the patients will have an opportunity to ask questions about study procedures, the required visit schedule, risks and benefits of the study treatment and alternative treatment options prior to signature of the ICF. The patient will receive a copy of the signed ICF to keep for their records.

A **minimum of twenty four (24) hours** must be allowed for the patient to consider and discuss participation in the study.

The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- checking that the current REC-approved version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has completed/initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e., information given, consent signed etc.)
- following registration, adding the patients' study number to all copies of the consent form, which should be filed in the patient's medical notes and Investigator Site File
- giving the patient a copy of their signed consent form, patient information sheet and patient contact card

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Patients will be informed of any revisions to the ICF and any revisions must be signed and kept in the patient study file.

Each time an ICF is administered (original and subsequent revisions as appropriate), the process of obtaining the patient's informed consent should be documented in the patient's medical record and the ICF signed and dated by the individual who conducted the informed consent discussion.

The right of the patient to refuse to participate in the study without giving reasons must be respected. All patients are free to withdraw at any time.

7.3.2. Demographics

The following demographic data will be obtained: date of birth/age, gender, child-bearing potential, race and ethnicity.

7.3.3. Medical History

Medical history deemed clinically significant by the Investigator will be collected per body system.

Diagnosis and medical history for HCC and mCRC will be recorded separately from other medical history.

All ongoing medical conditions and AEs arising from treatment of those conditions present for 30 days or more prior to entering the study are generally considered a part of the patient's medical history and must be recorded at Screening.

7.3.4. Physical Examination

A full physical examination, including height (required at Screening only) and weight, will be performed by a qualified licensed individual. A review of body systems will include the following:

- General appearance
- Skin
- Head, Ears, Eyes, Nose, Throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal Neurological

Any abnormalities or changes in intensity noted during the initial review of body systems should be documented in the patient's medical notes and CRFs. If a new clinically significant finding (i.e., not noted at Screening) or change in intensity occurs at subsequent visits, this must be documented as an AE. Resolution of any abnormal findings during the study will be noted in the patient's medical notes and CRFs.

7.3.5. Vital Signs

Assessments of vital signs (i.e., BP and HR) will be performed at all study visits. When possible, BP and HR will be determined after the patient has been in the sitting position for 5 minutes.

Any clinically significant changes from Screening will be recorded as an AE.

7.3.6. Performance Status

WHO performance status will be assessed according to the following categories:

Grade	WHO Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

7.3.7. Medication and Prior Treatment History

The use of concurrent medications (medications taken within 30 days of Screening and during the conduct of the study) will be obtained and documented in the patient's medical notes and CRFs.

Prior treatment history for HCC and mCRC will also be recorded.

7.3.8. Clinical Laboratory Evaluations – Biochemistry, Coagulation Parameters, Haematology

All clinical laboratory tests will be performed at the local laboratory according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal laboratory values, which are unexpected or not explained by the patient's clinical condition, should be repeated until confirmed, explained or resolved. Repeat evaluations should be performed as soon as possible after the original evaluation.

Changes from Screening will be recorded as an AE if assessed as clinically significant by the Investigator.

The following clinical laboratory assessments will be completed as per the Schedule of Visits:

Biochemistry

Blood samples for biochemistry will be taken.

- Sodium
- Potassium
- Calcium
- Magnesium
- Urea
- Creatinine
- Albumin
- Total Protein
- Alanine transaminase (ALT)
- Aspartate transaminase (AST), if ALT not available
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)

- Total bilirubin
- Random glucose
- Lactate Dehydrogenase (LDH)
- Urate
- Thyroid Stimulating Hormone (TSH)
- Calculated GFR (using a validated creatinine clearance calculation)

Coagulation Parameters

Blood samples for coagulation parameters will be taken.

- Prothrombin Time (PT)
- Partial Thromboplastin Time (PTT)
- International Normalised Ratio (INR)

Haematology

Blood samples for haematology will be taken.

- Haemoglobin
- Haematocrit
- White Blood Cell (WBC) Count
- Platelet Count
- WBC- differential and Absolute Neutrophil Count (ANC)
- Red Blood Cell (RBC) Count Mean corpuscular volume (MCV)

7.3.9. Pregnancy Test

All WOCBP will have a serum beta hCG pregnancy test at the Screening Visit to assess their suitability for entry into the study.

7.3.10. Serum Tumour Markers

The following clinical laboratory tests will be performed at the local laboratory according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes.

The following clinical laboratory assessments will be completed as per the Schedule of Visits:

Patients with HCC:

- serum alpha-fetoprotein (AFP) Patients with mCRC:
- serum CEA
- serum CA19-9
- serum CA125

7.3.11. Imaging including Dynamic Imaging

Since measurement of perfusion characteristics may improve understanding of liver tumour biology and behaviour, patients in this study will undergo dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) and perfusion Computed Tomography (pCT) at timepoints stated in the Schema. pCT and DCE-MRI will be combined with routine scans and study visits where possible, although additional visits to the Radiology Department may be required.

DCE-MRI

For DCE-MRI, patients will lie supine on the scanner table and an intravenous cannula placed in the antecubital fossa. No oral contrast is required. After acquisition of standard clinical MRI liver sequences, T1 mapping will be performed using three-dimensional volumetric gradient echo imaging with varying flip angles. A series of T1–weighted three-dimensional volumetric images will be acquired at baseline and at short intervals during administration of a bolus of intravenous paramagnetic MR contrast agent at a rate of 3-5 mL/s. Each acquisition takes approximately 5 seconds during which time patients are asked to hold their breath in full expiration or if necessary to breathe in a shallow fashion. The entire post contrast DCE series takes approximately 3-5 minutes.

Liver parenchyma and tumour signal intensity curves will be used to calculate semiquantitative and quantitative tissue parameters describing tumour perfusion, blood flow and vascularity, using a compartment model with an arterial and portal venous input function.

Assessment of changes in blood flow on DCE-MRI following treatment with BTG-002814. K^{trans}, K^{ep} and V^{e} will be derived from DCE-MRI images.

CT

CT will incorporate dual energy (DECT) and perfusion imaging (pCT) of the liver, in addition to standard clinical contrast enhanced imaging of the chest, abdomen and pelvis. CT should be performed before or at least 90 minutes after the MRI scan. Images will be acquired in a supine position using a cannula placed in the antecubital fossa, and no oral contrast is required. A combined CT protocol will be carried out as follows, with each volume acquired in inspiration:

1. dual energy (80+135 kV) acquisition of the liver prior to contrast administration
2. bolus of 0.5 mL/kg of iodinated contrast (300 mgI/mL) injected at a rate of no less than 5 mL/s (total <8 seconds).
3. volume perfusion acquisition of the liver, with intermittent scanning over 90 seconds
4. interval of at least 3 minutes to allow contrast washout
5. bolus of 1 mL/kg of iodinated contrast (300 mgI/mL) injected at a rate of 3-5 mL/s
6. late arterial phase (35 seconds post contrast bolus) volume of the chest and liver
7. portal venous phase (60 seconds post contrast bolus) volume of the abdomen and pelvis Data from CT and DCE-MRI will be used in developing the 3D modelling of the distribution of BTG-002814.

Following treatment with BTG-002814 a 4D CT scan will be performed to check and track the positioning of the beads in ‘real time’. This scan should be performed without contrast.

7.3.12. ECG Assessment

A 12-lead ECG reading will be taken as per the Investigator’s standard practice.

7.3.13. Blood Biomarkers

Approximately 4 mL of blood will be collected at the timepoints shown in the schedule of visits for the measurement of blood biomarkers. The analysis will be performed by the ECMC GCLP Laboratory at UCL Cancer Institute.
Blood biomarkers will be measured to indicate the activity of the investigational treatment on the target cancer, specifically cytokines, chemokines and growth factors relevant to cancer and inflammation.

Detailed information on sample handling, storage and shipping are provided in the Laboratory Manual.

7.3.14. Vandetanib and N-desmethyl metabolite Plasma Sampling and Analysis

Blood samples (approximately 4 mL) will be taken from an indwelling venous catheter in the antecubital fossa or another such suitably positioned catheter for obtaining blood samples. Sampling times will be pre-dose (0 min) and at 2 hours (± 15 mins), 4 hours (± 15 min) and 24 hours (± 1 hour) following the initial administration of BTG-002814. If patients require a longer hospital stay, an optional additional sample can be taken after 36 hours and up to the time of hospital discharge. Samples also to be taken within 24 hours prior to surgery (Visit 4) and at End of Study visit (Visit 6).

Plasma samples will be analysed by York Bioanalytical Solutions Ltd (YBS) (York, UK) using a validated assay.

Following the completion of the analysis, YBS will store plasma samples for up to 5 years; after which, upon written confirmation from the Sponsor, samples will be destroyed by YBS.

Detailed information on sample handling, storage and shipping are provided in the Laboratory Manual.

7.3.15. Vandetanib and N-desmethyl metabolite Liver Sampling and Analysis

Samples of resected liver tissue (both malignant and non-malignant) will be collected, processed and analysed by YBS using a validated assay.

Following the completion of the analysis, YBS will store the liver samples for up to 5 years; after which, upon written confirmation from the Sponsor, samples will be destroyed by YBS.

Detailed information on sample handling, storage and shipping are provided in the Laboratory Manual.

7.3.16. Surgical Resection and Local Histopathological Assessment and Procedures

Surgical resection is to be carried out as per standard care.

Participants will be asked for consent to access any stored pathology material from previous surgery or biopsy for HCC or colorectal cancer, so that histology pre-BTG-002814 treatment can be compared with histology post-treatment.

The date and type of liver surgery occurring during the protocol period must be recorded in the CRF. Surgical complications occurring within 30 days after surgical resection must be recorded in detail.

The histopathological stage and grade must be recorded (ypTN classification). The histological status of the resection margins must also be recorded (distance to nearest margin) and whether the resection was R0, R1 or R2.
Histopathological assessment of samples of resected liver tissue (both malignant and nonmalignant) will include microscopic examination to correlate radiologic extent of tumour cell

necrosis to microscopic extent of tumour cell necrosis. Sections of resected liver tissue will be paraffin-embedded.

H&E slides will be produced, which will be scanned to produce 3D pathology models of tumour volume. Additional slides will be stained to explore key immune, inflammatory and drug related mechanisms. These models can be used to investigate the tumour environment, such as extent of necrosis and neoangiogenesis.

These 3D models will be compared to the 3D models generated from clinical imaging.

7.3.17. Eligibility Review

Data documenting demographic information, medical history, physical examination, medication and prior treatment history, clinical laboratory tests, Child Pugh assessment (HCC patients only) and pregnancy test (for FOCP) will be reviewed against the eligibility criteria to determine eligibility. The determination will be recorded in the patient's medical notes and CRFs.

7.3.18. Patient Registration

Patient registration will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any study treatment. Pre-registration evaluations should be carried out as detailed in section 7.2.1.

Following consent of the patient, pre-treatment evaluations and confirmation of eligibility, the registration form must be fully completed and faxed to UCL CTC who will review the form to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting registration to discuss the patient and request updated forms to be faxed.

Once eligibility has been confirmed a unique numeric patient identity code will be assigned for the patient and should be added to the form by the site.

UCL CTC will fax/e-mail confirmation of the patient's inclusion in the study, their patient code to the Principal Investigator (PI), study staff and pharmacy.

REGISTRATION CONTACT DETAILS
VEROnA Trial Coordinator Cancer Research UK & UCL Cancer Trials Centre
General Queries: 020 7679 9887
Randomisation Fax Number: 020 7679 9871
Office hours: 9am to 5pm, Monday to Friday

7.3.19. Study Medication Treatment Record

The details of treatment administered at Visit 2 (Treatment day), including the volume administered and start/stop times will be recorded in the patient's medical notes and CRFs.

7.3.20. Concomitant Medication Record

At every study visit, new medications or changes in concomitant medications will be recorded in the patient's medical notes and CRFs. Documentation will include medication dosage and start/stop dates.

7.3.21. Observation and Recording of Adverse Events

All AEs will be documented from the date of signature of Informed Consent until the patient's last visit.

Refer to section 8.1.7 for information regarding the procedure for recording AEs.

The Investigator will assess all AEs for severity grading according to CTCAE v4.0, and relationship to BTG-002814 (relationship to vandetanib and the drug eluting beads/TACE procedure will be assessed separately). Definitions and procedures for assessment can be found in Section 8.

Pregnancy: any report of pregnancy or complications of pregnancy such as miscarriage or congenital abnormality recorded for any female trial participant or female partner of trial participant, should be reported within the same time-frame as required for an SAE (24 hours) to UCL CTC using the study specific Pregnancy Report. Every effort should be made to gather information regarding the pregnancy outcome until 8 weeks post-partum. It is the responsibility of the Investigator to obtain all pregnancy information.

8. ADVERSE EVENTS

8.1. Adverse Event Definitions

Adverse experience will be considered synonymous with the term adverse event and vice versa.

8.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence or undesirable event(s) experienced by a patient that begins or worsens following administration of the study drug, whether or not considered related to the treatment by the Investigator.

An undesirable event(s) can be, but is not limited to, symptoms experienced by a patient or objective findings, such as significant clinical laboratory abnormalities.

For the purpose of this study, the occurrence of a pregnancy is not considered to be an AE but should be reported within 24 hours to UCL CTC using the study specific Pregnancy Report. Reports of exposure during pregnancy will be followed up and the outcome of the pregnancy should be reported to UCL CTC by submitting a follow up Pregnancy Report. If the pregnancy results in an AE to the mother, foetus or neonate, then the SAE process should be followed and the event reported in accordance with Section 8.1.5.

8.1.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (“life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in a persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect important medical event, see below

Medical and scientific judgment should be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.1.3. Recording Adverse Events

All AEs will be documented from the date of signature of Informed Consent until the patient’s last visit.

Patients should be encouraged to report AEs spontaneously or in response to general, nondirected questions. At any time during the study, the patient may volunteer information that resembles an AE. Once it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE form. Where possible, a diagnosis, rather than a list of signs or symptoms, should will be recorded. Any medical management of an event and the date of resolution of the event must be recorded in the patient’s medical notes and on the appropriate CRF using medical terminology according to Sponsor instructions.

For each AE, the following information will be recorded:

- AE term

- Serious/non-serious
- Severity
- Action taken
- Relationship to study treatment
- Date of onset
- Date of resolution

If there are any AEs related to BTG-002814 continuing at the End of Study Visit, these should be recorded as 'ongoing' in the patient's medical notes and CRFs. These events should be managed according to sites local practice.

SAEs should be managed as discussed in Section 8.1.5.

Once the patient has been discharged from the study, the Investigator has no obligation to seek further follow-up with the patient in order to identify new AEs. However, if the Investigator becomes aware of an SAE that has occurred following the patient's discharge from the study and the Investigator considers the SAE to be related to BTG-002814, then the Investigator should report the SAE as described in Section 8.1.5.

8.1.4. Causality (Relationship to Drug) Assessment

The Investigator or physician sub-investigator must indicate whether he/she believes the AE is related (reasonable possibility that the investigational drug caused the AE), or not related (no reasonable possibility).

Relationship to vandetanib and the drug eluting beads/TACE procedure will be assessed separately.

8.1.5. Reporting Serious Adverse Events

All SAEs that occur between the signing of informed consent and Visit 6/End of Study visit **(or after this date if the site Investigator feels the event is related to study treatment)** must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the study specific SAE Report form. All sections of the SAE Report form must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report.

Patients experiencing an SAE should be followed clinically and with laboratory and/or diagnostic procedures, if appropriate, until medical treatment and/or medical monitoring of the event is no longer required because the event resolves or stabilises, returns to baseline if a baseline value is available, can be attributed to agents other than the study treatments or a referral for appropriate follow-up care has been made.

8.1.6. SAE Processing at UCL CTC

On receipt of an SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using information provided in the Investigator Brochure (IB).

UCL CTC will submit all SAE Reports concerning patients who have received BTG-002814 to BTG according to the timelines outlined in the agreement between UCL CTC and BTG. BTG will perform the Sponsor causality assessment. If UCL CTC has considered expectedness difficult to determine BTG will be consulted for their opinion at this time.

The Chief Investigator, or their delegate, may be contacted to review the SAE and to perform an evaluation of causality on behalf of the Sponsor.

If the event is a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA within the required timelines.

UCL CTC will fulfil the reporting requirements of the REC in relation to SAEs and SUSARs.

Each AE reported on an SAE form must also be reported on the AE section of the CRF.

8.1.7. Adverse Event Reporting

AEs will be recorded on the AE form and the severity grade using NCI CTCAE Version 4.0. The Investigator or physician sub-investigator will judge the severity of each AE and whether or not it is thought to be related to study treatment. All AEs that occur after signing the informed consent, including events likely to be related to the underlying disease or likely to represent concurrent illness, will be recorded, including events present at the Screening visit which worsen during the study

Development Safety Update Reports (DSURs) will be prepared by BTG and submitted to the competent authority and REC by UCL CTC.

8.1.8. Safety Profile of BTG-002814

There have been no patients treated with BTG-002814. This will be the first study of BTG-002814 in humans. The first patient recruited to the study will be observed until the completion of surgery before subsequent patients are recruited.

Safety data with the use of oral vandetanib to treat medullary thyroid cancer

Oral vandetanib is a standard therapy used to treat medullary thyroid cancer. Vandetanib produces repolarisation abnormalities in human myocardium that are consistent with blockade of the I_{KR} (potassium) channel. The most consistent electrophysiologic effects are a change in Twave morphology (flattening, broadening or notching) and prolongation of the QT interval, both of which occur more commonly as the dose is increased. Vandetanib can cause rash, diarrhoea and hypertension, all of which appear to be dose-related and are likely to be related to the pharmacologic activity of vandetanib.

For the full list of known Adverse Reactions and safety warnings, refer to the current version of the BTG-002814 IB.

Safety data with the use of radiopaque embolic beads

The clinical risks of the RO bead are mainly due to the embolisation procedure (e.g. non-target embolisation, post embolisation syndrome) itself and are the same as known for other similar products on the market. These risks can be minimised by following the warnings and precautions in the IB and the requirement that BTG-002814 is used only by well-trained physicians.

9. STATISTICAL CONSIDERATIONS

9.1. Study Design and Determination of Sample Size

The statistical analysis in this study will be primarily descriptive, to assess the safety and tolerability of the study treatment, as well as the distribution of the product following delivery. The study is not statistically powered. A staged enrollment will be performed, allowing for a safety

review after three patients have completed study treatment and follow up. Provided the safety committee deems that there is no significant toxicity related to BTG-002814, a further 9 patients will be enrolled in order to have a target sample size in the study of 6 patients with HCC and 6 patients with liver metastases from CRC. If up to two patients fail to complete study treatment and follow up, they will be replaced, giving a maximum total sample size of 14.

9.2. Statistical Analysis

The statistical analysis plan will be a separate document and will be updated as required prior to the analysis, in association with any protocol amendments. The plan will include descriptions of tables, listings and figures and will describe statistical programming considerations.

9.2.1. Analysis Populations and Sub-Groups

The Analysis Population will consist of all patients who received treatment with BTG-002814. The safety and efficacy analyses will be performed on the Analysis Population. Results will be presented separately for HCC and mCRC patients.

9.3. Baseline and Demographic Characteristics

The following demographic and baseline characteristics will be summarised descriptively, overall and by disease (HCC or mCRC):

- Gender, age, race and ethnicity.
- WHO Performance Status.
- Location and characteristics of tumour.
- Other characteristics (e.g. baseline laboratory profiles, vital signs, physical examination, child-bearing potential, ECG, blood biomarkers and serum tumour markers).

Medical history will be coded using MedDRA, and summarised by primary system organ class and preferred term.

The previous and concomitant medications will be summarised by ATC class and preferred term (WHO Drug Dictionary).

9.4. Efficacy Analyses

The following assessments are exploratory indicators of efficacy. Each will be summarised for all patients and by disease (HCC or mCRC):

9.4.1. Vandetanib concentration

Concentration of vandetanib and N-desmethyl vandetanib in plasma and in resected liver tissue following treatment with BTG-002814. Concentration profiles over time will be reported.

9.4.2. Distribution of BTG-002814

The distribution of BTG-002814 within the tumour vasculature and regions of interest will be assessed on non-contrast enhanced imaging. The findings will be summarised descriptively.

9.4.3. Histopathology of resected liver

An evaluation of histopathological features in both malignant and non-malignant liver tissue from the surgical specimen will be performed. The extent of tumour necrosis, viable tumour and any vascular changes observed will be summarised descriptively.

9.4.4. 3D modelling

The correlation between the distribution of BTG-002814 on imaging and within the pathological specimen will be explored using 3D modelling.

9.4.5. Blood flow following embolisation

Assessment of changes in blood flow will be assessed using DCE-MRI following treatment with BTG-002814. The parameters K^{trans}, K^{ep} and V^{e} will be derived from the DCE-MRI images and will be summarised descriptively.

9.4.6. Biomarker analysis

Levels of blood biomarkers (cytokines, chemokines and growth factors relevant to cancer and inflammation) will be measured following treatment with BTG-002814. The levels and changes in levels across the study will be summarised descriptively.

Levels of serum alpha-fetoprotein (AFP) in patients with HCC, and serum CEA, CA19-9 and CA125 in patients with mCRC will be measured following treatment with BTG-002814. The levels and changes in levels across the study will be summarised descriptively.

9.5. Safety Analyses

All safety results will be presented overall and by disease (HCC or mCRC):

9.5.1. Adverse Events

Adverse events will be graded by the Investigators using the NCI CTCAE v4.0 scale, and coded using MedDRA (the current version at the time of coding).

The number (n) and percentages (%) of patients affected by at least one AE, as well as the number of patients affected by at least one AE with causal relationship to the study treatment, will be summarised firstly overall, then by system/organ class and preferred term (MedDRA). Adverse events will also be tabulated by intensity, treatment for the AE, outcome and causality.

Deaths, SAEs, treatment-related complications, AEs leading to withdrawal and Unexpected Adverse Events (UAE) will be listed separately.

9.5.2. Laboratory Parameters

Observed values, changes from baseline, shifts in CTC grade and normal values/above and below normal values will be summarised with descriptive statistics. A listing of individual laboratory data will be provided with values outside normal ranges flagged.

9.5.3. Other Safety Parameters

Other safety parameters such as ECG, vital signs and physical examinations will be summarised.

9.6. Interim Safety Analysis

The interim safety analysis will incorporate a review of the following data for the first three patients who have completed study treatment and follow up:

- Baseline characteristics and demography
- Details of treatment
- All AEs, graded according to NCI CTCAE and coded using MedDRA.

10. DATA MANAGEMENT

All data management processes up to and including database lock will be detailed in the Data Management Plan (DMP), including the processes for import of external data (e.g. laboratory data).

Data will be collected from sites on version controlled CRFs designed for the study and supplied by UCL CTC. Data must be accurately transcribed onto the CRFs and must be verifiable from source data at site. Examples of source documents are hospital records which include patient's notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. CT/MRI scan images etc.) are being submitted for the study, the patient's study number must be clearly indicated on all material and any patient identifiers removed/redacted prior to sending to maintain confidentiality.

10.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialed. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site.

10.2. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

10.3. Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit.

Sites that persistently do not return data within the agreed timelines may be suspended from recruiting further patients into the study by UCL CTC and subjected to a 'for cause' monitoring visit.

10.4. Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests will be sent to the data contact at site. Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Request forms.

Raw data collected by third party vendors i.e., YBS will be electronically transferred to UCL CTC for inclusion in the UCL CTC Data Management study database. The transfer of derived data to UCL CTC will be described in the DMP.

Data verification and data validation checks will be performed by UCL CTC Data Management utilising electronic edit checks comprised of validated computer programs and manual data review. Any data discrepancies will be referred back to the Investigator via the site monitor. A clean database will be declared by UCL CTC after consistency checks have been run, all SAE reconciliations have been resolved, all data in a clean data transfer have been received including third party vendor data, all the data in the database has been accounted for, all edit checks have been run and data discrepancies have been resolved or accepted and a Quality Check on a sample of the data has been performed. After the database has been declared clean it will be locked and editing in the database will only be allowed with the proper documentation.

After database lock, data will be extracted to SAS® datasets (SAS Institute, Inc., Cary, NC, USA) for analysis as defined in the Statistical Analysis Plan (SAP). SAEs will be entered into the UCL CTC study safety database.

AEs and prior concomitant diseases will be coded according to the version of MedDRA agreed with the Sponsor. Concomitant medications will be coded using the version of the WHO Drug dictionary agreed with the Sponsor.

11. LEGAL/ETHICS and ADMINISTRATIVE PROCEDURES

11.1. Good Clinical Practice/Regulatory Compliance

The procedures set out in this study protocol, pertaining the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by the Declaration of Helsinki, Good Clinical Practice (GCP) and International Council for Harmonisation (ICH).

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate the potential for recruiting the required number of suitable patients within the agreed recruitment period. The Investigator will maintain a list of appropriately qualified person to whom the Investigator has delegated significant study-related tasks.

11.2. Study Site and Investigator Qualification

This study will be performed by appropriately qualified and licensed Investigators at two sites in the UK. All site staff must be appropriately qualified by education, training and experience to perform the study related duties allocated to them, which must be recorded on the site delegation log.

GCP training is required for all staff responsible for study activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

The study sites will be reviewed by UCL CTC (on behalf of the Sponsor) to verify that they are able to conduct the study.

11.2.1. Investigator Curriculum Vitae (CV)

The Investigator will provide the Sponsor or designee with his/her current curriculum vitae (CV), and any revisions/updates, as well as those of any sub-investigator or staff personnel with significant study responsibilities.

11.2.2. Site qualifications and study-specific procedural training

The Institution must have appropriately qualified Investigators, and clinical and administrative support staff in place to adequately conduct the study according to GCP in general and must have the adequate expertise and staff to conduct this study in compliance with the relevant guidelines and regulations and to treat patients with HCC and mCRC.

The physicians who will perform the treatment with BTG-002814 will be qualified Interventional Radiologists who are experienced with DEB-TACE treatments and will be accustomed to DC Bead® and its comparator products as spherical microsphere embolisation devices. However, prior to performing the first study-related treatment, the Interventional Radiologists who will be performing the treatment will undergo documented training in the use of RO bead.

11.2.3. Laboratory Certification and Normal Values

The Investigator will provide the Sponsor with the name and location of the clinical laboratory to be used for determination of laboratory assays, copy of certification, and a list of the normal range of values of all laboratory tests. Any changes in laboratory, certification or normal ranges will be communicated promptly to the Sponsor or UCL CTC.

11.3. Institutional Review Board (IRB)/Independent Ethics Committees (IEC)

11.3.1. Institutional Approval of the Protocol

It is the responsibility of UCL CTC to submit this protocol, the informed consent document (approved by the Sponsor or designee), relevant supporting information and all types of patient recruitment information to the Research Ethics Committee (REC) for review and approval prior to site initiation. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee prior to shipment of investigational product or recruitment of patients. Prior to implementing changes in the study, the Sponsor and REC must also approve any revised informed consent documents and amendments to the protocol with documentation of the approvals submitted to the Sponsor or designee. The approval document should clearly state the study reference, date of review and actions taken.

The Sponsor or designee will be responsible for keeping the REC apprised of the progress of the study, any changes to the protocol, deviations from the protocol and SAEs as required by the REC.

11.3.2. IRB/Ethics Committee Membership Roster

A complete and current membership roster of the REC should be provided to the Sponsor or designee.

11.4. Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent from patients prior to the conduct of any study procedures. All Informed Consent documentation must be in accordance with applicable regulations and GCP. Each patient is requested to sign the ICF after the patient has received and read the written information and received an explanation of the study, including but not limited to: the objectives, treatment plan, potential benefits and risk, inconveniences, alternative treatment options and the patient's rights and responsibilities. A copy of the Informed Consent documentation (Informed Consent Form or Patient Information and Informed Consent Form, as applicable) must be given to the patient or the patient's legally authorised representative.

Acquisition of the Informed Consent should be documented in the patient's medical record and the ICF should be personally signed and dated by the patient and the individual who conducted the Informed Consent discussion. Signed Informed Consent forms must remain in each patient's study file and must be available for verification by Study Monitors at any time.

The Sponsor must receive a copy of the REC- approved Informed Consent form and a copy of the REC written approval, prior to the start of the study. Additionally, if the REC required modification of the sample Patient Information and Informed Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

The Sponsor reserves the right to delay initiation of the study at a site where the Informed Consent forms do not meet the standards of applicable regulations and international GCP standards/guidelines.

11.5. Patient Privacy and Confidentiality

The Sponsor and Investigator affirm and uphold the principle for the patient's right to protection against invasion of privacy. Throughout this trial, all data collected and analysed by the Sponsor or designee will be treated confidentially and identified by an identification number.

To verify compliance with the protocol, the Sponsor will require the Investigator to permit its designee access to the patient's primary medical record to review those portions that directly concern this study (including but not limited to laboratory test results, radiology images, and hospital and outpatient records).

As part of required content of the Informed Consent, the patient must be informed that his/her records will be reviewed by the Sponsor, Sponsor representative and/or a representative of the appropriate competent authority and Safety Committee. The Informed Consent or related document will also state that patient privacy will be maintained pursuant to local regulations. Should access to such medical records require a waiver or authorisation separate from the statement of Informed Consent, the Investigator will obtain such permission in writing from the patient before the patient is entered in the study.

Patient identifiable data, including initials, gender and age, will be required for the registration process and will be provided to UCL CTC. UCL CTC and the Sponsor will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and studies conducted by UCL CTC are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

Data collected during this study may be used to support the development, registration or marketing of BTG-002814. Collected data may be reviewed by the Sponsor and/or its representatives, independent auditors who validate the data on behalf of the Sponsor, third parties with whom the Sponsor may develop, register or market BTG-002814, national or local competent authorities and the REC which granted approval for this study to proceed.

11.6. Study Monitoring

Monitoring of the study will be detailed in the Study Monitoring Plan and will be performed by qualified personnel from the Sponsor or Sponsor designee. At the monitoring visits, the progress of the study will be discussed with the Investigator or his/her representative. The ICFs will be reviewed for signatures and the CRFs checked for completeness and accuracy. Patient source data must be available for review. The Investigator and his/her staff are expected to cooperate with the Study Monitor and be available during at least a portion of the monitoring visit to review the CRFs and any queries/resolutions, answer questions, and provide any missing information.

The Study Monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing. Telephone and electronic mail contact will be made with the Investigator and study staff as necessary during the data collection and report writing periods.

11.7. Modification of the Protocol

UCL CTC (on behalf of the Sponsor) will be responsible for gaining ethical and regulatory approval(s), as appropriate, for amendments made to the protocol and other study-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

All amendments to the protocol must be documented in writing, reviewed and approved by the Chief Investigator and Sponsor and submitted to the REC and/or competent authority for approval prior to initiation. If the protocol amendment substantially alters the study design or potential risk to the patient, new written Informed Consent must be obtained from each patient for continued participation in the study.

11.8. Suspension or Termination of Study

If conditions arise requiring further clarification before the decision can be reached to proceed with or terminate the study, the study will be suspended until the situation has been resolved.

The Sponsor has the right to terminate this study and remove all study material from the site at any time. Examples of situations where this might occur include:

- It becomes apparent that patient enrollment is unsatisfactory with respect to quality and/or quantity or data recording is chronically inaccurate and/or incomplete.
- The incidence and/or severity of adverse events in the study indicate a potential health hazard caused by the trial treatment.

11.9. Departure from Protocol

No deviation may be made from the protocol unless an amendment has been agreed to in writing by both the Investigator and the Sponsor and approved by the REC and competent authority, if applicable. When an emergency occurs that requires a departure from the protocol for an individual, the Investigator or other physician in attendance will, if circumstances and time permit, contact UCL CTC or their representatives, immediately by telephone. Urgency is important to permit a decision as to whether or not the patient (for whom the departure from protocol effects) is to continue in the study. The source documents will completely describe the departure from the protocol and state the reasons for such departure. As appropriate, the REC will be notified in writing.

Urgent Safety Measures will be reported to the MHRA in accordance with the MHRA guidance on Reporting Urgent Safety Issues

11.9.1. Protocol Deviations

All protocol deviations will be documented and will be reviewed periodically by the Sponsor as detailed in the study Protocol Deviation Plan.

Protocol deviations will be tracked according to the following categories:

- Informed consent process not followed
- Screening tests or procedures out of window or not done
- Imaging tests not performed as required

- Dose delivery outside specified range Use of prohibited medications

Major protocol deviations are defined as:

- Enrollment violations: eligibility criteria deviations, informed consent issues,
- Data violations: those affecting primary study endpoints All others will be classified as minor protocol deviations

11.9.2. Serious Breaches

A “serious breach” is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, BTG will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

11.10. Recording, Access to and Retention of Source Data

Investigators are required to prepare and maintain adequate source documentation which includes:

- Documents relative to the patient medical history that verify Eligibility criteria
- Records covering patient participation in the study including basic identification information, results of physical examinations and diagnostic tests, original laboratory results (initialled and dated by the Investigator), study treatment administration, concurrent medication information, and visit notes.

Data must be recorded in the patient’s source documents including the date of Informed Consent.

The Investigator must permit authorised representatives of the Sponsor, the competent authority, the REC, and auditors to inspect facilities and records relevant to the study.

The monitor, auditors, REC or regulatory inspectors may check the CRF entries against the source documents. The Informed Consent form will include a statement by which the patients allow the above-named access to source data that substantiate information recorded in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medical information.

As described in the ICH GCP Guidelines, ‘essential documents’, including CRFs, source documents, Informed Consent forms, laboratory test results, IP inventory records, should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of a clinical development of the IP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator must obtain written permission from the Sponsor prior to destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required.

11.11. Source Documents and Case Report Forms

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into CRFs that have been designed to capture all observations and other data pertinent to the clinical investigation. CRFs should be completed by the Investigator or delegate as stated on the Delegation of Authority Log.

Overwriting of information or use of liquid correcting fluid is not allowed in source documentation. Once the Study Monitor has verified the contents of the completed CRF against the source data, queries may be raised if the data are unclear or contradictory.

11.12. End of Study

For regulatory purposes the end of the study will be the last visit of the last subject (LVLS), at which point the 'declaration of end of trial' form will be submitted to the MHRA and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the study at the site.

Once the end of study has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

11.13. Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the study will be prepared by the Chief Investigator and must be reviewed and approved in writing by the Sponsor, in advance of submission. The review is intended to protect Sponsor proprietary information existing either at the date of commencement of the study or generated during the study. No individual Investigator may publish results from his/her site until after publication of the primary manuscript describing the full study population.

The detailed obligations regarding the publication of any data, material results or other information that is generated or created in relation to the study shall be set out in the agreement between the Investigator and Sponsor.

In accordance with recommendations from the International Committee of Medical Journal Editors, the study will be listed in a publicly accessible registry of clinical trials such as clinicaltrials.gov.

11.14. Audit/Inspections

BTG Clinical Quality Assurance may audit the study sites at any time during the study. To ensure compliance with relevant regulations, data generated by this trial must be available for inspection upon request by representatives of the REC, competent authorities, the Sponsor and its representatives.

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Appendix 1. Medications Known to Prolong QT Interval and/or Induce Torsades de Pointes

Table 3. Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes (TDP)

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Amiodarone	Anti-arrhythmic/abnormal heart rhythm	*TDP risk regarded as low*
Arsenic trioxide	Anti-cancer/Leukaemia	
Astemizole	Antihistamine/Allergic rhinitis	
Azithromycin	Antibiotic/bacterial infection	
Bepridil	Anti-anginal/heart pain	
Chloroquine	Anti-malarial/malaria infection	

Chlorpromazine	Anti-psychotic/Antiemetic/schizophrenia/nausea	
Cisapride	GI stimulant/heartburn	
Citalopram	Anti-depressant/depression	
Clarithromycin	Antibiotic/bacterial infection	
Disopyramide	Anti-arrhythmic/abnormal heart rhythm	
Dofetilide	Anti-arrhythmic/abnormal heart rhythm	
Domperidone	Anti-nausea/nausea	
Droperidol	Sedative; Anti-nausea/anesthesia adjunct, nausea	
Erythromycin	Antibiotic; GI stimulant/bacterial infection; increase GI motility	
Escitalopram	Anti-depressant/Major depression/Anxiety disorders	
Flecainide	Anti-arrhythmic/abnormal heart rhythm	
Halofantrine	Anti-malarial/malaria infection	
Haloperidol	Anti-psychotic/schizophrenia, agitation	*TDS risk with IV or excess dosage*
Ibutilide	Anti-arrhythmic/abnormal heart rhythm	
Levomethadyl	Opiate agonist/pain control, narcotic dependence	
Mesoridazine	Anti-psychotic/schizophrenia	
Drug (Generic Names)	**Drug Class (Clinical Usage)**	**Comments**
Methadone	Opiate agonist/pain control, narcotic dependence	
Moxifloxacin	Antibiotic/bacterial infection	
Pentamidine	Anti-infective/pneumocystis pneumonia	
Pimozide	Anti-psychotic/Tourette's tics	
Probucol	Antilipemic/Hypercholesterolemia	
Procainamide	Anti-arrhythmic/abnormal heart rhythm	

Quinidine	Anti-arrhythmic/abnormal heart rhythm	
Sevoflurane	Anesthetic, general/anaesthesia	*Label warning for patients with congenital long QT or patients taking QT prolonging drugs*
Sotalol	Anti-arrhythmic/abnormal heart rhythm	
Sparfloxacin	Antibiotic/bacterial infection	
Terfenadine	Antihistamine/Allergic rhinitis	
Thioridazine	Anti-psychotic/schizophrenia	
Vandetanib*	Anti-cancer/Thyroid cancer	*Does not apply to this study

Table 4. Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Alfuzosin	Alpha1-blocker/Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral/Anti-infective/Parkinson's Disease	
Artenimol + Piperaquine	Anti-malarial	
Atazanavir	Protease inhibitor/HIV	
Bedaquiline	Anti-infective/Drug-resistant Tuberculosis	
Chloral hydrate	Sedative/sedation/insomnia	
Clozapine	Anti-psychotic/schizophrenia	
Dolasetron	Anti-nausea/nausea, vomiting	
Dronedarone	Anti-arrhythmic/Atrial Fibrillation	
Eribulin	Anti-cancer/metastatic breast neoplasias	
Famotidine	H2-receptor antagonist/Peptic ulcer/GERD	
Felbamate	Anti-convulsant/seizure	

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Fingolimod	Immunosuppressant/Multiple Sclerosis	

Foscarnet	Anti-viral/HIV infection	
Fosphenytoin	Anti-convulsant/seizure	
Gatifloxacin	Antibiotic/bacterial infection	
Gemifloxacin	Antibiotic/bacterial infection	
Granisetron	Anti-nausea/nausea and vomiting	
Iloperidone	Antipsychotic, atypical/Schizophrenia	
Indapamide	Diuretic/stimulate urine & salt loss	
Isradipine	Anti-hypertensive/high blood pressure	
Lapatinib	Anti-cancer/breast cancer, metastatic	
Levofloxacin	Antibiotic/bacterial infection	
Lithium	Anti-mania/bipolar disorder	
Mirtazapine	Anti-depressant	
Moexipril/HCTZ	Anti-hypertensive/high blood pressure	
Nicardipine	Anti-hypertensive/high blood pressure	
Nilotinib	Anti-cancer/Leukemia	
Octreotide	Endocrine/acromegaly, carcinoid diarrhea	
Ofloxacin	Antibiotic/bacterial infection	
Olanzapine	Anti-psychotic, atypical/Schizophrenia, bipolar	*Combo with fluoxetine: Symbyax*
Ondansetron	Anti-emetic/nausea and vomiting	
Oxytocin	Oxytocic/Labor stimulation	
Paliperidone	Antipsychotic, atypical/Schizophrenia	
Perflutren lipid microspheres	Imaging contrast agent/Echocardiography	
Quetiapine	Anti-psychotic/schizophrenia	
Ranolazine	Anti-anginal/chronic angina	
Risperidone	Anti-psychotic/schizophrenia	

Roxithromycin	Antibiotic/bacterial infection	
Sertindole	Antipsychotic, atypical/Anxiety, Schizophrenia	
Sunitinib	Anti-cancer/RCC, GIST	
Drug (Generic Names)	**Drug Class (Clinical Usage)**	**Comments**
Tacrolimus	Immunosuppressant/Immune suppression	
Tamoxifen	Anti-cancer/breast cancer	
Telithromycin	Antibiotic/bacterial infection	
Tizanidine	Muscle relaxant	
Vardenafil	Phosphodiesterase inhibitor/vasodilator	
Venlafaxine	Anti-depressant/depression	
Voriconazole	Anti-fungal/anti-fungal	
Ziprasidone	Anti-psychotic/schizophrenia	

Source: www.QTdrugs.org/

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