



Protocol Number:	C4251007/SGNTUC-028
Version:	Amendment 03; 27-Aug-2024
Protocol Title:	A randomized, double-blind, phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for metastatic HER2+ breast cancer (HER2CLIMB-05)
Investigational Product:	PF-07265792 Tucatinib
Phase:	3
US IND Number:	119421
EU Trial Number	2023-503826-37
Sponsor:	Seagen Inc., a wholly owned subsidiary of Pfizer 21823 30th Drive SE Bothell, WA 98021, USA
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Document History

Document	Version Date
Original	21-May-2021
Amendment 01	09-Aug-2021
Amendment 01, UK-1	31-Jan-2022
Amendment 02	07-Mar-2023
Amendment 02, CHN-1	26-Feb-2024
Amendment 03	27-Aug-2024

Protocol Amendment Summary of Changes Table

Amendment 03 (27-Aug-2024)

Overall Rationale for the Amendment: The primary purpose of this amendment is to align with Pfizer required safety reporting requirements and to incorporate other Pfizer specific text, requirements, and formatting across the document.

Description of Change	Brief Rationale	Change Section # and Name
Substantial Modification(s)		
Updated definition of women of childbearing and non-childbearing potential. Contraception and barrier guidance updated.	To align with Pfizer's Protocol Template.	Section 4.4 Childbearing Potential
Added section including definition and reporting of medication errors	To align with Pfizer's Protocol Template.	Section 7.8.1.2.7 subsection Medication Errors
Added section indicating lack of efficacy as reportable event to Pfizer Safety only if associated with an SAE.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1.2.8 subsection Lack of Efficacy
Updated section with additional required Pfizer protocol template language about AESI reporting.	To align with Pfizer's Protocol Template.	Section 7.8.1.6 Adverse Events of Special Interest
Non-Substantial Modification(s)		
Removed Medical Monitor's name and contact information	The medical monitor's name and contact information is personal identifiable information	Title page
Removed Eudra CT Number	Study has transitioned to CTIS	Title Page
Moved Document History table to front of document	Alignment with Pfizer document format and requirements.	Page 3 (no section number)
Added ClinicalTrials.gov and Pediatric Investigational Plan numbers	Alignment with Pfizer document format and requirements.	Synopsis
Added Study Rationale, Ethical Considerations	Alignment with Pfizer document format and requirements.	Synopsis
Revised inclusion/exclusion criteria to include key criteria only; changed formatting to bullets instead of numbering	Alignment with Pfizer document format and requirements.	Synopsis
Deleted exploratory objectives and endpoints	Alignment with Pfizer document format and requirements.	Synopsis
Deleted references to Appendix G.	Prior Appendix G Country-Specific Requirements for China deleted	Synopsis/Biomarker Assessment

Description of Change	Brief Rationale	Change Section # and Name
		Section 7.2.1 Confirmation of HER2 Expression for Study Eligibility Section 7.4 Pharmacokinetic Assessments Section 7.5 Biomarker Assessments Section 7.5.1 Characterization of Tumor Tissue Section 7.5.2 Characterization of Blood Samples
Updated EOT timing to 30-37 days from last dose.	To align with Section 6.4	Schedule of Events
Updated footnote H to add that participants of childbearing potential should be counseled on adequate contraception methods	To align with Pfizer's Protocol Template.	Schedule of Events
Added footnote "X" indicating that bone scans are not required at EOT if conducted 4 weeks prior to EOT.	Clarification to align requirements for end of treatment imaging	Schedule of Events
Added that participants who discontinue study treatment in the absence of RECIST-PD are expected to continue tumor assessments at the same intervals as while on study treatment based on the C1D1 assessment date.	To clarify the timing of tumor assessments in participants who discontinue study treatment in the absence of RECIST-PD.	Schedule of Events (Footnote Y) Section 6.5 Follow-up Period (Visits Every 12 weeks [±1 week])
Added that CCI [REDACTED]	To clarify that CCI [REDACTED]	Section 3.1.1 Continuation on Study Treatment After CNS--Only Progression Section 6.3.3.3 Every 27 weeks (±21 days) after Cycle 1 Day 1 Section 7.3.1 Evaluation of Brain Metastases
Added: "Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that	To align with Pfizer's Protocol Template.	Section 3.2.3 Blinding and Unblinding

Description of Change	Brief Rationale	Change Section # and Name
randomization/dispensing has been done accurately.”		
Identified “sensitive” clinical data, ie, variables that have the potential to unblind a participant’s treatment assignment	To align with Pfizer’s Protocol Template.	Section 3.2.3 Blinding and Unblinding
Revisions to contraception text to use preferred Pfizer contraception wording and follow all Pfizer contraception guidelines.	To align with Pfizer’s Protocol Template.	Section 4.3 Contraception
Updated definition of women of childbearing and non-childbearing potential.	To align with Pfizer’s Protocol Template.	Section 4.4 Childbearing Potential
Referenced the SoE for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. Added that the withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow up.	To align with Pfizer’s Protocol Template.	Section 4.5.1 Discontinuation of Study Treatment
Added: “If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected except for publicly available information. The sponsor may retain and continue to use any data collected before such withdrawal of consent.”	To align with Pfizer’s Protocol Template	Section 4.5.2 Participant Withdrawal from Study

Description of Change	Brief Rationale	Change Section # and Name
Storage and Handling, Packaging and Labeling, Preparation incorporated into Section 5.1 Treatments Administered Preparation, Handling, Storage and Accountability	To align with Pfizer's Protocol Template.	From prior amendment: Sections 5.1.1.4, 5.1.2.4 - Storage and Handling Sections 5.1.1.5, 5.1.2.5, 5.1.3.4, 5.1.4.4 Packaging and Labeling Sections 5.1.1.6, 5.1.2.6, 5.1.3.5, 5.1.4.5 Preparation
Details on storage temperature recording, temperature excursion management, product complaint reporting, IMP preparation and destruction added.	To align with Pfizer's Protocol Template.	Section 5.1 Treatments Administered Preparation, Handling, Storage, and Accountability
Added section to augment existing study intervention information as it relates to preparation and dispensing	To align with Pfizer's Protocol Template.	Sections 5.3.1.4, 5.3.2.4, 5.3.3.4, 5.3.4.5 Preparation and Dispensing
Added Single Reference Safety Document (SRSD) information	To provide SRSD information for each study intervention and to align with Pfizer's Protocol Template	Section 5.2 Single Reference Safety Documents
Added that any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued	To clarify dose modification guidelines for trastuzumab	Section 5.4.2 Trastuzumab
Updated dose modification guidelines for pertuzumab; deleted Table 4 Recommendations Regarding Delayed or Missed Doses of Pertuzumab	To update dose modification guidelines for pertuzumab	Section 5.4.3 Pertuzumab
Language revised to have overdose reported to Pfizer Safety only when associated with an SAE.	To align with Pfizer's safety reporting process.	Section 5.7.7 Management of Overdose
Added that continued access to study intervention will be provided for participants who continue to derive clinical benefit from treatment (as judged by the PI and discussed with the sponsor) at the time the end of study has been reached, and who have no other treatment options outside a clinical study.	To support study transition to Pfizer Pharmacovigilance processes and systems.	Section 5.9 Continued Access to Study Intervention After the End of the Study
Referenced Appendix C for pregnancy test and contraception monitoring review. Added counseling on adequate contraception methods for	To align with Pfizer's Protocol Template.	Section 6.2.3 Baseline Visit (Days -7 to Day 1)

Description of Change	Brief Rationale	Change Section # and Name
participants of childbearing potential		
Added: "Blood sample collection for biomarker at Cycle 3 predose"	To include biomarker blood sample collection information described in SGNTUC-028 Administrative Letter 01 (05-Jun-2023)	Section 6.3.1 Treatment Period Day 1
Clarified that EOT visits should occur 30 to 37 days after the last dose of the last study intervention unless delayed due to an AE. However, because EOT evaluations must be performed before initiation of subsequent cancer therapy, if EOT evaluations are completed before 30 days after the last study treatment, the participant will be contacted 30 to 37 days following the last study treatment to assess for AEs; the other EOT evaluations do not need to be repeated.	To clarify the timing of EOT evaluations.	Section 6.4 End of Treatment: Visit (30 to 37 days after last dose of last study intervention)
Added: "Blood sample collection for biomarker"	Include biomarker blood sample collection information content described in SGNTUC-028 Administrative Letter 01 (05-Jun-2023)	Section 6.4 End of Treatment: Visit (30 to 37 days after last dose of last study intervention)
Biomarker blood sample at Cycle 3 Day 1 footnoted "b" to indicate "predose" only	To include biomarker blood sample collection information described in SGNTUC-028 Administrative Letter 01 (05-Jun-2023)	Section 7.4 Pharmacokinetic Assessments
Moved sections on Overdose, Medication Error, Misuse, and Abuse	Overdose is described in Section 5.7.7 Management of Overdose Medication errors are discussed under Section 7.8.1.2 Procedures for Eliciting and Recording Adverse Events	Section 7.8.1.1 Definitions
Added that complications that occur during hospitalization are AEs. Clarified that the term disabling/incapacitating does not include experiences of relatively minor medical significance.	To further define the definitions of hospitalization and disabling/incapacitating	Section 7.8.1.1 Definitions
Added text to provide additional details in the event the investigator does not know	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1.1.4 Definitions, under table in the subsection "Relationship of the Adverse Event to Study Treatment"

Description of Change	Brief Rationale	Change Section # and Name
whether or not the study intervention caused the event.		
Added language regarding exposure during pregnancy and added information on environmental and occupational exposure as well as exposure during breastfeeding.	To align with Pfizer's Protocol Template.	Section 7.8.1.2.6 subsections Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
Safety reporting period clarified in case a participant begins a new anticancer therapy.	To align with Pfizer's Protocol Template.	Section 7.8.1.3 Reporting Period for AEs and SAEs
Updated section to add required Pfizer protocol template language and remove redundant text due to this update. PSSA added as electronic tool for reporting.	To align with Pfizer's Protocol Template.	Section 7.8.1.4 SAE Require Immediate Reporting
Updated section with additional required Pfizer protocol template language about SUSARs or other specific safety information.	To support study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1.7 Sponsor Safety Reporting to Regulatory Authorities
Added guidance on pregnancy testing	To align with Pfizer's Protocol Template.	Section 7.8.5 Pregnancy Testing
Section 8.2 was incorporated into Section 10 with updates to be consistent with Pfizer Pharmacovigilance processes.	To align with Pfizer's Protocol Template.	Section 8.2 Data Management Procedures
Section 8.3 was incorporated into Section 10 with updates to be consistent with Pfizer Pharmacovigilance processes.	To align with Pfizer's Protocol Template.	Section 8.3 Access to Source Data
Section 8.5 was incorporated into Section 10.	To support Study transition to Pfizer processes and systems.	Section 8.5 Quality Assurance Procedures
Section 8.6 was incorporated into Section 10.	To support Study transition to Pfizer processes and systems.	Section 8.6 Data Handling and Record Keeping
Section 8.6.1 was incorporated into Section 10.	To support Study transition to Pfizer processes and systems.	Section 8.6.1 Data Handling
Section 8.6.2 was incorporated into Section 10.	To support Study transition to Pfizer processes and systems.	Section 8.6.2 Investigator Record Retention
Added language requiring a protocol amendment incorporating any major modifications of the primary endpoint definitions or their analyses in the SAP.	To align with Pfizer's Protocol Template.	Section 9.3 Statistical and Analytical Considerations

Description of Change	Brief Rationale	Change Section # and Name
Investigator's responsibility added	To align with Pfizer's Protocol Template.	Section 10.1.1 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP
Language on public disclosure of study results added	To align with Pfizer's Protocol Template.	Section 10.5 Dissemination of clinical Study Data
Section added	To align with Pfizer's Protocol Template.	Section 10.9 Use of Medical Records
Section added	To align with Pfizer's Protocol Template.	Section 10.11 Sponsor's Medically Qualified Individual
Removal of Investigator's agreement and the investigator's signature.	The investigator's agreement and signature is personal identifiable information.	Appendix D from prior amendment
Deleted section for country-specific requirements for China.	Biomarker analyses will not be performed for China.	Appendix G from prior amendment
Added AE definition, AE/SAE recording/reporting requirements and procedures	To support study transition to Pfizer Pharmacovigilance processes and systems.	Appendix G Adverse Events: Definitions and Procedures for Recording and Reporting
Removal of Investigator's agreement and the investigator's signature.	The investigator's agreement and signature is personal identifiable information.	Appendix H from prior amendment
Added Appendix H for Country-Specific Requirements	Once a study is governed by Pfizer SOPs, any amendment created for the study needs to reflect a single global version of the protocol. Differences across countries or regions are specified by country or region in Appendix H.	Appendix H: Country Specific Requirements
The term "subject" has been updated to "participant" when referring to an individual who has consented to participate in the clinical study. The term "subject" has been updated to "patient" when used to describe the wider population beyond the trial. The term "study drug" has been updated to "study intervention".	Alignment with Pfizer document format and requirements.	Throughout protocol
Minor editorial modifications in the text, which are not provided in this summary of changes, were made for additional clarity.	Minor updates and clarifications.	Throughout protocol

PROTOCOL SYNOPSIS

Protocol Number C4251007/SGNTUC-028 Version Amendment 03; 27-Aug-2024 Phase 3	Product Name PF-07265792 (Tucatinib) Sponsor Seagen Inc., a wholly owned subsidiary of Pfizer 21823 30th Drive SE Bothell, WA 98021, USA
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Protocol Title

A randomized, double-blind, phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for metastatic HER2+ breast cancer (HER2CLIMB-05)

Regulatory Agency Identification Number(s):

US IND Number:	119421
EU Clinical Trial (CT) Number:	2023-503826-37
ClinicalTrials.gov ID:	NCT05132582
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4251007/SGNTUC-028
Phase:	3

Study Rationale:

C4251007 is a phase 3, global, randomized, double-blind study of tucatinib vs placebo in combination with trastuzumab and pertuzumab as maintenance therapy in patients with advanced breast cancer who last received trastuzumab, pertuzumab, and a taxane with no evidence of progression. The purpose of this study is to optimize first-line (1L) therapy by prolonging the chemotherapy-free period by adding a tyrosine kinase inhibitor (TKI) to dual anti-human epidermal growth factor 2 (HER2) mAb therapy and to address a growing segment of patients with HER2+ breast cancer with brain metastasis as an early site of relapse.

Study Objectives and Endpoints

Primary Objective	Corresponding Primary Endpoint
• Compare progression--free survival (PFS) by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms	• PFS, defined as the time from randomization to investigator-assessed documented disease progression per RECIST v1.1, or death from any cause, whichever occurs first
Key Secondary Objective	Corresponding Key Secondary Endpoint
• Compare overall survival (OS) between treatment arms	• OS, defined as the time from randomization to death from any cause
Other Secondary Objectives	Corresponding Secondary Endpoints

Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1	PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST v1.1), or death from any cause, whichever occurs first
Assess the change in health-related quality of life (HRQoL)	Time to deterioration of HRQoL, defined as time to 10-point decrease in the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30)
Evaluate PFS in the brain	Central nervous system (CNS)-PFS, defined as the time from randomization to investigator assessed- disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first
Evaluate the safety and tolerability of tucatinib in combination with trastuzumab and pertuzumab	- Adverse events (AEs) - Clinical laboratory assessments - Incidence of dose holding, dose reductions, and discontinuations of tucatinib - Incidence of dose holding and discontinuations of trastuzumab - Incidence of dose holding and discontinuations of pertuzumab
Evaluate the pharmacokinetics (PK) of tucatinib	Plasma concentrations of tucatinib

Study Population

Key Inclusion Criteria

Participants must meet the following criteria to be eligible for the study:

- Have centrally confirmed HER2+ breast carcinoma according to the 2018 American Society of Clinical Oncologists (ASCO)-College of American Pathologists (CAP) guidelines prior to randomization (defined as a 3+ score on immunohistochemistry (IHC) and/or 2+ IHC and concurrent positive by ISH).
 - a. Tissue blocks or tumor slides must be submitted and confirmed as HER2+ by a sponsor designated central laboratory prior to randomization
- 2. Have unresectable locally advanced or metastatic (hereafter referred to as “advanced”) disease; if recurrent (after [neo]adjuvant therapy), there must be a minimum 6month -treatment free interval from any trastuzumab and pertuzumab received in the early breast cancer setting to the diagnosis of advanced HER2+ disease. Prior standard of care therapy for early breast cancer is permitted (eg, prior

- ado-trastuzumab- emtansine [T-DM1]); however, Exclusion Criterion 1 should be noted.
- Have received 4-8 cycles of pre-study induction therapy including only trastuzumab, pertuzumab, and taxane as first-line therapy for the treatment of advanced breast cancer prior to study enrollment. Participants are eligible provided they are without evidence of disease progression (per investigator judgement, ie, CR, PR, or SD) following completion of induction therapy.
 - Participants receiving <6 cycles (ie, 4-5 cycles) of taxane are only eligible if the taxane was stopped early due to intolerable toxicity (eg, documented neuropathy impacting function).
 - Participants are permitted to receive trastuzumab and pertuzumab for 2 additional cycles (after completion of chemotherapy) to allow completion of screening procedures. Study treatment should begin within 6 weeks ($\pm$ 3 days) from the start of the last cycle of trastuzumab and pertuzumab.
 - Participants are permitted to receive up to 2 cycles of carboplatin during the start of induction therapy in combination with trastuzumab, pertuzumab, and taxane (eg, to obtain confirmation of metastatic breast cancer diagnosis)
 - Participants who received traditional medications (eg, traditional Chinese medication) and/or supplements with potential anti-cancer effects during induction therapy will remain eligible if they discontinue these treatments at least 4 weeks prior to the start of study treatment.
 - Known hormone receptor status (per local guidelines; may be hormone receptor positive [HR+] or negative [HR-])
 - Have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
 - **CNS Inclusion** – Based on screening contrast-enhanced brain magnetic resonance imaging (MRI), participants may have any of the following:
 - No evidence of brain metastases
 - Untreated brain metastases which are asymptomatic, not needing immediate local treatment and, if identified on prior brain imaging, without evidence of progression since starting first-line induction therapy with trastuzumab, pertuzumab, and taxane
 - Previously treated brain metastases which are asymptomatic
 - Brain metastases previously treated with local therapy must not have progressed since treatment
 - Time since whole brain radiation therapy (WBRT) is $\geq$ 14 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is $\geq$ 7 days prior to first dose of study treatment, or time since surgical resection is $\geq$ 28 days prior to first dose of study treatment

- Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

Key Exclusion Criteria

Participants will be excluded from the study for any of the following reasons:

- Have previously been treated with any tyrosine kinase inhibitor targeting HER2 and/or epidermal growth factor receptor (EGFR) including pyrotinib, lapatinib, tucatinib, neratinib, and afatinib (except neratinib if given in the extended adjuvant setting and at least 12 months have elapsed from the last neratinib dose to the start of study intervention) or are currently participating in another interventional clinical trial.
- Unable for any reason to undergo contrast-enhanced MRI of the brain
- **CNS Exclusion** – Based on screening brain MRI and clinical assessment, participants must not have any of the following:
 - Symptomatic brain metastasis after CNS-directed local therapy
 - Progression of brain metastases since starting first-line trastuzumab, pertuzumab, and taxane
 - Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent). For participants requiring systemic steroids for control of comorbidities (eg, asthma or autoimmune diseases), daily dose must not exceed 2 mg dexamethasone (or equivalent).
 - Any untreated brain lesion in an anatomic site which may pose risk to participant (eg, brain stem lesions). Participants who successfully undergo local treatment for such lesions may be permitted to rescreen, if otherwise eligible, after discussion with, and approval by, the medical monitor.
 - Known or suspected leptomeningeal disease (LMD) as documented by the investigator
 - a. Poorly controlled (>1/week) seizures, or other persistent neurologic symptoms despite CNS directed therapy for brain metastasis

Number of Planned Participants

Approximately 650 participants may be randomized in the study.

Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and pertuzumab as maintenance therapy in participants with advanced HER2+ breast cancer who have had prior treatment with a taxane, trastuzumab, and pertuzumab. After signing informed consent and meeting all eligibility criteria, participants will be

randomized in a 1:1 ratio to receive 21-day cycles of either tucatinib or placebo in combination with trastuzumab and pertuzumab. Randomization will be stratified by diagnosis (de novo versus recurrent), hormone receptor status (positive versus negative), and presence or history of brain metastases (yes versus no).

Dose reductions of tucatinib or placebo will be allowed. Dose holding or discontinuation of tucatinib or placebo, trastuzumab, and/or pertuzumab will also be allowed as needed for participant safety. In the absence of progression, participants who discontinue trastuzumab and pertuzumab due to intervention related toxicity may continue receiving tucatinib/placebo alone, and participants who discontinue tucatinib/placebo may continue to receive trastuzumab and pertuzumab. If a participant discontinues trastuzumab or pertuzumab, they are required to discontinue both. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued. These participants will still be required to complete all assessments as outlined in the Schedule of Events.

Safety will be monitored in an ongoing, blinded basis by the sponsor throughout the study. An External Data Monitoring Committee (E-DMC) will regularly review all relevant unblinded safety data as outlined in a separate E-DMC charter. After approximately 30 participants are randomized and have received at least 2 full cycles of study treatment, the E-DMC will sponsor or convene to review safety data. Enrollment will continue during the initial safety assessment of these 30 participants. Ad hoc meetings of the E-DMC may be held upon the request of the E-DMC.

Study Treatment, Dose, and Mode of Administration

Tucatinib will be administered at 300 mg orally twice a day (PO BID) every day for 21 days.

Placebo for tucatinib will be administered PO BID every day for 21 days.

Trastuzumab and pertuzumab will be administered as follows:

- Trastuzumab will be given intravenously (IV) at a dose of 6 mg/kg or subcutaneously (SC) at a fixed dose of 600 mg, once every 21 days.

AND

- Pertuzumab will be given IV at 420 mg every 21 days.

OR

- Fixed dose combination of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase will be given SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.

Trastuzumab and pertuzumab will be supplied in an open-label manner by the sponsor, where required. If supplied by the sponsor, the provided intervention and formulation must be utilized.

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression (ideally verified radiologically per RECIST v1.1), withdrawal of consent, or study closure. No crossover from placebo to tucatinib will be allowed.

Efficacy Assessments

Disease response per RECIST v1.1 will be assessed by both investigator and BICR. This will include measurement of all known sites of tumor (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline and every 9 weeks until progression per RECIST (irrespective of dose holds) or end of treatment (EOT), whichever is later. Any imaging that is conducted as per standard of care will be collected for retrospective BICR. Positron emission tomography (PET)/CT (if -diagnostic quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other sites of disease (eg, skin lesion photography for skin lesions, imaging of the neck, or imaging by CT or MRI of bone metastases not captured by imaging of the chest, abdomen, or pelvis). Bone scans will be required at screening only for participants with known or suspected bone metastases and are to be repeated every 27 weeks (~6 months). Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. PET-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study. Contrast-enhanced brain MRI is required for all participants at screening and at EOT and is to be repeated only for participants with a history of, or baseline, brain metastasis every 9 weeks. For participants without a history of, or baseline, brain metastasis, contrast-enhanced brain MRI is to be repeated every 27 weeks (~6 months). Additional contrast MRIs of the brain may be performed as clinically appropriate.

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each participant will continue until disease progression per RECIST v1.1 by investigator assessment has been documented or EOT, whichever is later. Survival and other follow-up assessments will continue until study closure or withdrawal of consent.

Pharmacokinetic Assessments

Blood samples for PK assessment of trough tucatinib drug concentrations will be collected in all participants on Day 1 of Cycles 2 to 6, prior to administration of tucatinib. CCI

Plasma concentrations of tucatinib will be determined using validated liquid chromatography (LC) mass spectrometry (MS)/MS methods. PK parameters will be summarized using descriptive statistics. Additional analytes may be evaluated as necessary.

Biomarker Assessments

HER2 status will be confirmed at a central laboratory as determined by IHC/ISH prior to randomization. Refer to Inclusion Criterion #1 for more details.

Tumor tissue will be collected at screening/baseline. Peripheral blood samples will be collected at baseline, at Cycle 3 Day 1, and at disease progression/end of treatment.

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Safety Assessments

Participants will be assessed throughout the study for safety. Safety assessments including physical examinations, vital signs, collection of AEs and laboratory values (including pregnancy testing) and concomitant medications will be performed on Day 1 of each cycle throughout study treatment and approximately 30 days after the last dose of the last study intervention. Day 1 of each cycle is determined by the dosing date of trastuzumab and pertuzumab. If participants have discontinued trastuzumab and pertuzumab, cycles will be defined as 21 days for tucatinib/placebo dosing. Laboratory assessments will be performed locally. Additional assessments may be added as clinically indicated. Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation irrespective of dose delays or interruption, and at the EOT visit (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). AE and laboratory abnormality severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.

Other Assessments

Health-related QoL will be assessed at protocol-specified time points using standardized assessment tools including the EORTC QLQ-C30 CCI

Statistical Methods

Sample Size Considerations

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of PFS events (hazard ratio [HR] of 0.70; median PFS of 15 months in the control arm and 21.4 months in the experimental arm).

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CCI [REDACTED]

Analysis Methods

For the primary endpoint of PFS by investigator assessment, the 2 treatment groups will be compared using a 2sided stratified log-rank test. Estimation of the HR will be based upon the stratified Cox regression model. PFS will also be summarized using the Kaplan Meier method. All randomized participants will be included in the primary analysis of PFS. Kaplan Meier methodology will be used to estimate the PFS time curves, including the median. Similar methods will be used for the key and other secondary time-to-event endpoints and other exploratory time-to-event endpoints.

No interim analyses will be performed for the primary endpoint. CCI [REDACTED]

The stopping boundaries will be determined using Lan-DeMets spending functions for the O'Brien and Fleming boundaries.

Ethical Considerations:

The results of previous clinical and non-clinical studies of tucatinib in combination with trastuzumab and pertuzumab support the investigation of tucatinib in combination with trastuzumab and pertuzumab for metastatic HER2+ breast cancer, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with tucatinib in combination with trastuzumab and pertuzumab are justified by the anticipated benefits that may be afforded to participants with metastatic HER2+ breast cancer. Participants may experience improvements during the study and will benefit from more intense monitoring and more frequent assessments compared to usual standard of care. Participants may benefit from contributing to the understanding of metastatic HER2+ breast cancer. Based on the experience with tucatinib, the potential risks for tucatinib in combination with trastuzumab and pertuzumab include diarrhea and elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods and avoid vaccination with live attenuated vaccines. When relevant, it is recommended that participants keep their diet habits constant throughout the study.

The use of placebo in this study is necessary to determine the effect of adding tucatinib to the combination of trastuzumab and pertuzumab as maintenance therapy for 1L locally advanced unresectable or metastatic HER2+ breast cancer. The placebo group is currently the standard of care for this patient population. The placebo group will allow for the comparison of the investigational regimen to current standard of care in a blinded manner typically expected for phase 3 studies.

SCHEDULE OF EVENTS

		Screening/Baseline ^A		Every 21-Day Cycle	C1, C2	Every 9 Weeks, Starting at C1D1	Every 27 Weeks, Starting at C1D1	Every 12 Weeks	EOT	F/U
		D -28 to 1	D -7 to 1	D1 ^B	D12				30-37 D from last dose ^C	Every 12 wks
				±2d	±2d	±1 wk	±3 wks	±1 wk		±1 wk
Screening/Baseline Assessments	Informed consent ^D	X								
	Inclusion/Exclusion, medical history ^E	X								
	Randomization		X							
	Central confirmation of HER2 status ^F	X								
Safety Assessments	Physical examination ^G		X	X					X	
	Height		X							
	Weight		X	X					X	
	Pregnancy test (participants of childbearing potential) ^H		X	X					X	
	CBC with ANC ^I	X ^J	X ^J	X					X	
	Chemistry panel ^{I,K}	X ^J	X ^J	X					X	
	Liver function tests ^L	X ^J	X ^J	X	X				X	
	Serology for hepatitis B and C ^M	X								
	ECOG performance status		X	X					X	
	ECHO or MUGA	X						X ^N	X ^N	
	ECG	X								
	Concomitant medications	Related to study procedures ^O		Collect from Day 1 predose through safety reporting period of study intervention(s) ^P						X ^Q
	Adverse event collection									X
Treatment	Study intervention administration			X						
	Follow-up cancer therapy									X
PRO/QoL	EORTC QLQ-C30 ^R		X	X					X	X ^S
	CCI		X	X					X	X ^S
PK	Blood sample collection			X ^T		C3D1 and EOT. See Table 7 for sample collection details.				
Biomarker	Blood sample collection ^U		X	X ^V					X ^W	
	CT of chest, abdomen, pelvis	X				X			X ^{X,Y}	X ^Y

		Screening/Baseline ^A		Every 21-Day Cycle	C1, C2	Every 9 Weeks, Starting at C1D1	Every 27 Weeks, Starting at C1D1	Every 12 Weeks	EOT	F/U
Response Assessments ^{AA}	Additional imaging (of other known sites of disease, as appropriate)	X				X			X ^{X,Y}	X ^Y
	Brain MRI	X ^Z				X ^Z	X ^Z		X ^{X,Z}	X ^Y
	Bone scan (if known or suspected bone metastases)	X ^{BB}					X ^{BB}		X ^{X,Y,BB}	X ^Y
	Survival status									X ^{CC}

- A. Certain screening evaluations may not need to be repeated outside the 28-day screening window with medical monitor approval. These include the following: ECHO/MUGA and CT scans. All other safety labs and assessments will need to be repeated per the schedule of events for these participants. If local CNS therapy involves surgical resection, a postoperative contrast MRI of the brain is required prior to starting study treatment.
- B. For Screening/Baseline and Safety Assessments: Assessments do not need to be repeated, if already done within 2 days of study visit. Confirm laboratory results prior to study treatment dosing.
- C. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the participant's last study treatment (ie, last dose of any study intervention) to ensure that AEs are reviewed.
- D. Informed consent does not expire at 28 days.
- E. All prior breast cancer treatment will be collected.
- F. HER2 samples may be submitted up to 6 months prior to the Screening Visit. Participants must sign the pre-screening consent prior to submission. HER2 status must be centrally confirmed prior to randomization. If archival tissue is unavailable, a fresh tumor biopsy must be obtained.
- G. Includes collection of vital signs.
- H. Participants of childbearing potential only: can be performed within 7 days prior to study treatment dosing on Day 1 of cycle. Confirm negative pregnancy test prior to continuing study treatment dosing. In addition, participants of childbearing potential should be counseled on adequate contraception methods as outlined in [Appendix C](#).
- I. Complete blood count (CBC) assessment will include white blood cell count, hemoglobin, platelet count, and absolute neutrophil count (ANC).
- J. Assessments may be collected between D -28 and D1 to demonstrate eligibility. If performed between D -28 and D -8 and any value is out of eligibility range, the given test(s) may be repeated between D -7 and D1 and confirmed as meeting eligibility before dosing.
- K. At a minimum, blood urea nitrogen, creatinine, chloride, potassium, and sodium should be collected.
- L. Liver function tests will include alkaline phosphatase, ALT, AST, and total bilirubin.
- M. Hepatitis B surface antigen, antibodies to hepatitis B core, and antibodies to hepatitis C are to be assessed. If hepatitis C serology is positive, hepatitis C virus RNA test by polymerase chain reaction is required to confirm hepatitis C infection.
- N. Scheduling is determined by date of most recent ECHO/MUGA. Not required at EOT visit if an ECHO or MUGA scan was done on study treatment within the previous 12 weeks (excluding the Screening/Baseline assessment).
- O. From time of informed consent.
- P. The safety reporting period for all AEs and SAEs is from study Cycle 1 Day 1 (predose) through 30 days after the last dose of study intervention. SAEs and non-serious AEs will be followed until significant changes return to baseline, the event stabilizes or is no longer considered clinically significant by the investigator, or the participant dies or withdraws consent. All treatment-related SAEs that occur after the safety reporting period should be reported (see Section 7.7.1.3).
- Q. Concomitant medications given for treatment-related SAEs should be recorded.
- R. Participant should complete questionnaires prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days. Questionnaires will be completed at baseline, D1 of cycle 2, 3, 4, and then every 2 cycles.
- S. Applies to first follow up visit only
- T. Cycles 2-6

		Screening/Baseline ^A	Every 21- Day Cycle	C1, C2	Every 9 Weeks, Starting at C1D1	Every 27 Weeks, Starting at C1D1	Every 12 Weeks	EOT	F/U
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- U. Samples will be collected where permitted as per local regulations.
- V. Cycle 3 Day 1 predose only
- W. For participants who discontinue treatment due to progressive disease as defined by RECIST v1.1 or discontinue treatment for any other reason (eg, toxicities).
- X. Not required if conducted 4 weeks prior to EOT.
- Y. Only required if participants ended study treatment for reasons other than RECIST-PD. All types of tumor assessments will be collected as per the previous schedule, as defined by the C1D1 assessment date, if not yet progressed by RECIST, and will continue until RECIST-PD.
- Z. Contrast-enhanced brain MRI is required for all participants at screening and at end of treatment and is to be repeated only for participants with a history of, or baseline, brain metastasis every 9 weeks. For participants without a history of, or baseline, brain metastasis, contrast-enhanced brain MRI is to be repeated every 27 weeks (~6 months). Additional contrast MRIs of the brain may be performed as clinically appropriate.
- AA. Assessments performed as a part of standard care prior to signed informed consent may be used for baseline disease evaluation if they were completed within the 28-day screening window.
- BB. Bone scans will be required at screening only for participants with known or suspected bone metastases at baseline and are to be repeated every 27 weeks (± 21 days). Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. Positron emission tomography (PET)-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study.
- CC. May be either an in-person assessment, contact by telephone, or review of publicly available information (if reasonable efforts to contact the participant are unsuccessful).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncologists
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BICR	Blinded Independent Central Review
BID	twice a day
CAP	College of American Pathologists
CBC	complete blood count
CFR	Code of Federal Regulation
CHF	congestive heart failure
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DCC	Data Coordinating Center
DDI	drug-drug interaction
DFS	disease-free survival
DILI	drug-induced liver injury
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
E-DMC	External Data Monitoring Committee
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality-of-life questionnaire

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EOT	end of treatment
CCI	
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	gastrointestinal
HER2+	human epidermal growth factor receptor 2-positive
HIV	Human immunodeficiency virus
HR	hazard ratio
HR-	hormone receptor-negative
HR+	hormone receptor-positive
HRQoL	health-related quality of life
HRT	hormone replacement therapy
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IND	investigational new drug
IP	investigational product
IRB	institutional review board
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
LAM	lactational amenorrhea method
LC	liquid chromatography
LFT	liver function test
LMD	leptomeningeal disease
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median overall survival
mPFS	median progression-free survival

MQI	medically qualified individual
MRI	magnetic resonance imaging
MS	mass spectrometry
MUGA	multiple-gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	Progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	orally
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRO	Patient reported outcome
PSSA	Pfizer SAE submission assistant
QTc	corrected QT intervals
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SoE	schedule of events
SOP	standard operating procedure
SRS	stereotactic radiosurgery
SRSD	single reference safety document
SRT	stereotactic radiation therapy
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitors
T-DM1	ado-trastuzumab emtansine
TTP	time to progression

ULN	upper limit of normal
US/USA	United States
VAS	visual analog scale
WBRT	whole brain radiation therapy
WOCP	women of childbearing potential

1. INTRODUCTION

1.1. HER2+ Breast Cancer

Breast cancer is the most common form of cancer in women worldwide, the second leading cause of cancer-related death in the US (Siegel 2020), and the fourth leading cause of cancer-related death globally (Sung 2021). The estimated number of new patients diagnosed in the US with breast cancer for 2018 is 266,120, among whom 40,920 will die due to the disease (Siegel 2018). Approximately 15% to 22% of breast cancers overexpress HER2 (Howlander 2014; Parise 2014; American Cancer Society (ACS) 2018). HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and, prior to the advent of HER2-directed therapy, were associated with poorer overall survival (OS) compared to HER2-negative cancers (Slamon 1987).

1.1.1. Treatment of Early and First-Line Advanced HER2+ Breast Cancer

The introduction of HER2-targeted therapy using either antibody-based therapies or small molecule tyrosine kinase inhibitors (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the neoadjuvant/adjuvant and metastatic settings (Slamon 2001; Geyer 2006; Baselga 2012; Verma 2012). The current standard of care for most patients with HER2+ metastatic disease in the first-line (1L) setting is pertuzumab plus trastuzumab and a taxane, based on results of the pivotal CLEOPATRA study (Baselga 2012; Giordano 2014). Given the multiple HER2-targeted agents now available in the early breast cancer setting, it is expected that patients with recurrent disease will already have exposure to pertuzumab and/or trastuzumab, and a subset may have had exposure to ado-trastuzumab emtansine (T-DM1) and/or a TKI. The modern population with HER2+ advanced breast cancer therefore may be markedly different from that enrolled in CLEOPATRA.

1.1.1.1. Trastuzumab

The first FDA-approved HER2-targeted therapy for advanced HER2+ breast cancer was trastuzumab (Herceptin®), a humanized anti-HER2 monoclonal antibody (mAb) that binds to the HER2 extracellular domain. In a pivotal, phase 3 study, the safety and efficacy of trastuzumab in combination with chemotherapy (anthracycline plus cyclophosphamide or paclitaxel) versus chemotherapy alone were evaluated as 1L treatment for HER2+ metastatic breast cancer. Results from 469 patients showed that the addition of trastuzumab improved time to progression (TTP) significantly (7.6 versus 4.6 months, $P=0.0001$) compared with chemotherapy alone. Median follow-up of 29 months revealed a significantly increased median survival in participants receiving trastuzumab plus chemotherapy compared with those receiving chemotherapy alone (25.4 versus 20.3 months, $P<0.025$) (Eiermann 2001).

1.1.1.2. Pertuzumab

The next approved anti-HER2 mAb was pertuzumab (Perjeta®), which binds to the HER2 receptor at a site different from trastuzumab. It was approved in combination with trastuzumab and docetaxel as 1L therapy for patients with metastatic disease (Swain 2015). This current 1L standard is based upon data demonstrating a significant improvement in OS

in the CLEOPATRA study as initial therapy in the metastatic setting, where median OS was 56.5 months (95% CI: 49.3, not reached) in the pertuzumab + trastuzumab + docetaxel combination group versus 40.8 months (95% CI: 35.8, 48.3) in the trastuzumab + docetaxel group (hazard ratio [HR]=0.68) (Swain 2015). Of interest, in the pertuzumab arm, the median number of docetaxel cycles was 8, whereas the median number of study treatment cycles was 24. In the majority of patients in whom docetaxel was stopped but mAb was continued once 6 cycles was reached, the reason for this decision was “standard practice” or “adequate therapy.” In patients receiving more than 6 cycles of docetaxel, the vast majority still discontinued chemotherapy while mAb continued, though in these patients, “AE/intercurrent illness” was more commonly the reason (Miles 2017). This pattern of dropping taxane after an “induction” phase and continuing mAb therapy in a “maintenance” phase was also seen in the subsequent open-label single-arm 1L PERUSE study, in which the median number of chemotherapy cycles was 6 and the median number of study treatment cycles was 24 (Bachelot 2019). Despite the even lower chemotherapy exposure in PERUSE, the median OS was 65.3 months (95% CI: 60.9-70.9 months), similar to that seen in the CLEOPATRA study (Miles 2017).

1.1.2. Optimizing Treatment in the First-Line Metastatic Setting by Maintenance Therapy

The CLEOPATRA study profoundly impacted the up-front management of participants with HER2+ advanced breast cancer and set the current standard of care as trastuzumab, pertuzumab, and taxane. Ultimately however, most patients experienced progression on maintenance therapy, with a median progression free survival (mPFS) of 18.7 months (Swain 2015). Further extending the time to progression, including in the central nervous system (CNS), with a biologic-only regimen could offer the opportunity to prolong survival while maintaining quality of life.

Since the CLEOPATRA study the treatment landscape in the neoadjuvant/adjuvant setting has changed. Whereas only approximately 10% of participants enrolled in CLEOPATRA received prior trastuzumab, trastuzumab-based chemotherapy is now the standard approach to HER2+ breast cancer in the neoadjuvant/adjuvant setting. Pertuzumab and T-DM1 are also now established in the neoadjuvant/adjuvant and residual disease adjuvant settings, respectively, and neratinib is an option for some patients in an extended adjuvant setting. Among trastuzumab-exposed patients, lower mPFS was observed both in the 1L CLEOPATRA and PERUSE studies, and lower mOS was observed in PERUSE. Further optimizing 1L therapy, including de-novo metastatic breast cancer (mBC) as well as for patients previously treated with HER2-targeted agents, remains an unmet medical need.

Perhaps the greatest unmet medical need in the post-trastuzumab era is treatment and prevention of brain metastases. Recent data suggest that the incidence of first relapse occurring in the brain is increasing in patients who have received trastuzumab-based adjuvant therapy (Clayton 2004) and up to 50% of patients with HER2+ metastatic disease will develop brain metastases (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013). The increasing prevalence of brain metastases in patients with HER2+ breast cancer may be due to several factors (Lin 2004). First, HER2+ breast cancer appears to display tropism for the brain. Second, with better control of non-CNS disease, patients may be living

longer, allowing brain metastases to become more of a critical clinical issue. Finally, the brain may represent a sanctuary site for HER2+ disease, as large molecules such as trastuzumab and pertuzumab may not penetrate the blood-brain barrier to any meaningful extent at approved doses. The evidence suggests that drug blood-brain barrier permeability is most likely a function of not only P-glycoprotein (P-gp) expression but also the interplay of molecule size, charge, lipophilicity, tumor neovasculature anatomy, and plasma protein binding ([Gerstner 2007](#)).

Treatment options for brain metastases are limited, but include surgical resection, radiosurgery, and/or whole brain radiotherapy in addition to continuation of systemic anti-HER2 therapy. Unfortunately, these local treatments often result in significant morbidity. Stereotactic radiosurgery (SRS) has been increasingly used to avoid the neurologic toxicities of whole brain radiotherapy but the trade-off for this decrease in toxicity has been inferior control of brain relapse outside of the radiation fields ([Chang 2009](#); [Brown 2016](#); [Kaidar-Person 2016](#)). Approved systemic therapies with CNS efficacy are needed in the 1L mBC setting. The presence of CNS metastases is a negative prognostic factor dramatically impacting the quality of life of these patients. Data from retrospective studies suggest that the incidence of brain metastases in patients with HER2+ disease ranges from 21% to 50% ([Clayton 2004](#); [Goldhirsch 2013](#); [Lin 2013](#); [Pestalozzi 2013](#)).

The current HER2+ breast cancer population treated in the 1L setting with taxane, trastuzumab, and pertuzumab and exposed to HER2-targeted agents in the early breast cancer setting has been shown to have a shorter mPFS as compared to the original results from the CLEOPATRA trial ([Miles 2021](#)). With the increased use of effective therapy for early-stage disease, cure rates have increased and contemporary patients with relapsed metastatic disease are likely to have already been exposed to 1 or more HER2-targeted therapies. Patients treated with taxane, trastuzumab, and pertuzumab as treatment of *de novo* mBC also remain with unmet need as they will ultimately experience disease progression of their cancer. The goal of this study is to update the CLEOPATRA regimen to better address the needs of a modern 1L mBC population.

1.2. Tucatinib

Tucatinib (ONT-380) is an orally available, reversible HER2 small molecule TKI. Following tucatinib's initial approval in combination with trastuzumab and capecitabine in previously treated advanced HER2+ breast cancer, clinical trials are ongoing to examine the safety and efficacy of tucatinib when combined with other anti-HER2 therapies.

One of the key features of tucatinib is its potency and selectivity for HER2 compared to the closely related kinase epidermal growth factor receptor (EGFR). With a >1000-fold increase in potency for HER2 inhibition compared to EGFR, tucatinib has the potential to inhibit HER2 signaling while avoiding known EGFR-related side effects (eg, severe skin rash and gastrointestinal [GI] toxicity). This unique feature differentiates tucatinib from other HER2 inhibitors, including neratinib and lapatinib, which inhibit HER2 and EGFR with similar potency and have been associated with side effects associated with EGFR inhibition.

A complete summary of the clinical and nonclinical data relevant to the study treatment and its study in human patients is provided in the Investigator's Brochure.

1.3. Rationale for Use of Tucatinib in Combination with Trastuzumab and Pertuzumab

Tucatinib has demonstrated improvement in mPFS and mOS in advanced HER2+ breast cancer previously treated with trastuzumab and pertuzumab. This study is intended to extend 1L therapy by adding a TKI to dual anti-HER2 mAb therapy to improve overall disease control. Tucatinib is a promising candidate TKI based on the results of the pivotal HER2CLIMB study, in which risk of overall progression or death was reduced with the addition of tucatinib to trastuzumab and capecitabine (HR=0.54; 95% CI: 0.42-0.71) ([Lin 2020](#); [Murthy 2020](#)). Importantly, mOS was improved with the addition of tucatinib (HR=0.66; 95% CI: 0.50-0.88) ([Murthy 2020](#)).

Available safety and response data with tucatinib in absence of chemotherapy support the strategy of combining TKI with anti-HER2 mAb, or in the present study, with dual anti-HER2 mAb. Tucatinib was initially evaluated in a phase 1 monotherapy dose-escalation study in HER2+ advanced solid tumors (ARRAY-380-101; NCT00650572) ([Moulder 2017](#)), followed by a subsequent phase 1b clinical trial evaluating the combination of tucatinib with capecitabine and/or trastuzumab in advanced HER2+ mBC with and without brain metastases (ONT-380-005; NCT02025192) ([Murthy 2018](#)). Both studies demonstrated a lower incidence and severity of diarrhea and rash with tucatinib than that typically associated with dual HER2/EGFR inhibitors as well as notable antitumor activity in heavily pretreated patients. Among the 18 patients treated with tucatinib and trastuzumab in ONT 380-005 (all at 300 mg PO twice a day [BID]), there was a 40% objective response rate, and 40% stable disease rate observed.

Resistance to anti-HER2 mAb can result both during sustained HER2 inhibition and HER2 signal reactivation through a variety of mechanisms, including acquisition of HER2 mutations, variants, increased activity of the other HER2-family tyrosine kinases, and activation of HER2 by other receptor tyrosine kinases. TKIs can be effective where anti-HER2 mAb no longer are ([Schiff 2021](#)). In a highly HER2-amplified, trastuzumab-resistant breast cancer xenograft model (SUM190), tucatinib in combination with trastuzumab and pertuzumab provided greater tumor inhibition than trastuzumab and pertuzumab alone ([O'Brien 2019](#)).

Patients with HER2+ brain metastases have a worse prognosis relative to those without CNS disease, and improvements in therapy options for these patients, in particular, are needed. Beyond the broadest goal of extending overall disease control in the 1L setting, the present study aims to address a growing segment of patients with HER2+ breast cancer with brain metastasis as an early site of relapse. In population-based registries of patients with HER2+ mBC enrolled at diagnosis, presence of brain metastases is associated with a shortened survival relative to absence of brain metastases ([Brufsky 2011](#)). Among the 377 patients in the registHER study with brain metastases, median OS from the date of initial mBC diagnosis was 26.3 months (range: 1.0 to 60.9 months) compared to 44.6 months (range: 0.5 to 59.7 months) in the 635 participants who did not have brain metastases ([Brufsky 2011](#)).

Prevalence of brain metastasis in the 1L setting varies widely in observational studies, from 37.3% in the registHER study which enrolled from 2003-2006, to 8.9% in the SystHERs study which enrolled from 2012-2016 (Brufsky 2011; Tripathy 2014). Development of new brain metastasis in these studies was 30% and 21.7%, respectively, and ~15% in the pertuzumab arm of the CLEOPATRA study. In the early breast cancer studies KATHERINE and APHINITY, despite higher cure rates, among participants developing distant relapse, 56% and 35% had CNS as a first site of metastasis, respectively (von Minckwitz 2017; von Minckwitz 2019). Given this high prevalence at first relapse in these 2 trials, it is suggestive that agents with demonstrated CNS activity in HER2+ breast cancer may be optimally used by incorporating them into 1L regimens. In HER2CLIMB participants with brain metastasis, the risk of progression or death was reduced by 52% (HR=0.48; 95% CI, 0.34-0.69) (Murthy 2020). At median follow-up of 29.6 months (range, 0.1-52.9 months), median OS was 9.1 months longer in the tucatinib combination (tucatinib + trastuzumab + capecitabine) group (21.6 months; 95% CI: 18.1-28.5) vs the placebo combination group (12.5 months; 95% CI: 11.2-16.9). The tucatinib combination group showed greater clinical benefit in CNS-PFS and intracranial objective response rate compared with the placebo combination group. The duration of cranial response was 8.6 months (95% CI: 5.5-10.3 months) in the tucatinib combination group and 3.0 months (95% CI: 3.0-10.3 months) in the placebo combination group. Risk of developing new brain lesions as the site of first progression or death was reduced by 45.1% in the tucatinib combination group vs the placebo combination group (hazard ratio, 0.55 [95% CI: 0.36-0.85]) (Lin 2022). Incorporating tucatinib after completion of taxane might improve clinical efficacy while minimizing safety and quality of life concerns.

1.4. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tucatinib may be found in the Investigator's Brochure.

1.4.1. Risk Assessment

Clinical data from the pivotal HER2CLIMB clinical trial showed that the addition of tucatinib to trastuzumab and capecitabine resulted in a comparable safety profile to trastuzumab and capecitabine alone. Discontinuation of tucatinib or placebo due to treatment emergent adverse events (TEAEs) was infrequent (5.7% and 3.0%, respectively). These events were mostly Grades 1 and 2 and were manageable with dose modifications and treatment with antidiarrheals.

Hepatotoxic events have been observed in clinical tucatinib studies, but these events and laboratory abnormalities were primarily Grades 1 and 2, transient, asymptomatic, reversible, and manageable with dose modification. Furthermore, SGNTUC-020 demonstrated tucatinib had no effects on renal function, and elevations of serum creatinine are the result of tucatinib inhibiting kidney transporters responsible for renal secretion of creatinine.

Based on the overlapping toxicities of the study drugs, diarrhea is expected to potentially increase with the combination of pertuzumab and tucatinib. However, this is expected to be primarily low grade and manageable with standard anti-diarrheal agents and supportive care.

Based on findings from animal studies and its mechanism of action, tucatinib may cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of this potential risk to a fetus, and participants of childbearing potential must use effective contraception during treatment until the end of systemic exposure (Section 4; Appendix C).

The following risk mitigation measures will be employed to ensure safety of participants in this trial:

- Formation of an external data monitoring committee (E-DMC) to monitor safety of tucatinib in combination with trastuzumab and pertuzumab in participants.
- Early evaluation by the E-DMC after enrollment of approximately 30 participants who receive at least 2 full cycles of study treatment.
- Identification of AEs, and implementation of preventative mitigation measures for each, when appropriate (see Section 5.4), that are informed by prior clinical trials.

1.4.2. Benefit Assessment

Overall, tucatinib has been associated with an acceptable safety profile and has demonstrated both single-agent and combination anti-tumor activity, including in patients with progression after multiple prior HER2-directed therapies, and in patients with either untreated or previously radiated brain metastases.

Importantly, clinical data from HER2CLIMB showed that the addition of tucatinib to trastuzumab and capecitabine reduced the risk of disease progression or death by 46% in the primary analysis population, comprised of heavily pretreated participants with advanced HER2+ breast cancer. Tucatinib reduced the risk of disease progression or death by 52% in participants with brain metastasis. Tucatinib also reduced the risk of death by 34% in the overall population in this study.

1.4.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with tucatinib are justified by the anticipated benefits that may be afforded to participants with advanced HER2+ breast cancer.

2. OBJECTIVES

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of tucatinib in combination with trastuzumab and pertuzumab as maintenance therapy in participants with advanced HER2+ breast cancer. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and Corresponding Endpoints

Primary Objective	Corresponding Primary Endpoint
Compare PFS by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms	PFS, defined as the time from randomization to investigator-assessed documented disease progression per RECIST v1.1, or death from any cause, whichever occurs first
Key Secondary Objective	Corresponding Key Secondary Endpoint
Compare OS between treatment arms	OS, defined as the time from randomization to death from any cause
Other Secondary Objectives	Corresponding Secondary Endpoints
Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1	PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST v1.1), or death from any cause, whichever occurs first
Assess the change in health-related quality of life (HRQoL)	Time to deterioration of HRQoL, defined as time to 10-point decrease in the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30)
Evaluate PFS in the brain	CNS-PFS, defined as the time from randomization to investigator-assessed disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first
Evaluate the safety and tolerability of tucatinib in combination with trastuzumab and pertuzumab	- AEs - Clinical laboratory assessments - Incidence of dose holding, dose reductions, and discontinuations of tucatinib - Incidence of dose holding and discontinuations of trastuzumab - Incidence of dose holding and discontinuations of pertuzumab
Evaluate the PK of tucatinib	Plasma concentrations of tucatinib
Exploratory Objectives	Corresponding Exploratory Endpoints
CCI	

Table 1: Objectives and Corresponding Endpoints

CCI	
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3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and pertuzumab as maintenance therapy in participants with advanced HER2+ breast cancer who have had prior treatment with a taxane, trastuzumab, and pertuzumab. After signing informed consent and meeting all eligibility criteria, participants will be randomized in a 1:1 ratio to receive 21-day cycles of treatment in 1 of the following 2 treatment groups:

- Control arm: Placebo given PO BID plus trastuzumab and pertuzumab every 21 days
- Experimental arm: Tucatinib 300 mg PO BID plus trastuzumab and pertuzumab every 21 days

Trastuzumab and pertuzumab will be administered as follows:

- Trastuzumab will be given intravenously (IV) at a dose of 6 mg/kg or subcutaneously (SC) at a fixed dose of 600 mg, once every 21 days.

AND

- Pertuzumab will be given IV at 420 mg every 21 days.

OR

- Fixed dose combination of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase will be given SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.

Trastuzumab and pertuzumab will be supplied in an open-label manner by the sponsor, where required. If supplied by the sponsor, the provided intervention and formulation must be utilized. Randomization will be stratified by diagnosis (*de novo* versus recurrent), hormone receptor status (positive versus negative), and presence or history of brain metastases (yes versus no).

Tucatinib or placebo will be dispensed to participants in a double-blinded manner. Cycles will be planned to be 21 days in length, with dispensation of tucatinib or placebo planned for Day 1 of each cycle (see [Schedule of Events](#) and Section 5.4). Study treatment will continue until unacceptable toxicity, disease progression (ideally verified radiologically per RECIST v1.1), withdrawal of consent, or study closure. No crossover from placebo to tucatinib will be allowed.

Disease response per RECIST v1.1 ([Eisenhauer 2009](#)) will be assessed by both investigator and BICR (Section 7.3). Treatment decisions will be made based upon local radiologic assessment. Response assessments for each participant will continue until disease progression per RECIST v1.1 by investigator assessment has been documented, or end of treatment (EOT), whichever is later. Survival and other follow-up assessments will continue until study closure or withdrawal of consent.

Safety will be monitored on an ongoing, blinded basis by the sponsor throughout the study. An E-DMC will regularly review all relevant unblinded safety data as outlined in a separate IDMC charter. After approximately 30 participants are randomized and have received at least 2 full cycles of study treatment, the E-DMC will convene to review safety data. Enrollment will continue during the initial safety assessment of these 30 participants. Ad hoc meetings of the E-DMC may be held upon the request of the sponsor or E-DMC.

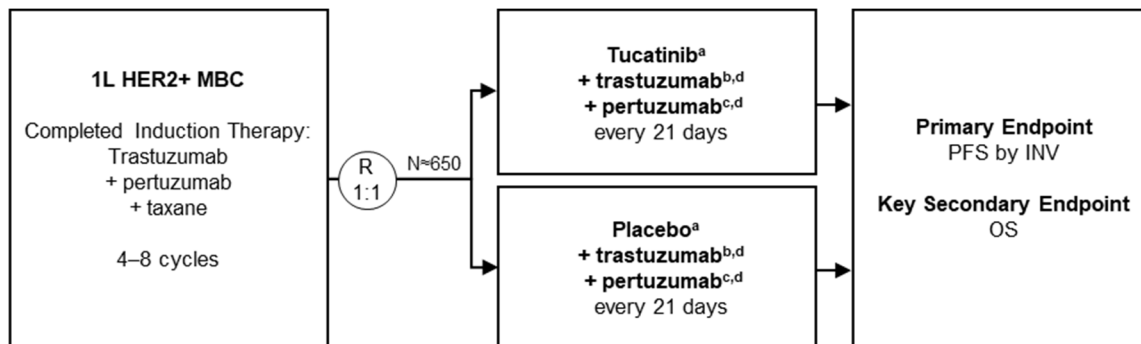
Blood samples for PK assessment of trough tucatinib drug concentrations will be collected in all participants on Day 1 of Cycles 2 to 6, prior to administration of tucatinib. CCI

Plasma concentrations of tucatinib will be determined using validated liquid chromatography (LC)-mass spectrometry (MS)/MS methods. Additional analytes may be evaluated as necessary. PK parameters will be summarized using descriptive statistics.

Health-related QoL will be assessed at protocol-specified time points using standardized assessment tools including the CCI instrument and the EORTC QLQ-C30.

Approximately 650 participants (approximately 325 participants per treatment arm) will be randomized in this study. See Figure 1 for study schema. A Schedule of Events is also provided.

Figure 1: Study design schema



1L = first-line, MBC = metastatic breast cancer, OS = overall survival, PFS = progression-free survival

Single-agent endocrine therapy (with or without ovarian suppression) is allowed during the study treatment (see also Section 5.6.2)

a See Section 5.3.1.3 for dosing instructions.

b See Section 5.3.2.3 for dosing instructions and options.

c See Section 5.3.3.3 for dosing instructions and options.

d See Section 5.3.4.3 for dosing instructions and options.

3.1.1. Continuation on Study Treatment After CNS--Only Progression

If a participant is found to have radiographic progressive disease per RECIST v1.1 based on isolated progression in the CNS (including either parenchymal brain or dural metastases but not skull base or leptomeningeal metastases) without progression of disease outside the CNS, the participant may be eligible to continue on study interventions after completion of local

treatment (radiotherapy or surgery) of the brain/dural metastases to allow for clinical benefit. Such participants with isolated parenchymal brain or dural metastases who are eligible to continue study treatment will be considered to have RECIST-PD (contributing to the primary endpoint). Continuation of study treatment requires discussion with and documented approval from the study medical monitor and may continue until either systemic progression or a second isolated CNS progression. The participant will remain on the same treatment regimen that they were receiving prior to receipt of CNS-directed therapy, and may continue on study provided the following criteria are met and the participant continues to receive clinical benefit:

- The participant is not experiencing any worsening of cancer-related symptoms. Participants who are clinically deteriorating and unlikely to receive further benefit from continued treatment should discontinue study treatment.
- The participant is tolerating study intervention
- Approval by the medical monitor
- Participant has no evidence of unequivocal systemic progression
- Participant has not had a previous isolated CNS progression while on study

Study treatment may be held up to 6 weeks to allow local CNS therapy. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued. Oral study interventions (tucatinib/placebo) are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib is unknown. Trastuzumab/pertuzumab are not known to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study interventions may be re-initiated 7 days or more after completion of SRS/stereotactic radiation therapy (SRT), 14 days or more after whole brain radiation therapy (WBRT) and 28 days or more after surgical resection. CCI

[REDACTED]

Because the primary endpoint of the study is PFS (reached in individual participants by overall RECIST-PD), every effort should be made to avoid radiation and/or surgery to target lesions in the brain in the absence of progressive disease by RECIST v1.1 (eg, for symptoms but without RECIST-PD). Target lesions, once treated with local CNS therapy, cannot be adequately assessed for subsequent response to systemic therapy.

CCI

[REDACTED]

3.1.2. External Data Monitoring Committee

The E-DMC will be responsible for monitoring the safety of participants in the study at regular intervals. The E-DMC will review unblinded data including deaths, discontinuations, dose reductions, AEs, and serious adverse events (SAEs) on a regular basis. The E-DMC will

make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or modification, or early discontinuation of the study for excessive toxicity. A separate E-DMC Charter will outline the committee's composition, members' roles and responsibilities, and describe E-DMC procedures. The sponsor will communicate each E-DMC overall recommendation to the investigators.

3.1.3. Stopping Criteria

Reasons for prematurely terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants, either through a safety review by the sponsor or an independent safety assessment by the E-DMC.
- Participant enrollment is unsatisfactory.
- Sponsor discretion

3.1.4. End of Study

The study will end after the last visit of the last patient. It is estimated that this will occur ~5 years after the first participant is enrolled and after the final OS analysis is completed. In addition, the sponsor may terminate the study at any time (see Section 10).

3.1.5. Retreatment

In the event that all study treatment has been discontinued, no component may be resumed.

3.2. Discussion and Rationale for Study Design

3.2.1. Method of Assigning Participants to Treatment Groups

Following informed consent and screening assessments, participants will be randomly assigned to study treatment in a 1:1 ratio. Randomization will be performed centrally using a stratified permuted block randomization method. Randomization procedures are detailed in the Study Manual.

Randomization will be stratified by:

- Diagnosis: *de novo* versus recurrent
- Hormone receptor status: negative versus positive
- Presence or history of brain metastases: yes versus no

3.2.2. Rationale for Selection of Doses

3.2.2.1. Tucatinib

In the pivotal HER2CLIMB study (ONT-380-206) in participants with HER2+ mBC, the combination of tucatinib 300 mg PO BID with trastuzumab and capecitabine was found to be well tolerated, with a manageable safety profile. The most frequent AEs included diarrhea (80.9% in the tucatinib, trastuzumab, and capecitabine arm versus 53.3% in the placebo,

trastuzumab, and capecitabine arm), palmar-plantar erythrodysesthesia (PPE) syndrome (63.4% versus 52.8%), nausea (58.4% versus 43.7%), fatigue (45.0% versus 43.1%), and vomiting (35.9% versus 25.4%). Elevated liver function test (LFT) AEs were observed, with all grade aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin elevations reported in 21.3%, 20.0% and 18.6% of participants in the experimental arm, respectively, and 11.2%, 6.6%, and 10.2% in the control arm. Grade ≥ 3 AEs included PPE syndrome (13.1% versus 9.1%), diarrhea (12.9% versus 8.6%), increased AST (4.5% versus 0.5%), increased ALT (5.4% versus 0.5%), and increased bilirubin (0.7% versus 2.5%).

The Phase 1b studies ONT-380-004 and ONT-380-005 evaluated the safety of tucatinib 300 and 350 mg PO BID in combination with T-DM1 and trastuzumab/capecitabine, respectively, in participants with HER2+ mBC. Both studies determined the recommended tucatinib clinical dose to be 300 mg PO BID.

In the 18 participants in ONT-380-005 who received tucatinib 300 mg BID plus trastuzumab, the most frequent AEs were diarrhea (56% of 18 participants), nausea (33%), constipation (28%), and arthralgia, vomiting, and dizziness (22% each). No Grade ≥ 3 AEs occurred in more than 1 participant. All grade AST, ALT, and bilirubin laboratory abnormalities reported in 67%, 44%, and 22%, respectively. There were no Grade ≥ 3 LFT laboratory abnormalities.

In the tucatinib plus trastuzumab and capecitabine cohort, the most frequent AEs were diarrhea (74% of 27 participants), nausea (78%), PPE syndrome (67%), vomiting (52%), and fatigue (44%). Grade ≥ 3 AEs occurring in $>10\%$ of participants were fatigue (15%), and diarrhea and PPE syndrome (11% each). All grade AST, ALT, and bilirubin laboratory abnormalities were reported in 89%, 78%, and 52% of participants, respectively. Grade ≥ 3 LFT laboratory abnormalities were reported in 2 participants (7%) each.

Based on these studies, the proposed starting dose of tucatinib combined with trastuzumab is 300 mg BID.

3.2.2.2. Trastuzumab

Trastuzumab will be administered every 3 weeks at the dose and schedule specified in the trastuzumab label for treatment of participants with advanced breast cancer. Given that participants will have already started this prior to randomization, no loading dose is planned while on the study.

3.2.2.3. Pertuzumab

Pertuzumab will be administered every 3 weeks at the dose and schedule specified in the pertuzumab label for treatment of participants with advanced breast cancer. Given that participants will have already started this prior to randomization, no loading dose is planned while on the study.

3.2.2.4. Trastuzumab + Pertuzumab

A fixed dose combination of trastuzumab + pertuzumab (pertuzumab, trastuzumab, and hyaluronidase) will be administered SC every 3 weeks at the dose and schedule specified in

the trastuzumab + pertuzumab label for treatment of participants with advanced HER2+ breast cancer.

3.2.3. Blinding and Unblinding

The study will be double-blinded, and every attempt will be made to maintain the blind throughout the study. Participants and their caregivers will be blinded to their assigned study intervention. Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The investigator, study center personnel, clinical research organization staff, and sponsor personnel (except for pre-specified Safety personnel) will not have access to the randomization scheme during the study except in the case of an emergency. Safety data will be monitored by an E-DMC. Suspected unexpected serious adverse reactions (SUSARs) will be unblinded in accordance with local regulatory reporting requirements.

As per local regulatory reporting requirements, the sponsor Safety Department will unblind the identity of study medication for any unexpected (as per the reference safety information) SAEs that are considered to be related to the blinded study intervention (tucatinib/placebo). All other sponsor personnel will remain blinded. Please see study binders for further detail regarding unblinding procedures.

In the case of a concerning intervention related safety event, it is recommended that the Investigator contact and consult with the Medical Monitor. In emergency situations related to the safety of the patient, the Investigator may break the treatment code immediately, or as quickly as possible if they find it is in the best interest of the trial participant. The investigator has unrestricted and immediate access to break the treatment code through the IRT system. The investigator will not provide the sponsor with the results of the unblinding. In the event of any unblinding, the sponsor must be notified within 1 working day (if not involved in the unblinding decision). The participant must subsequently be discontinued from study treatment but should continue in the long-term follow-up period of the study.

Unblinding for ongoing safety monitoring and risk/benefit assessment by the E-DMC, will be performed through an independent Data Coordinating Center (DCC) to ensure integrity of the study.

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variable is considered sensitive clinical data: study intervention PK concentrations.

4. STUDY POPULATION

Participants must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator or sponsor and are participant to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1. Inclusion Criteria

1. Have centrally confirmed HER2+ breast carcinoma according to the 2018 American Society of Clinical Oncologists (ASCO)-College of American Pathologists (CAP) guidelines prior to randomization (defined as a 3+ score on immunohistochemistry (IHC) and/or 2+ IHC and concurrent positive by ISH).
 - a. Tissue blocks or tumor slides must be submitted and confirmed as HER2+ by a sponsor-designated central laboratory prior to randomization.
2. Have unresectable locally advanced or metastatic (hereafter referred to as “advanced”) disease; if recurrent (after [neo]adjuvant therapy), there must be a minimum 6-month treatment-free interval from any trastuzumab and pertuzumab received in the early breast cancer setting to the diagnosis of advanced HER2+ disease. Prior standard of care therapy for early breast cancer is permitted (eg, prior T-DM1); however, Exclusion Criterion 1 should be noted.
3. Have received 4-8 cycles of pre-study induction therapy including only trastuzumab, pertuzumab, and taxane as first-line of therapy for the treatment of advanced breast cancer prior to study enrollment. Participants are eligible provided they are without evidence of disease progression (per investigator judgement, ie, CR, PR, or SD) following completion of induction therapy.
 - a. Participants receiving <6 cycles (ie, 4-5 cycles) of taxane are only eligible if the taxane was stopped early due to intolerable toxicity (eg, documented neuropathy impacting function).
 - b. Participants are permitted to receive trastuzumab and pertuzumab for 2 additional cycles (after completion of chemotherapy) to allow completion of screening procedures. Study treatment should begin within 6 weeks ($\pm$ 3 days) from the start of the last cycle of trastuzumab and pertuzumab.
 - c. Participants are permitted to receive up to 2 cycles of carboplatin during the start of induction therapy in combination with trastuzumab, pertuzumab, and taxane (eg, to obtain confirmation of metastatic breast cancer diagnosis).
 - d. Participants who received traditional medications (eg, traditional Chinese medication) and/or supplements with potential anti-cancer effects during induction therapy will remain eligible if they discontinue these treatments at least 4 weeks prior to the start of study treatment.
4. Known hormone receptor status (per local guidelines; may be hormone receptor positive [HR+] or negative [HR-])

5. Be at least 18 years of age, and legally an adult at time of consent and $\geq$ the age of majority per regional requirements
6. Have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
7. Have adequate hepatic function as defined by the following:
 - a. Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), except for participants with known Gilbert's disease who may enroll if the conjugated bilirubin is $\leq 1.5 \times$ ULN
 - b. Transaminases (AST/serum glutamic oxaloacetic transaminase [SGOT] and ALT/serum glutamic pyruvic transaminase [SGPT]) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN if liver metastases are present)
8. Have adequate baseline hematologic parameters as defined by:
 - a. Absolute neutrophil count (ANC) $\geq 1 \times 10^3/\mu\text{L}$
 - b. Platelet count $\geq 100 \times 10^3/\mu\text{L}$
 - c. Hemoglobin ≥ 9 g/dL
 - d. In participants receiving any transfusion before study entry, the above hematologic parameters must be met in absence of any transfusion for ≥ 14 days prior.
 - e. In participants receiving growth factors before study entry, the above hematologic parameters must be met in absence of relevant growth factor use for ≥ 14 days prior.
9. Have a serum or plasma creatinine $\leq 1.5 \times$ institutional ULN.
10. Have left ventricular ejection fraction (LVEF) $\geq 50\%$ as assessed by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment.
11. For participants of childbearing potential, the following stipulations apply:
 - a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β -hCG]) result within 7 days prior to the first dose of study treatment. A participant with a false positive result and documented verification that the participant is not pregnant is eligible for participation. Documentation must include either an ultrasound or repeat pregnancy test to verify the false-positive nature of the pregnancy test.
 - b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study intervention
 - c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through at least 7 months after the final dose of study intervention
 - d. If sexually active in a way that could lead to pregnancy, must consistently use at least 2 acceptable methods of birth control (contraception), at least 1 of which

must be highly effective, as defined in [Appendix C](#), starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention

12. For male participants, the following stipulations apply:

- a. Must agree not to donate sperm starting at the time of informed consent and continuing throughout the study period and for at least 7 months after the final dose of study intervention
- b. If able to father children and sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use at least 2 acceptable methods of birth control (contraception), at least 1 of which must be highly effective, as defined in [Appendix C](#), starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention
- c. Male participants who are sexually active with a person who is pregnant or breastfeeding, must consistently use a male condom, starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study intervention

13. Provide signed informed consent per a consent document that has been approved by an institutional review board or independent ethics committee (IRB/IEC) prior to initiation of any study related tests or procedures that are not part of standard-of-care for the participant's disease

14. Be willing and able to comply with study procedures

15. **CNS Inclusion** – Based on screening contrast-enhanced brain magnetic resonance imaging (MRI), participants may have any of the following:

- a. No evidence of brain metastases
- b. Untreated brain metastases which are asymptomatic not needing immediate local treatment and, if identified on prior brain imaging, without evidence of progression since starting first-line induction therapy with trastuzumab, pertuzumab, and taxane
- c. Previously treated brain metastases which are asymptomatic
 - 1) Brain metastases previously treated with local therapy must not have progressed since treatment
 - 2) Time since whole brain radiation therapy (WBRT) is ≥ 14 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days prior to first dose of study treatment
 - 3) Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

4.2. Exclusion Criteria

1. Have previously been treated with any tyrosine kinase inhibitor targeting HER2 and/or epidermal growth factor receptor (EGFR) including pyrotinib, lapatinib, tucatinib, neratinib, and afatinib (except neratinib if given in extended adjuvant setting and at least 12 months have elapsed from the last neratinib dose to the start of study intervention) or are currently participating in another interventional clinical trial
2. Unable for any reason to undergo contrast-enhanced MRI of the brain
3. History of allergic reactions to trastuzumab, pertuzumab, or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 infusion-related reactions (IRRs) to trastuzumab or pertuzumab that were successfully managed, known allergy to one of the excipients in the study interventions, or hypersensitivity to murine proteins
4. Are positive for Hepatitis B by surface antigen expression, positive for active Hepatitis C infection, or the presence of known chronic liver disease. Participants who have been treated for Hepatitis C infection are permitted if they have documented sustained virologic response of at least 12 weeks, as documented per local guidelines. The latest local guidelines should be followed regarding the testing of Hepatitis B DNA levels by polymerase chain reaction (PCR). Participants with Hepatitis B DNA levels by PCR that require nucleoside analogue or other therapies are not eligible for the trial.
5. Participants known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
 - a. CD4+ T-cell count of <350 cells/ μ L
 - b. Detectable HIV viral load
 - c. History of an opportunistic infection within the past 12 months
 - d. On stable antiretroviral therapy for <4 weeks
6. Are pregnant, breastfeeding, or planning a pregnancy from time of informed consent until 7 months after the final dose of study intervention
7. Have inability to swallow pills or have significant GI disease or surgery which would preclude the adequate oral absorption of medications
8. Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 days prior to first dose of study treatment (see [Appendix D](#) and [Appendix E](#))
9. Have current conditions of symptomatic congestive heart failure, unstable angina pectoris, uncontrolled hypertension, or cardiac arrhythmia or history of myocardial infarction within 6 months prior to randomization
10. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

11. Have evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment
12. Have ongoing $\geq$ Grade 2 toxicity from first line induction therapy (ie, trastuzumab, pertuzumab, and taxane) with the exceptions of alopecia, neuropathy, and nail toxicity
13. Have ongoing $\geq$ Grade 2 diarrhea
14. **CNS Exclusion** – Based on screening brain MRI and clinical assessment, participants must not have any of the following:
 - a. Symptomatic brain metastasis after CNS-directed local therapy
 - b. Progression of brain metastases since starting first line trastuzumab, pertuzumab, and taxane
 - a. Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent). For participants requiring systemic steroids for control of comorbidities (eg, asthma or autoimmune diseases), daily dose must not exceed 2 mg dexamethasone (or equivalent).
 - b. Any untreated brain lesion in an anatomic site which may pose risk to participant (eg, brain stem lesions). Participants who successfully undergo local treatment for such lesions may be permitted to rescreen, if otherwise eligible, after discussion with, and approval by, the medical monitor.
 - c. Known or suspected leptomeningeal disease (LMD) as documented by the investigator
 - c. Poorly controlled (>1 /week) seizures, or other persistent neurologic symptoms despite CNS directed therapy for brain metastasis

4.3. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see [Appendix C](#)) and will confirm that the participant has been instructed in its consistent and correct use.

At time points indicated in the SoE, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of contraception methods as outlined in [Appendix C](#).

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

4.4. Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator judgment will determine childbearing status and study eligibility.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

- Postmenopausal female: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
 - a high FSH level in the postmenopausal range (as per the reference range used by the laboratory) must also be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
 - females on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

4.5. Removal of Participants from Therapy or Assessment

If a participant is withdrawn from study treatment and/or from the study, the reason(s) for withdrawal must be documented in the participant's medical records and case report form (CRF).

4.5.1. Discontinuation of Study Treatment

A participant's study treatment may be discontinued for any of the following reasons:

- Progressive disease (CNS only progressive disease is allowed)
- Adverse event (AE)
- Pregnancy
- Investigator decision, non-AE

- Participant decision, non-AE
- Study termination by sponsor
- Other, non-AE

See the [Schedule of Events](#) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

In the absence of progression:

- participants who discontinue trastuzumab and pertuzumab due to intervention-related toxicity may continue receiving tucatinib/placebo alone.
- participants who discontinue tucatinib/placebo may continue to receive trastuzumab and pertuzumab.
- if a participant discontinues trastuzumab or pertuzumab, they are required to discontinue both.

Tumor assessments should be conducted as per the Schedule of Events until unequivocal evidence of radiologic progression occurs (see [Schedule of Events](#)), as defined in RECIST v1.1. If study treatment is discontinued for reasons other than participant withdrawal of consent or death, participants should continue in long-term follow-up, as per the Schedule of Events, through study termination.

Participants who withdraw consent from the interventional portion will continue to be followed for survival status until death or administrative study closure unless the participant withdraws consent for this follow-up. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow up. Survival follow up includes, but is not limited to, follow-up through medical records, public records, or other public platform only as appropriately directed in accordance with local law. Every attempt should be made to follow the participant until death or administrative study closure.

4.5.2. Participant Withdrawal from Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include

- Participant withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly. If the participant withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected except for publicly available information. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5. TREATMENTS

5.1. Treatments Administered

Participants will be randomized in a 1:1 ratio to receive 1 of the following study treatments, either:

1. Control arm: Placebo tablets PO BID (twice a day) every day plus trastuzumab and pertuzumab on Day 1 of a 21-day cycle
2. Experimental arm: Tucatinib 300 mg PO BID every day plus trastuzumab and pertuzumab on Day 1 of a 21-day cycle

Trastuzumab and pertuzumab will be administered as:

- Trastuzumab will be given IV at a dose of 6 mg/kg or SC at a fixed dose of 600 mg, once every 21 days.

AND

- Pertuzumab will be given IV at 420 mg once every 21 days.

OR

- Fixed dose combination of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase will be given SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.

Trastuzumab and pertuzumab will be supplied in an open-label manner by the sponsor, where required. If supplied by the sponsor, the provided intervention and formulation must be utilized.

Study interventions are all prespecified MPs intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to tucatinib/placebo, trastuzumab, and pertuzumab.

5.2. Single Reference Safety Documents for Study Interventions

Single reference safety documents (SRSD) for each of the study interventions are summarized in [Table 2](#).

Table 2 Single Reference Safety Documents for Study Interventions

Study Intervention	SRSD
Tucatinib	Investigator's brochure
Trastuzumab	EU SmPC
Pertuzumab	EU SmPC
Pertuzumab/Trastuzumab/Hyaluronidase	EU SmPC

5.3. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the Pharmacy Instructions/IP Manual.
1. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take home study intervention.
5. Study interventions should be stored in their original containers.
6. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the Study Drug Accountability log. All study interventions will be accounted for using a study intervention accountability form/record. Study intervention, ie, tucatinib/placebo, that is taken home by the participant, both used and unused bottles, must be returned to the investigator by the participant. **Returned tucatinib/placebo bottles must not be redispensed to the participants.**
7. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Instructions/IP Manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

5.3.1. Study Intervention (Tucatinib or Placebo)

Detailed information describing the preparation, administration, and storage of the study treatment (tucatinib or placebo) is located in the Pharmacy Instructions/IP Manual.

5.3.1.1. Description

Tucatinib drug product, intended for oral administration, is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

Tucatinib matching placebo tablets are formulated with common pharmaceutical excipients, but they do not contain the active ingredient. They are coated to be identical in appearance to active tablets and are supplied in the same format to maintain blinding.

5.3.1.2. Method of Procurement

The study treatment (tucatinib or placebo) will be provided by the sponsor.

5.3.1.3. Dose and Administration

Tucatinib/placebo will be administered according to the following:

- Route of administration: PO
- Dose: Tucatinib/placebo 300 mg will be administered PO BID from Cycle 1 Day 1 onwards.
- Dosing schedule: BID on each day of study treatment. Tucatinib/placebo should be taken once in the morning and once in the evening, with approximately 8 to 12 hours between doses in the same calendar day.

Dose modifications of tucatinib/placebo are described in Section 5.4.1. Participants will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, participants will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

It is recommended that if a participant misses a scheduled dose of tucatinib/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the participant should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid. Doses that are vomited will not be replaced.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study participants and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Participant compliance with study treatment dosing instructions will be assessed by study drug accountability.

5.3.1.4. Preparation and Dispensing

Detailed drug preparation instructions are provided in the Pharmacy Binder.

A qualified staff member will dispense tucatinib/placebo in the bottles provided, in quantities appropriate according to the [SoE](#). The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

5.3.2. Trastuzumab

5.3.2.1. Description

Trastuzumab is a humanized immunoglobulin G1 (IgG1) kappa mAb which binds to the extracellular domain of HER2; it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which over express the HER2 protein. Trastuzumab is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative breast cancer, in combination with paclitaxel or docetaxel for first-line treatment of HER2-overexpressing mBC and in combination with an aromatase inhibitor for HR+ mBC, as a single agent for treatment of HER2-overexpressing breast cancer in participants who have received 1 or more chemotherapy regimens for metastatic disease. Multiple forms have been approved for clinical use based on bioequivalence testing (eg, IV or SC trastuzumab, biosimilar trastuzumab).

5.3.2.2. Method of Procurement

Trastuzumab will be supplied in an open label manner by the sponsor, where required. If supplied by the sponsor, the provided drug and formulation must be utilized. Where not supplied by the sponsor, any approved form of trastuzumab may be utilized, for every-21-day use.

5.3.2.3. Dose and Administration

Trastuzumab will be administered IV or SC under the direction of the investigator.

5.3.2.3.1. Intravenous

Trastuzumab will be given at a dose of 6 mg/kg IV once every 21 days. Trastuzumab infusion rates and any premedication will be per investigator judgment, following any applicable institutional guidelines. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued.

It is recommended to observe participants from the start of the infusion for fever, chills and other infusion-related symptoms. Interruption or slowing of the infusion may help control

such symptoms and may be resumed when symptoms abate. All infusion-related symptoms must have resolved before the participant is discharged unless deemed clinically not significant by the investigator. See Section 5.7.4.1 for recommended treatment of IRRs and premedication for subsequent administrations.

5.3.2.3.2. Subcutaneous

Alternatively, trastuzumab may be administered as a SC dose, given as a fixed dose of 600 mg once every 21 days. SC trastuzumab does not require a loading dose. For information on SC trastuzumab + pertuzumab, see Section 5.3.4.3.

5.3.2.3.3. Biosimilar

Any approved trastuzumab may be used as determined to be appropriate by the investigator. Trastuzumab biosimilar may only be used during the study if approved for use by the relevant national regulatory authority.

5.3.2.4. Preparation and Dispensing

See the trastuzumab product labeling for instructions on how to prepare trastuzumab for administration. Trastuzumab should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.3. Pertuzumab

5.3.3.1. Description

Pertuzumab is an anti-HER2 mAb that binds to the HER2 receptor at a site different from trastuzumab. Pertuzumab is indicated in combination with trastuzumab and docetaxel for treatment of HER2+ mBC in participants who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease, and in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of participants with early-stage breast cancer (either greater than 2 cm in diameter or node positive) (Gianni 2016) and adjuvant treatment of participants with HER2+ early breast cancer at high risk of recurrence (von Minckwitz 2017), PERJETA® [prescribing information]. San Francisco, CA: Genentech Inc; Revised Jan 2020).

5.3.3.2. Method of Procurement

Pertuzumab will be supplied in an open-label manner by the sponsor, where required. If supplied by the sponsor, the provided drug and formulation must be utilized.

5.3.3.3. Dose and Administration

Pertuzumab will be administered every 21 days by IV administration. The 420 mg infusion will be given over 30 to 60 minutes. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued.

5.3.3.4. Preparation and Dispensing

See the pertuzumab product labeling for instructions on how to prepare pertuzumab for administration. Pertuzumab should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.4. Trastuzumab + Pertuzumab

5.3.4.1. Description

Fixed dose trastuzumab + pertuzumab (pertuzumab, trastuzumab, and hyaluronidase) is a combination of trastuzumab and pertuzumab and is indicated in combination with docetaxel for treatment of HER2+ mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

5.3.4.2. Method of Procurement

Trastuzumab + pertuzumab will be supplied in an open-label manner by the sponsor, where required. If supplied by the sponsor, the provided drug and formulation must be utilized.

5.3.4.3. Dose and Administration

A fixed dose of trastuzumab + pertuzumab (600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase) will be administered every 21 days by SC administration, in lieu of trastuzumab and pertuzumab individually.

5.3.4.4. Packaging and Labeling

Each vial of trastuzumab + pertuzumab will be labeled in compliance with applicable regulatory requirements.

5.3.4.5. Preparation and Dispensing

See the trastuzumab and pertuzumab product labelings for instructions on how to prepare trastuzumab and pertuzumab for administration. Trastuzumab and pertuzumab should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.4. Dose Modifications

5.4.1. Tucatinib or Placebo

Refer to [Table 3](#) and [Table 4](#) for the tucatinib or placebo dose modification requirements. Dose reductions larger than those required by these tables may be made at the discretion of the investigator. Up to 3 dose reductions of tucatinib or placebo are allowed, but dose reductions to below 150 mg BID are not allowed. Participants who, in the opinion of the investigator, would require a dose reduction to <150 mg BID, or who would require a potential fourth dose reduction of tucatinib, should discontinue study treatment.

Tucatinib or placebo dose should not be re-escalated after a deliberate dose reduction is made.

Table 3: Recommended Tucatinib or Placebo Dose Reduction Schedule

Starting Dose ^a	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
300 mg PO BID	250 mg PO BID	200 mg PO BID	150 mg PO BID

a Dose reduction of greater steps than those listed in this table (ie, more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator. However, tucatinib or placebo may not be dose reduced below 150 mg BID.

Table 4 describes dose modifications of tucatinib or placebo for clinical AEs other than hepatotoxicity (Section 5.7.2).

Table 4: Dose Modifications of Tucatinib or Placebo for Clinical Adverse Events Other Than Hepatocellular Toxicity Related to Either Tucatinib or Placebo*

Clinical Adverse Event	Related to Tucatinib or Placebo
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal use of anti-emetics or anti-diarrheals.	Hold until severity $\leq$ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITH optimal use of anti-emetics or anti-diarrheals.	Hold until severity $\leq$ Grade 1 or pretreatment level. Restart at next lowest dose level.
Grade 4 nausea, vomiting, or diarrhea regardless of use of anti-emetics or anti-diarrheals.	Permanently discontinue.
Grade 3 rash WITHOUT optimal use of topical corticosteroids or anti-infectives.	Hold until severity $\leq$ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 rash WITH optimal use of topical corticosteroids or anti-infectives.	Hold until severity $\leq$ Grade 1 or pretreatment level. Restart at next lowest dose level.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives.	Permanently discontinue.

Table 4: Dose Modifications of Tucatinib or Placebo for Clinical Adverse Events Other Than Hepatocellular Toxicity Related to Either Tucatinib or Placebo*

Clinical Adverse Event	Related to Tucatinib or Placebo
Grade 3 AEs other than Grade 3 fatigue lasting ≤ 3 days; alopecia ^a ; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to $\leq$ Grade 1 within 7 days.	Hold until severity $\leq$ Grade 1 or pretreatment level. Restart at next lowest dose level.
Other Grade 4 AEs	Permanently discontinue.

* Note that if the AE in question does not recover to the Grade required for restarting study medication as outlined in the table, the participant may need to discontinue the intervention completely. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued. ^a No dose modifications are required for alopecia.

5.4.2. Trastuzumab

There are no dose reductions permitted for trastuzumab. In the event of Grade ≥ 3 trastuzumab-related AEs, hold trastuzumab and pertuzumab until the AE has resolved to Grade ≤ 1 or pretreatment levels.

As trastuzumab may be given as an IV infusion, IRRs may occur. If a significant IRR occurs, the infusion should be interrupted, and appropriate medical therapies should be administered (see Section 5.7.4.1). Permanent discontinuation should be considered in participants with severe IRR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

Trastuzumab dose modification guidelines for left ventricular dysfunction and cardiomyopathy are presented in Section 5.7.3.1, for IRR in Section 5.7.4.1, and for hypersensitivity reactions in Section 5.7.6.

Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued.

5.4.3. Pertuzumab

There are no dose reductions permitted for pertuzumab. In the event of Grade ≥ 3 pertuzumab-related AEs, hold trastuzumab and pertuzumab until the AE has resolved to Grade ≤ 1 or pretreatment levels.

As pertuzumab may be given as an IV infusion, IRRs may occur. If a significant IRR occurs, the infusion should be interrupted, and appropriate medical therapies should be administered (see Section 5.7.4.2). Permanent discontinuation should be considered in participants with

severe IRR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

Pertuzumab dose modification guidelines for left ventricular dysfunction and cardiomyopathy are presented in Section 5.7.3.1, for IRR in Section 5.7.4.2, and for hypersensitivity reactions in Section 5.7.6.

Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued.

5.4.4. Trastuzumab + Pertuzumab

No loading doses will be permitted. Any study intervention that requires a delay ≥ 6 weeks between sequential doses should be discontinued. Dose of trastuzumab + pertuzumab may be modified for observed LVEF events (Section 5.7.3.1).

5.5. Required Premedication and Postmedication

Any premedication for the initial administration of trastuzumab and pertuzumab should follow the investigator's judgement. Participants who experience infusion-related or injection-related symptoms should be strongly considered for premedication with paracetamol and antihistamines for subsequent infusions/injections.

5.6. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent through the safety reporting period. Concomitant medications given for treatment-related SAEs should be recorded during follow-up period.

5.6.1. Required Concomitant Therapy

There are no required concomitant therapies.

5.6.2. Allowed Concomitant Therapy

Participants may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria.

- Single agent endocrine therapy (with or without ovarian suppression)
- Supportive care to include bisphosphonates, denosumab, hematologic/anti-infectious support, and pain management.
- Supportive care medications such as anti-diarrheals, anti-emetics, antacids, and laxatives are permitted. Prophylactic use of anti-diarrheals may be permitted.
- Thoracentesis or paracentesis may be performed, if needed for comfort.
- If surgery or localized radiation are indicated (either for palliation or down-staging of previously nonresectable tumor), these concomitant procedures are

permitted for non-target non-CNS lesions only in situations where other lesions remain assessable by RECIST v1.1. These interventions should be avoided if clinically feasible until after the second response assessment. The medical monitor should be consulted prior to the intervention occurring.

- In participants that have CNS only progression, local therapy and study treatment continuation is permitted after RECIST-PD is captured and discussed with the medical monitor.
- Oral study drugs (tucatinib/placebo) are to be held 1 week prior to planned radiotherapy. The potential for radiosensitization with tucatinib is unknown. Trastuzumab/pertuzumab are not known to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study drugs may be re-initiated 7 days or more after the completion of radiotherapy. For CNS-directed therapy guidelines, please refer to Section 3.1.1.
- After initiation of study treatment, corticosteroids may be initiated for control of CNS symptoms. It should be confirmed that symptoms are not indicative of progression. Premedication with corticosteroids solely for contrast use for imaging can be used without discussion with the medical monitor.
- Transfusion support with blood products (Note that hematologic eligibility parameters must be met without recent blood product use; see Section 4)
- Treatment for COVID-19, after discussion with the medical monitor

The sponsor has conducted a risk assessment for the concomitant use of COVID-19 vaccines. It has determined that the administration of a COVID-19 vaccine during this trial is considered a simple concomitant medication that does not require advice on timing of the vaccine beyond the guidance already outlined in this study protocol (Section 5.6). This patient population is at risk for moderate to severe COVID-19 disease and therefore will benefit from administration of a vaccine that prevents severe disease.

5.6.3. Prohibited Concomitant Therapy

The following therapies are prohibited while participants are receiving study treatment (unless otherwise noted):

- Investigational interventions and devices
- Non-protocol anti-cancer therapy aside from single agent endocrine therapy (with or without ovarian suppression)
- Radiation therapy to target lesions or CNS lesions
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of study treatment. For additional information, including elimination half-lives of strong CYP3A4 inducers, see [Appendix D](#).

- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of tucatinib/placebo treatment. For additional information, including elimination half-lives of strong inhibitors and inducers, see [Appendix E](#).
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (see [Appendix F](#)). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.
- Concomitant use of tucatinib with digoxin, a P-gp substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

5.7. Management of Treatment-Emergent Adverse Events

5.7.1. Dose Modifications for Diarrhea

Tucatinib and pertuzumab may cause severe diarrhea. Diarrhea should be treated according to standard practice and guidelines. Participants should be counseled to report diarrhea to investigators at the first sign or symptom to ensure that appropriate actions are taken. If diarrhea persists >48 hours or if there is an increase of >7 stools per day over baseline, participants should also be instructed to promptly inform the investigator for potential dose modifications and proper management. Early intervention with anti-diarrheal medications, fluids and electrolyte replacement should be considered. Tucatinib/placebo should be modified before pertuzumab (see Section 4.5.1). See [Table 4](#) for dose modifications guideline of tucatinib for diarrhea. Interruption of treatment with pertuzumab should be considered if no improvement in the participant's condition is achieved. When diarrhea is under control, treatment with pertuzumab may be reinstated.

5.7.2. Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities.

For dose modifications of tucatinib or placebo, see [Table 5](#) below. Dose modification of trastuzumab is not required but dosing can be held at investigator discretion. For participants with documented Gilbert's disease, baseline value (instead of ULN) will be used as the reference for bilirubin. Dose modifications and interruptions of any study intervention due to Gilbert's disease will be documented in the source documents and the CRF.

Table 5: Dose Modifications of Tucatinib/Placebo for LFT Abnormalities, Regardless of Relationship to Tucatinib/Placebo

Laboratory Abnormality	Tucatinib/Placebo Dose Modification
Bilirubin elevation $>1.5\text{--}3 \times \text{ULN}$ ($>1.5\text{--}3 \times$ baseline for participants with documented Gilbert's disease)	Hold until recovery to $\leq 1.5 \times \text{ULN}$ Resume at same dose
Bilirubin elevation $>3\text{--}10 \times \text{ULN}$ ($>3\text{--}10 \times$ baseline for participants with documented Gilbert's disease)	Hold until recovery to $\leq 1.5 \times \text{ULN}$ Reduce dose.
Bilirubin elevation $>10 \times \text{ULN}$ ($>10 \times$ baseline for participants with documented Gilbert's disease)	Permanently discontinue.
ALT or AST elevation $>5\text{--}20 \times \text{ULN}$	Hold until recovery to $\leq 3 \times \text{ULN}$ or return to baseline level in participants with known liver metastasis Reduce dose.
ALT or AST elevation $>20 \times \text{ULN}$	Permanently discontinue.
ALT or AST elevation $>3 \times \text{ULN}$ AND bilirubin elevation $>2 \times \text{ULN}$ ($>2 \times$ baseline for participants with documented Gilbert's disease)	Permanently discontinue.

5.7.3. Left Ventricular Dysfunction and Cardiomyopathy

5.7.3.1. Trastuzumab and Pertuzumab

Trastuzumab and pertuzumab can cause asymptomatic decline in LVEF and left ventricular cardiac dysfunction, including congestive heart failure. Trastuzumab can also cause arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death.

Trastuzumab + pertuzumab can cause asymptomatic decline in LVEF, hypertension, arrhythmias, left ventricular cardiac dysfunction, disabling cardiac failure, cardiomyopathy, and cardiac death.

Trastuzumab and pertuzumab (including trastuzumab + pertuzumab) dose modification guidelines for left ventricular dysfunction, regardless of relationship to study intervention, are provided in [Table 6](#).

Table 6: Trastuzumab and Pertuzumab Dose Modification Guidelines for Left Ventricular Dysfunction

LVEF at Assessment	Action
LVEF $\geq 50\%$	Continue treatment with trastuzumab and pertuzumab
LVEF 45% to $<50\%$ with $<10\%$ absolute decrease from baseline	Continue treatment with trastuzumab and pertuzumab
LVEF $<45\%$ or 45% to $<50\%$ with $\geq 10\%$ absolute decrease from baseline	Hold trastuzumab and pertuzumab, repeat LVEF in 3 weeks
Repeat LVEF at 3 weeks:	
- LVEF $\geq 50\%$	Resume treatment with trastuzumab and pertuzumab
- LVEF 45% to 49%	
$<10\%$ absolute decrease from baseline	Resume treatment with trastuzumab and pertuzumab
$\geq 10\%$ absolute decrease from baseline	Discontinue trastuzumab and pertuzumab
- LVEF $<45\%$	Discontinue trastuzumab and pertuzumab

Trastuzumab and pertuzumab should be discontinued in participants who develop symptomatic left ventricular dysfunction.

5.7.4. Infusion-related Reaction and its Management

An IRR is characterized by an adverse reaction to the infusion of pharmacological or biological substances. IRRs occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension (Kang 2007).

5.7.4.1. Trastuzumab

If participants develop an IRR, participants should be treated according to the following guidelines, or according to institutional guidelines, at discretion of the investigator:

- Stop infusion and notify physician.
- Assess vital signs.
- Administer acetaminophen 650 mg PO.
- Consider administration of: meperidine 50 mg intramuscular, diphenhydramine 50 mg IV, ranitidine 50 mg IV or cimetidine 300 mg IV, dexamethasone 10 mg IV, or famotidine 20 mg IV.
- If vital signs are stable, resume trastuzumab infusion.

No standard premedication is required for future treatments if participants have developed an infusion syndrome. Participants may be given acetaminophen prior to treatments. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids, and withdrawal of study agent as indicated.

5.7.4.2. Pertuzumab

Participants should be placed under close observation for 60 minutes after the first dose and for 30 minutes after subsequent doses of pertuzumab. Institutional guidelines should be followed. If a significant IRR occurs, slow or interrupt the infusion, and administer appropriate medical therapies. Participants will be monitored carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in participants with severe IRRs.

5.7.5. Injection-Related Reaction and its Management

5.7.5.1. Trastuzumab + Pertuzumab

Participants should be placed under close observation during and for 30 minutes after the first dose and during and for 15 minutes after subsequent doses. If a significant injection-related reaction occurs, slow down or pause the injection and administer appropriate medical therapies.

Trastuzumab + pertuzumab should be permanently discontinued if participants experience anaphylaxis or severe injection-related reactions.

5.7.6. Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of study intervention. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, ie, a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension.

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death (NCI-CTCAE, version 5.0 and [Rosello 2017](#)).

Any allergic/hypersensitivity reaction related to trastuzumab and/or pertuzumab should be managed according to the product label and/or institutional standard of care. If anaphylaxis occurs, administration of study intervention should be immediately and permanently discontinued.

5.7.7. Management of Overdose

In the event of an overdose of study treatment (tucatinib or placebo), defined as any dose greater than the prescribed dose, study personnel should:

- Care for and medically stabilize the participant until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of tucatinib or placebo administered, participant weight) and AEs, if any.

Overdose is reportable to Pfizer Safety only when associated with an SAE.

Refer to the product labeling for overdose information for trastuzumab and pertuzumab.

5.8. Treatment Compliance

Study intervention compliance will be assessed on a participant-by-participant basis by study site staff and documented in source documents and the CRF.

The pharmacist or designee will record the number of study treatment (tucatinib or placebo) tablets dispensed to each individual participant, and the number of tablets returned to the clinic at the end of each cycle.

Data regarding the administration, formulation, and dose of trastuzumab and/or pertuzumab will also be collected by the site after each cycle. Dose modifications and interruptions of any study intervention will be documented in the source documents and the CRF.

5.9. Continued Access to Study Intervention After the End of the Study

Continued access to study intervention may be made available to participants who continue to derive clinical benefit from treatment (as judged by the PI and sponsor) and have no other treatment options outside a clinical study.

6. STUDY ACTIVITIES

6.1. Schedule of Events

Adverse events and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related adverse event (defined in Section 7.8.1.1) as well as any concomitant medications given for treatment of the adverse event, should be recorded from the time of informed consent.

Clinical assessments (eg, physical exam, vital signs, laboratory values), noted in the Schedule of Events, should be performed with results reviewed prior to the initial administration of all study interventions. Results from tumor assessments, as soon as they are available to the investigator, should be applied to the decision of whether to continue with study treatment.

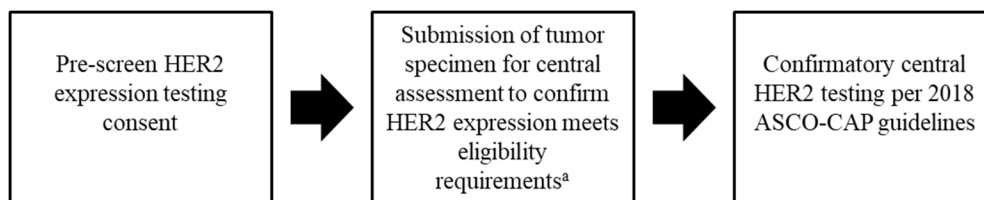
A [Schedule of Events](#) is provided. Rows provide descriptions of all study assessments; columns provide the timings for these assessments. Further details are presented in Section 7.

6.2. Screening and Baseline Period

6.2.1. Pre-screening (Up to 6 Months Before the Screening Visit)

Participants may consent to submit a tumor specimen for central assessment to complete HER2 expression testing up to 6 months before the Screening Visit (Pre-screening period; [Figure 2](#)). Participants must be informed that HER2 testing consent is not informed consent for the main study and participation in HER2 testing does not guarantee study eligibility.

Figure 2: Pre-Screen HER2 Testing



^a See Section 7.2 for more information.

6.2.2. Screening Period (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- Confirmation of HER2+ status
 - Tissue blocks or slides must be submitted and confirmed as HER2+ by a sponsor designated central laboratory prior to randomization
- Safety assessments (see [Schedule of Events](#))
- Response assessments (see [Schedule of Events](#))

- Radiographic disease assessments will evaluate all known sites of disease, preferably using high quality spiral contrast computed tomography (CT) (with oral and/or IV contrast), and covering, at a minimum, the chest, abdomen, and pelvis.
- Positron emission tomography (PET)-CT scans (if high quality CT scan is included) and/or MRI scans may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study, unless contraindicated.
- Contrast-enhanced MRI of the brain
- Bone scan in participants with known or suspected bone metastasis. Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. PET-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study.

Informed consent and certain screening evaluations may not need to be repeated outside the 28-day screening window with medical monitor approval. These include the ECHO/MUGA examinations and CT scans. All other safety labs and assessments will need to be repeated per the schedule of events for these participants. If local CNS therapy involves surgical resection, a postoperative contrast MRI of the brain is required prior to starting study treatment.

6.2.3. Baseline Visit (Days –7 to Day 1)

- Height and weight
- Physical exam
- Pregnancy test for participants of childbearing potential and contraception monitoring review as outlined in [Appendix C](#). In addition, participants of childbearing potential should be counseled at screening on adequate contraception methods.
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate)
- ECOG performance status ([Appendix A](#))
- Blood samples for laboratory testing (see [Schedule of Events](#))
- Blood sample for biomarker (see [Schedule of Events](#))
- Patient reported outcome (PRO)/Quality of Life (QoL) questionnaires
 - CCI [REDACTED]
 - EORTC QLQ-C30 questionnaire

6.3. Treatment Period (21-day cycles)

If the following Baseline/Screening activities occur within 7 days prior to Cycle 1, Day 1 (C1D1) and meet eligibility requirements, they do not need to be repeated at the C1D1 Visit:

- ECOG Performance status ([Appendix A](#))
- Serum chemistry panel
- Complete blood count (CBC)
- LFTs

Concomitant medications and adverse events will be documented from Day 1 predose through safety reporting period of study interventions. Day 1 of each cycle is determined by the dosing date of trastuzumab and pertuzumab. If participants have discontinued trastuzumab and pertuzumab, cycles will be defined as 21 days for tucatinib/placebo dosing. Refer to the [Schedule of Events](#) for interpretation of assessments conducted during study treatment.

6.3.1. Day 1 (±2d)

- Results from clinical laboratory assessments must be reviewed and must confirm no contraindication to dosing prior to study intervention
- Safety assessments (see [Schedule of Events](#))
- PRO/QoL questionnaires (see [Schedule of Events](#))
- Dispense tucatinib (if participant has not discontinued intervention). Administer the first dose of tucatinib. (Participant will self-administer the remainder of doses during the treatment cycle.)
- Administer trastuzumab and pertuzumab (if participant has not discontinued intervention).
- Tucatinib PK samples (Cycles 2 to 6)
 - CCI [REDACTED]
- Blood sample collection for biomarker at Cycle 3 predose

CCI [REDACTED]

6.3.2. Day 12 (±2 days; applicable only to Cycles 1 and 2)

- LFTs (see [Schedule of Events](#))

6.3.3. Radiological Assessment Schedule

6.3.3.1. Every 9 weeks (±1 week) after Cycle 1 Day 1

- Response assessments (see [Schedule of Events](#))

6.3.3.2. Every 12 weeks (± 1 week)

- ECHO or MUGA scan (scheduling is determined by date of most recent screening or on treatment ECHO/MUGA)

6.3.3.3. Every 27 weeks (± 21 days) after Cycle 1 Day 1

- Contrast MRI scan of the brain for participants with no history of, or baseline, brain metastasis
- Bone scan (only for participants with bone metastases at baseline). Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. PET-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study.

- CCI [REDACTED]

6.4. End of Treatment Visit (30 to 37 days after last dose of last study intervention)

EOT visits should occur 30 to 37 days after the last dose of the last study intervention taken/administered unless delayed due to an AE.

Note: EOT evaluations must be performed before initiation of a new subsequent cancer therapy. If EOT evaluations are completed before 30 days after the last study treatment, the participant will be contacted 30 to 37 days following the last study treatment to assess for AEs; the other EOT evaluations do not need to be repeated.

- Safety assessments (see [Schedule of Events](#))
- PRO/QoL questionnaires (see [Schedule of Events](#))
- Tucatinib PK samples (see [Schedule of Events](#))
- Response assessments (see [Schedule of Events](#))
- Blood sample collection for biomarker (see [Schedule of Events](#))

6.5. Follow-up Period (Visits Every 12 weeks [± 1 week])

Treatment-related SAEs and concomitant medications for these SAEs will be collected throughout the follow-up period. Survival status will also be assessed. Participants who discontinue study treatment in the absence of RECIST-PD are expected to continue tumor assessments at the same intervals as while on study treatment (based on the C1D1 assessment date). They may undergo these assessments as performed previously (while on study treatment), or alternatively may provide images performed as part of clinical care outside of this study, with the investigator to enter the RECIST assessment. See the [Schedule of Events](#) for more detailed information.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only participants who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing to determine participant eligibility; confirmatory HER2 testing may be performed on archival tissue or a newly obtained (preferred) baseline biopsy of an accessible tumor lesion that has not been previously irradiated.

Participant medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies, and any concomitant medications.

All known lesions will be assessed and documented at Screening/Baseline (see Section 7.1). Participants with non-measurable disease by RECIST v1.1 at baseline may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 4. For participants with non-measurable disease at baseline, progression will be determined based on the appearance of new lesions. A contrast MRI of the brain is performed to evaluate the presence of brain metastases (see Section 7.3.1). Participants with brain metastases at study entry may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 4.

A physical examination including height and weight (Section 7.8.4), vital signs (Section 7.8.2), ECOG performance status (Appendix A), clinical laboratory testing (Section 7.8.3), and pregnancy testing (Section 7.8.5) will be done at Screening/Baseline.

7.2. End of Study/End of Follow-up

The date the participant met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7.2.1. Confirmation of HER2 Expression for Study Eligibility

Archival or freshly obtained tumor tissue (freshly obtained tumor tissue sample preferred) must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing prior to randomization. Tissue block or slides should be submitted to allow for central HER2 testing as well as biomarker analyses (see Appendix H). Please refer to the Central Laboratory Manual for details. Tumor samples must be formalin-fixed and paraffin-embedded.

HER2 expression will be analyzed centrally per 2018 ASCO-CAP Guidelines for standardization of HER2 status.

7.3. Response/Efficacy Assessments

Disease response to study treatment and the occurrence of disease progression will be determined according to RECIST v1.1 (Eisenhauer 2009), as assessed by both investigator and BICR. Any imaging that is conducted as per standard of care will be collected for retrospective BICR. Radiographic scans and additional imaging assessments (if applicable)

will be performed at protocol specified- time points outlined in Section 6 and the Schedule of Events.

Response assessments will be performed at baseline and every 9 weeks until RECIST progression (irrespective of dose interruptions) or EOT, whichever is later. Response assessments include measurement of all known sites of tumor (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast CT. PET/CT (if diagnostic quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other sites of disease (eg, skin lesion photography for skin lesions, imaging of the neck, or imaging by CT or MRI of bone metastases not captured by imaging of the chest, abdomen, or pelvis). Bone scans will be required- at screening only for participants with known or suspected bone metastases and are to be repeated every 27 weeks (~6 months). Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. PET-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study. Contrast enhanced brain MRI is required- for all participants at screening and at EOT and is to be repeated only for participants with a history of, or baseline, brain metastasis every 9 weeks. For participants without a history of, or baseline, brain metastasis, contrast enhanced brain MRI is to be repeated every 27 weeks (~6 months). Additional contrast MRIs of the brain may be performed as clinically appropriate (Section 7.3.1).

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each participant will continue until disease progression per RECIST v1.1 by investigator assessment has been documented, or EOT, whichever is later. Survival and other follow up- assessments will continue until study closure or withdrawal of consent (see [Schedule of Events](#)).

Participants' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.3.1. Evaluation of Brain Metastases

Brain MRI, as with all tumor imaging, will be performed locally and collected prospectively for centralized independent review. Treatment decisions will be made on the basis of local imaging assessment.

Contrast MRI scan of the brain will be performed for all participants at Screening/Baseline to assess tumor burden in the brain and/or dura and identify participants with brain metastases at baseline. CT of the brain alone will not be sufficient, and participants with known contraindications to undergo contrast MRI imaging will be excluded from the study. Participants are considered to have brain metastases at baseline with any of the following:

- Any history of brain metastases
- Any brain metastases at baseline
- Brain lesions of equivocal significance at baseline

Only participants with documented brain metastases at baseline, as defined above, or participants who are continuing study treatment for clinical benefit after isolated CNS

progression defined in Section 3.1.1 will continue to have follow-up contrast MRIs of the brain on the same schedule as non-CNS response assessments (Section 6 and [Schedule of Events](#)). In participants without known brain metastases at baseline, contrast MRIs of the brain will be performed every 6 months and may also be performed as clinically indicated. All participants will have an additional contrast MRI of the brain at the EOT visit, unless 1 has been performed within 4 weeks of discontinuing study treatment or the reason for going off treatment was radiologically documented progression in the brain.

In participants with baseline brain lesions, at least 1 brain lesion should be included in the baseline RECIST lesion selection as either a target or non-target lesion. Treated lesions that have not progressed since local treatment should not be selected as target lesions but as non-target lesions for the purpose of disease assessment by RECIST v1.1 ([Appendix B](#)).

Untreated lesions, if measurable, should be prioritized as target lesions rather than non-target lesions.

7.4. Pharmacokinetic Assessments

Blood samples for PK assessment of trough tucatinib drug concentrations will be collected in all participants on Day 1 of Cycles 2 to 6 (prior to administration of tucatinib) and at EOT.

CCI [REDACTED] (Table 7). Plasma concentrations of tucatinib will be determined using validated LC-MS/MS methods. Additional analytes may be evaluated as necessary. Dose holds or discontinuations of tucatinib, trastuzumab, or pertuzumab may impact the need for tucatinib PK sample collections. Decision trees (see Pharmacy Instructions/IP Manual) have been developed to address these scenarios.

Table 7: Pharmacokinetic and Biomarker Sample Collection Timepoints

	Study day	Time	Window	Relative Time	Blood Samples		FFPE Tumor
					PK	Bio-marker	Specimen
Pre-screening	- 6 months to Day -29	N/A	N/A	N/A			X
Screening	Day -28 to 1	N/A	N/A	N/A			X ^a
Baseline	Day -7 to 1	N/A	N/A	N/A		X	
Cycle 2	Day 1	Predose	Should be taken within 2 hours prior to administration of tucatinib.	Time of administration of tucatinib	X		
Cycle 3	Day 1	Predose, Post-dose	N/A CCI [REDACTED]	Time of administration of tucatinib	X	X ^b	

Table 7: Pharmacokinetic and Biomarker Sample Collection Timepoints

	Study day	Time	Window	Relative Time	Blood Samples		FFPE Tumor
					PK	Bio-marker	Specimen
Cycles 4, 5, and 6	Day 1	Predose	N/A	Time of administration of tucatinib	X		
End of Treatment					X	X ^c	

FFPE=formalin fixed paraffin embedded; N/A=not applicable.

a If not obtained during pre-screening.

b Predose only

c These blood samples should be collected for participants who discontinue treatment due to progressive disease (as defined by RECIST v1.1) or discontinue treatment for any other reason (eg, toxicities).

7.5. Biomarker Assessments

Relationships of biomarker parameters to efficacy, safety and PK parameters may be explored in peripheral blood and tumor tissue as outlined in this section. CCI

. Correlative studies may be conducted to gain a better understanding of target response relationships, CCI and mechanisms of resistance. Samples will be collected where permitted as per local regulations (see Appendix H).

7.5.1. Characterization of Tumor Tissue

Participants will have HER2 status determined at a central laboratory by immunohistochemistry (IHC) and in situ hybridization (ISH) in samples prior to randomization. Confirmation of HER2 status will be determined prior to enrollment to ensure population is standardized using a single test and a single scoring algorithm due to known historical changes in scoring algorithm and known variability observed in local HER2 testing. CCI

Samples will be collected where permitted as per local regulations (see Appendix H).

Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.

HER2 status will be confirmed centrally. See Table 7 for the schedule of biomarker assessments.

7.5.2. Characterization of Blood Samples

CCI

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7.6. Biospecimen Repository

In the US only, for participants who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Pfizer and used for future research, including the evaluation of targets for novel therapeutic agents. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.7. Patient Reported Outcomes (PROs)

PROs will be administered as specified in the [Schedule of Events](#) and Section 6. The objective is to assess change in improvements, deteriorations, and stabilization in health-related QoL and time to deterioration (TTD) between treatment arms. During study treatment, these questionnaires must be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days.

7.7.1. EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC) QLQ was developed to measure aspects of health-related QoL pertinent to participants with a broad range of cancers who are participating in international clinical trials ([Aaronson 1993](#); [Bjordal 1994](#); [Sneeuw 1998](#)). The core instrument, the QLQ-C30 (Version 3.0), is a 30-item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social)
- 3 symptom scales (fatigue, pain, nausea, and vomiting)
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease
- 2 global items (health, overall QoL)

7.7.2. CCI

CCI

7.8. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an E-DMC as described in Section 9.3.11.

7.8.1. Adverse Events

7.8.1.1. Definitions

The recording and reporting of AEs and SAEs is further detailed in [Appendix G](#).

7.8.1.1.1. Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether to record a test result, medical condition, or other incident on the Adverse Events CRF:

- From the time of informed consent through the day prior to study Cycle 1 Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Cycle 1 Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing predose on study Cycle 1 Day 1 that worsen in severity, increase in frequency, become related to study intervention, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study intervention) should be recorded from study Cycle 1 Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value (eg, hematology, clinical chemistry, or urinalysis) should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, requires additional diagnostic testing or medical/surgical intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE

resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record “anemia” rather than “low hemoglobin”).

- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.8.1.1.2. Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the participant at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent

Fatal:	AE resulted in death
	in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the participant’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a participant exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the participant and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.8.1.2 for the definition of potential DILI.)

7.8.1.1.3. Adverse Event Severity

AE severity should be graded using the NCI-CTCAE, version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. ‘Severity’ characterizes the intensity of an AE. ‘Serious’ is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

7.8.1.1.4. Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib or placebo, trastuzumab, or pertuzumab) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the intervention and the AE, such as: - A single occurrence of an event that is uncommon and known to be strongly associated with intervention exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) - One or more occurrences of an event that is not commonly associated with intervention exposure, but is otherwise uncommon in the population exposed to the intervention (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the PSSA and in accordance with the SAE reporting requirements.

7.8.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during participant questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

7.8.1.2.1. Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

7.8.1.2.2. Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Please refer to [Appendix G](#) for additional guidance on recording of AEs.

7.8.1.2.3. Diagnosis versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study intervention. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

7.8.1.2.4. Recording Serious Adverse Events

For SAEs, record the event(s) on the CRF and report the SAE to Pfizer Safety using PSSA. Please refer to [Appendix G](#) for additional guidance on recording and reporting of SAEs.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.

- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

7.8.1.2.5. Progression of Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease”, or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. Complications from progression of the underlying malignancy should be recorded as AEs or SAEs in the CRF.

7.8.1.2.6. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

Please refer to [Appendix G](#) for additional guidance on recording and reporting of environmental exposure.

Exposure During Pregnancy

An EDP occurs if:

- A participant is found to be pregnant while receiving or after discontinuing study intervention.
- A participant who is receiving or has discontinued study intervention inseminates a partner.
- A nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
 - A family member or healthcare provider reports that they are pregnant after exposure (e.g., ingestion, inhalation, or skin contact) to study intervention.
 - A family member or healthcare provider who has been exposed to the study intervention by ingestion, or skin contact then inseminates their partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred as shown in [Table 8 \(Appendix G\)](#). The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner after the start of study intervention and until 7 months, the investigator must report this information to Pfizer Safety via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 7 months after the last dose of the last study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

Follow up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow up to the initial EDP. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly, the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow up of birth outcomes will be handled on a case-by-case basis (eg, follow up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to their partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to their partner.

Please refer to [Appendix G](#) for additional guidance on recording and reporting of exposure during pregnancy.

Exposure During Breastfeeding

An EDB occurs if:

- A participant is found to be breastfeeding while receiving or after discontinuing study intervention until 7 months after the last dose of the last study intervention. A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports breastfeeding after having been exposed to study intervention by ingestion or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed PSSA is maintained in the investigator site file. Please refer to [Appendix G](#) for additional guidance on reporting/recording EDB.

Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA must be maintained in the investigator site file.

7.8.1.2.7. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded in the CRF	Recorded on the AE Page of the CRF	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention; examples include, but are not limited to:
 - The administration of expired study intervention;
 - The administration of an incorrect study intervention;
 - The administration of an incorrect dosage;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the CRF and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE**. In the event of a significant medication dosing error, the sponsor should be notified within 24 hours.

7.8.1.2.8. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

7.8.1.2.9. Potential Drug-Induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study intervention may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential drug-induced liver injury (DILI) in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation $> 3 \times \text{ULN}$

AND

2. Total bilirubin $> 2 \times \text{ULN}$, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

All participants presenting with the above abnormal laboratory tests and/or suspicious of DILI, can be discussed with the medical monitor and Sponsor. **Reporting Requirements**

Any potential Hy's Law case is to be handled as a SAE and reported promptly to the Sponsor.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to $>3 \times$ ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study intervention.

7.8.1.2.10. Left Ventricular Ejection Fraction Decreased

For asymptomatic declines in LVEF leading to a change in study treatment or discontinuation of study treatment, the term "ejection fraction decreased" should be used, and severity Grades 2 to 4 used to report asymptomatic LVEF decrease.

For symptomatic CHF, the term "heart failure" should be used, and severity Grades 2 to 5 used to report symptomatic CHF.

7.8.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Cycle 1 Day 1 (predose) through 30 days after the last study treatment. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the participant dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started. SAEs occurring during the safety reporting period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

7.8.1.4. Serious Adverse Events Require Immediate Reporting

All SAEs occurring in a participant during the safety reporting period are reported to Pfizer Safety on the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Participant number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

7.8.1.5. Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.8.1.6. Adverse Events of Special Interest

An AESI can be any serious or nonserious AE that is of scientific or medical concern as defined by the sponsor and specific to the program, for which ongoing monitoring and rapid communication to the sponsor may be appropriate.

All AESIs must be reported as an AE or SAE following the procedures described in Section 7.8.1.3. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the PSSA.

AESIs for this study are:

- **≥ Grade 3 diarrhea**
- **Hepatotoxicity:** either of the following types of LFT elevation:
 - AST or ALT elevations that are $>3 \times$ ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin $\geq 2 \times$ ULN, except in participants with documented Gilbert's syndrome
 - AST or ALT elevations $>20 \times$ ULN
 - Bilirubin elevations $>10 \times$ ULN

Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. The sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.8.1.7. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.8.1.4). The sponsor will report all SAEs, including SUSARs, to regulatory authorities as required per local legislation or regulatory reporting requirements. An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

7.8.2. Vital Signs

Vital signs measures are to include heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature.

7.8.3. Clinical Laboratory Tests

Samples will be drawn for local laboratory testing and will utilize the relevant laboratory's range of normal for evaluating safety and making clinical decisions. The following laboratory assessments will be performed by the local lab to evaluate safety at scheduled time points (see [Schedule of Events](#)) during the course of the study:

- At a minimum, the chemistry panel is to include the following tests: blood urea nitrogen, creatinine, chloride, potassium, and sodium.
- LFTs: alkaline phosphatase, ALT, AST, and total bilirubin
- The CBC is to include the following tests: white blood cell counts with hemoglobin, neutrophils, and platelet count.
- A serum or urine β -hCG pregnancy test for participants of childbearing potential

7.8.4. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological, as well as any other areas with tumor assessable by physical examination (eg, breast or skin). Measurements of height obtained within the prior 12 months may be utilized.

7.8.5. Pregnancy Testing

For participants of childbearing potential, a serum or urine β -hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at the times listed in the [SoE](#). Following a negative pregnancy test result at screening, appropriate contraception must be commenced or continued and a second negative pregnancy test result will be required at the baseline visit prior to starting study intervention. A negative pregnancy result is required before the participant may receive study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive. Pregnancy tests will be performed once a month for 7 months after the last dose of study treatment.

7.8.6. Cardiac Function

7.8.6.1. MUGA or Echocardiogram

Assessment of cardiac ejection fraction will be performed by MUGA scan or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation irrespective of dose delays or interruption, and at the EOT visit (unless done within 12 weeks prior to the EOT visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

7.8.6.2. Electrocardiogram

Electrocardiograms (ECGs) (12-lead) will be performed at screening. To correct for heart rate, corrected QT intervals (QTc) should be calculated using the Fridericia formula.

7.9. Appropriateness of Measurements

Response will be assessed according to RECIST v1.1 ([Eisenhauer 2009](#)), which are standardized criteria for evaluating response in solid tumors. The schedule for tumor balances measurement of tumor control (and thus appropriateness of continuing study treatment) with the burden of imaging.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. Additional safety assessments may be performed as clinically appropriate. AEs and clinical laboratory data will be graded using standardized criteria for oncology (NCI-CTCAE version 5.0).

Pharmacokinetic assessments are common in clinical studies to help characterize dose exposure response relationships.

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The QLQ-C30 (Version 3.0) is a validated questionnaire developed by the EORTC to assess the QoL of cancer participants ([Aaronson 1993](#); [Sneeuw 1998](#)). These PROs have been incorporated into previous clinical trials that seek to quantify the QoL in participants.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of participants at the site, Pfizer or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current Investigator's Brochure/product labeling
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Study treatment storage, accountability, labeling, dispensing, and record keeping
- Participant coding and randomization
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Pfizer representative will typically review regulatory documentation, CRFs, source documentation, and study treatment storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study participants, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Pfizer or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of progression or death (HR of 0.70; median PFS of 15 months in the control arm and 21.4 months in the experimental arm).

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9.2. Study Endpoint Definitions

9.2.1. Primary Endpoint: PFS per Investigator Assessment

PFS per investigator is defined as the time from the date of randomization to the investigator assessment of disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. Participants without documentation of PD, or death at the time of analysis, will be censored at the date of the last tumor assessment with an overall response of CR, PR, SD, or non-CR/non-PD.

If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of randomization.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the Statistical Analysis Plan (SAP).

9.2.2. Key Secondary Endpoint: Overall Survival

OS is defined as the time from randomization to death from any cause.

For a participant who is not known to have died by the end of study follow-up, observation of OS is censored on the date the participant was last known to be alive (ie, the date of last contact). Participants lacking data beyond the day of randomization will have their survival time censored on the date of randomization (ie, OS duration of 1 day).

9.2.3. Other Secondary Endpoints

9.2.3.1. PFS per BICR

PFS per BICR is defined as the time from the date of randomization to the documented disease progression assessed by BICR according to RECIST v1.1 or death from any cause, whichever occurs first.

9.2.3.2. Patient Reported Outcomes

Time to deterioration of HRQoL, defined as time to 10-point decrease in the global health status/QoL scale of the EORTC QLQ-C30, will be measured based on PROs.

9.2.3.3. CNS-PFS

CNS-PFS is defined as the time from randomization to investigator assessed disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first.

9.2.3.4. PK Analysis

Individual plasma tucatinib concentrations will be used for PK assessments. Additional exploratory PK analyses may be conducted.

9.2.4. Exploratory Endpoints

9.2.4.1. CCI [REDACTED]

[REDACTED]

9.2.4.2. CCI [REDACTED]

[REDACTED]

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in the protocol amendment. The SAP will be finalized prior to database lock.

9.3.1. General Considerations

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

9.3.1.1. Randomization and Blinding

This is a randomized, double-blind, phase 3 study that will enroll approximately 650 participants. Participants will be randomized in a 1:1 ratio to receive either tucatinib or placebo in combination with trastuzumab and pertuzumab. Randomization will be stratified

by diagnosis (de-novo versus recurrent), hormone receptor status (positive versus negative), and presence or history of brain metastases (yes versus no).

Randomization will be performed centrally using a system that will assign a unique participant randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

9.3.1.2. Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 3.2.1). If the sample size of 1 stratum by a stratification factor is too small, the statistical analysis will not include this randomization stratification factor in the statistical analysis, such as stratified log-rank test and stratified Cox regression model. This minimum sample size requirement will be specified in the SAP. Covariates may be considered for adjustment in exploratory analyses.

9.3.1.3. Handling of Dropouts and Missing Data

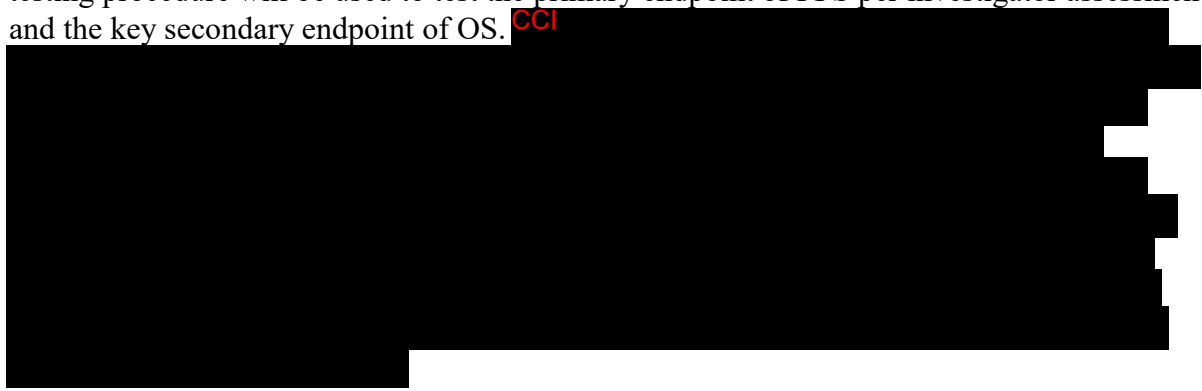
With the exception of time-to-event endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP.

9.3.1.4. Multicenter Studies

This study will be conducted at multiple study centers; however, it is not anticipated that any center will accrue enough participants to warrant an analysis by center.

9.3.1.5. Multiple Comparisons and Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05, a fixed sequential testing procedure will be used to test the primary endpoint of PFS per investigator assessment and the key secondary endpoint of OS. CCI



9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study treatment unless otherwise specified in the analysis plan.

9.3.1.7. Analysis Sets

The intent-to-treat (ITT) analysis set will include all randomized participants. Participants will be included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints will be based on the ITT analysis set.

The safety analysis set will include all randomized participants who receive at least 1 dose of study treatment (tucatinib, placebo, trastuzumab or pertuzumab). Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment.

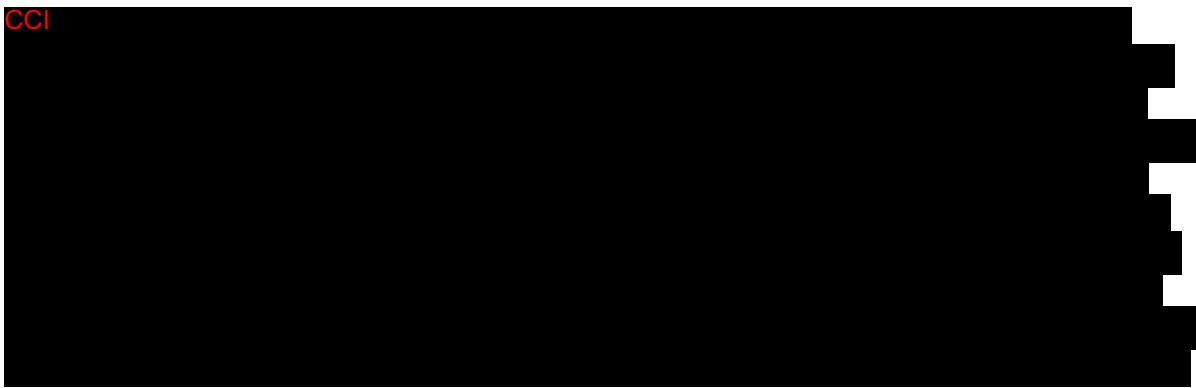
Additional analysis sets of participants may be defined in the SAP.

9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

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9.3.2. Participant Disposition

An accounting of study participants by disposition will be tabulated and the number of participants in each analysis set will be summarized. Participants who discontinue study treatment and participants who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3. Participant Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4. Concomitant and Further Therapy

Concomitant medications will be listed and summarized by treatment group. The frequency and types of further anticancer therapies started after study treatment discontinuation will be summarized.

9.3.5. Treatment Compliance

Treatment administration will be summarized by treatment. Summary statistics for duration of therapy (weeks) and the number of cycles per participant will be presented. The frequency

of dose reductions, interruption and holds as well as dose intensity will be summarized. Details will be provided in the SAP.

9.3.6. Efficacy Analyses

9.3.6.1. Primary Efficacy Analyses

For the primary endpoint of PFS by investigator assessment, the 2 treatment groups will be compared using a 2-sided stratified log-rank test at significance level of 0.05. Estimation of the HR and the 95% CI will be based upon the stratified Cox regression model. Kaplan-Meier methodology will be used to estimate the PFS time curves, including the median. Both stratified log-rank and Cox regression models will take into account the stratification factors for randomization. If the sample size of 1 stratum from a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a stratum to be included in the statistical model will be specified in the SAP. All randomized participants will be included in the primary analysis of PFS. Similar methods will be used for the key and other secondary time-to-event endpoints.

9.3.6.2. Key Secondary Efficacy Analyses

Statistical analysis of the key secondary endpoint of OS will follow the methodology described for primary efficacy analyses (Section 9.3.6.1).

9.3.6.3. Secondary Efficacy Analyses

Statistical analysis of the secondary endpoints of PFS by BICR and CNS-PFS by investigator assessment will follow the methodology described for primary efficacy analyses (Section 9.3.6.1).

9.3.7. Pharmacokinetic Analyses

Individual (participant) plasma tucatinib concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated.

9.3.8. Biomarker Analysis

Relationships of biomarker parameters to efficacy, safety, and PK parameters may be explored. Relationships and associated data that are determined to be of interest may be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.9. Patient Reported Outcomes (PRO) Analyses

Patient -reported outcomes (PRO) assessments based on the CCI and EORTC QLQ-C30 questionnaires will be analyzed to evaluate if treatment affects PRO scores. CCI and time to deterioration (defined as time to 10-point decrease) will be assessed for the EORTC QLQ-C30 global health status/QoL scale, and physical and role function scales. All subscales and individual item scores will be tabulated or plotted. Descriptive summaries of observed data will be provided at each scheduled assessment time point. Further details on the PRO analyses as well as investigation of missing patterns and details of imputation, will be provided in the SAP.

9.3.10. Safety Analyses

Safety is assessed through summaries of AEs, changes in laboratory test results, changes in vital signs and physical examination findings. AEs will be classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE criteria.

9.3.10.1. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study intervention. In the event of multiple occurrences of the same AE with the same preferred term in 1 participant, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study intervention will be summarized and listed in the same manner.

9.3.10.2. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.10.3. Clinical Laboratory Results

For laboratory values (eg, chemistry and hematology), summary statistics for actual values and for change from baseline may be tabulated as appropriate by treatment arms. Laboratory values will be listed with grade per NCI-CTCAE version 5.0 and flagged when values are outside the normal reference range.

Additional analytical methods for a more thorough investigation of LFTs (including temporal/simultaneous summaries and figures) will be specified in the SAP.

9.3.10.4. Other Safety Analyses

9.3.10.4.1. Vital Signs and Physical Examinations

Post-baseline clinically significant vital signs and abnormal physical examination findings may be collected as AEs.

9.3.10.4.2. ECOG Status

ECOG status will be listed. Shifts from baseline to the best and worst post-baseline score may be tabulated.

9.3.10.4.3. MUGA or Echocardiogram

Assessment of cardiac ejection fraction will be performed by MUGA scan or echocardiogram at screening and at least once every 12 weeks thereafter until treatment discontinuation, and at the EOT visit (unless done within 12 weeks prior to the EOT visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent echocardiogram

or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

Cardiac ejection fraction data will be summarized by treatment group by baseline and post-baseline assessment. Corresponding shift tables will also be provided by treatment group and baseline and post-baseline assessment.

9.3.11. Interim Analyses

No interim analyses will be performed for the primary endpoint. CCI

The stopping boundaries will be determined using Lan-DeMets spending functions for the O'Brien and Fleming boundaries.

An E-DMC will regularly review all relevant unblinded safety data as outlined in a separate E-DMC charter. After approximately 30 participants are randomized and have received at least 2 cycles of study treatment, the E-DMC will convene to review safety data. Enrollment will continue during the initial safety assessment of these 30 participants. Ad hoc meetings of the E-DMC may be held upon the request of the sponsor or E-DMC.

10. REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

10.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in a secure location with access by authorized personnel only to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal

data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

For clinical sites covered by the General Data Protection Regulation (GDPR), personal data in this study will be protected in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) including those which govern the transfer of data and the management of any potential personal data breaches. The sponsor will ensure equivalent guarantees regarding personal data protection standards before transferring the encoded data to non-EU countries by the use of standard contractual clauses which are included in data protection agreements. In accordance with the GDPR, clinical sites must immediately report security incidents to the Sponsors' Clinical Research Associate as well as to the Sponsor Data Protection Officer at privacy.officer@pfizer.com and to the site's data privacy officer for evaluation of a potential personal data breach and reporting requirements.

For all other clinical sites, in the event of a security incident or potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notification as required by law.

10.4. Committees Structure

10.4.1. Data Monitoring Committee

This study will use an E-DMC. The E-DMC is independent of the Pfizer study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities and investigators, as appropriate.

10.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of “bonafide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.6. Data Quality Assurance

All participant data relating to the study will be recorded on an electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

The investigator must permit study related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or onsite monitoring), are provided in the Data Management Plan and clinical monitoring plan, as well as centralized monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document for ePROs. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source document and its origin can be found in the Source Document Identification Log, which is maintained by the site.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered on the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.8. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered

closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of tucatinib, participants may continue to receive tucatinib as per Section 5.9 and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 3.1.4.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address,

city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).
- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US licensed physicians or other healthcare professionals. All authors will have access to the

relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

10.11. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent, which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

10.12. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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Appendix A. ECOG Performance Status

ECOG	
Score	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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Appendix B. RECIST Version 1.1 Criteria

RECIST v1.1 is to be used to assess all sites of disease. Selected sections from RECIST v1.1 criteria are provided below. For detailed guidelines, see study binder and/or published guideline ([Eisenhauer 2009](#)).

Measurability of Tumor Lesions at Baseline

Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least 1 dimension [longest diameter to be recorded] with a minimum size of 10 mm with spiral contrast CT scan with slice thickness no greater than 5 mm or if CT scan with slice thickness >5 mm, the minimum lesion size must have a longest diameter twice the actual slice thickness) or non-measurable (all other lesions, including small lesions [longest diameter <10 mm with spiral CT scan] and truly non-measurable lesions). Participants with non-measurable disease may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 4. For participants with non-measurable disease at baseline, progression will be determined based on the appearance of new lesions.

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (approximately 30 days) before the beginning of treatment.

Lesions considered to be truly non-measurable include the following: blastic bone lesions, LMD, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques. Lytic bone lesions and cystic lesions must meet criteria detailed in the study binder and RECIST v1.1.

Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

- Clinical Examination – Clinically detected lesions will be considered measurable only when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is required.
- Contrast CT and MRI – CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional contrast CT and MRI should be performed with

contiguous cuts of 10 mm or less in slice thickness. Spiral contrast CT should be performed by use of a 5-mm or less contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, whereas head and neck tumors and those of the extremities usually require specific protocols.

Tumor Response Evaluation

Baseline Evaluation

Assessment of Overall Tumor Burden and Measurable Disease – To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Baseline Documentation of “Target” and “Nontarget” Lesions – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline (this means in instances where participants have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded). Lymph nodes are considered 1 organ. Only 2 lymph nodes should be measured as target lesions (Schwartz 2016). Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

New Lesions

If a new lesion is equivocal (for example because of its small size [< 5 mm in diameter] or due to differences in scanning technique) therapy should be continued, and follow-up assessment performed will confirm whether it represents truly new disease.

Lesions identified in anatomic locations not scanned at baseline and > 5 mm in diameter are considered new.

New lesions identified on ultrasound should be confirmed on contrast CT/MRI.

Treatment Effect or Pseudoprogression or Equivocal Progression

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or treatment effects in existing lesions) in clinically stable participants, treatment may continue until the next scheduled assessment or until unequivocal progression is confirmed.

Response Criteria

Evaluation of Target Lesions – This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: CR—the disappearance of all target lesions; PR—at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters; PD—at least a 20% increase in the sum of the of diameters of target lesions, taking as reference the smallest sum of diameter recorded since the treatment started or the appearance of 1 or more new lesions; SD—neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameter since the treatment started.

Evaluation of Non-target Lesions – This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: CR—the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/SD—the persistence of 1 or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; and PD—the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response – The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

Overall Responses for All Possible Combinations of Tumor Responses in Target and Non-Target Lesions With or Without the Appearance of New Lesions^{a,b}

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

a Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).

b In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the CR status).

Frequency of Tumor Re-Evaluation – Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment.

Appendix C. Guidance on Contraception

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 1 week after the last dose of tucatinib, 6 months after the last dose of pertuzumab, or 7 months after the last dose of trastuzumab; see Section 4.1). If a subject is abstinent meeting the above definition, a second form of effective birth control is not required.

Acceptable Effective Methods of Birth Control (Contraception)

Subjects who are of childbearing potential or whose partners are of childbearing potential, and who are sexually active in a way that could lead to pregnancy must choose TWO of the following acceptable methods of birth control (contraception), at least ONE of which must be highly effective:

Highly Effective Methods of Birth Control	Effective Methods of Birth Control
Abstinence (as defined above)	Progestin-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
Combined (estrogen and progestin containing) oral, intravaginal, or transdermal hormonal contraception with inhibition of ovulation	Male or female condom with or without spermicide
Oral, implantable, or injectable progestogen-only hormonal contraception associated with inhibition of ovulation	Cap, diaphragm, or sponge with spermicide
Intrauterine hormone-releasing system	A combination of a male condom with either a cap, diaphragm, or sponge with spermicide (double barrier)
Intrauterine device with failure rate <1%	
Bilateral tubal occlusion/ligation	
Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)	

The following methods of birth control (contraception) are not considered acceptable or effective

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method (LAM)

Appendix D. CYP3A4 Inducers and Their Elimination Half-Lives

Cytochrome P450 (CYP) 3A4 inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug ^{a,b}	Elimination Half-Life ^c (hours, unless indicated otherwise)
Strong Inducers	
Apalutamide	3 days ^a
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Enzalutamide	5.8 days ^b
Mitotane	18 to 159 days ^c
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours ^g

Note: Any additional CYP3A4 inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers” (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency>).

b EMA. “Guideline on the investigation of drug interactions” (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf).

c Drug product labeling.

d ERLEADA drug label 2018.

e XTANDI drug label 2018.

f LYSODREN drug label 2017.

g (Kerb 1996)

Appendix E. CYP2C8 Inhibitors/Inducers of CYP2C8 and Their Elimination Half-Lives

Drug ^{a, b}	Elimination Half-life ^c (hours)
Strong Inhibitors	
Clopidogrel	6 hours
Gemfibrozil	1–2 hours
Montelukast	3–6 hours
Moderate Inducer	
Rifampin	3–5 hours

a FDA. “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers” (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency>).

b EMA. “Guideline on the investigation of drug interactions”

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

c Drug product labeling

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

Appendix F. Examples of Clinical Substrates for CYP3A-Mediated Metabolism

Sensitive (AUC increase ≥ 5 -fold with strong index inhibitor)	Moderate Sensitive (AUC increase 2 to 5-fold with strong index inhibitor)
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir ^c , ebastine, everolimus, ibrutinib, lomitapide, lovastatin ^d , midazolam, naloxegol, nisoldipine, saquinavir ^c , simvastatin ^d , sirolimus, tacrolimus, tipranavir ^c , triazolam, vardenafil	alprazolam, aprepitant, atorvastatin ^a , colchicine, eliglustat ^b , pimozone, rilpivirine, rivaroxaban, tadalafil
budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir ^c , lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolcapten	

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 5 -fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥ 2 to < 5 -fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥ 10 -fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010).

a Listed based on pharmacogenetic studies.

b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.

d Acid form is an OATP1B1 substrate.

Source:

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1>

Appendix G. ADVERSE EVENTS: DEFINITIONS and PROCEDURES for RECORDING and REPORTING

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs via PSSA to Pfizer Safety throughout the safety reporting period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

Table 8: Requirements for Recording AEs on the CRF and for Reporting SAEs via PSSA

Safety Event	Recorded on the CRF	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB Note: Instances of EDP or EDB not associated with an AE or SAE are not captured on the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE) **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety via PSSA.

****EDB** is reported to Pfizer Safety via PSSA, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety via PSSA.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception

of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

SAE Reporting to Pfizer Safety via an electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

Appendix H. Country-Specific Requirements

European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The sponsor will notify EU Member States concerned of the following:

- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event
- Any serious breach, as described in Section 10.1.1, no later than 7 days of becoming aware of that breach
- Any urgent safety measure, as described in Section 10.1.1, no later than 7 days of the measure being taken
- Any inspection report of a third-country authority concerning the study

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other pean Union law.

France

Contrat Unique

1. GCP Training
Before enrolling any participants, the investigator and any sub-investigators will complete the Pfizer provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.
2. Study Intervention
No participants or third-party payers will be charged for study intervention.
3. Urgent Safety Measures
In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.
4. Termination Rights
Pfizer retains the right to discontinue development of tucatinib at any time.

China

Biomarker sample collection and analysis will not be performed in China. Additionally, the changes described in [Table 9](#) are applicable in China.

Table 9: Summary of China-specific Changes

Section	Description of Change
Synopsis, Study Treatment, Dose, and Mode of Administration); also applicable to Section 3.1 Summary of Study Design; Section 5.1 Treatments Administered (see also Section 3.2.2.4 below)	In the Synopsis, Section 3.1, and Section 5.1, the following text is not applicable for China: “Fixed dose combination of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.”
Synopsis, Biomarker Assessments,	In the Synopsis, Biomarker Assessments, the following text is not applicable to China: CCI [REDACTED] See Appendix H for further information.”
Synopsis, Schedule of Events	Footnotes U, V, and W related to biomarker collection are not applicable to China
Section 2, Objectives	In Section 2 Objectives, the following text is not applicable to China: Exploratory Objective: CCI [REDACTED] Corresponding Exploratory Endpoints: CCI [REDACTED]
Section 3.2.2.4 Trastuzumab + Pertuzumab	In Section 3.2.2.4, the following text is not applicable to China: A fixed dose combination of trastuzumab + pertuzumab (pertuzumab, trastuzumab, and hyaluronidase) will be administered SC every 3 weeks at the dose and schedule specified in the trastuzumab + pertuzumab label for treatment of participants with advanced HER2+ breast cancer.
Section 5.1.4 Trastuzumab + Pertuzumab	Section 5.1.4 and all subsections (5.1.4.1 through 5.1.4.5) are not applicable in China (trastuzumab + pertuzumab is not a treatment option in China)
Section 5.2.4 Trastuzumab + Pertuzumab	Section 5.2.4 is not applicable in China (trastuzumab + pertuzumab is not a treatment option in China)

Table 9: Summary of China-specific Changes

Section	Description of Change
Section 5.5.3.1 Trastuzumab and Pertuzumab subsection of Left Ventricular Dysfunction and Cardiomyopathy	In China, Section 5.5.3.1 is adjusted to read as follows: Trastuzumab and pertuzumab can cause asymptomatic decline in LVEF and left ventricular cardiac dysfunction, including congestive heart failure. Trastuzumab can also cause arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab and pertuzumab dose modification guidelines for left ventricular dysfunction, regardless of relationship to study drug, are provided in Table 6.
Section 5.5.5.1 Trastuzumab + Pertuzumab (this is a subsection of Section 5.5.5 Injection Related Reaction and its Management)	Section 5.5.5.1 is not applicable to China (trastuzumab + pertuzumab is not a treatment option in China)
Section 6.2.3 Baseline Visit (Day2 -7 to Day 1),	In Section 6.2.3, the following text is not applicable to China: Blood sample for biomarker (see Schedule of Events)
Section 6.3.1 Day 1 (±2d)	In Section 6.3.1, the following text is not applicable to China: Blood sample for biomarker at Cycle 3 predose
Section 7.2.1 Confirmation of HER2 Expression for Study Eligibility	In Section 7.1.1, the following text is not applicable to China: “....as well as biomarker analyses.”
Section 7.4 Pharmacokinetic Assessments, Table 7	In China, Table 7 is as follows: Table 7: Pharmacokinetic and Tumor Tissue Sample Collection Timepoints

Table 9: Summary of China-specific Changes

Section	Description of Change																																																								
	<table><tr><td></td><td>Study day</td><td>Time</td><td>Window</td><td>Relative Time</td><td>PK Blood Samples</td><td>FFPE Tumor Specimen</td></tr><tr><td>Pre-screening</td><td>-6 months to Day -29</td><td>N/A</td><td>N/A</td><td>N/A</td><td></td><td>X</td></tr><tr><td>Screening</td><td>Day -28 to 1</td><td>N/A</td><td>N/A</td><td>N/A</td><td></td><td>X^a</td></tr><tr><td>Baseline</td><td>Day -7 to 1</td><td>N/A</td><td>N/A</td><td>N/A</td><td>X</td><td></td></tr><tr><td>Cycle 2</td><td>Day 1</td><td>Predose</td><td>Should be taken within 2 hours prior to administration of tucatinib.</td><td>Time of administration of tucatinib</td><td>X</td><td></td></tr><tr><td>Cycle 3</td><td>Day 1</td><td>Predose, Post-dose</td><td>N/A CCI</td><td>Time of administration of tucatinib</td><td>X</td><td></td></tr><tr><td>Cycles 4, 5, and 6</td><td>Day 1</td><td>Predose</td><td>N/A</td><td>Time of administration of tucatinib</td><td>X</td><td></td></tr><tr><td colspan="5">End of Treatment</td><td>X</td><td></td></tr></table> FFPE=formalin-fixed paraffin-embedded; N/A=not applicable. ^a If not obtained during pre-screening.		Study day	Time	Window	Relative Time	PK Blood Samples	FFPE Tumor Specimen	Pre-screening	-6 months to Day -29	N/A	N/A	N/A		X	Screening	Day -28 to 1	N/A	N/A	N/A		X ^a	Baseline	Day -7 to 1	N/A	N/A	N/A	X		Cycle 2	Day 1	Predose	Should be taken within 2 hours prior to administration of tucatinib.	Time of administration of tucatinib	X		Cycle 3	Day 1	Predose, Post-dose	N/A CCI	Time of administration of tucatinib	X		Cycles 4, 5, and 6	Day 1	Predose	N/A	Time of administration of tucatinib	X		End of Treatment					X	
	Study day	Time	Window	Relative Time	PK Blood Samples	FFPE Tumor Specimen																																																			
Pre-screening	-6 months to Day -29	N/A	N/A	N/A		X																																																			
Screening	Day -28 to 1	N/A	N/A	N/A		X ^a																																																			
Baseline	Day -7 to 1	N/A	N/A	N/A	X																																																				
Cycle 2	Day 1	Predose	Should be taken within 2 hours prior to administration of tucatinib.	Time of administration of tucatinib	X																																																				
Cycle 3	Day 1	Predose, Post-dose	N/A CCI	Time of administration of tucatinib	X																																																				
Cycles 4, 5, and 6	Day 1	Predose	N/A	Time of administration of tucatinib	X																																																				
End of Treatment					X																																																				
Section 7.5 Biomarker Assessments	Section 7.5 is not applicable in China																																																								
Section 7.5.1 Characterization of Tumor Tissue	In Section 7.5.1, the following text is not applicable in China: CCI Samples will be collected where permitted as per local regulations																																																								
Section 7.5.2 Characterization of Blood Samples	Section 7.5.2 is not applicable in China																																																								
Section 7.6 Biospecimen Repository	Section 7.6 is not applicable in China.																																																								
Section 9.2.4.1 CCI	Section 9.2.4.1 is not applicable in China.																																																								

Table 9: Summary of China-specific Changes

Section	Description of Change
Section 9.3.3 Participant Characteristics	In China, Section 9.3.3 is adjusted to read as follows: Demographics and other baseline characteristics, including age, gender, ethnicity, race, and ECOG, will be summarized. Details will be provided in the SAP
Section 9.3.8 Biomarker Analysis	Section 9.3.8 is not applicable in China.

United Kingdom

The changes described in [Table 10](#) are applicable in the United Kingdom.

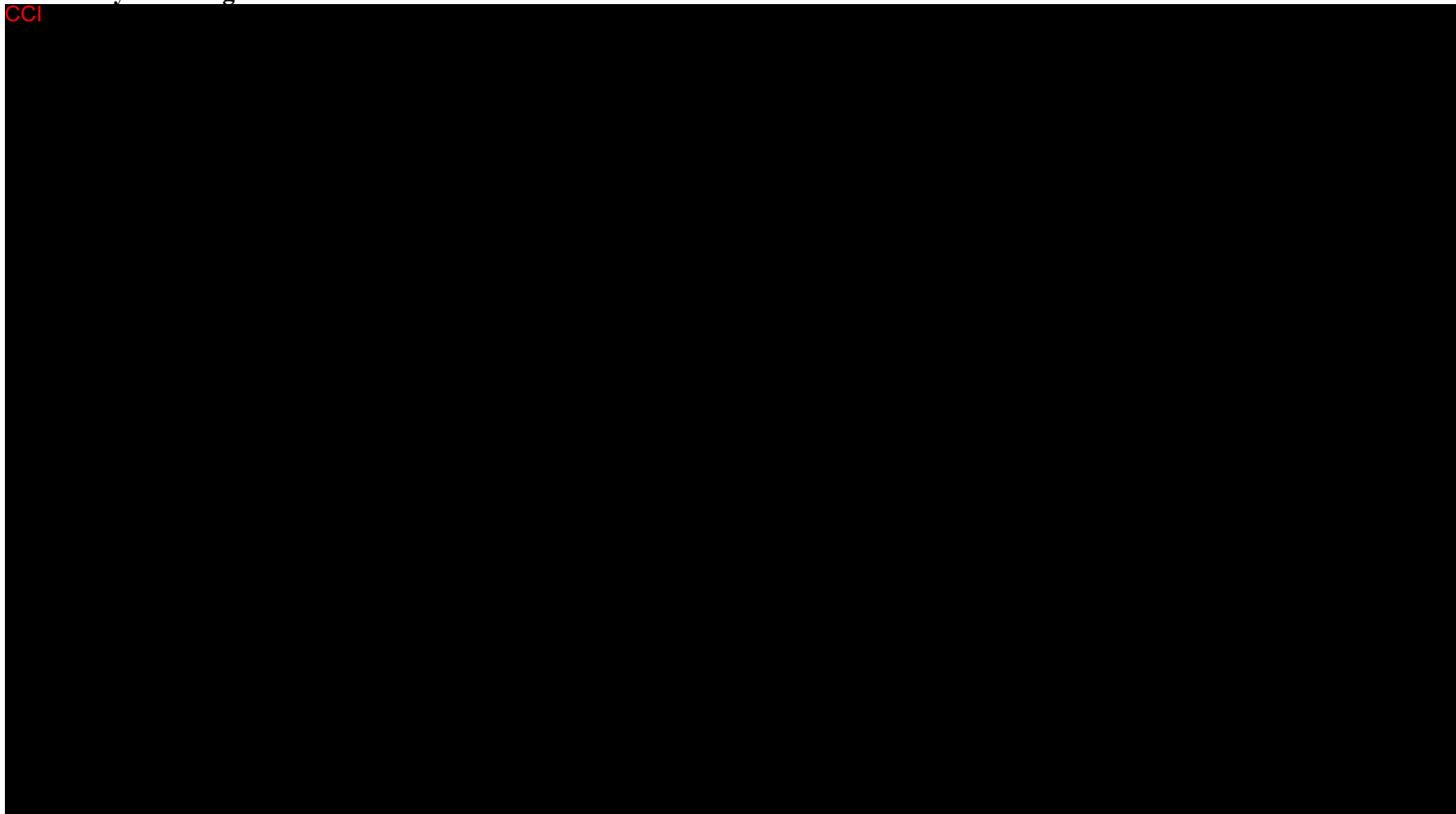
Table 10 Summary of UK-specific Changes

Section(s)	Change	Rationale
Synopsis, Section 4.1	Inclusion Criteria #11a: “A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.” Added: “Documentation must include either an ultrasound or repeat pregnancy test to verify the false-positive nature of the pregnancy test.”	To clarify “documented verification” as an ultrasound or repeat pregnancy test
	Inclusion Criteria #11d, 12b: Updated contraceptive inclusion criteria for subjects of child-bearing potential to include “at least 2 acceptable methods of birth control (contraception), at least 1 of which must be highly effective”	For consistency with Appendix C
Appendix C	Updated Guidance on Contraception to define effective and highly effective methods of birth control.	To clarify definitions of effective and highly effective methods of birth control in alignment with CTFG guidance

Appendix I. Summary of Changes for Prior Amendments

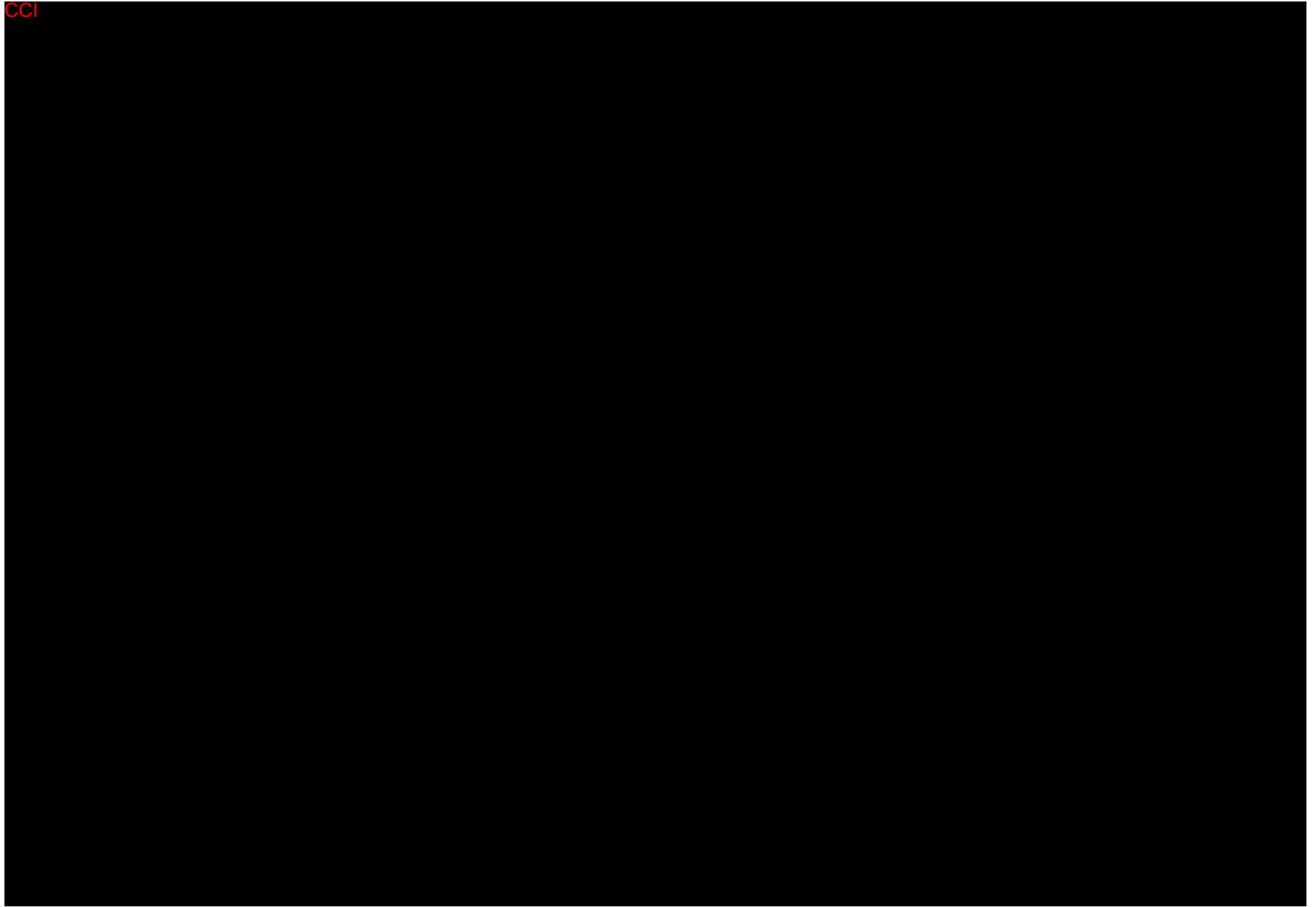
Summary of Changes in Amendment 01

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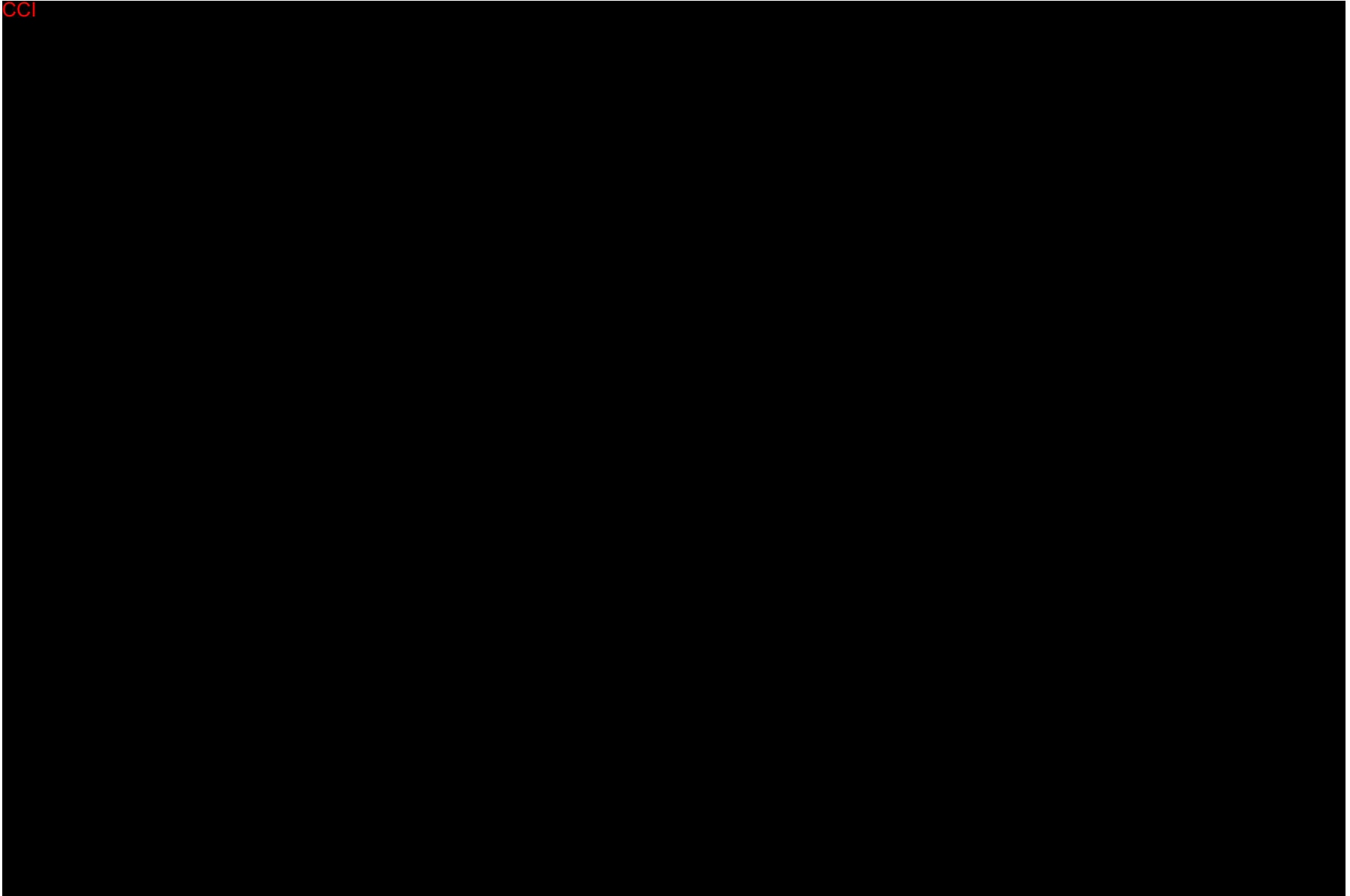
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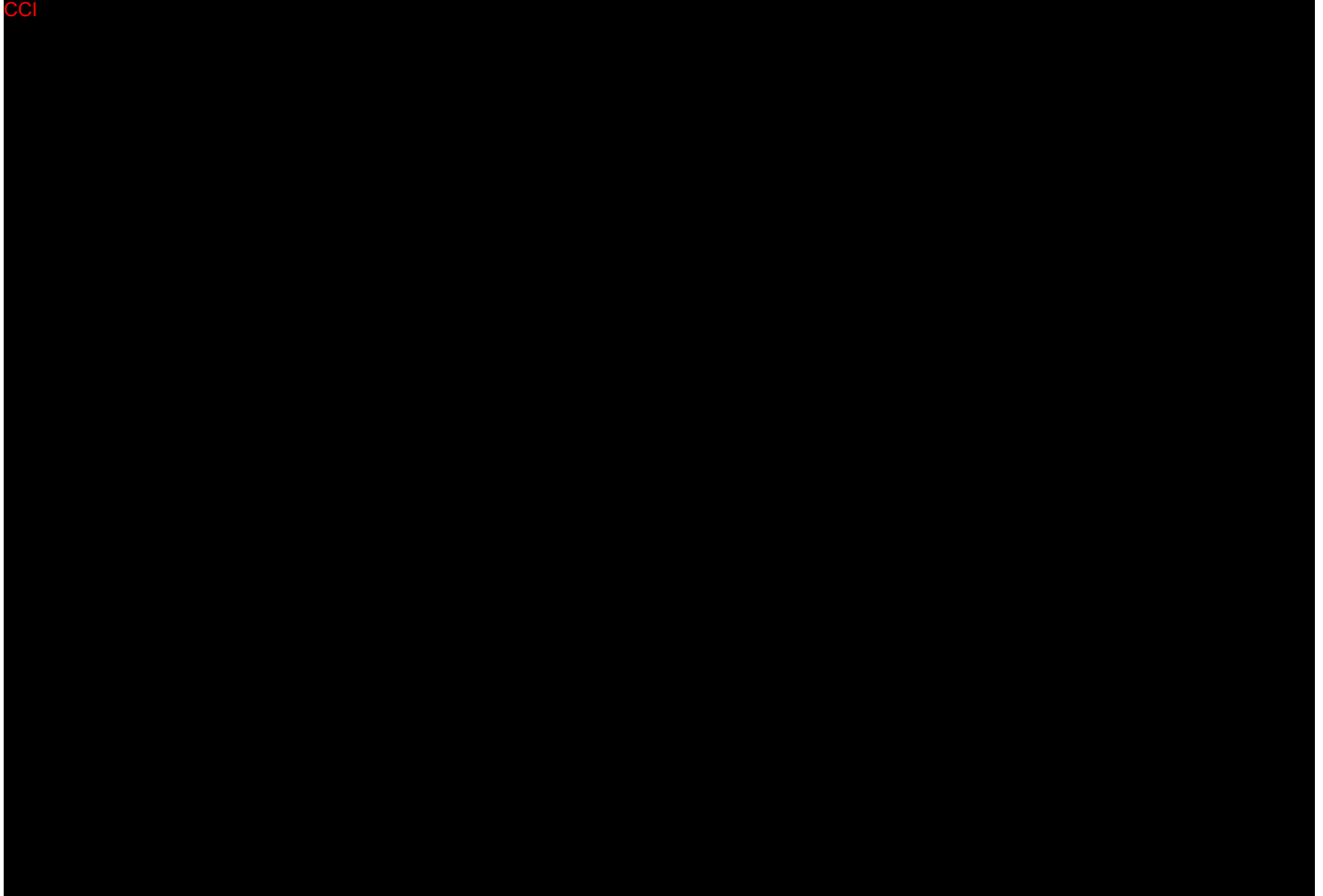
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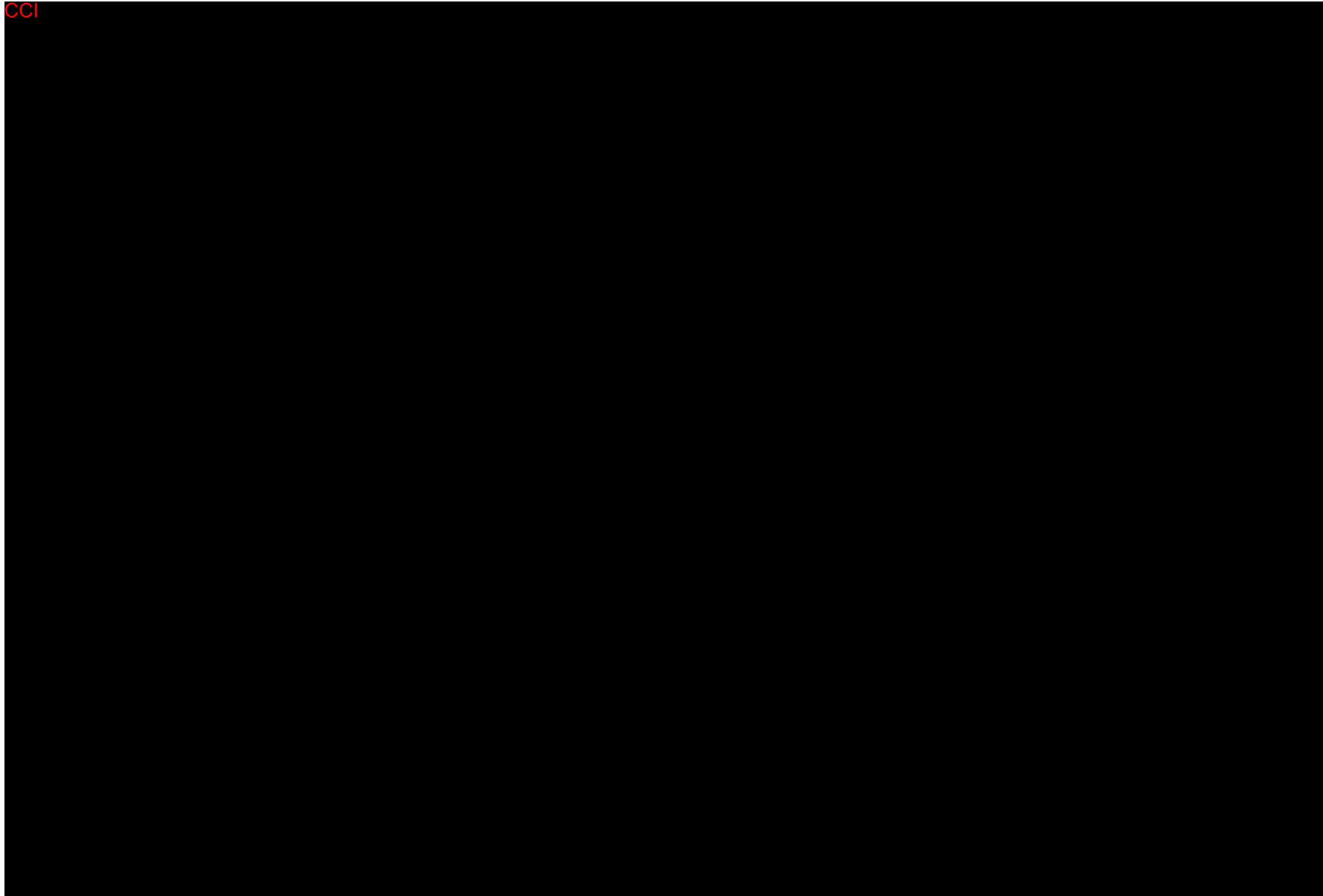
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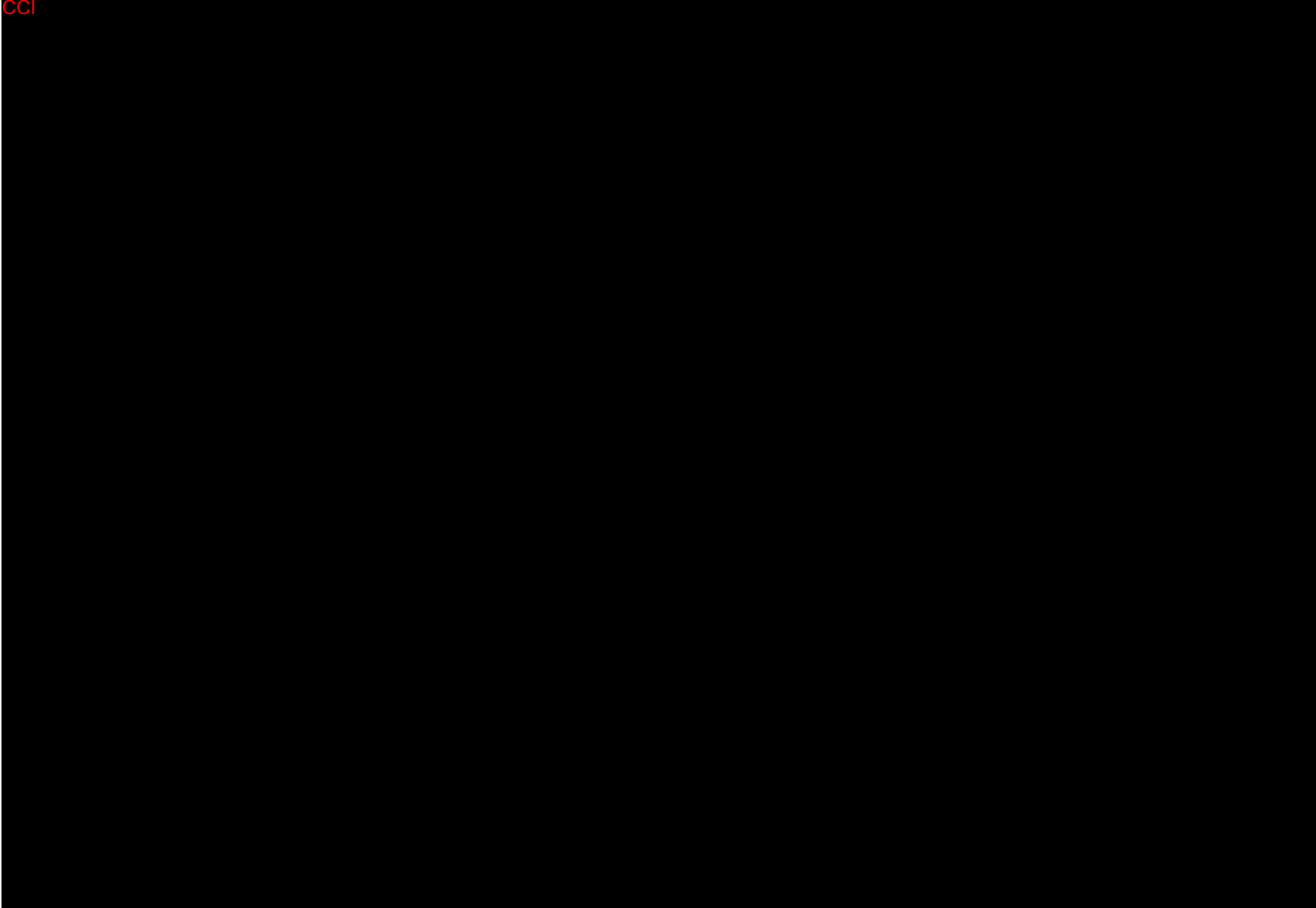
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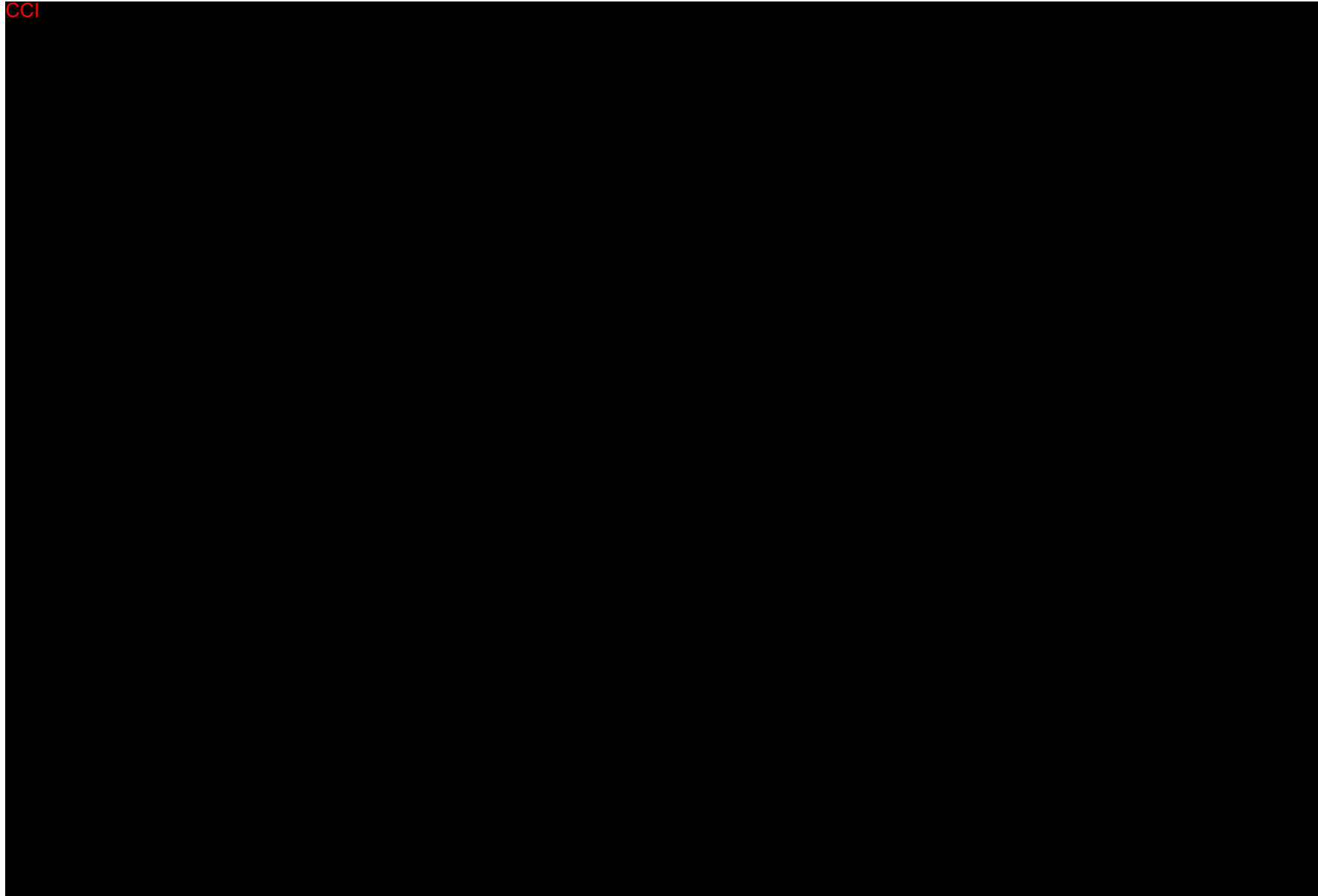
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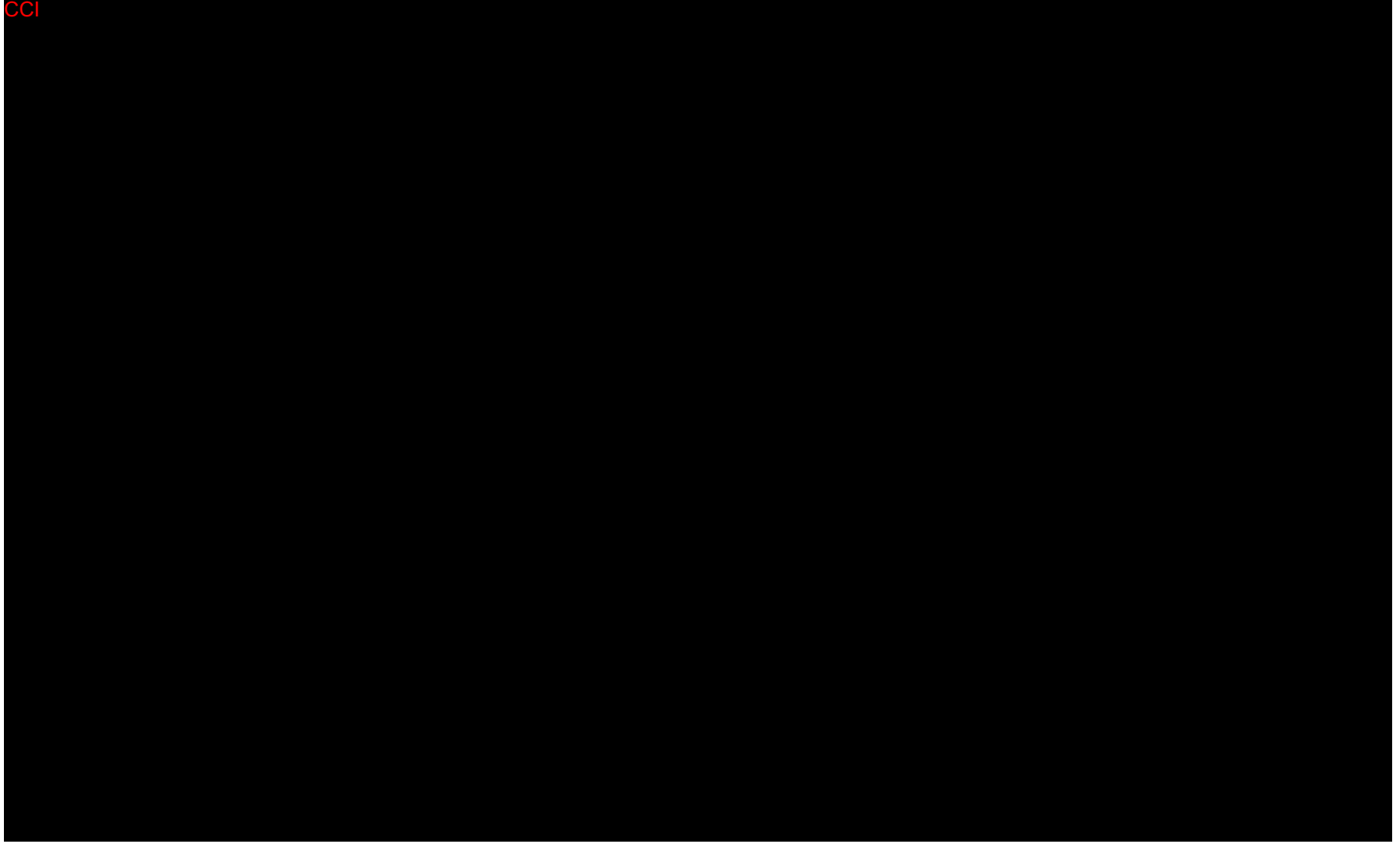
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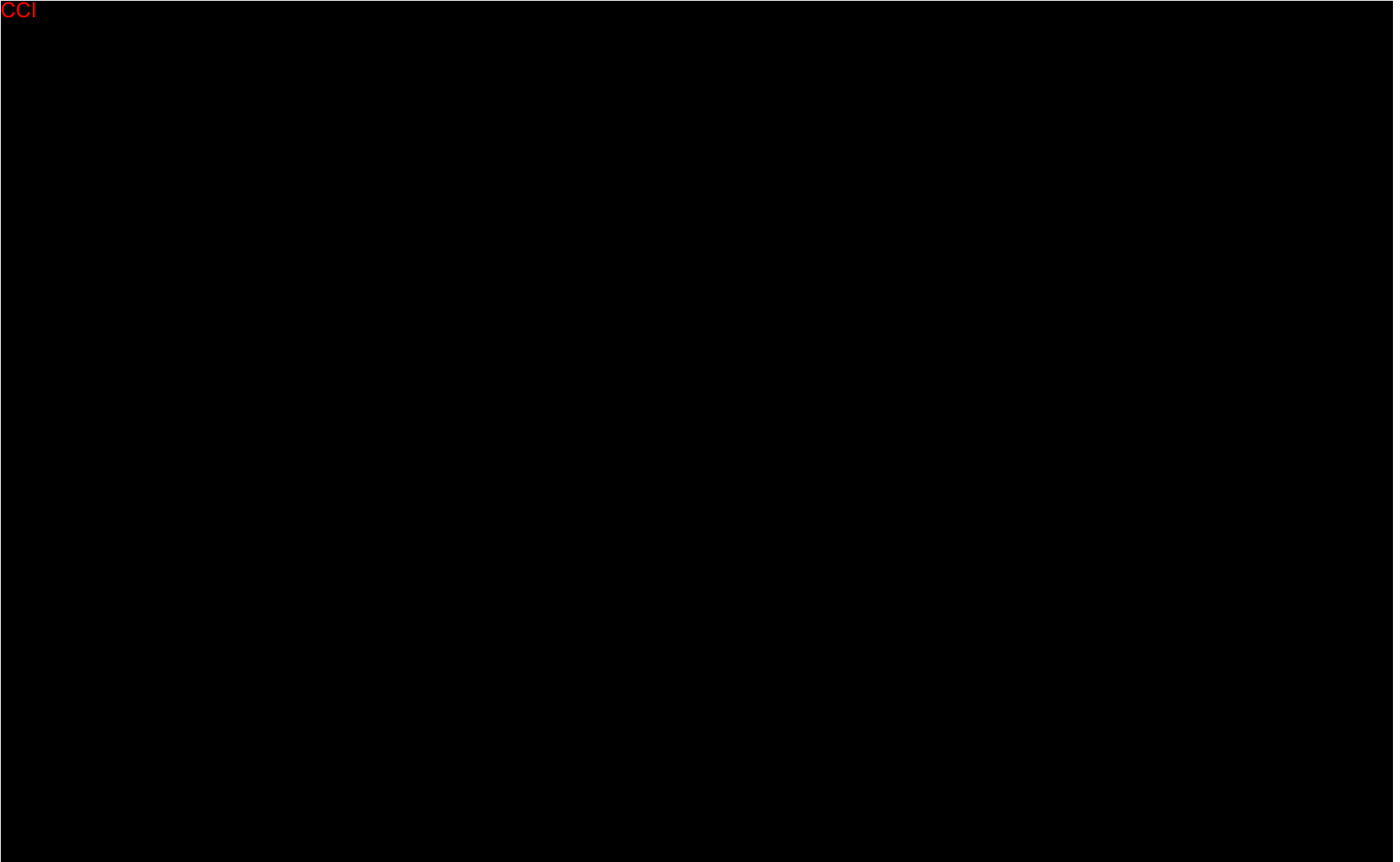
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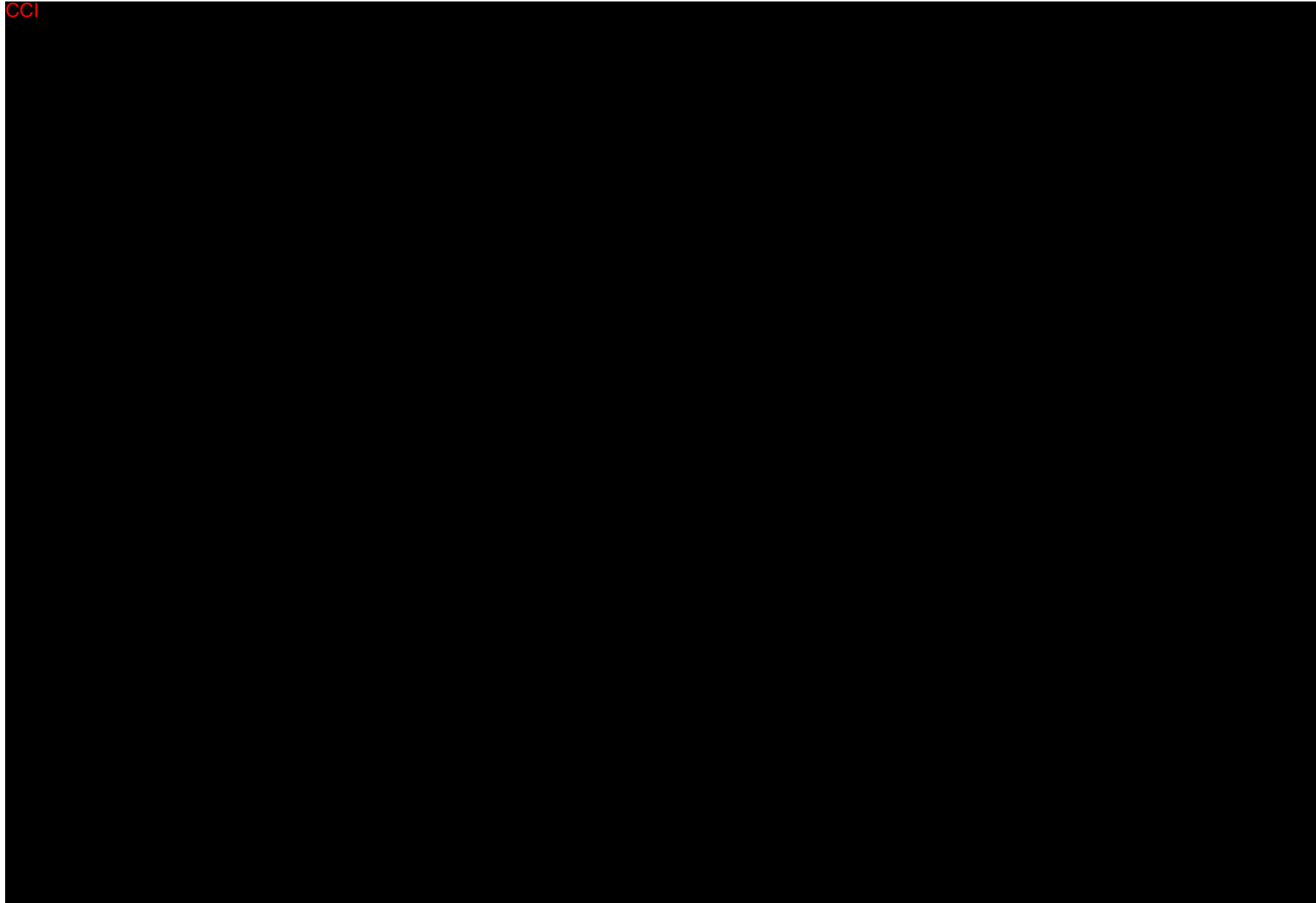
Summary of Changes in Amendment 02

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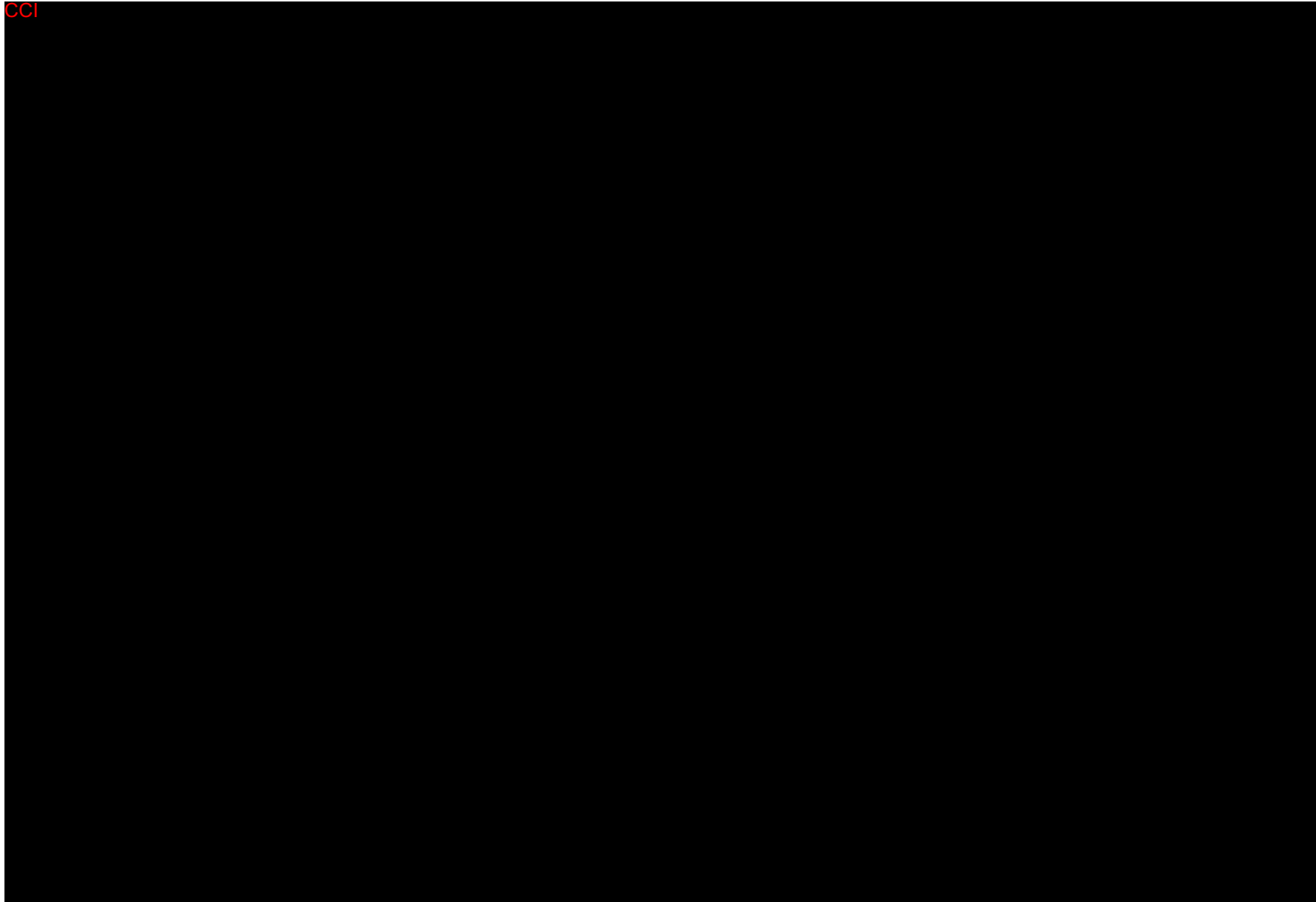
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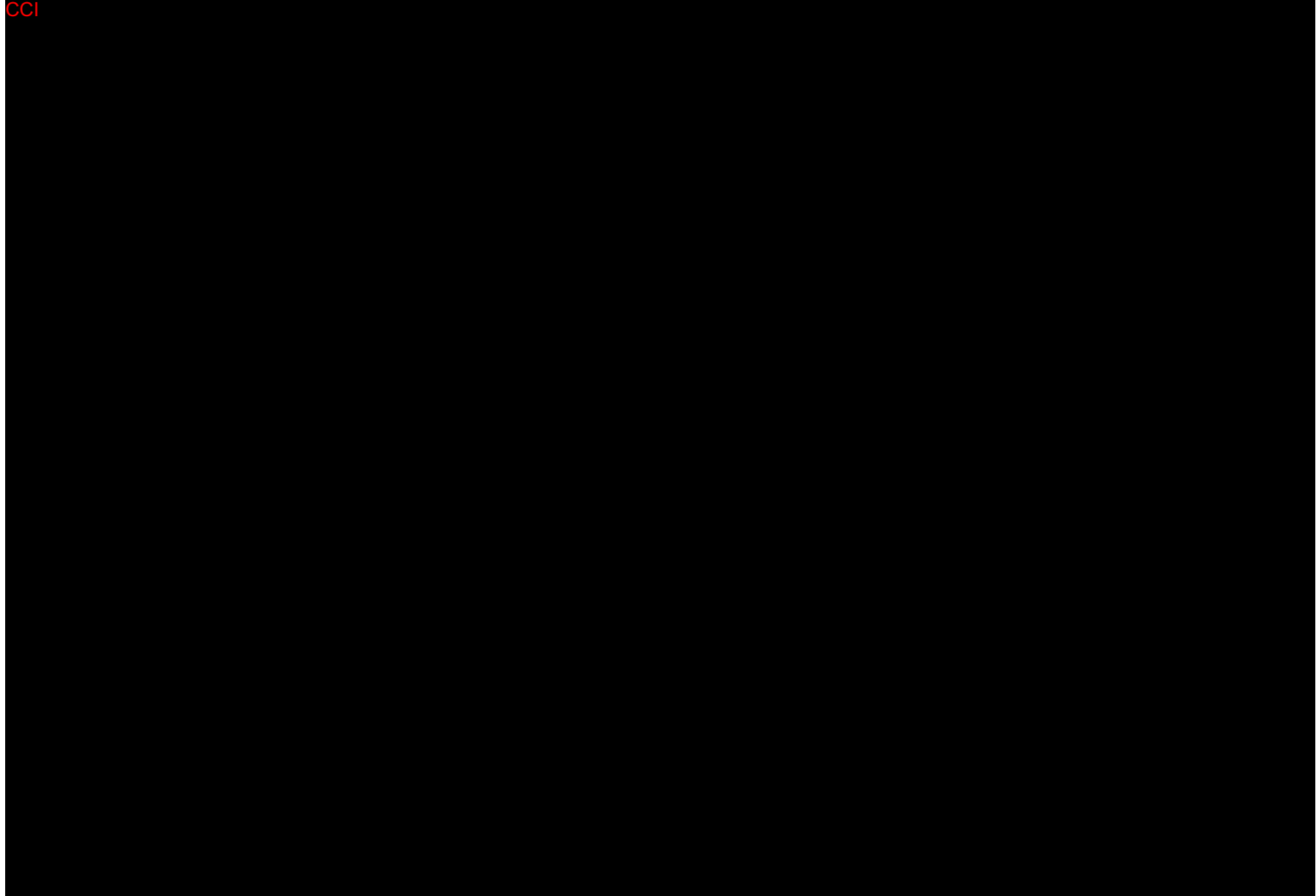
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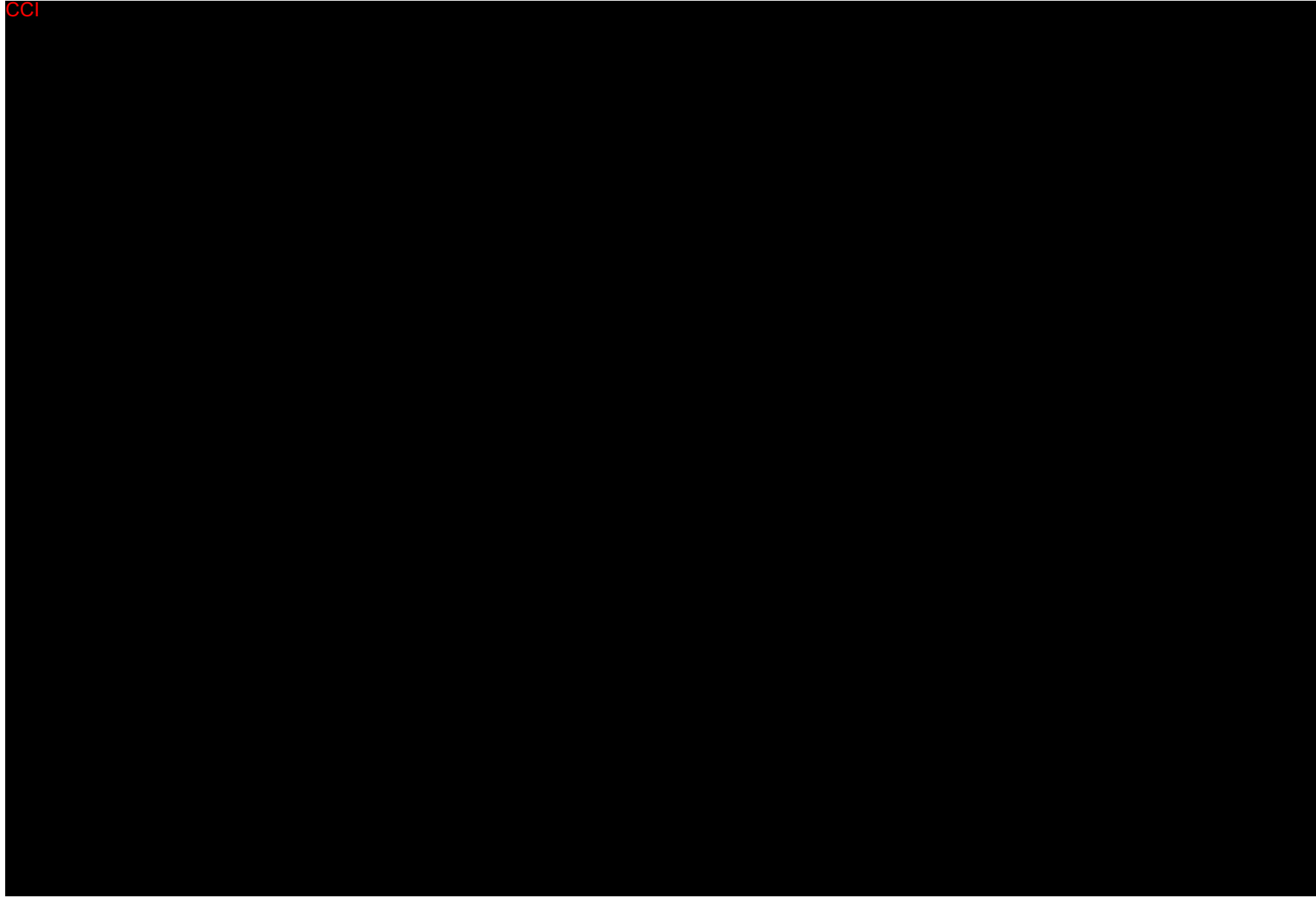
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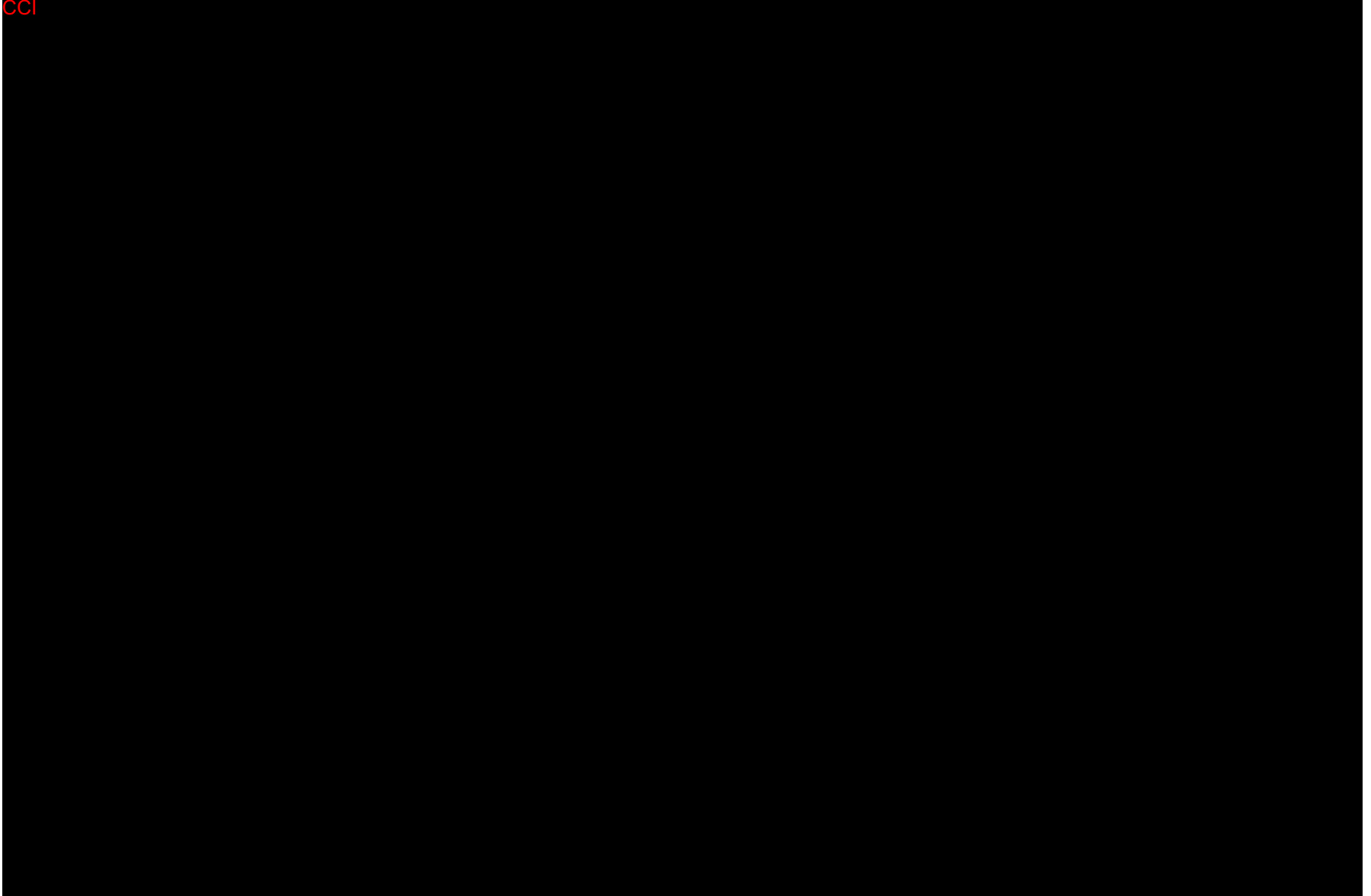
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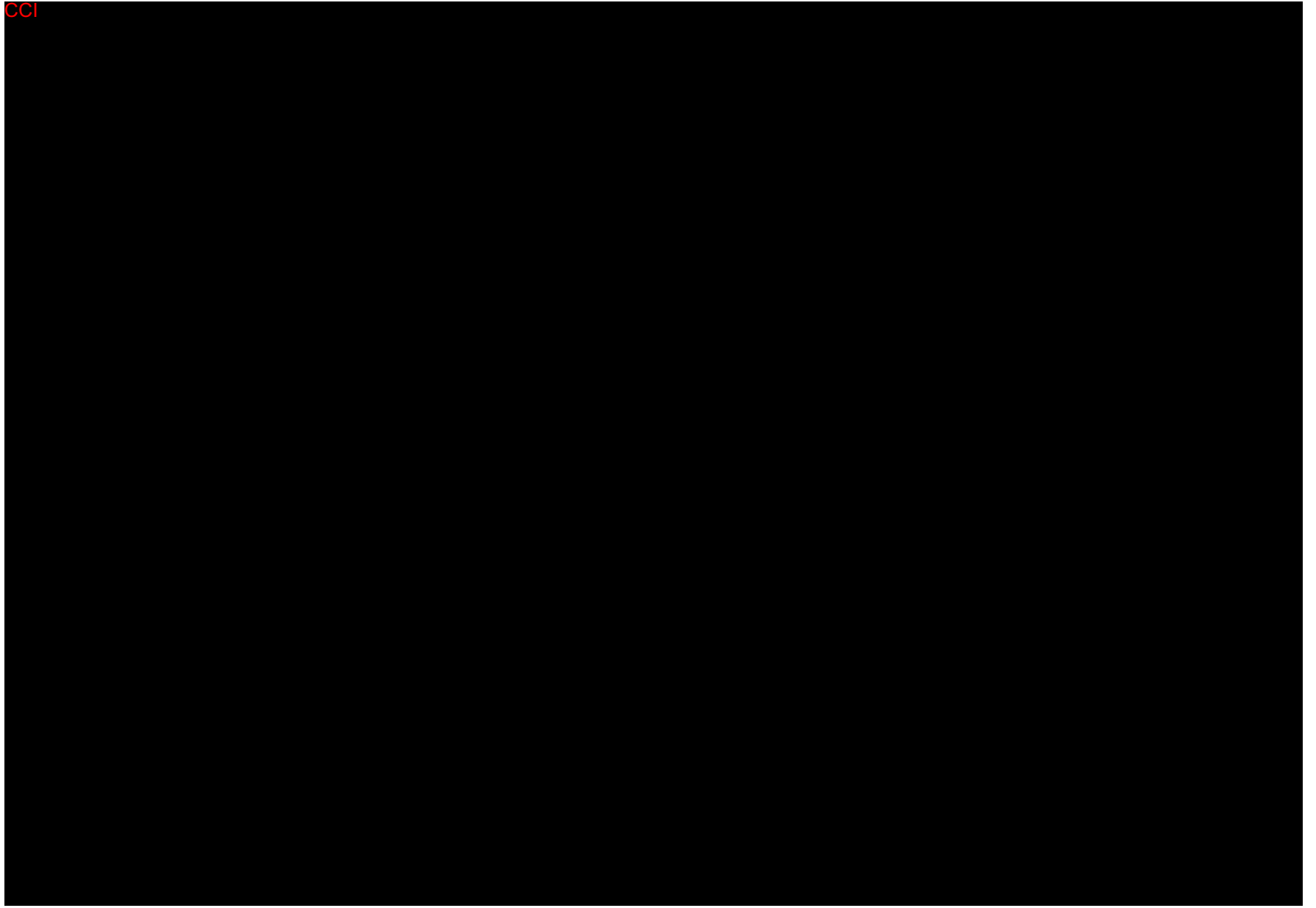
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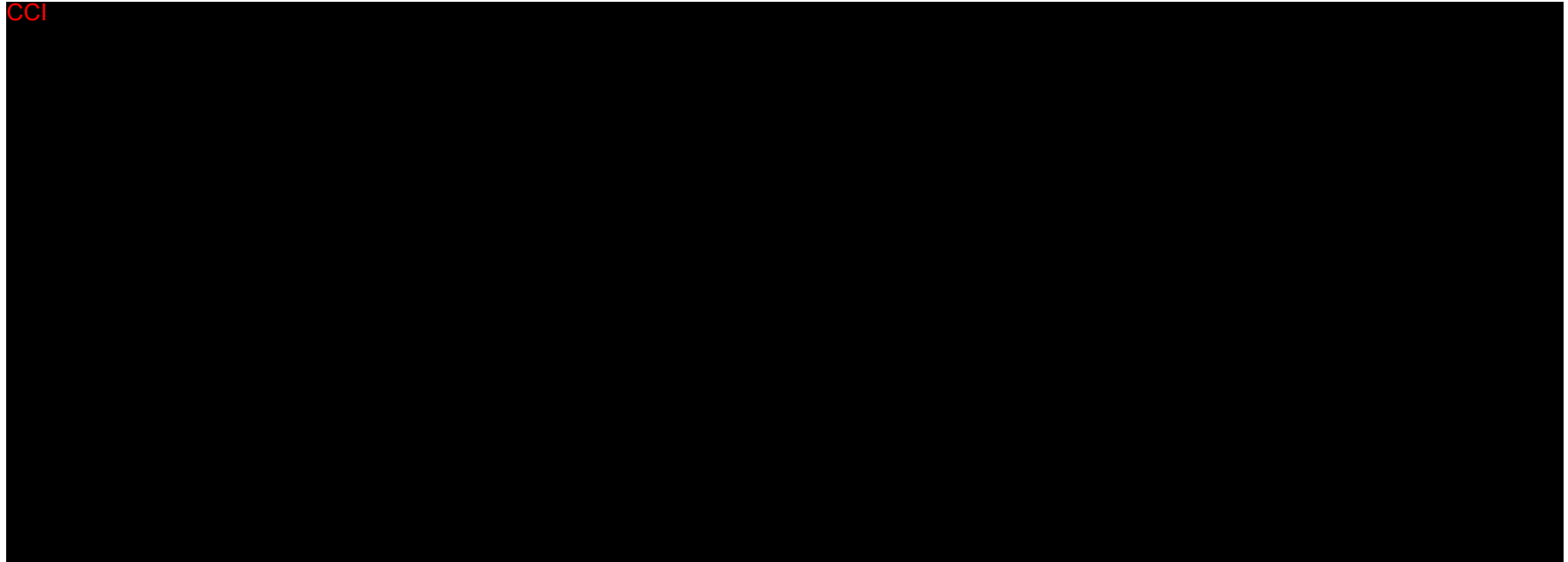
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