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Clinical Protocol

Study CS3008(BLU-554)-101

Study Title: A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Document Date: 28Jul2020

NCT Number: NCT04194801

A Multi-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Version 2.1

Clinical Study Protocol

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Protocol No.:	**CS3008 (BLU-554) - 101**
Version Number:	**V. 2.1/Jul. 28, 2020**
Investigational Drug:	**CS3008(BLU-554); CS1001**
Study Phase:	**Phase Ib/II**
Sponsor:	**CStone Pharmaceuticals (Suzhou) Co., Ltd.** **CStone Pharmaceuticals (Shanghai) Co., Ltd.** Unit E618, 2F, North Tower, Building A1, SIP BioBay, 218 Xinghu Street, Suzhou Industrial Park, Suzhou, China Room 211-20, 2nd Floor, Building 1, No. 38, Debao Road, Experimental Zone, Free Trade Zone, Shanghai, China Blueprint Medicines Corporation 45 Sidney Street Cambridge, MA 02139, USA

Signature Page

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This protocol is a confidential document of **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.** for confidential circulation. I confirm I have read through and understand this protocol and will follow the protocol in the study. Furthermore, I will abide by the ethics principles in Declaration of Helsinki and GLP and applicable laws and regulations during the study. By signing for this document, I agree that I will not make public or disclose any non-public information herein without prior written permission from **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.**

Note to investigator: Please sign your name and date on this signature page. Fill in the printed names of you and your site where this trial will be conducted. A copy of this signature page will be returned to **CStone Pharmaceuticals (Suzhou) Co., Ltd. and CStone Pharmaceuticals (Shanghai) Co., Ltd.**

I have read through the full text of the protocol and agree to follow it in the study.

Investigator Name: _____

_____ _____

Investigator Signature **Date**

Protocol Approval Page

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CStone Pharmaceuticals will carefully fulfill the duties of sponsors according to current Good Clinical Practice of relevant countries and regions and be responsible for the initiating, submitting, organizing, sponsoring and monitoring this clinical study. Patients with serious adverse events during the clinical study will be provided with active intervention and the corresponding treatment expense will be covered by sponsor according to applicable national regulatory requirements. Adequate financial compensation will be offered to subjects who experience damage confirmed to be consequence of investigational product-induced serious adverse effect.

I have participated in the development of and discussion on this study protocol and agree to its contents. I have fully understood sponsor's duties related with this trial protocol and agree to conduct clinical study per this protocol and applicable regulatory requirements.

Sponsor: CStone Pharmaceuticals (Suzhou) Co., Ltd.

CStone Pharmaceuticals (Shanghai) Co., Ltd.

Blueprint Medicines Corporation

_____ _____

[redacted] **Date**

Senior Vice President, Chief Translational Medicine Officer

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1. PROTOCOL SYNOPSIS

1.1. SYNOPSIS

Sponsor: CStone Pharmaceuticals (Suzhou) Co., Ltd., CStone Pharmaceuticals (Shanghai) Co., Ltd., Blueprint Medicines Corporation	
Final product name: NA	
Investigational product: CS3008 (fisogatinib, BLU-554), CS1001	
Names of active substances: Fibroblast growth factor receptor 4 inhibitor, completely humanized IgG4-type recombinant anti- Programmed death ligand 1 (PD-L1) monoclonal antibody	
Title of study:	**A Muti-center, Open-label, Multiple-dose Phase Ib/II Study to Assess the Safety, Tolerability, Pharmacokinetics, Anti-tumor Efficacy of CS3008 (BLU-554) in Combination with CS1001 in Subjects with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC)**
CAT No.:	**JXHL1900045, CXSL900017**
Protocol No.:	**CS3008 (BLU-554) - 101**
Sites:	**20 sites as planned**
Duration of the study (first subject in to last subject out):	**Screening period (28 days prior to the initial administration), treatment period (at most 24 months) and follow-up period (safety follow-up period: at most 90 days; survival follow-up period: every 12 weeks until withdrawl of subjects or termination of study)**
Study Phase:	**Phase Ib/II**

This is a multi-center, open-label, multi-dose, dose-finding and extension study for evaluating the safety, tolerance, pharmacokinetics and antitumor efficacy profiles of BLU-554 in combination with CS1001 in subjects with locally advanced or metastatic HCC.

The study consists of 2 parts, including a Part 1 (phase Ib) dose escalation and part 2 (phase II) dose expansion. Part 1 is a dose escalation study for determination of the MTD (Maximum tolerated dose) and/or RP2D (Recommended Phase II dose) of BLU-554 in the combination regimen and assess primary safety and tolerance of the combination regimen. Part 2 is a dose extension study in which preliminary evaluate the antitumor efficacy and the further evaluate the safety, tolerance, PK and immunogenicity of combination regimen.

Phase 1b: Dose Escalation

Primary Objectives	**Primary Endpoints**
• To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of BLU-554 when being in combination with CS1001 in subjects with locally advanced or metastatic HCC. • To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Incidence of DLT (Dose-limiting toxicity) during the administration of BLU-554 in combination with CS1001. • Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
Secondary Objectives	**Secondary Endpoint**

• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When being administered in combination with BLU-554, area under the serum concentration-time curve (AUC); Maximum serum concentration (C_{max}); Time to maximum serum concentration (t_{max}); Clearance at steady state (CL_{ss}); accumulation ratio of CS1001. • When being administered in combination with CS1001, AUC, C_{max}, t_{max}, CL_{ss}/F, accumulation ratio of BLU-554.
• To assess the preliminary anti-tumor activity of BLU-554 in combination with CS1001.	• To assess Objective response rate (ORR), the duration of response (DOR), disease control rate (DCR), time to progression (TTP), progression free survival (PFS) and overall survival (OS) based on RECIST v1.1.
• To assess the immunogenicity of CS1001 when being administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

Phase II: Dose expansion

Primary Objectives	**Primary Endpoints**
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess ORR based on RECIST v1.1.
Secondary Objectives	**Secondary Endpoint**
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess the DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To evaluate the safety and tolerability of BLU-554 in combination with CS1001.	• Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When being administered in combination with BLU-554, AUC, C_{max}, t_{max}, CL_{ss}, accumulation ratio of CS1001. • When being administered in combination with CS1001, AUC, C_{max}, t_{max}, CL_{ss}/F, accumulation ratio of BLU-554.
• To assess the immunogenicity of CS1001 when being administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

Study design:

Both Phase Ib and Phase II can be divided into 3 periods, screening period, treatment period and follow-up period:

- The screening period is the 28 days prior to the first dose.
- During the treatment period, the subjects will be administered the study drug once every 21 days (3 cycles). BLU-554 is taken orally (PO) once daily (QD); CS1001 is administered intravenously once every 21 days (Q3W). Subjects with advanced stage solid tumor will be imageologically evaluated by the investigators every 9 weeks (i.e. every 3 dosing periods) during the 1st year of treatment and every 12 weeks after treatment for more than 1 year against Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The investigator may increase evaluation frequency if clinically indicated. The drug may be administered continually until presence of intolerable adverse reaction, disease progression, withdrawal of informed consent, loss to follow up, death or study termination. The duration of treatment may be up to 24 months.
- Follow-up period consists of safety follow-up period and survival follow-up period. The safety follow-up period includes 90 days after the last dose of study drug, or until the initiation of a new anti-tumor treatment, whichever occurs earlier. Survival follow-up period will be performed every 12 weeks for collection of the survival status, subsequent anti-tumor therapies and study drug-related SAEs of the subjects until the death, loss to follow-up, withdrawal or termination of study, whichever occurs first. Refer to the Section 1.2 SOA for the study schedule.

Phase Ib: Dose Escalation

The MTD and/or RP2D of BLU-554 in the combination regimen will be determined using a BOIN dose escalation design. 2 dose levels of BLU-554 will be assessed with CS1001 1,200 mg Q3W as the fixed dose (RP2D in single-dose study). The planned dose escalation scheme is shown in Table 1 with 400 mg QD as the starting dose of BLU-554. Every 21 days (3 weeks) will be considered as one cycle. DLT assessment will be done within 21 days (Cycle 1) after the administration. Using BOIN design, the target toxicity probability of the MTD is 0.3 with a maximum sample size of 12. The cohort size included 3 enrolled and treated subjects. The number can be modified based on subject's enrollment. As shown in Figure 13, the starting dose is dose level 1, i.e. BLU-554 400 mg QD in combination with fixed dose CS1001 1,200 mg Q3w. After complete DLT assessment for each cohort, the dose level for the next cohort was determined according to the dose escalation/decreasing rule in Table 7. Repeat the step with every 3 subjects until a maximum sample size of 12 is reached, the dose escalation is ended (See Dose Escalation Flowchart for details). CS1001 is administered intravenously once every 3 weeks (21 days). BLU-554 is taken orally once daily from Day 1 to Day 21; In case that the two study drugs would be administered on the same day, BLU-554 should be administered firstly.

Table 1:Planned Dose Escalation Scheme

Cohort	BUL-554	CS1001
1	400 mg QD	1,200 mg Q3W
2	600 mg QD	1,200 mg Q3W

During the study period, an SMC consisting of the principle investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representative will be established to review the safety data, PK data, efficacy data from the study and determine the escalation dose level and dosage regimen in dose escalation study so as to determine the MTD and RP2D selected for the extension study. The SMC will also decide whether or not to include unscheduled dose levels for the study.

Phase II: Dose expansion:

The primary objective of the dose expansion phase is to primarily evaluate the antitumor efficacy as well as to further evaluate the safety, tolerability, PK and immunogenicity of the combination regimen. In this part, subjects will be enrolled into 2 groups according to the expression of FGF19 immunohistochemistry (IHC): Group 1 will be advanced hepatocellular carcinoma subjects with FGF19 IHC-, the cancellation of which will be based on phase Ib data (see protocol 4.1 for details); Group 2 will be advanced hepatocellular carcinoma subjects with FGF19 IHC+. In case of being within the statistically pre-defined assessment range, additional subjects may be enrolled for further evaluation (see Protocol 4.1 for details). FGF19 expression will be determined at central laboratory by immunohistochemistry (IHC) with the inclusion criteria of FGF19 IHC+ defined as ≥ 1%.
In Phase Ib and Phase II, archived or fresh tumor samples must be provided for FGF19 and PD-L1 IHC test which will be employed at central laboratory.
The tumors shall be evaluated in accordance with RECIST v1.1. During the 1st year of the treatment, subjects will receive CT/MRI examination every 9 weeks (every 3 cycles). After 1 year of treatment, CT/MRI examinations shall be carried out once every 12 weeks (The investigator may increase the frequency of tumor evaluations where clinically indicated).
The data from subjects on anti-tumor activity, safety, tolerability, PK profile and host immunogenicity will be reviewed from the day of first administration of study drugs up to 90 days after the last administration or up to two-year treatment period of combination regimen

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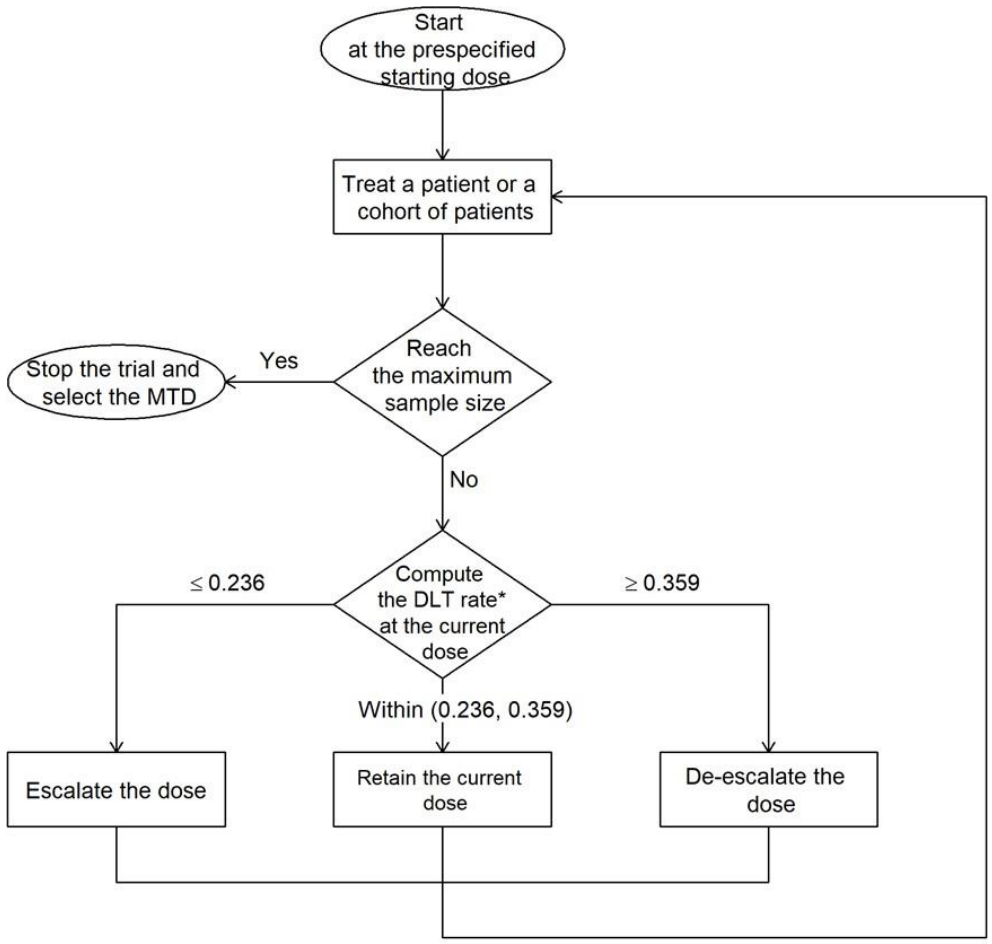
- *Dose Escalation Process:*



$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$$

Planned number of subjects:	Phase Ib: Approximately 12 subjects will be enrolled Phase II: Approximately 40 subjects will be enrolled
Dose limiting toxicity (DLT) definition:	Definition of DLT: All toxicity or adverse events (AEs) are graded according to NCI-CTCAE 5.0. Any AE occurring during C1 (21 days) that is not clearly caused by something other than investigational drug: Hematological toxicity: ● Grade 4 neutropenia that lasts for ＞7 days; ● Grade ≥3 febrile neutropenia (ANC<1,000/mm^3, with a single temperature of ≥38.3℃ or a sustained temperature of ≥38℃ for more than one hour); ● Grade 3 neutropenia with infection; ● Grade 3 thrombocytopenia with clinically significantly bleeding;

	● Grade 4 thrombocytopenia; ● Grade ≥4 anemia
	Non-hematological toxicity: ● Grade ≥4 toxicity; ● Grade 3 toxicity that fails to be resolved to ≤Grade 2, with the exception of diarrhea, nausea and vomiting; ● Grade ≥3 immune-related adverse event (irAE); ● Any Grade 3 tumor flare reaction (local pain, irritation or rash at known or suspected tumor focus) that lasts for 7 days or above; ● Grade 3 or Grade 4 non-hematological laboratory abnormalities, if meet any of the followings: –need medical intervention – require hospitalization – last for >7 days and other toxicity of any grade that requires premature termination of the study as determined by the investigator and the sponsor through discussion. Definition of MTD: Based on BOIN design, MTD is the highest dose level at which 30% of the subjects experience DLT within 21 days (Cycle 1) among which at least 6 subjects are available for DLT evaluation. The RP2D will be determined by SMC based on comprehensive data of safety and tolerability, PK, pharmacodynamics, and preliminary anti-tumor efficacy obtained during the dose escalation phase. The RP2D will not exceed the MTD and will be determined at a dose escalation meeting.
Study Population:	**<u>Inclusion Criteria:</u>** To meet the conditions for participation in this clinical study, subjects must: 1. Voluntarily participate in the clinical study. Fully understand and get informed of this study and sign the Informed Consent Form (ICF). 2. ≥18 years of age on day of signing the informed consent. 3. Unresectable locally advanced or metastatic hepatocellular carcinoma as confirmed by histology or cytology. 4. Stage B or C based on Barcelona Clinic Liver Cancer (BCLC) staging system; In case of Stage B, subject must be ineligible for surgery and/or local therapy, or has progressed after surgery and/or local therapy or refuses surgery and/or

	local treatment. 5. For Phase Ib, subject has failed after or is unsuitable for the standard systemic therapy against HCC. For Phase II, subject has not previously received systemic therapy [systemic therapies mainly include: chemotherapy, molecular target drugs (e.g. tyrosine kinase inhibitors, TKI), immunotherapy (e.g. anti PD-1/PD-L1, CTLA-4 etc.), biological therapy (e.g. tumor vaccine), cytokines, etc.)]. 6. At least one measurable lesion as evaluable by RECIST version1.1, Target lesions within the field of prior efficacy irradiation or in the area of local treatment (intervention or ablation therapy) are considered measurable in case of confirmation of progression. 7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 point. 8. A-level Child-Pugh score. 9. Expected survival≥3 months. 10. For Phase Ib and II, 9 formalin fixed-paraffin embedded and unstained tumor tissue slides should be provided for FGF19 IHC and PD-L1 analysis in the central laboratory. • Patients to be enrolled in the FGF19 IHC + arm in the Phase II study must be FGF19 IHC +; • Patients to be enrolled in the FGF19 IHC - arm in the Phase II study must be FGF19 IHC – (whether this arm will be initiated or not will be decided based on Phase Ib data) 11. Clinical laboratory screening criteria: • Absolute neutrophil count (ANC)≥1.5 × 10^9/L • Platelet count≥ 75 × 10^9/L • Hemoglobin≥90 g/L • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × ULN • Total bilirubin ≤ 2 ×ULN • International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 ×ULN (INR ⩽ 1.5 × ULN and PT ⩽ 1.5 × ULN, if both available) • Serum creatinine ≤ 1.5 ×ULN or creatinine clearance (CL)≥60 mL/min (Cockcroft-Gault Formula) Female: $\frac{\text{CrCl}=(140-\text{age}) \times \text{weight (Kg)} \times 0.85}{72 \times \text{serum creatinine(mg/dL)}}$ Male: $\frac{\text{CrCl}=(140-\text{age}) \times \text{weight (Kg)} \times 1.00}{72 \times \text{serum creatinine(mg/dL)}}$ 12. For subjects with hepatitis C virus (HCV) infection, treatment with locally approved and available anti-HCV therapy is required if HCV RNA is detected. 13. For subjects with hepatitis B virus (HBV) infection, HBV DNA ≤ 2,000 IU/ml at Screening. • Subject with HBV DNA (+), treatment with HBV antiviral therapy (as per the local standard of care) is required at least 14 days prior to the initiation of study.

	• Subject with HBsAg (+) and/or HBcAb (+), based on investigator assessment, HBV antiviral therapy may be applied if needed. 14. For female subjects of childbearing potential, serum pregnancy test must be negative within 7 days prior to randomization. Except for female subjects who have been recorded as surgically sterilized or who are postmenopausal, female subjects of childbearing potential or male subjects and their partners must agree to use effective contraception from the signature of the informed consent form (ICF) until at least 6 months after the last dose of study drug. Appendix 6: Effective Contraceptive Methods **Exclusion Criteria:** Subjects who meet any of the following criteria will not be eligible to participate in the study: 1. Portal vein tumor thrombosis in the main trunk or contralateral first branch (VP4), involvement of the inferior vena cava or the heart as revealed by imaging at baseline. 2. Prior or current history of hepatic encephalopathy. 3. History of liver surgery and/or local treatment for HCC (intervention, ablation therapy, absolute alcohol injection, etc.) or radiotherapy, etc. within 4 weeks prior to first dose. 4. Active or documented gastrointestinal bleeding within 6 months (e.g. esophageal or gastric varices, ulcer bleeding). 5. Presence of ascites detected by physical examination or clinical symptoms caused by ascites during the screening period, or ascites that need for special treatment, such as repeated drainage, or intraperitoneal drug infusion, etc. (Note: subjects with a small amount of ascites that can only be detected by imaging may be enrolled). Presence of uncontrolled pleural effusion or pericardial effusion (with clinical symptoms, requiring repeated drainage, or intrapleural or pericardial drug infusion, etc.) during the screening period. 6. Presence of meningeal metastasis or central nervous system (CNS) metastatic lesions. 7. According to the New York Heart Association (NYHA) Classification, subject has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure; myocardial infarction or unstable angina (within 6 months), uncontrolled hypertension (systolic blood pressure≥150 mmHg and diastolic blood pressure≥100 mmHg) or clinically significant uncontrolled arrhythmias, including bradycardia that may result in prolonged QT (e.g. Grade II or III heart block). Left ventricular ejection fraction (LVEF)<50%. QTc interval >480 msec (corrected using Fridericia's formula). 8. Subjects who have current interstitial lung disease or noninfectious pneumonitis, and prior history of interstitial lung disease or noninfectious pneumonitis that may affect the assessment or management of study drug-related pulmonary toxicity. Presence of active tuberculosis

	infection. 9. Any serious acute, chronic infections that require systemic antimicrobial, antifungal or antiviral therapy at screening, excluding viral hepatitis. 10. Malabsorption syndrome or inability to take the study drug orally for other reasons. 11. Had primary malignancies other than HCC within 5 years. The following prior malignancies were excluded: completely excised skin basal cells and squamous cell carcinoma, local prostate cancer responsive to treatment, and carcinoma in situ with complete resection at any site. 12. Subject has had major surgery within 4 weeks prior to first dose (procedures such as central venous cannulation, biopsy, and feeding tube placement are not considered as major surgery). 13. Previously received FGFR4 inhibitor treatment. 14. Blood transfusion, use of hematopoietic stimulating factors [including G-CSF (granulocyte colony stimulating factor), GM- CSF (granulocyte-macrophage colony stimulating factor), EPO (erythropoietin) and TPO (thrombopoietin)] and human albumin preparations within 14 days prior to first dose. 15. Requiring corticosteroids (dose equivalent to > 10 mg/day of Prednisone) or other immunosuppressive drugs within 14 days prior to first dose for systemic therapy. Note: For the absence of active autoimmune disease, it is allowed to use inhaled or topical steroids or adrenal hormone replacement therapy with equivalent dose of ≤10 mg/day prednisone. Short-term (≤ 7 days) use of corticosteroids for prophylaxis (e.g., contrast allergy) or for the treatment of non- autoimmune diseases (e.g., delayed hypersensitivity reactions due to contact allergens) is permitted. For subjects requiring hormone therapy, the dose administration should be done at least two days before and after the injection of CS1001. 16. Use of traditional Chinese medicine (elemene, Kanglaite, Cinobufacin, Xiaoaiping, Huaier granule, Ganfule, Jinlong capsule, Aidi, etc.) with anti-liver cancer indication within 14 days prior to the first dose. 17. Subject has received potent CYP3A4 inhibitors and/or inducers within 2 weeks prior to first dose. See Appendix 8: Strong Inhibitors and Inducers of CYP3A4. 18. Concurrent HBV and HCV infection (History of HCV infection, but subjects with HCV RNA(-) can be considered as not being infected with HCV). 19. Subjects with human immunodeficiency virus (HIV) infection. 20. Pregnant or lactating women. 21. Subjects with a history of hypersensitivity or hypersensitivity to any of the components of the investigational drug. 22. Any previous or current clinically significant diseases, medical conditions, history of surgery, signs, or abnormal laboratory parameters that, in the opinion of the investigator, may increase the risks associated with study participation and study drug administration, or affect the subject's ability to receive study drug and reliability of study results; other circumstances that in the opinion of the

	investigator would preclude participation in the study. 23. Subjects who are unwilling or unable to follow the study procedures as defined. Subjects with no or limited disposing capacity and with psychiatric disorders that may affect study compliance. 24. With the exception of alopecia, all toxicities from prior anticancer therapies and other therapies did not recover to ≤ Grade 1 (per CTCAE v5.0) prior to the first dose of study drug. 25. Subjects who have received prior allogeneic stem cell or solid organ transplantation.
Definition of end of study:	All subjects completed the treatment period, EOT visit, disease progression follow-up and survival follow-up or the Sponsor terminated the study (whichever occurred first).
Test product, dose and mode of administration:	BLU-554 capsule 100 mg will be taken by oral administration once daily. CS1001 injection 600 mg/20 ml/Bottle will be given via intravenous infusion on the first day of each treatment cycle, once every 21 days (3 weeks).
Planned trial and treatment duration per subject:	No more than 35 cycles (24 months) of study treatment followed by a 90-day safety follow-up.

Statistical methods:	**Analysis Populations** Safety analysis set: consists of all subjects receiving at least one dose of investigational product. Efficacy analysis set: consists of all subjects with measurable baseline disease who received at least one dose of investigational product. It will be the primary analysis set for efficacy in this study. Note: Subjects who were screened but never started treatment will be listed, but not included in any efficacy analysis set. Therefore, these subjects will not be included in any of the summary tables. Dose-determining set: consists of all subjects from the safety analysis set who, in Cycle 1, meet the minimum exposure criterion and complete the follow-up on Cycle 1 Day 21 or discontinue the treatment due to DLT. A subject is considered to have met the minimum exposure criterion if in Cycle 1 the subject has received ≥75% of the treatment (not necessarily consecutively). Subjects who do not meet these minimum safety evaluation requirements are considered to be ineligible for the dose-determining set. Determination of the MTD uses subjects eligible for the dose-determining set. Pharmacokinetic analysis set: consists of all subjects who received at least one dose of investigational product and had at least one post-baseline pharmacokinetic assessment. Immunogenicity analysis set: consists of all subjects receiving at

	least one dose of investigational product and having available ADA data. Biomarker analysis set: consists of all subjects receiving at least one dose of investigational product and having available biomarker data. All analysis sets will be determined before the database is locked. **Primary Analysis Method** Safety: Safety assessments will include adverse events, vital signs, physical examination, electrocardiogram (ECG), echocardiography and laboratory tests. The incidence of DLT for each dose group will be assessed. All treatment-emergent adverse events (TEAEs) in each dose group are summarized by system organ classification and preferred terms. The relationship of the incidence and severity of all TEAEs to the investigational drug will be summarized. Descriptive summaries of laboratory tests and vital signs for each dose group will be made separately. Abnormal findings of laboratory tests, vital signs, ECG, echocardiograms will be listed. Efficacy: Efficacy assessments will be conducted according to RECIST v1.1, including ORR, PFS, DCR and DOR. The efficacy endpoint is the ORR assessed by the investigator and ORR for the subjects in each dose group and overall ORR will be summarized. OS and PFS will be expressed by a Kaplan-Meier curve. **Sample Size Determination** According to efficacy result of BLU-554-1101 study (data cut-off date: 16 Jun 2018), ORR was 17% (11/63) for FGF19 IHC+ subjects (1st line and above) and 0 (0/38) for FGF19 IHC- subjects. ORR of PD-1/PD-L1 monotherapy was reported around 10~20% for 1st line and 2nd line HCC subjects. Based on the data above, BLU-554 in combination with CS1001 is targeting 40% ORR for 1st line and 2nd line FGF19 IHC+ subjects and 30% ORR for 1st line and 2nd line FGF19 IHC- subjects. Combining all subjects treated at RP2D in Phase Ib and Phase II, gating criteria in Bayesian framework are developed as the following: Gating based on 25 FGF19 IHC+ subjects • A non-informative ORR prior is assumed at Beta (0.45, 0.55). • Timing - when all 25 subjects finish at least two post-baseline tumor assessments • Go - 12 responses or more, corresponding ORR 48%, the

probability of combo ORR > 40% is 0.788.

- No go - 8 (32%) responses or fewer, the probability of combo ORR<40% is 0.797.
- Evaluate - 9 (36%) to 11 (44%) responses, evaluate other efficacy endpoints (DOR, DCR etc.) and safety.

Gating based on 40 FGF19 IHC+ subjects (if enrichment of 15 FGF19 IHC+ subjects as decided)

- A non-informative ORR prior is assumed at Beta (0.45, 0.55).
- Timing - when all 40 subjects finish at least two post-baseline tumor assessments
- Go - 18 responses or more, corresponding ORR 45%, the probability of combo ORR > 40% is 0.737.
- No go - 14 (35%) responses or fewer, the probability of combo ORR<40% is 0.744.
- Evaluate - 15 (37.5%) to 17 (42.5%) responses, evaluate other efficacy endpoints (DOR, DCR, etc.) and safety.

Gating based on FGF19 IHC - subjects treated at RP2D in Phase Ib

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - only conducted if at least 6 FGF19 IHC- subjects are treated at RP2D in Phase Ib, when they finish at least two post-baseline tumor assessments
- No go - 0 response, the probability of combo ORR<30% is greater than 0.99, Phase II will only include the FGF IHC+ cohort
- Evaluate - 1 response or more, the cohort of FGF IHC- subjects will be included in Phase II

Gating based on 15 FGF19 IHC- subjects

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - when all 15 subjects finish at least two post-baseline tumor assessments
- Go - 6 responses or more, corresponding ORR 40%, the probability of combo ORR > 30% is 0.757. If the final

decision for FGF19 IHC+ subjects is “go” (Gating based on 15 or 40 FGF19 IHC+ subjects, as above said), FGF19 IHC- subjects may also be included in the target population of future development.

- No go - 3 (20%) responses or fewer, the probability of combo ORR<30% is 0.845. Future development will not include FGF19 IHC- subjects in the target population.
- Evaluate - 4 (26.7%) to 5 (33.3%) responses, evaluate other

	efficacy endpoints (DOR, DCR, etc.) and safety. The sample sizes of 25 or 40 FGF19 IHC+ subjects and 15 FGF19 IHC- subjects are selected to have reasonably high probability of ORR exceeding the target when the go criteria are met or ORR being lower than the mono therapies when no-go criteria are met. The go and no-go criteria are set up to guide future development of the combination. **They are not binding decision-making rules.** If the actual numbers of evaluable subjects are different from those planned above, the same method will be used to calculate the posteriori probability that ORR will reach the predefined target for reference in subsequent development.

1.2. SCHEDULE OF ACTIVITIES

Table 2:tudy Assessments and Procedures Schedule in Dose Escalation Part (Phase Ib)

Phase Ib[a]	**Screening**	**Treatment (21d for each cycle)**								**Follow-up**			
		Cycle 1				**Cycle 2**		**≥Cycle 3**	**EOT visit[b]**	**Safety follow-up[c]**			**Survival follow-up[c]**
										1	**2**	**3**	
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**0-7 days post EOT date**	**30 days post last dose**	**60 days post last dose**	**90 days post last dose**	**Every 12 weeks post last dose**
Time Window				**±2**	**±2**	**±4**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed Consent [d]	X												
Inclusion/Exclusion Criteria	X	X											
Demographics	X												
Medical History [e]	X	X											
Physical Examination [f]	X	X		X	X	X	X	X	X	X			
Vital Signs	X	X		X	X	X	X	X	X	X			
ECOG PS	X	X				X		X	X	X			
Serum or Urine Pregnancy Test [g]	X							X [h]	X	X			
12-lead ECG [i]	X	X	X			X		X	X	X			
Echocardiogram [j]	X	As clinically indicated							X				
Tumor Imaging [k]	X	**Within 1 year**: every 9 weeks ± 7 days (end of every 3 dose cycles), **after 1 year**: every 12 weeks ± 7 days; or based on the clinical needs.											
Blood test [l]	X	X		X	X	X	X	X	X	X			
Serum Chemistry, CK-MB [l]	X	X		X	X	X	X	X	X	X			
HIV, HBV, HCV [m]	X							X	X	X			
AFP [m]	X							X	X				
Coagulation [l]	X	X				X		X	X	X			
Routine Urine Test	X	X				X		X	X	X			
Thyroid Function [n]	X	X				X		X	X	X			

Tumor Sample	X [o]												
CS1001 Administration [p]		X				X		X					
BLU-554 Administration [q]		X											
PK blood sample [r]		X											
Immunogenicity Blood Sample [r]		X											
Subsequent anti-tumor therapy [s]										X	X	X	X
AE Monitoring	X												
SAE Monitoring [t]	X												
Concomitant Medications	X												
Survival Status [u]	X												

Abbreviations: AFP, Alpha-Fetoprotein; CT, computed tomography; CK-MB, creatine kinase-MB; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PK, pharmacokinetics.

a. All visits should be performed as noted in Table 2. Additional safety tests (e.g., blood test, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Unless otherwise indicated, all tests and procedures must be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately. Re-screening is permitted for one time, but need to decide by medical monitor and sponsor assessment.

b. The date of the End of Treatment (EOT) visit is defined as the date on which the investigator decided to stop dosing. The EOT visit should be performed 0-7 days post the EOT date. If the EOT visit and a treatment visit occur within 7 days, no tests are required for repeated items. If the EOT visit occurs within the safety follow-up window, no tests are required for repeated items. If an alternate treatment is started within 7 days of the EOT date, the EOT visit should be conducted prior to the first dose of alternate therapy. The last administration date is defined as the later last administration date of the two study drugs. It should be noted that the date on which the investigator decided to stop dosing may not coincide with the date of last dose.

c. Safety visits: For subjects who have completed treatment, a safety visit should be conducted on the 30th day (±7 days), 60 days (±7 days), and 90 days (± 7 days) post the last dose; the safety follow-up at 90 day post the last dose can be conducted at the same day as that for the first survival follow-up. Survival follow-up: subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until the death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

d. Consent for the study may be obtained from the subjects by written.

e. A complete medical history will be obtaining at the Screening visit. Only disease-related symptoms and changes from the previous visit need to be collected on C1D1.

f. A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be disease- and AE-focused.

g. To be performed for women with childbearing potential within 7 days of C1D1. A serum pregnancy test should be performed at Screening; thereafter, a serum or urine pregnancy test should be performed on every odd cycle (e.g., C3, C5).

h. To be performed on D1 (±4 days) of every odd cycle starting with C3.

i. ECGs (12-lead) exams will be performed after at least a 10 minute rest in the supine position. ECGs will be performed at Screening and during treatment, at EOT, and at Safety Follow-Up. In case of PK sampling, ECG should be performed for 3 consecutive times with an interval of 5 minutes each time in Cycle 1, 2 and 4. Refer to Table 4 and Table 5 for specific time. For other treatment cycles ECG should be performed at predose of any Cycle Day 1 dosing. For C1D2,

ECG should be collected at predose. Frequency of ECGs may be increased if clinically indicated.

j. To be performed as clinically indicated.

k. Imaging assessment of tumors: Tumor assessment is conducted according to the standard RECIST v1.1. See the specific assessment standards in Appendix 2.

The imaging assessment method of tumors may adopt CT or MRI as decided by the investigator, however, the assessment method, machine and technical parameters should remain consistent in the entire study period; if there is no contraindication, a contrast medium should be used. The imaging results will be interpreted by the investigator or radiologist of each site. In case a tumor assessment has been conducted within 28d before initial administration and by the same method and machine in the same hospital, the result can be adopted as baseline tumor assessment. Baseline tumor assessment should cover chest, abdomen, pelvic cavity and any other site suspected of tumor lesion (such as brain, bone lesions). Subjects with bone metastases during screening should be followed up using CT/MRI/X-ray at subsequent visits. Imaging (CT or MRI) assessments per RECIST v1.1 will be performed within 28 days prior to the first dose (baseline assessment), every 9 weeks during the first year of the study, and every 12 weeks thereafter until (1) disease progression, (2) initiation of a new anti-tumor therapy, (3) withdrawal of informed consent, (4) loss of follow-up, (5) death, and (6) termination of the study, whichever occurs first. In case medication is discontinued permanently for a subject due to the reasons other than those above said (such as AEs), the tumor assessment will still be conducted as scheduled. The investigator can schedule additional imaging examination based on the subject's clinical condition. If an unscheduled tumor assessment is carried out and the disease has not progressed, subsequent tumor assessments should also be performed as scheduled. The confirmatory assessment must be completed 4 weeks after the efficacy is assessed as complete response (CR) or partial response (PR). If the investigator suspects that the progression of disease is pseudoprogression, then progression of disease must be confirmed in the imaging examination four weeks later or at the next scheduled imaging assessment time point (note: the time point of the next imaging examination may not be later than 9 weeks after the initial confirmation of progression of disease). For a subject whose treatment is stopped before any clearly- disease progression, imaging examination results should be obtained as far as possible to conduct tumor efficacy assessment. In case a subject discontinues study treatment due to disease progression (excluding pseudoprogression), it will be unnecessary to repeat the step of imaging assessment in the last visit. If the subject has completed the imaging assessment of the tumor within 28 days prior to the EOT visit or safety visit, it is not required to repeat such examinations at the two visits.

l. If the Screening visit tests are performed within 7 days of C1D1, clinical laboratory tests do not need to be repeated on C1D1 (i.e. there is a -7-day window for C1D1 labs). When laboratory tests (including blood test, blood biochemistry, myocardial enzyme, coagulation function, urinalysis, and thyroid function, if applicable) and study drug administration are scheduled to be conducted on the same day (e.g., Day 1 [D1] of each treatment cycle), the test results should be available before the administration can be scheduled. Except for the first dose, laboratory tests at each dosing visit should be completed within 3 days prior to dosing. If the subject has received relevant laboratory tests within the first 7 days of the EOT visit or safety visit 1, there is no need to repeat such tests at these two visits.

m. Screening visit will be performed at the local laboratory, which includes HCV antibody, HBsAg, HIV antibodies. Subjects with HBsAg positive will further assess HBV DNA test, subject with HCV antibody positive will further assess HCV RNA test. Subjects with HBsAg positive need to be retested for HBV DNA every 12 weeks until safety follow-up 1; subjects with HCV antibody positive need to be retested for HCV RNA every 12 weeks until safety follow-up 1; APF test will be done every 12 weeks until the EOT visit.

n. Thyroid function examination covers free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) analysis, conducted respectively in the screening period, dosing in the first and second administration cycle, dosing every two subsequent administration cycles, EOT and in the safety follow-up visit. If the thyroid function test at screening is performed within 7 days prior to the first dose (C1D1), it does not need to be repeated before the first dose (i.e., there is a -7-day window for the thyroid function test on C1D1). When thyroid function tests and study drug administration are scheduled to be conducted on the same day (eg, on Day 1 [D1] of the respective treatment cycle for thyroid function tests), the test results should be available before the administration can be scheduled. Except for the first dose, the specified thyroid function tests performed at each dosing visit should be completed within 3 days prior to

dosing. If subjects have completed the thyroid function examination within 7 days prior to the end of treatment visit or safety visit 1, there is no need to repeat such at these two visits.

o. The tumor tissue used for FGF19 and PD-L1 IHC test will be sampled at screening and be analyzed at central laboratory.

p. CS1001 will be given on D1 of each 21-day cycle. Each infusion should be completed over 60-120 minutes. The recommended infusion time for PK blood sample collection is 90 minutes, as shown in table 4 and table 5.

q. BLU-554 will be administered qd in the morning with no food intake from 2 hours before until 1 hour after study drug administration. On study visit days when PK samples are collected, subjects will take their BLU-554 dose at the site. When the 2 study drugs are administered on the same day, BLU-554 should be administered before CS1001 infusion completion. After BLU-554 is administered, the subject should be given with CS1001 through intravenous infusion as soon as possible.

r. Blood samples for PK and immunogenicity assessment refer to Table 4 and Table 5.

s. Subsequent anti-tumor treatment: Information on subsequent (after the end of study treatment) anti-tumor therapies will be collected, including the name of all components of the treatment and the start and end dates of administration.

t. If the investigator learns of any SAE (including death) in a subject after the subject has completed safety follow-up or has withdrawn from the study, and there is a reasonable cause to believe that the event is possibly related to the study drug, the investigator should notify the sponsor's pharmacovigilance team or representative.

u. Survival status: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

Table 3:Study Assessments and Procedures Schedule in Expansion Part (Phase II)

Phase II[a]	**Screening**	**Treatment (21d for each cycle)**						**Follow-up**			
		Cycle 1			**Cycle 2**	**≥Cycle 3**	**EOT visit [b]**	**Safety follow-up [c]**			**Survival follow-up [c]**
								1	**2**	**3**	
Days	**-28 to -1**	**1**	**2**	**15**	**1**	**1**	**0-7 days post EOT date**	**30 days post last dose**	**60 days post last dose**	**90 days post last dose**	**Every 12 weeks post last dose**
Time Window				±2	±4	±4	±7	±7	±7	±7	±7
Informed Consent [d]	X										
Inclusion/exclusion Criteria	X	X									
Demographics	X										
Medical History [e]	X	X									
Physical Examination [f]	X	X		X	X	X	X	X			
Vital Signs	X	X		X	X	X	X	X			
ECOG PS	X	X			X	X	X	X			
Serum or Urine Pregnancy Test [g]	X					X [h]	X	X			
12-lead ECG [i]	X	X	X		X	X	X	X			
Echocardiogram [j]	X	As clinically indicated					X				
Tumor Imaging [k]	X	**Within 1 year**: every 9 weeks ± 7 days (end of every 3 dose cycles), **after 1 year**: every 12 weeks ± 7 days; or based on the clinical needs.									
Blood test[l]	X	X		X	X	X	X	X			
Serum Chemistry, CK-MB [l]	X	X		X	X	X	X	X			
HIV, HBV, HCV [m]	X					X	X	X			
AFP[m]	X					X	X				
Coagulation [l]	X	X			X	X	X	X			
Routine Urine Test	X	X					X				
Thyroid Function [n]	X	X			X	X	X	X			
Tumor Sample	X [o]										
CS1001 Administration [p]		X			X	X					

BLU-554 Administration [q]		X					
PK Blood Sample [r]		X					
Immunogenicity Blood Sample [r]		X					
Subsequent anti-tumor therapy [s]				X	X	X	X
AE Monitoring [t]	X						
SAE Monitoring	X						
Concomitant Medications	X						
Survival Status [u]	X						

Abbreviations: AFP, Alpha-Fetoprotein; CT, computed tomography; CK-MB, creatine kinase-MB; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; PK, pharmacokinetics.

a. All visits should be performed as noted in Table 3. Additional safety tests (e.g., blood test, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Unless otherwise indicated, all tests and procedures must be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately. Re-screening is permitted for one time, but need to decide by medical monitor and sponsor assessment. Repeated screening is allowed for once and central laboratory-confirmed FGF19 IHC results obtained at screening # 1 may be used in the assessment of FGF19 IHC status at repeated screening without recollecting tumor samples for testing. It is recommended that the screening of FGF19 IHC status be performed first and then clinical screening continue when FGF19 IHC screening results are acceptable.

b. The date of the End of Treatment (EOT) visit is defined as the date on which the investigator decided to stop dosing. The EOT visit should be performed 0-7 days after the EOT date. If the EOT visit and a treatment visit occur within 7 days, no tests are required for repeated items. If the EOT visit occurs within the safety follow-up window, no tests are required for repeated items. If an alternate treatment is started within 7 days of the EOT date, the EOT visit should be conducted prior to the first dose of alternate therapy. The last administration date is defined as the later last administration date of the two study drugs. It should be noted that the date on which the investigator decided to stop dosing may not coincide with the date of last dose.

c. Safety visits: For subjects who have completed treatment, a safety visit should be conducted on the 30th day (±7 days), 60 days (±7 days), and 90 days (± 7 days) post the last dose; the safety follow-up at 90 day post the last dose can be conducted at the same day as that for the first survival follow-up. Survival follow-up: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

d. Consent may be obtained from the subjects by written.

e. A complete medical history will be obtaining at the Screening visit. Only disease-related symptoms and changes from the previous visit need to be collected on C1D1.

f. A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be disease- and AE-focused.

g. To be performed for women of childbearing potential within 7 days of C1D1. A serum pregnancy test should be performed at Screening; thereafter, a serum or urine pregnancy test should be performed on every odd cycle (e.g., C3, C5).

h. To be performed on D1 (±4 days) of every odd cycle starting with C3.

i. ECGs (12-lead) exams will be performed after at least a 10 minutes rest in the supine position. ECGs will be performed at Screening and during treatment, at EOT, and at Safety Follow-Up. In case of PK sampling, ECG test should be perfomed for 3 consecutive times with an interval of 5 minutes each time in Cycle 1,

2 and 4. Refer to Table 4 and Table 5 for specific time.For other treatment cycles ECG should be performed at predose of any Cycle Day 1 dosing. For C1D2, ECG should be collected at predose. Frequency of ECGs may be increased if clinically indicated.

j. To be performed as clinically indicated.

k. Imaging assessment of tumors: Tumor assessment is conducted according to the standard RECIST v1.1. See the specific assessment standards in Appendix 2. The imaging assessment method of tumors may adopt CT or MRI as decided by the investigator, however, the assessment method, machine and technical parameters should remain consistent in the entire study period; if there is no contraindication, a contrast medium should be used. The imaging results will be interpreted by the investigator or radiologist of each site. In case a tumor assessment has been conducted within 28d before initial administration and by thesame method and machine in the same hospital, the result can be adopted as baseline tumor assessment. Baseline tumor assessment should cover head, chest, abdomen, pelvic cavity and any other site suspected of tumor lesion (such as brain, bone lesions). Subjects with bone metastases during screening should be followed up using CT/MRI/X- ray at subsequent visits. Subjects who have no brain metastases confirmed by imaging at screening will not be required to undergo regular brain imaging at subsequent visits, which may be scheduled by the investigator as clinically indicated. Imaging (CT or MRI) assessments per RECIST v1.1 will be performed within 28 days prior to the first dose (baseline assessment), every 9 weeks during the first year of the study, and every 12 weeks thereafter until (1) the disease progression, (2) initiation of a new anti-tumor therapy, (3) withdrawal of informed consent, (4) loss of follow-up, (5) death, and (6) the termination of the study, whichever occurs first. In case medication is discontinued permanently for a subject due to the reasons other than those above said (such as AEs), the tumor assessment will still be conducted as scheduled. The investigator can schedule additional imaging examination based on the subject's clinical condition. If an unscheduled tumor assessment is carried out and the subject has not progressed, subsequent tumor assessments should also be performed as scheduled. The confirmatory assessment must be completed 4 weeks after the efficacy is assessed as complete response (CR) or partial response (PR). If the investigator suspects that the progression of disease is pseudoprogression, then progression of disease must be confirmed in the imaging examination four weeks later or at the next scheduled imaging assessment time point (note: the time point of the next imaging examination may not be later than 9 weeks after the initial confirmation of progression of disease). For a subject whose treatment is stopped before any clearly- disease progression, imaging examination results should be obtained as far as possible to conduct tumor efficacy assessment. In case a subject discontinues study treatment due to the progression of disease (excluding pseudoprogression), it will be unnecessary to repeat the step of imaging assessment in the last visit. If the subject has completed the imaging assessment of the tumor within 28 days prior to the EOT visit or safety visit, it is not required to repeat such examinations at the two visits.

l. If the Screening visit tests are performed within 7 days of C1D1, clinical laboratory tests do not need to be repeated on C1D1 (i.e. there is a -7-day window for C1D1 labs). When laboratory tests (including blood test, blood biochemistry, myocardial enzyme, coagulation function, urinalysis, and thyroid function, if applicable) and study drug administration are scheduled to be conducted on the same day (e.g., Day 1 [D1] of each treatment cycle), the test results should be available before the administration can be scheduled. Except for the first dose, laboratory tests at each dosing visit should be completed within 3 days prior to dosing. If the subject has received relevant laboratory tests within the first seven days of the EOT visit or safety visit 1, there is no need to repeat such tests at these two visits.

m. Screening visit will be performed at the local laboratory, which includes HCV antibody, HBsAg and HIV antibodies. Subjects with HBsAg positive will further assess HBV DNA test, subject with HCV antibody positive will further assess HCV RNA test. Subjects with HBsAg positive need to be retested for HBV DNA every 12 weeks until safety follow-up 1; subjects with HCV antibody positive need to be retested for HCV RNA every 12 weeks until safety follow-up 1; AFP test is required at baseline, and will be done every 12 weeks until the EOT visit..

n. Thyroid function examination covers free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) analysis, conducted respectively in the screening period, dosing in the first and second administration cycle, dosing every two subsequent administration cycles, EOT and in the safety follow-up visit. If the thyroid function test at screening is performed within 7 days prior to the first dose (C1D1), it does not need to be repeated before the first dose (i.e., there is a -7-day window for the thyroid function test on C1D1). When thyroid function tests and study drug administration are scheduled to be conducted on the same day (eg, on Day 1 [D1] of the respective treatment cycle for thyroid function tests), the test results should be available before the administration

can be scheduled. Except for the first dose, the specified thyroid function tests performed at each dosing visit should be completed within 3 days prior to dosing. If subjects have completed the thyroid function examination within 7 days prior to the end of treatment visit or safety visit, there is no need to repeat such at these two visits.

o. The tumor issue used for FGF19 and PD-L1 IHC test will be sampled at screening and be analyzed at central laboratory.

p. CS1001 will be given on D1 of each 21-day cycle. Each infusion at Cycle 1 should be completed over 60-120 minutes. The recommended infusion time for PK blood sample collection is 90 minutes, as shown in table 4 and table 5.

q. BLU-554 will be administered qd in the morning with no food intake from 2 hours before until 1 hour after study drug administration. On study visit days when PK samples are collected, subjects will take their BLU-554 dose at the site. When the 2 study drugs are administered on the same day, BLU-554 should be administered before CS1001 infusion completion. After BLU-554 is administered, the subject should be given with CS1001 through intravenous infusion as soon as possible.

r. Blood samples for PK and immunogenicity assessment refer to Table 4 and Table 5.

s. Subsequent anti-tumor treatment: Information on subsequent (after the end of study treatment) anti-tumor therapies will be collected, including the name of all components of the treatment and the start and end dates of administration.

t. If the investigator learns of any SAE (including the death) in a subject after the subject has completed safety follow-up or has withdrawn from the study, and there is a reasonable cause to believe that the event is possibly related to the study drug, the investigator should notify the sponsor's pharmacovigilance team or representative.

u. Survival status: Subjects will be contacted by telephone or in person every 12 weeks from the last dose of study drug to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

Table 4: Schedule for PK and Immunogenicity Blood Sampling by Study Drugs in Phase Ib

		BLU-554[a]			CS1001[a]				ECG[a, e]
Day		**Time**	**Time window**	**PK Sampling**	**Time**	**Time window**	**PK Sampling**	**ADA Sampling of CS1001**	
Cycle 1	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h[c, e]	± 10 min	X	EOI+30 min[c, e]	± 15 min	X		X
		4h	± 15 min	X					
		6h	± 15 min	X					
		7.5h			EOI+6h	± 30 min	X		
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X	EOI+22.5h[d]	± 1h	X		X
	D8	168h			EOI+168 h	± 1 day	X		
	D15	336h			EOI+336h	± 1 day	X		
Cycle 2	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosingb				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h	± 10 min	X					X
		4h	± 15 min	X					
		6h	± 15 min						
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X					

Day		BLU-554[a] Time	BLU-554[a] Time window	BLU-554[a] PK Sampling	CS1001[a] Time	CS1001[a] Time window	CS1001[a] PK Sampling	CS1001[a] ADA Sampling of CS1001	ECG[a, e]
Cycle 4	D1				0 (Predose	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
					EOI+30 min	± 15 min	X		X
					EOI+6h	± 30 min	X		
	D2				EOI+22.5h[d]	± 1 h	X		
	D8				EOI+168 h	± 1 d	X		
	D15				EOI+336h	± 1 d	X		
Cycle 5	D1				0 (Predose)	30 min prior to dosing	X	X	
C7, C10、C13 and C16, and every 8 cycles afterwards	D1				0 (Predose)	30 min prior to dosing	X	X	

Abbreviations: EOI, end of infusion; ADA, anti-drug antibody; PK, pharmacokinetics

a. It is important that PK sampling occurs as close as possible to the scheduled time. PK and immunogenicity sampling and ECG collection should be performed on the same day. Detailed sequential procedures are: 1) Scheduled triplicate ECG with an interval of at least 5 mins; 2) Vital sign measurements; 3) PK blood sampling; and 4) Any other tests and assessment required by the study.
b. After BLU-554 is administered, the subject should be intravenously infused with CS1001 as soon as possible. For PK blood sampling, the recommended infusion time of CS1001 is 90 minutes.
c. Collect two samples at one time point with BLU-554 blood sample be collected firstly and then CS1001 blood sample.
d. The 24h PK sample of BLU-554 and the EOI+22.5h PK sample of CS1001 must be collected prior to dosing on the same day.
e. Cycle 1 Day 1: "2 hours post BLU-554 dosing" ECG collection is allowed at 1 - 4 h post BLU-554 dosing; "end of CS1001 infusion + 30 min" ECG collection is allowed from the time after the completion of CS1001 infusion to 2.5 h post the completion of CS1001 infusion. If the ECG collection windows for these two time points on C1D1 do not overlap, i.e. two sets of ECG data will be collected.

Table 5:Schedule for PK and Immunogenicity Blood Sampling by Study Drugs in Phase II

		BLU-554[a]			CS1001[a]				ECG[a, e]
Day		**Time**	**Time window**	**PK sampling**	**Time**	**Time window**	**PK sampling**	**ADA sampling of CS1001**	
Cycle 1	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		2h[c, e]	±10 min	X	EOI+30 min[c, e]	± 15 min	X		X
	D2	24h[d]	± 1h	X	EOI+22.5h[d]	± 1h	X		X
Cycle 2	D1	0 (Predose)	30 min prior to dosing	X	0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
		30 min	± 5 min	X					
		1h	± 5 min	X					
		2h	± 10 min	X					X
		4h	± 15 min	X					
		6h	± 15 min	X					
		8h	± 30 min	X					
	D2	24h[d]	± 1h	X					
Cycle 4	D1				0 (Predose)	30 min prior to dosing	X	X	X
		BLU-554 dosing[b]			CS1001 dosing[b]				
					EOI+30 min	± 15 min	X		X
					EOI+6h	± 30 min	X		
	D2				EOI+22.5h[d]	± 1 h	X		
	D8				EOI+168 h	± 1 d	X		
	D15				EOI+336h	± 1 d	X		

		BLU-554[a]			CS1001[a]				ECG[a, e]
Day		**Time**	**Time window**	**PK sampling**	**Time**	**Time window**	**PK sampling**	**ADA sampling of CS1001**	
Cycle 5	D1				0 (Predose)	30 min prior to dosing	X	X	
C7, C10、C13 and C16, and every 8 cycles afterwards	D1				0 (Predose)	30 min prior to dosing	X	X	

Abbreviations: EOI, end of infusion; ADA, anti-drug antibody; PK, pharmacokinetics

a. It is important that PK sampling occurs as close as possible to the scheduled time. PK and immunogenicity sampling and ECG collection should be performed on the same day. Detailed sequential procedures are: 1) Scheduled triplicate ECG with an interval of at least 5 mins; 2) Vital sign measurements; 3) PK blood sampling; and 4) Any other tests and assessment required by the study.
b. After BLU-554 is administered, the subject should be intravenously infused with CS1001 as soon as possible. For PK blood sampling, the recommended infusion time of CS1001 is 90 minutes.
c. Collect two samples at one time point with BLU-554 blood sample be collected firstly and then CS1001 bloodsample.
d. The 24h PK sample of BLU-554 and the EOI+22.5h PK sample of CS1001 must be collected prior to dosing on the same day.
e. Cycle 1 Day 1: "2 hours post BLU-554 dosing" ECG collection is allowed at 1 - 4 h post BLU-554 dosing; "end of CS1001 infusion + 30 min" ECG collection is allowed from the time after the completion of CS1001 infusion to 2.5 h after the completion of CS1001 infusion. If the ECG collection windows for these two time points on C1D1 do not overlap, i.e. two sets of ECG data will be collected.

2. INTRODUCTION

2.1. INTRODUCTION OF THE INVESTIGATIONAL DRUG

BLU-554 capsules, also known as BLU111362 or X439161, are a highly potent selective small molecule inhibitor of FGFR4, which are developed by Blueprints for the treatment against HCC and other solid tumors with positive FGF19 expression.

CS1001 injection is a completely humanized IgG4-type recombinant anti-Programmed death ligand 1 (PD-L1) monoclonal antibody developed by CStone Pharmaceutical, which exerts an anti-tumor effect by recovering T-cell immune killer function after blocking the PD-L1 signaling pathway. It is currently developed for indications of advanced solid tumors such as HCC, lung cancer, gastric cancer, esophageal cancer etc.

2.2. MECHANISM OF ACTION AND BACKGROUND

- **Background**

Hepatocellular Carcinoma

Primary liver cancer mainly includes three different pathological types, which include Hepatocellular Carcinoma (HCC), Intrahepatic Cholangiocarcinoma (ICC) and HCC-ICC, with great differences in the terms of pathogenesis, biological behavior, histologicalmorphology, treatment method and prognosis, with hepatocellular carcinoma accounting for > 85-90%**[2]**

HCC is the sixth most common cancer and the second leading cause of death in subjects with cancer, which accounts for 7% of all cancers worldwide. Each year, 750,000 subjects could be present with HCC, among which almost 700,000 cases of subjects die **[1]** HCC is the fourth most common malignant tumor in China and the third leading cause of death in subjects with tumor **[2]**. Each year, 466 thousand cases of subjects could be present with newly diagnosed HCC in China, among which, about 422 thousands cases of subjects could die**[3]**, which significantly threats to the lives and well-beings of the people in China.

Treatment of HCC

Treatment of HCC is based on the staging of the disease. The Barcelona Clinic Liver Cancer (BCLC) staging criteria **[4]**, having been validated in a large series of subjects**[5]**, have become the standard by which treatment decisions are made. At this time, only tumor resection and liver transplantation are curative for HCC. It has been estimated that, in the US, 20–30% of subjects who present with HCC may fall into the very early, or early stages of the

BCLC criteria**[1]**, and so would be candidates for surgical treatment. However, only about 5% of subjects present with very early HCC, where resection and transplant have had the best results, and in many others presenting with early stage disease, chronic liver disease and cirrhosis preclude the use of surgery as a treatment modality. Even in subjects who are thought to be good candidates and successfully undergo resection, recurrence rates can be 55% at 2 years, and may reach 60-100% by 5 years[**6]**. Localized therapies such as trans-arterial chemo-embolization have had some long-term success, but only in very select groups of subjects.

The majority of subjects with HCC ultimately require systemic therapy, but development of systemic treatment for HCC has been severely limited. The current standard of care is sorafenib, a multikinase inhibitor, which received marketing approval in 2007. Sorafenib was evaluated in two Phase 3 trials against a control of best supportive care (BSC), with one trial conducted in

Western subjects with HCC, and the other in subjects from the Asia-Pacific region. In the Western trial, median overall survival (OS) improved from 7.9 months in the BSC arm to 10.7 months in the sorafenib arm (hazard ratio 0.69, p <0.001) reflecting an improvement of 30% **[7]**. In the Asia-pacific trial, a similar degree of improvement was seen, although with a subject population with more advanced disease, the actual survival times were different (4.2 months in the BSC arm vs. 6.5 months in the sorafenib arm) **[8].**

Although other multi-kinase inhibitors including linifanib, sunitinib and brivanib have been tested as first-line treatment for HCC, none has shown a statistically significant improvement in OS compared to sorafenib in Phase 3 studies **[9][10][11]**. Lenvatinib was approved by the FDA as first-line treatment for HCC in August 2018. In a non-inferiority Phase III study of lenvatinib versus sorafenib, the results showed that the median survival was 13.6 months in the lenvatinib arm and 12 months in the sorafenib arm (HR, 0.92; 95% CI, 0.79-1.06), indicating that the lenvatinib was not inferior to sorafenib **[12]**. However, this was accompanied by significant toxicity and frequent dose interruptions and reductions **[13]**.

In the second-line treatment for HCC in subjects who have received prior sorafenib, the multi-kinase inhibitor, regorafenib, and the PD-1 inhibitor, nivolumab have shown clear clinical activity and gained approval in the second line setting **[14][15]**. However, ORR and

OS remain low with these agents and there are no diagnostics to select subjects more likely to benefit. Thus, there remains a substantial medical need for novel agents for the systemic treatment for HCC in both the first and second line settings.

Immune checkpoint is a class of molecules that are immunosuppressed. Their physiological function is to regulate the intensity and breadth of immune response, thereby avoiding damage of normal tissue. While tumor cells tend to utilize such profile of the immune checkpoints to evade attacks of the immune cells. Currently, the immune checkpoints that have been clinically validated include CTLA-4 and PD1/PD-L1, and the immune checkpoint inhibitors targeting the PD1/PD-L1 have better clinical application prospect due to their better safety and broader indications. The combination with many types of drugs is possible due to the good safety and potential improvement of immune micro-environment properties of PD1/PD-L1 inhibitors. PD1/PD-L1 inhibitors in combination with many types of drugs has also been explored in multiple clinical studies, including anti-PD1/PD-L1 inhibitors in combination with CTLA-4 inhibitors such as nivolumab in combination with ipilimumab, durvalumab in combination with tremepilimumab; PD1/PD-L1 inhibitors in combination with molecular targeted agents such as lenvatinib in combination with pembrolizumab, PDR- 001 in combination with sorafenib. It was reported that lenvatinib in combination with pembrolizumab had a response rate of 52. 2% in subjects with advanced endometrial cancer and 63% in subjects with renal cell carcinoma, indicating that the combination regimen has the more prospective clinical treatment prospects [16]

- BLU-554

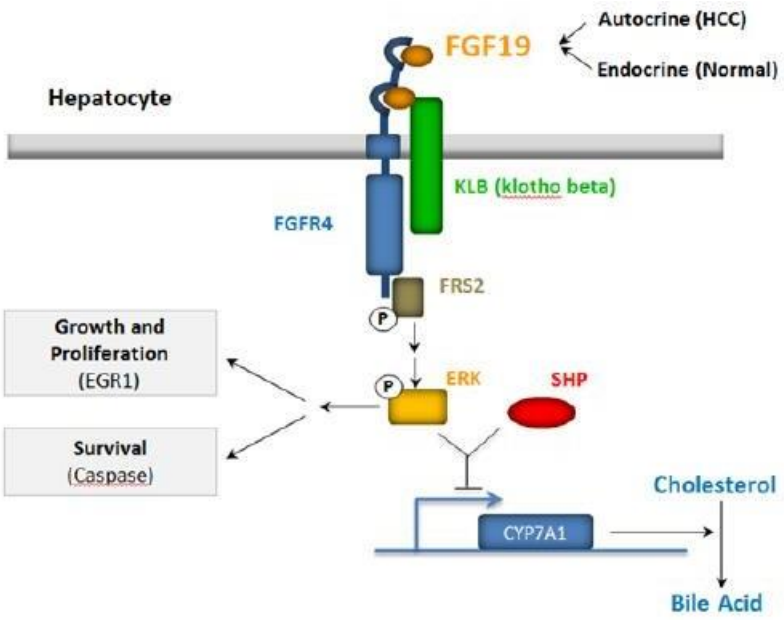
BLU-554 was designed as a highly potent, selective small molecule inhibitor of FGFR4 and has a unique selectivity profile for the FGFR family.

In normal physiology, FGF19 controls bile acid homeostasis and promotes hepatocyte survival and proliferation via binding to FGFR4 and co-receptor, Klotho-beta (KB), which initiates activation of the extracellular signal-regulated kinase (ERK) signaling pathway (**Figure 1**) **[17]**. Extracellular signal-regulated kinase activation attenuates bile acid

production by repressing expression of cholesterol-7α-hydroxylase (CYP7A1), an enzyme which catalyzes the first and rate-limiting step of bile acid production from cholesterol.

Extracellular signal-regulated kinase additionally promotes hepatocyte proliferation via EGR1 and hepatocyte survival via anti-apoptotic mechanisms.

Figure 1:FGF19-FGFR4 Pathway in Normal Physiology and HCC



The FGF19 pathway normally functions as an endocrine system in which post-prandial bile acids trigger FGF19 production in the ileum for delivery to the liver via the portal circulation. Liver expresses high levels of FGFR4 and KLB, which bind the released FGF19 and initiate signaling. Hepatocellular carcinomas likely to remain FGF19 responsive, suggesting that targeting the FGF19 pathway may have therapeutic benefit in HCC.

- CS1001

PD-L1, primarily expressed on the surface of tumor cells and antigen presenting cells, is the main ligand of T-cell inhibitory receptor PD-1 [18]. Binding of PD-L1 on tumor cells to PD-1 on the surface of T cell may cause signaling cascade reaction, inhibiting the proliferation of T cells and secretion of activated cytokines, reducing the activity of T cells, and reducing the tumor-cell killing ability of T cells; PD-L1 inhibitors impair the activity of T cells and tumor-cell killing ability by blocking the interaction between PD-1 and PD-L1 **[19].**

CS1001 is a completely humanized IgG4-type recombinant anti-Programmed death ligand 1 (PD-L1) monoclonal antibody, which exerts an anti-tumor effect by recovering T-cell immune killer function after blocking the PD-L1 signaling pathway.

2.3. PRECLINICAL STUDY

2.3.1. PHARMACOLOGY

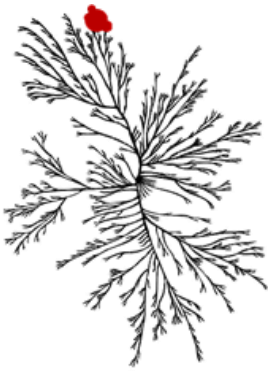
2.3.1.1. BLU-554

Inhibition of FGFR4 In Vitro

BLU-554 was designed as a highly potent, selective small molecule inhibitor of FGFR4 and has a unique selectivity profile for the FGFR family. BLU-554 forms a covalent interaction with cysteine 552 of FGFR4. This cysteine is located near the adenosine triphosphate (ATP)

binding site in FGFR4 and is unique among FGFR family members as well as rare among other kinases. It demonstrated biochemical in vitro activity on the FGFR4 kinase domain at a half-maximal inhibitory concentration (IC_{50}) of 5 nM and is at least 100-fold less active against the other FGFR paralogs. No kinases outside of the FGFR family are significantly bound by BLU-554.**Figure 2** below shows the high selectivity of BLU-554 across the human kinome.

Figure 2:The Activity of BLU-554 against the Human Kinome



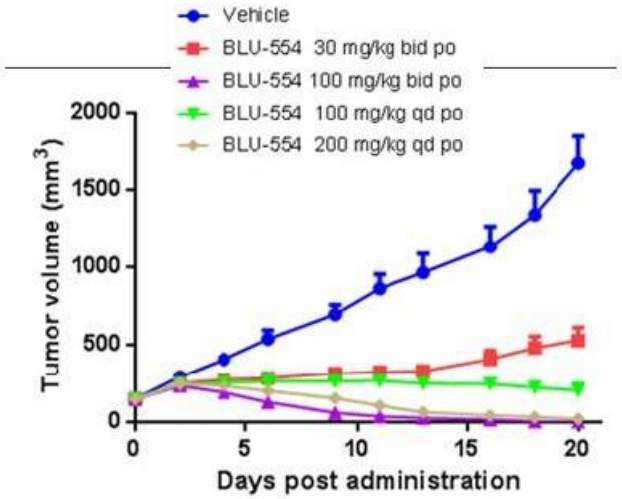
Each branch of the dendrogram above represents an individual human kinase. BLU-554 was screened at 3 µM against each kinase. Kinases inhibited at 3 µM are indicated by red circles on the kinome tree. The degree of inhibition corresponds to the size of the circle. No kinases outside of the FGFR family are significantly bound by BLU-554. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc (www.cellsignal.com).

In vitro, in human breast cancer cell line MDA-MB-453, BLU-554 exhibited dose-dependent inhibition of FGFR4 activity as well as modulation of key effector pathways known to be involved in tumorigenesis.

Inhibition of FGFR4 In Vivo

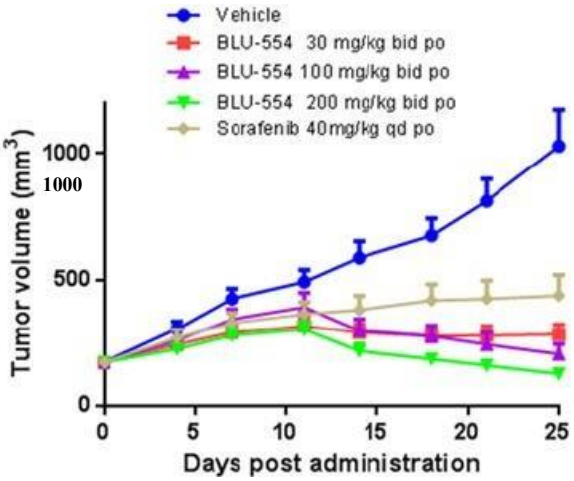
In vivo, anti-tumor efficacy with BLU-554 was demonstrated in a Hep3B human HCC xenograft model (genomic amplification and overexpression of FGF19) and in a LIX-066 subject-derived tumor xenograft model (overexpression of FGF19 without amplification). In the Hep3B model **Figure 3**), tumor regression was observed following administration of BLU-554 on both once daily (qd) and twice daily (bid) dosing schedules with no corresponding weight loss. In the LIX-066 primary human tumor model (**Figure 4**), tumor stasis was observed with a significant reduction in tumor growth upon administration of BLU-554; efficacy and tolerability were improved compared to sorafenib. Together, these data provide a rationale for selecting subjects with FGF19 overexpression and/or gene amplification for treatment with BLU-554.

Figure 3:BLU-554 Efficacy in a Xenograft Tumor Model with Amplified FGF19



Mice bearing Hep3B xenograft tumors were dosed orally on a once daily (qd) or twice daily (bid) schedule with 30, 100, or 200 mg/kg BLU-554. The Hep3B xenograft models HCC tumors that are IHC+, FISH+. BLU-554 100 mg/kg bid and 200 mg/kg qd resulted in equivalent tumor growth inhibition. Data points represent group mean and error bars represent standard error of the mean (SEM).

Figure 4:Efficacy Measurements for BLU-554 in a Subject-derived Xenograft Tumor Model with FGF19 Up-regulation in the Absence of Genomic Amplification



Mice bearing LIX-066 xenograft tumors were dosed orally with 30, 100, or 200 mg/kg BLU- 554 bid. The LIX-066 xenograft models HCC tumors that are IHC+, FISH-. A significant decrease in tumor growth was observed. Data points represent group mean, and error bars represent standard error of the mean (SEM).

Safety pharmacology studies revealed that BLU-554 inhibits human ether-a-go-go-related gene (hERG) channel activity in vitro with an average IC50 of 6.26 µM by single cellular electrophysiological recordings. The pharmacologic specificity of BLU-554 was assessed against a panel of 55 pharmacological targets including receptors, transporters, and enzymes. Compound binding was calculated as percentage inhibition of the binding of a radioactively labeled ligand specific for each target. Assays for the following targets showed >50% inhibition by BLU-554 at 10 µM screening concentration: A3 adenosine receptor, α2 adrenergic receptor, cholecystokinin A receptor, chloride ion channel, κ-opioid receptor,

melatonin receptor MT1, sodium ion channel site 2, and the nociceptin receptor. The relevance of this binding was not apparent in the dog and mouse 28-day Good Laboratory Practice (GLP) toxicology studies and so the clinical significance of these interactions is unknown.

2.3.1.2. CS1001

In Vitro Pharmacology

In vitro pharmacology studies were conducted, including: the binding capacity with cell surface human PD-L1, the binding capacity with recombinant PD-L1 protein in human, cynomolgus monkey or mouse, the binding kinetics to recombinant PD-L1 protein, the binding capacity with human PD-L2 protein, the member of PD-L1 family, competitive blocking of ligation of PD-L1 with PD-1/CD80, activation on human CD4+ T cells, ADCC and CDC.

In the binding assay of PD-L1 on the cell surface, CS1001 antibody effectively bound to PD-L1-transfected CHO cells with an EC_{50} value being 1.10 nM.

Cross-species reactivity test showed that CS1001 specifically binds to human and cynomolgus monkey PD-L1 protein with the comparable binding capacity, but cannot bind to mouse PD-L1 protein.

The calculated result of affinity with WBP315.hPro1.ECD.mFc showed that CS1001 has strong affinity with PD-L1 protein and its affinity constant is 1.38 nM.

Cross-reactivity assay with proteins of PD-L1 family showed that CS1001 specifically binds to human PD-L1 protein but not to human PD-L2, indicating that this PD-L1 antibody would not potentially cause side effects due to non-specific binding.

From the results of competitive inhibition of PD-L1/PD-1 ligation, it is clear that CS1001 can effectively block the ligation of PD-L1 with PD-1 protein with IC50 value being 1.93 nM. It is also showed that CS1001 can effectively block the ligation of PD-L1 with CD80 similarly as the reference antibody WBP315BMK1 (BMS).

Together, above results showed that CS1001 can inhibit the PD-1/PD-L1 interaction via specific binding to PD-L1. Its effect on T cell immune function was further studied in *in vitro* functional experiments.

The effect of CS1001 on T lymphocyte activation was tested using mixed lymphocyte reaction (MLR). The results showed that CS1001 can significantly enhance the secretion of IL-2 and IFN-γ by CD4+ T lymphocytes, and promote the proliferation of CD4+ T lymphocytes.

On the other hand, the ADCC and CDC effect of CS1001 were tested. The results indicated that CS1001 had no ADCC and CDC on PD-L1-positive lymphocytes, thereby without potential damage to surrounding immune cells *in vivo*.

In Vivo Pharmacology

Because CS1001 does not recognize mouse PD-L1, the activity of CS1001 was evaluated in a syngeneic mouse tumor model humanized with human PD-L1 in the tumor graft (MC38- B7H1) and human PD-1 in animal host (i.e. B-hPD-1 C57BL/6 humanized mouse). The drug was

administered through intraperitoneal injection, once every 2 days for 6 consecutive doses. The results (**Figure 5**) showed that the tumor volume in the solvent control group increased rapidly during the test period (the mean tumor volume was 2359 mm^3 at the end of the study), while the tumor volumes were substantially lower in the CS1001 low (3mg/kg), medium (10 mg/kg), and high (30 mg/kg) dose groups than the control group (the mean tumor volumes were 949 mm^3, 1416 mm^3, and 1115 mm^3, respectively), and all 3 doses showed effective anti-tumor activity (Tumor Growth Inhibition [TGIs] were 62.8%, 42.0%, and 55.4%, respectively; p=0.019, 0.149, and 0.039, respectively). On the other hand, mice in different groups showed no significant difference in body weight changes during administration (**Figure 6**), and were in good state of activity and food consumption, indicating that the mice were well tolerated with CS1001. The consistent results were achieved in a repeated study using the same animal model.

Figure 5:Tumor Growth in Each Group during the Test

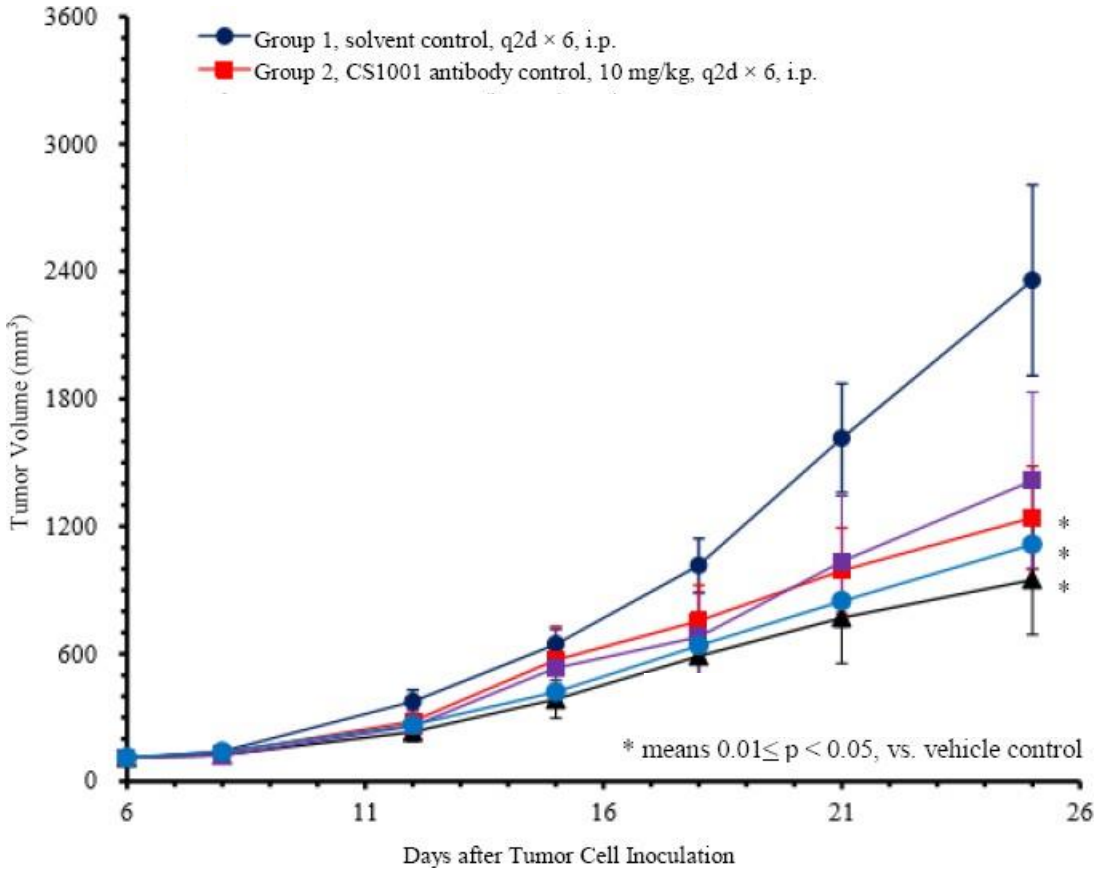
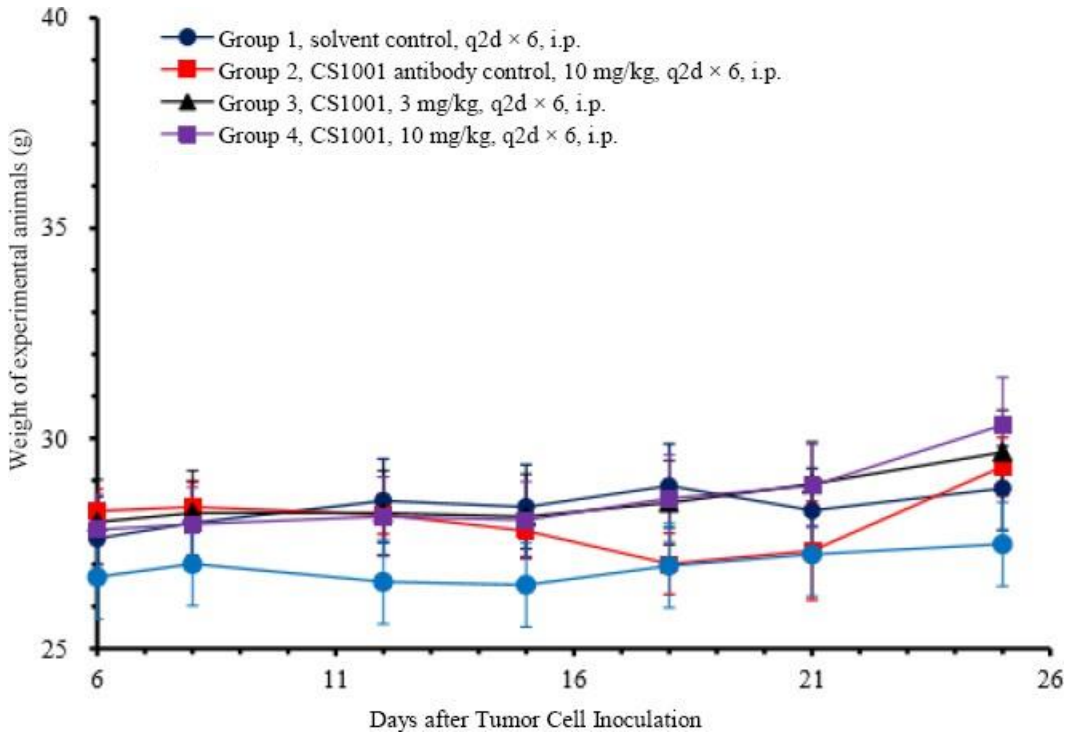


Figure 6: Body Weight Changes of Mice in Each Group during the Administration



2.3.2. PHARMACOKINETICS

2.3.2.1. BLU-554

Single-Dose Pharmacokinetics

Upon single dose administration in nonclinical species, plasma clearance upon IV administration was moderate in mouse and rat, at ~ 20% liver blood flow. Plasma clearance in nonrodent species, dog, and monkey, was low at ≤20% liver blood flow. The volume of distribution at steady state was low-to-moderate in all species, either approximating or slightly higher than published values for the volume of total body water. The oral bioavailability of BLU-554 dosed as a solution was moderate in mouse, rat, and dog, ranging from 62% to 82%, and was low in monkey (29%).

Repeat-dose Pharmacokinetics

In repeat-dose toxicology studies in mice, plasma exposure to BLU-554 increased less than proportionally to dose upon repeat-dosing for 7 or 28 days. Systemic exposure to BLU-554 was similar in both sexes of mice (Report WIL-124511).

In repeat-dose toxicology studies in dogs, BLU-554 exposure in terms of C_{max} increased in a dose proportional manner, but $AUC_{0\text{-}24}$ increased greater than proportionally to dose upon repeat-dosing for 28 days. Exposure was similar in both sexes of dogs (Report WIL-124512).

2.3.2.2. CS1001

Single-Dose Pharmacokinetic Study

Serum PK characteristics and ADA on CS1001 were assessed when 18 male and 18 female naïve cynomolgus monkeys were administered intravenously once at 10, 30 and 90 mg/kg.

The results showed that in the dose range of 10 mg/kg to 90 mg/kg, the C_0 of CS1001 increased in a dose-dependent manner, and the rate of $AUC_{0\text{-last}}$ increased greater than proportional over the above-mentioned dose range.

The female: male ratio of CS1001 systemic exposure (AUC0-last) (**Table 2**) was 0.58, 0.94 and 0.85 in the low, medium and high dose groups respectively, all of which were within 2 folds, suggesting that no significant gender difference on CS1001 systemic exposure in cynomolgus monkeys.

ADA was mainly occurred at 648, 984 and 1320 hours after administration; in the 10 mg/kg treatment group, the number (%) of monkeys with a positive ADA sample was 22.2% for both male and female, and in the 30 mg/kg treatment group, the number (%) of monkeys with a positive ADA sample was 22.2% for the male and 11.1% for the female. No monkeys had positive ADA sample in the 90 mg/kg treatment group. The data showed that compared with the low-dose group, the positive rate of ADA in the high-dose group showed a decreasing trend. No abnormalities were observed in all the experimental animals during the whole experiment.

Please refer to Investigator's brochure (IB) of CS1001.

2.3.3. TOXICOLOGY

2.3.3.1. BLU-554

The toxicity profile of BLU-554 was evaluated in vitro in a bacterial reverse mutation assay and in vivo in CD-1 mice, Sprague-Dawley rats, and Beagle dogs. CD-1 mice and Beagle dogs were chosen as the nonclinical test species for assessing chemical structure- and pharmacology-mediated toxicity of BLU-554 on the basis of the following criteria: a) these species are pharmacologically responsive to the effects of BLU-554; b) these species have historically been utilized to assess potential human adverse effects, and; c) these species are qualitatively similar in hepatocyte metabolism profiles to humans.

Repeat-Dose Toxicity

In the 28-day GLP-compliant repeat-dose toxicology study in CD-1 mice, only minimal effects were noted at a limit dose of 2,000 mg/kg/day. Resultant end-of-study sex-averaged maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) in the mouse were higher than the predicted C_{max} and $AUC_{0\text{-}24}$ at the projected human efficacious dose of 1,000 mg/day; (581 mg/m^2/day).

In the 28-day GLP-compliant repeat-dose toxicology study in Beagle dogs, the lethal dose effects, the highest non-severely toxic dose (HNSTD) effects, and the dose-limiting toxicities (DLT) have been carefully characterized. In the dog, the DLT is attributed to inanition, gastrointestinal malfunction, and metabolic perturbations evidenced by changes in body weights, food consumption, serum, and urine chemistry values, and contributed to by hematologic and tissue effects. The severely toxic dose (STD) in the dog is 50 mg/kg/day (1,000 mg/m^2/day) and the HNSTD is 25 mg/kg/day (500 mg/m^2/day). At the HNSTD, the predominant change in serum biochemistry was hyperphosphatemia. However, this was modest (maximum increase of 30% on Day 15) and readily reversible, with complete recovery by Day 42. Hyperphosphatemia was

associated with minimal to mild tissue mineralization as detailed in the Investigator's Brochure. Effects noted in dogs are considered to be related to the pharmacologic activity of FGFR4 signaling by BLU-554 or the sequelae of these effects, except for the myxomatous change noted in the heart. All adverse effects are monitorable. All adverse effects were resolving or resolved after the 14-day recovery period,except effects in the stomach, heart, and aorta. No functional effects on the cardiovascular system were noted based on electrocardiogram (ECG) analyses and in-life examinations.

Genotoxicity

BLU-554 was negative in the bacterial reverse mutation and micronucleus in vitro assays with and without metabolic activation (rat liver S9).

Developmental and Reproductive Toxicity

Reproductive toxicology studies have not been initiated. Studies on the potential toxicity of BLU-554 on reproductive function and fetal development are not available. No information is available on the safety or efficacy of BLU-554 in pregnant or lactating females. In the GLP-compliant 28-day repeat-dose toxicity studies in CD-1 mice (Study WIL-124511) and Beagle dogs (Study WIL-124512), adverse effects in reproductive tissues were noted only in male dogs (effects in the testes and epididymis). Pregnant women will not be enrolled in the Phase 1 clinical trial and lactating women will be instructed not to nurse while receiving BLU-554.

Local Tolerance

Local tolerance was assessed by reviewing the digestive tract changes in the GLP-compliant 28-day toxicology studies in mouse (Study WIL-124511) and dog (Study WIL-124512). No evidence of local gastrointestinal effects occurred in the CD-1 mouse even at the highest tested dose of 2,000 mg/kg/day at which local mucosal surface concentrations would be anticipated to be high relative to human exposure. In the Beagle dog at lethal doses, esophageal effects were attributed to gavage trauma and gastric mucosal effects to stress.

BLU-554 did induce emesis and diarrhea in the dog at the HNSTD, without any gastrointestinal tissue histologic correlate.

Other Toxicity Studies

Phototoxicity Studies: Definitive tissue distribution studies have yet to be performed. In GLP- and non-GLP-compliant toxicology studies in CD-1 mice and Beagle dogs, there were no lesions in the epidermis of the skin or in the eye. In a non-GLP in vitro neutral red uptake photoxicity assay in 3T3 fibroblasts, BLU-554 was classified as a compound with phototoxicity potential. On the basis of the molar extinction coefficient of BLU-554, the in

vitro neutral read uptake photoxicity assay in 3T3 fibroblasts, and the lack of definitive tissue distribution data, a risk of phototoxicity cannot be ruled out. Subjects should therefore use clothing and sunscreen to avoid direct sun exposure.

Toxicokinetics

The allometrically scaled HNSTD in the dog is 500 mg/m^2 (25 mg/kg/day). The highest nontoxic dose in the mouse is 2,000 mg/kg/day or 6,000 mg/m^2. Based on allometrically scaled dosages as well as on systemic exposures ($AUC_{0\text{-}24}$), the dog is the most sensitive species. The

mouse tolerates these exposures without toxic consequences. The mean exposure in the dog at the HNSTD approximates the steady state AUC_{0-24} and C_{max} values at the human MTD/RP2D of 600 mg/day (370 mg/m^2/day), while the STD exposure AUC_{0-24} and C_{max} values exceed the maximum tolerated human exposure.

See Investigator's brochure (IB) of BLU-554 for more details.

2.3.3.2. CS1001

Single-Dose Toxicity Test

To evaluate the potential toxicity and the MTD of CS1001, following single intravenous infusion to cynomolgus monkeys, and to assess the reversibility, persistence, or delayed occurrence of toxic effects following a 14-day observation period. In conclusion, administration of CS1001 to cynomolgus monkeys by a single intravenous infusion at dose levels of 100, 300, and 1,000 mg/kg followed by a 14-day observation period was well tolerated and did not result in any treatment-related mortality, and any effects in clinical signs, changes in body weight, food intake, or gross pathology. Under the conditions of the study, the MTD was considered to be no less than 1,000 mg/kg.

Repeat-Dose Toxicity Test

To determine the potential toxicity to cynomolgus monkey of CS1001, by intravenous infusion once weekly for a total of 5 doses and to assess the reversibility, persistence, or delayed occurrence of toxic effects following a 4-week recovery period.

CS1001 was given via intravenous infusion by the doses of 30, 75 and 200 mg/kg, and, at the end of the trial, no CS1001-related significant change was observed in survival rate, clinical symptoms, weight, food intake, temperature or clinical pathology (blood test, coagulation parameters, biochemistry and urine analysis). One case of retinal depigmentation was observed in the 200 mg/kg dose group, and the possibility of drug-related pigmentary degeneration of the retina could not be excluded; no other CS1001-related ophthalmological change was seen.

The results of pathological test showed that, in the late administration period and late recovery period, no CS1001-related obvious lesion visible to naked eyes was observed; there was no significant change in the weight of any organ; the microscopic examination of various organs also showed no CS1001-related histopathological change.

Consequently, under the conditions of the study, the NOAEL was considered to be 200 mg/kg.

Safety Pharmacology Evaluation

The safety pharmacological parameters (cardiovascular and respiratory systems) were evaluated in the repeated dose toxicity test.

According to the results, in the repeated dose toxicity test, the changes in the blood pressure, heart rate, ECG and respiratory system parameters of cynomolgus monkeys in various administration groups all fell within the ranges of normal physiological fluctuations, and no CS1001-related significant change was observed.

Local Irritation Study

Local irritation was evaluated in repeated dose toxicity study. The results showed that during the administration period, very slight to obvious erythema could be observed at the injection site of animals in all groups (including the control group). The histopathological examination showed hemorrhage and/or neutrophil-dominated inflammatory infiltration in blood vessels/peripheral tissues. No obvious dose dependence was observed regarding the severity, duration or incidence. Local reactions at injection sites lasted for different durations in various administrations, but all of them disappeared within 7d after administration. Therefore, these findings were considered related to the dose administration procedure and not related to CS1001.

In Vitro Hemolysis Studies

The in vitro hemolysis test was conducted to detect whether two concentrations of CS1001 injection could incur hemolysis and/or RBC coagulation. There was no hemolysis or coagulation of red blood cell in negative control group (sodium chloride), and obvious hemolysis in positive control group (purified water), which indicated the study system was valid. No hemolysis or red blood cell coagulation was noted in CS1001 (6 and 30.3 mg/mL) or CS1001 placebo.

Anaphylaxis Study

An active systemic anaphylaxis study was performed in guinea pigs to determine the potential anaphylaxis of CS1001. According to the results, the animals in the positive control group showed the allergic reactions of piloerection, nose scratching, dyspnea and gait instability 5 min after challenge dosing; however, no allergic reaction was observed after provocation and administration on any animal in the negative control group or the administration groups. No animal showed any CS1001-related change in clinical symptoms or weight in either the induction phase or the challenge phase, and there was no unexpected death during the trial.

Immunotoxicity/Immunogenicity Test

The immunological characteristic assessment was also carried out during the repeated dose toxicity test, and mainly consisted of four aspects, i.e., ADA analysis, B, T lymphocyte phenotype analysis, cytokine analysis, and immune globulin & complement.

As shown by the ELISA method-based detection in this study, no positive anti-CS1001 antibody result was detected on any animal, suggesting that CS1001 had no immunogenicity for cynomolgus monkeys under these doses. Flow cytometry was employed for B, T lymphocyte phenotype detection, and the results showed that, no statistical difference or dose-related change was observed in the peripheral blood and immune organ lymphocyte subset percentage before and after administration or among various dose groups. Trace- sample multi-index flow cytometry-based protein quantitative counting (Becton-Dickinson FACSCanto II flow cytometry) was used to analyze the TNF-α, IL-2, IL-4, IFN-γ, IL-5 and IL-6 in the peripheral blood, and the results showed that no CS1001-related change was observed in cytokines and that all cytokine changes fell within the ranges of normal physiological fluctuations. Immunoturbidimetry was adopted to analyze the immune globulin & complement in serum via the detection indexes of C3c, C4, IgG, IgA and IgM, and the results showed that no CS1001-related change was observed in immune globulin & complement and that all the changes fell within the ranges of normal physiological fluctuations.

Tissue Cross-reactivity Study

Immunohistochemistry was employed to analyze the tissue cross-reactivity of CS1001 in human, cynomolgus monkey and rat tissues. According to the results: Immunohistochemistry was

employed to analyze the binding activity of biotinylated CS1001 and biotinylated control (135-Human Ctrl) in 33 kinds of fresh frozen normal rat tissues, cynomolgus monkey tissues and human tissues (each kind of tissues coming from three individuals). At 1 μg/mL and 10 μg/mL, specific staining by biotinylated CS1001 was observed only on the cell membrane of CHO PD-1 positive cell line (positive control). No specific staining by biotinylated CS1001 or biotinylated 135-Human Ctrl was seen in any fresh frozen rat tissue; no specific staining by biotinylated CS1001 or biotinylated 135-Human Ctrl was seen in any fresh frozen cynomolgus monkey tissue; no specific staining by biotinylated 135-Human Ctrl was seen in any fresh frozen human tissue, and only specific staining by biotinylated CS1001 was seen in the placenta tissue.

Toxicokinetic study

Toxicokinetics was studied in a repeated dose trial in cynomolgus monkeys. 40 cynomolgus monkeys were randomly assigned into four groups, that is, the placebo group and the dose groups of CS1001 30 mg/kg, 75 mg/kg and 200 mg/kg; the drug was given once a week for a total of five times (respectively on D1, D8, D15, D22 and D29), and the blood would be sampled at the planned time for the serum concentrations of CS1001 and ADA test. See Table **3** for the summary of the toxicokinetic parameters of CS1001.

According to the results of CS1001 administered to male and female cynomolgus monkeys through repeated intravenous infusion, the T_{max} median of CS1001 occurred between 0.3 and 8.0 hours postdose. No significant gender difference was observed among various dose groups in term of the systemic exposure; as the dose was increased from 30 mg/kg to 200 mg/kg, systemic exposures of both female and male cynomolgus monkeys on Days 1 and 22 increased proportionally. Based on the change in $AUC_{0\text{-}168h}$, the ratio of systemic exposure on Day 22 to that on Day 1 ranged between 2.2 and 3.0 and the growth in systemic exposure of CS1001 in the test animals of any dose group indicated the existence of drug accumulation. No ADA was observed in the animals of any dose group.

See the Investigator's brochure (IB) of CS1001for more details.

2.4. CLINICAL STUDIES

2.4.1.1. BLU-554

As of 16 June 2018 (data cut-off), there is 1 ongoing Phase 1 study in subjects with BLU-554 Study BLU-554-1101 is a Phase 1, open-label, FIH study designed to evaluate the safety, tolerability, PK, PD, and preliminary antineoplastic activity of BLU-554 administered orally in subjects with HCC. The study consists of 3 parts. Part 1 consists of dose escalation employing a 3+3 design to determine MTD/RP2D by exploring both QD and BID dosing schedules. Additional accrual to dose levels that had been declared safe was allowed to further assess the safety, PK, PD, and preliminary antitumor activity of BLU-554. Part 2 consists of dose expansion exploring the MTD/RP2D for the QD dosing schedule. Part 3 is a continuation of expansion for the QD dosing schedule in subjects with FGF19 immunohistochemistry positive (IHC+) HCC who have not received prior TKI therapies such as sorafenib, regorafenib, lenvatinib, or other kinase inhibitor (TKI-naïve). Part 1 and Part 2 of the study have completed enrollment. Part 3 (Expansion FGF19 IHC+, TKI-naïve) is ongoing with BLU-554 being administered at the RP2D of 600 mg QD. At the time of the data cut-off date (16 June 2018), 115 subjects have received BLU-554, including 34 subjects in Part 1 (QD and BID dosing) and 81 subjects in Part 2 (QD dosing).

Part 1 Dose Escalation

A total of 25 subjects received BLU-554 according to the QD dose escalation schedule during Part 1 of the study at doses ranging from 140 mg to 900 mg. In the QD dose schedule, no DLTs were observed at doses ranging from 140 to 600 mg QD. Two DLTs were noted at 900 mg QD including 1 subject with Grade 3 abdominal pain and 1 subject with Grade 3 fatigue lasting more than 7 days. BLU-554 600 mg QD was determined to be the MTD. Based on the safety profile, PK, and preliminary antitumor activity, 600 mg QD was considered the recommended dose for Part 2 (dose expansion).

A total of 9 subjects received BLU-554 according to the BID dose escalation schedule during Part 1 of the study at doses of 200 mg or 300 mg. In the BID dose schedule, 2 DLTs were noted at 200 mg BID, including 1 subject with Grade 3 fatigue lasting greater than 7 days and 1 subject with clinically important AEs (Grade 1 headache, nausea, diarrhea, abdominal pain, and Grade 3 fatigue) that were determined by the Investigator to be a DLT. At 300 mg BID, 1 DLT was noted in 1 subject with Grade 3 pulmonary edema. Pharmacokinetic modelling suggested that 100 mg BID would provide exposure below xenograft efficacy levels as well that of the 280 mg QD dose level. Therefore, further study of the BID schedule is not planned.

Part 2 Expansion

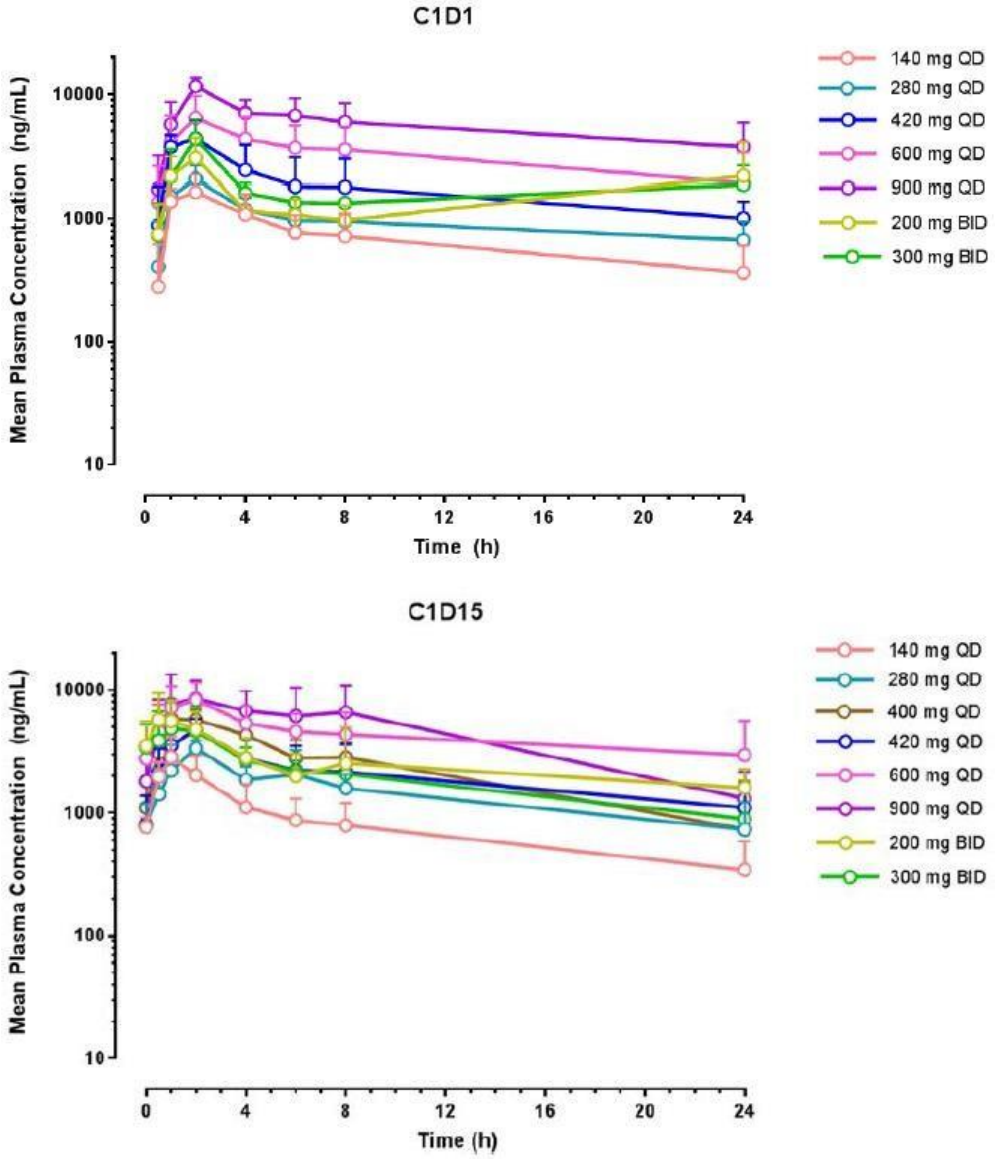
A total of 81 subjects have received BLU-554 at the RP2D of 600 mg QD in Part 2 QD dose expansion.

Pharmacokinetics

The single dose (Cycle 1 Day 1 [C1D1]) and steady state (Cycle 1 Day 15 [C1D15]) pharmacokinetics of BLU-554 following QD and BID oral administration have been evaluated in subjects in Study BLU-554-1101. The mean plasma BLU-554 concentration-time profiles for each dose level on C1D1 and C1D15 are shown in **Figure 7**

Following administration of single oral doses of BLU-554 ranging from 140 to 900 mg, the median time to peak concentration (T_{max}) ranged from 1.5 to 2 hours postdose, and the mean (of all dose groups) plasma elimination half-life ($t_{½}$) of BLU-554 was 16.5 hours. After a single dose and repeat dosing of BLU-554, systemic exposure increased in a dose-dependent manner. No significant drug accumulation (Rac ≤1.6) was observed after repeat dosing of BLU-554 (dose range: 140 – 900 mg QD; 200 and 300 mg BID), consistent with the observed half-life. The steady state (C1D15) geometric mean (%CV; n) C_{max} and $AUC_{0-\tau}$ of BLU-554 at the RP2D of 600 mg QD was 8733 ng/mL (36.1%; n=72) and 91386 h•ng/mL (41.8%; n=65), respectively.

Figure 7: Mean (+StdDev) Plasma Concentration-Time Profiles of BLU-554 on C1D1 (Single Dose) and C1D15 (Steady State) Following Once Daily or Twice Daily Oral Administration (Study BLU-554-1101)



Abbreviations: BID = twice daily; C1D1 = Cycle 1, Day 1; C1D15 = Cycle 1, Day 15; QD = once daily; StdDev = standard deviation.
Data cut-off date: 22 June 2018.

Safety

As of the data cutoff, a total of 115 subjects were evaluable for the safety analysis evaluation. Most adverse events (AEs) observed in these subjects were Grade 1 or 2. The most common (≥20%) suspected to be related to study drug include diarrhea (N = 87, 76%), nausea (N = 48, 42%), ALT increased (N = 38, 33%), vomiting (N = 42, 37%), AST increased (N = 33, 29%), fatigue (N = 32, 28%) and decreased appetite (N = 22, 19%). Serious adverse events (SAEs) were reported in 49 (43%) subjects, and SAEs considered related to study drug occurred in 18 (16%) subjects, mainly including vomiting, anemia, hyponatremia, and pyrexia, etc.

At the time of the data cut-off, 10 of 115 subjects remained on treatment, including 9 subjects

who are FGF19 IHC+. Of the 105 subjects (91%) who discontinued treatment with BLU-554,78 subjects ended treatment due to disease progression, 18 due to AEs, 6 due to withdrawal of consent, and 3 due to Investigator decision. No deaths due to drug-related AEs have been reported.

Efficacy

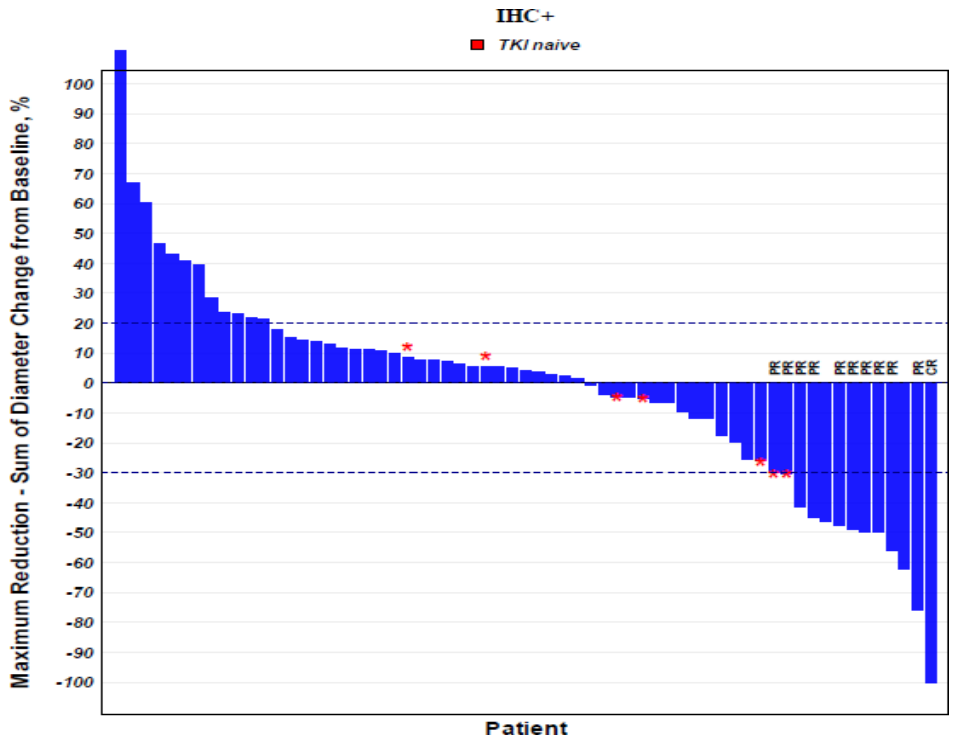
A total of 101 subjects were evaluated for disease assessment per RECIST 1.1 (Investigator-assessed response). Of the 38 subjects who were FGF19 IHC–, there were no responders. Eleven of 63 (17%) subjects who were FGF19 IHC+ had documented responses per RECIST1.1. One subject had an unconfirmed complete response before disease progression, which was documented at the subsequent assessment due to a new lesion. Best response is shown in Table 7. Maximum tumor reduction as measured by shrinkage in target lesions in 63 FGF19 IHC+ subjects is shown in **Figure 8**. Twenty-seven (43%) subjects have had a reduction in tumor burden, including 5 of the 7 TKI naviïe subjects (71%) as shown in **Figure 9**

Table 7: Best Response (Response-Evaluable Population, N=101)

Best Response	**FGF19 IHC+ N=63 N (%)**	**FGF19 IHC- N=38 n (%)**
Complete response	1 (2)[a]	0
Partial response	10 (16)	0
Stable disease	30 (48)	21 (55)
Disease progression	22 (35)	17 (45)

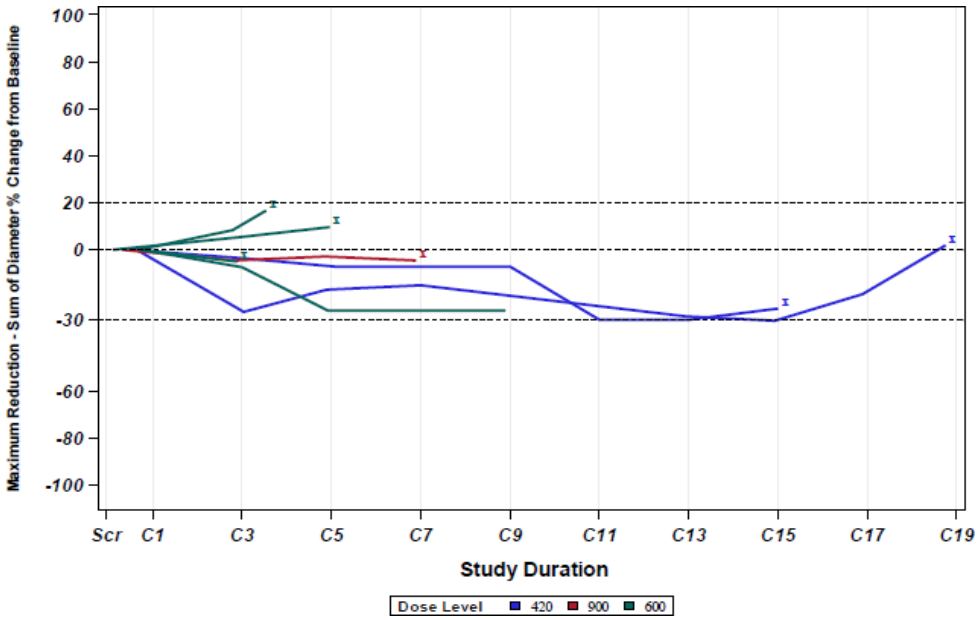
Abbreviations: IHC = immunohistochemistry.
Data cut-off date: 16 June 2018.

Figure 8:Waterfall Plot of Maximum Tumor Reduction in Target Lesions (Response-Evaluable Population, IHC+, N=63)



Abbreviations: CR = complete response; IHC = immunohistochemistry; PR = partial response; TKI = tyrosine kinase inhibitor.
Data cut-off date: 16 June 2018.

Figure 9:Spider Plot of Tumor Reduction and Study Duration in Tyrosine Kinase Inhibitor Naïve Subjects (Response-Evaluable Population, IHC+, N=7)



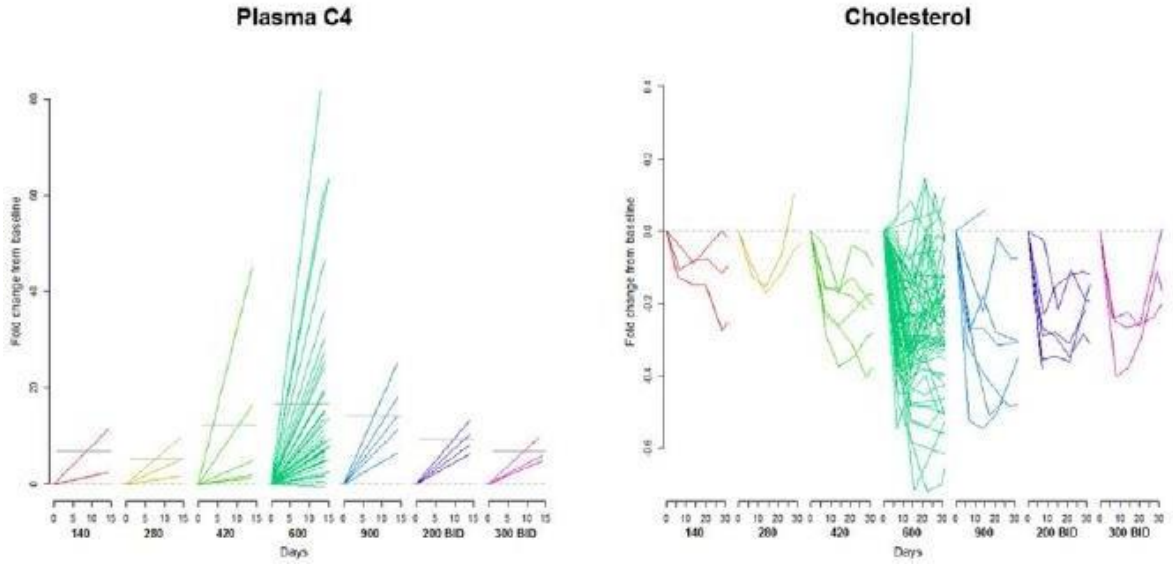
Abbreviations: C = cycle; IHC = immunohistochemistry; Scr = Screening; TKI = tyrosine kinase inhibitor; x = treatment discontinuation.
Data cut-off date: 16 June 2018.

Pharmacodynamics

During BLU-554 dose escalation in both the QD and BID dosing schedules, plasma-based PD markers are collected predose, and 1 hour, 2 hours, and 15 days thereafter. Cholesterol and the bile acid precursor, 7α-hydroxy-4-cholesten-3-one (C4), were selected as biomarkers as they constitute reactants of the FGFR4-regulated bile acid synthesis pathway under physiologic liver conditions. Cholesterol and C4 are substrate and product respectively of CYP7A1 and CYP17A1 catalytic conversion that are repressed by FGFR4 signaling. As shown in **Figure 10** inhibition of FGFR4 by BLU-554 leads to a release of the CYP7A1/CYP17A1 expression blockade and subsequently to the accumulation of C4 and depletion of total cholesterol as expected. This relationship is apparent starting from the lowest 30 mg BLU-554 dose and becomes more pronounced with increasing dose levels. No change of magnitude is apparent beyond 600 mg, which indicates that pathway modulation plateaued. This indicates adequate FGFR4 target coverage.

Gut-derived endocrine FGF19 represents a feedback loop to prevent oversupply of bile acids. Due to the perturbance of the bile acid homeostasis by BLU-554, FGF19 levels rise accordingly (data not shown).

Figure 10: Plasma-Based Pharmacodynamic Markers (Once Daily Dosing)



Please refer to the latest Investigator's Brochure for the latest data from clinical study of BLU-554.

2.4.1.2. CS1001

Study CS1001-101 has been conducted in Mainland China since October 2017. CS1001-101 is an ongoing Phase 1a/1b, multi-center, open-label, multiple-dose, dose finding and expansion first in human (FIH) study for assessing the safety, tolerability, PK profile and anti-tumor efficacy of CS1001 in subjects with advanced solid tumors or lymphoma. Phase

1a part was a dose finding study and used a classic 3+3 design. Phase 1a part is a dose finding study in which subjects received CS1001 intravenously across 5 cohorts at 3 mg/kg, 10 mg/kg, 20 mg/kg, 1,200 mg fixed dose and 40 mg/kg once every 3 weeks (Q3W). Phase Ib part is an expansion study conducted in subjects with different solid tumors and subjects with lymphoma. As of November 30, 2018, a total of 29 subjects were enrolled into each of the dose- escalation groups and began to receive CS1001 at 5 dose levels, i.e. 3 mg/kg, 10 mg/kg, 20 mg/kg, fixed dose 1,200 mg and 40 mg/kg from October 19, 2017 to June 5, 2018 for dose finding. No dose limiting toxicity (DLT) was observed in all dose groups after assessment by the Safety Monitoring Committee (SMC) and maximum tolerated dose (MTD) was not reached. As of 30 November 2018, the overall safety and tolerability were good. Based on data on safety, PK and preclinical pharmacology, the fixed dose 1,200 mg as infused every 3 weeks was identified as the study drug dose for CS1001 in Phase Ib and subsequent studies. Preliminary safety data and antitumor activity supported the subsequent studies of CS1001 in subjects with advanced tumors. As the design of Phase Ib study, it was planned to enroll 250- 300 subjects. 162 subjects had been enrolled as of 15 March 2019 and the study is still ongoing.

Pharmacokinetics

As of 30 November 2018, serum concentrations of CS1001 were observed from 29 subjects in

5 dose groups in the Phase Ia study of CS1001-101. Pharmacokinetic (PK) analysis indicated that the median T_{max} was between 2.05 to 4.55 hours after a single intravenous infusion (3 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, fixed dose 1,200 mg). The exposure of CS1001 (C_{max} and AUC) increased proportional to dose escalation with moderate individual variability. Calculated based on plasma concentration profile after single dose, the arithmetic mean $t_{1/2}$ ranged from 12.19 to 17.56 days; geometric mean V_{ss} ranged from 3.29 to 4.43 L, indicating that CS1001 was mainly distributed in blood and extracellular fluid; mean $t_{1/2}$ and V_{ss} were comparable across dose groups. The in vivo pharmacokinetic property of CS1001 is consistent with the IgG4-type antibodies. In addition, PK values after multiple intravenous infusions (every 3 weeks, Q3W) showed a consistent proportional increase in exposure compared with the Cycle 1 with moderate individual variability.

Safety

As of 30 November 2018, the safety profile of all subjects at 5 different dose levels in the dose escalation phase (Phase Ia) CS1001 was summarized.

All 5 dose levels had been assessed by the Safety Monitoring Committee (SMC). No dose limiting toxicity (DLT) was observed in all dose groups, and the maximum tolerated dose (MTD) was not reached.

As of the data cutoff, enrolled subjects had received a median of 6 cycles of CS1001, with a range from 1 cycle to 20 cycles; the median duration of CS1001 treatment was 126 days, ranging from 21 days to 408 days. No subjects experienced treatment-emergent adverse events (TEAEs) leading to study drug infusion interruption, TEAEs leading to death, and infusion-related TEAEs.

29 (100%) subjects experienced TEAEs during the study. The most common (≥ 20.0%) TEAEs were anemia (48.3%), proteinuria (44.8%), blood bilirubin increased (27.6%), alanine aminotransferase increased (24.1%), aspartate aminotransferase increased (24.1%), conjugated bilirubin increased (24.1%), white blood cell count decreased (24.1%) and appetite decreased (20.7%). TEAE will be replaced with AE (adverse event) in the following description.

Most subjects (93.1%) experienced CS1001-related AEs during the study. The most frequent CS1001-related AEs were anemia (48.3%), followed by proteinuria (44.8%), blood bilirubin increased (27.6%), alanine aminotransferase increased (24.1%), aspartate aminotransferase increased (20.7%), conjugated bilirubin increased (20.7%), white blood cell count decreased (20.7%), etc.

Of the CS1001-related AEs, most were Grade 1 to 2 in severity according to Common Terminology Criteria for Adverse Events (CTCAE), and Grade 3 events included platelet count decreased (1 in group 20 mg/kg) and anemia (2 in group 1,200 mg fixed dose). There were no Grade 4 or 5 CS1001-related AEs.

Of the 29 subjects enrolled, 6 (20.7%) experienced serious adverse reactions (SAEs), none of which were related to CS1001. 2 (6.9%) subjects experienced AEs that led to permanent treatment discontinuation, which were abnormal hepatic function (3.4%) and pulmonary tuberculosis (3.4%) respectively. Both were in group 1,200 mg fixed dose and both were judged to be unrelated to CS1001.

13 (44.8%) subjects experienced AEs leading to delayed treatment cycle, which occurred in

groups 3 mg/kg (2 subjects), 10 mg/kg (2 subjects), 20 mg/kg (2 subjects) and 1,200 mg fixed dose (7 subjects), respectively. 2 (6.9%) of these subjects reported increased conjugated bilirubin (in groups 3 mg/kg and 1,200 mg fixed dose, respectively), and the incidence of other AEs leading to delayed treatment cycle was 3.4%.

7 (24.1%) subjects experienced immune-related adverse reactions (irAEs), which occurred in groups 10 mg/kg (1 subject), 20 mg/kg (3 subjects) and 1,200 mg fixed dose (3 subjects), all of which were CTCAE grade 1 or 2 in severity. IrAEs with an incidence of ≥ 5.0% included hypothyroidism (13.8%) and pruritus (6.9%).

A total of 8 (27.6%) cases of death occurred during the study across all the groups, with the exception of group 20 mg/kg. 7 cases were due to the subject's disease, and 1 case with unknown cause. No subject died due to study treatment.

Efficacy

A total of 29 subjects in the CS1001-101 phase Ia study began treatment with CS1001 every 3 weeks from October 19, 2017 to June 05, 2018. As of November 30, 2018, 20 subjects had discontinued the treatment and 9 subjects continued to receive CS1001 in this study. Of these 29 subjects, 7 subjects achieved partial responses, of which 6 subjects were with confirmed responses and one subject was with unconfirmed response due to failure to reach the next imaging assessment follow-up time. All 7 subjects who achieved objective responses remained in sustained response with unreached median time to response. The median progression-free survival (PFS) for all subjects was 4.3 months and the 6-month progression- free survival rate was 42.0%; the median survival time (OS) was not reached and the 6-month overall survival rate was 75.1%.

Findings from the phase Ia study demonstrated that CS1001 demonstrated preliminary efficacy in subjects with advanced solid tumors or lymphoma.

Please refer to the latest Investigator's Brochure for the latest data from clinical study of CS1001.

2.5. OVERALL BENEFIT/RISK ASSESSMENT

HCC is a highly fatal tumor in the world. Most HCC subjects have lost their opportunities to receive curative treatment at the time of the first diagnosis and the recurrence rate at 2 years and 5 years after surgery remains high (see 2.2 for details), seriously threating to the lives and well-beings of the subjects in China. Most HCC subjects in China are complicated with underlying liver disease (e.g., chronic hepatitis B, chronic hepatitis C, cirrhosis, etc.) which makes the treatment more difficult[**2**]. Existing available therapies are limited with not good efficacies, so there is still a huge unmet clinical need. Therefore, a new combination regimen is urgently needed.

BLU-554 showed highly selectivity in non-clinical, phase I BLU-554-1101 study and showed a better response rate in subjects in group FGF19 IHC + (see Section 2.4.1.1). For the safety of BLU-554, reactions mainly are gastrointestinal system disorders or increased hepatic transaminase, of which, nausea, vomiting, diarrhea and abdominal pain can be relieved by supportive treatments while for transaminase and bilirubin elevation, liver function should be monitored closely.

Anti-PD-1 and anti-PD-L1 monoclonal antibodies targeting PD-1 and PD-L1 have achieved

major advances in treatment for various advanced malignancies. Opdivo ® (nivolumab) has been approved by the US FDA as the second-line therapy for treatment against advanced hepatocellular carcinoma, providing breakthrough advancement to anti-PD-1/PD-L1 antibody drug in the treatment for liver cancer. The results of the recently reported KEYNOTE-224 study also showed encouraging efficacy and acceptable safety of pembrolizumab in subjects with advanced hepatocellular carcinoma who had previously failed sorafenib treatment, or who were intolerant to sorafenib.

Based on the mechanism of action of CS1001 and the clinical safety information of the like product, it is expected that the adverse events that may occur during clinical trials mainly include various inflammation caused by the activation of the immune system, such as pneumonia, colitis, hepatitis, nephritis and inflammation of endocrine system, etc. According to the available clinical data of anti-PD-L1 and anti-PD-1 monoclonal antibody drugs, although the incidence of adverse reactions is high, such drugs are well tolerated, and only a small proportion of subjects have discontinued the drugs due to adverse reactions, and most adverse reactions can be relieved after treatment. Due to the variable early symptoms of immune-related adverse reactions, investigators should pay special attention to the early signs and symptoms of various immune-related reactions in clinical study, make timely judgments and adjust the dose according to the protocol and provide corresponding effective therapy, so as to reduce the medication risk in subjects.

Based on the current clinical data and pre-clinical pharmacological and toxicological profiles, it is expected that the combination regimens would show positive risks and benefits balance, and will provide more safe and effective treatment options for HCC subjects in China.

3. OBJECTIVES AND ENDPOINTS

3.1. PRIMARY OBJECTIVES AND PRIMARY ENDPOINTS OF THE STUDY

Objectives:	Endpoints:
Primary	
Phase Ib:	
• To determine the MTD and/or RP2D of BLU- 554 when being in combination with CS1001 in subject with advanced HCC. • To evaluate the safety and tolerability of BLU- 554 in combination with CS1001.	• Incidence of DLT during the administration of BLU-554 in combination with CS1001. • Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
Phase II:	
• To assess the anti-tumor efficacy of BLU-554 in combination with CS1001	• To assess ORR based on RECIST v1.1

3.2. SECONDARY OBJECTIVES AND SECONDARY ENDPOINTS OF THE STUDY:

Objectives:	Endpoints:

Secondary	
Phase Ib	
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When combination with BLU-554, AUC, Cmax, tmax, CLss , accumulation ratio of CS1001. • When combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554
• To preliminary assess the anti-tumor activity of BLU-554 in combination with CS1001	• To assess ORR, DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To assess the immunogenicity of CS1001 when administered in combination with BLU-554	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression • level with efficacy of BLU-554 in combination with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level
Phase II	
• To assess the anti-tumor activity of BLU-554 in combination with CS1001.	• To assess DOR, DCR, TTP, PFS and OS based on RECIST v1.1
• To evaluate the safety and tolerability of BLU- 554 in combination with CS1001.	• Safety: incidence and severity of AEs and SAEs, including laboratory tests, vital signs, and ECG • Tolerance: discontinuation and reduction of study drug dose
• To assess the pharmacokinetics (PK) profile of BLU-554 in combination with CS1001.	Pharmacokinetic parameters include, but are not limited to: • When combination with BLU-554, AUC, Cmax, tmax, CLss, accumulation ratio of CS1001. • When combination with CS1001, AUC, Cmax, tmax, CLss/F, accumulation ratio of BLU-554.
• To assess the immunogenicity of CS1001 when • administered in combination with BLU-554.	• Occurrence of anti-CS1001 antibody
• To correlate FGF19 and PD-L1 expression level with efficacy of BLU-554 in combination • with CS1001	• ORR, DOR, DCR, TTP, PFS and OS by FGF19 protein and PD-L1 protein level

4. STUDY DESIGN

4.1. OVERALL STUDY DESIGN

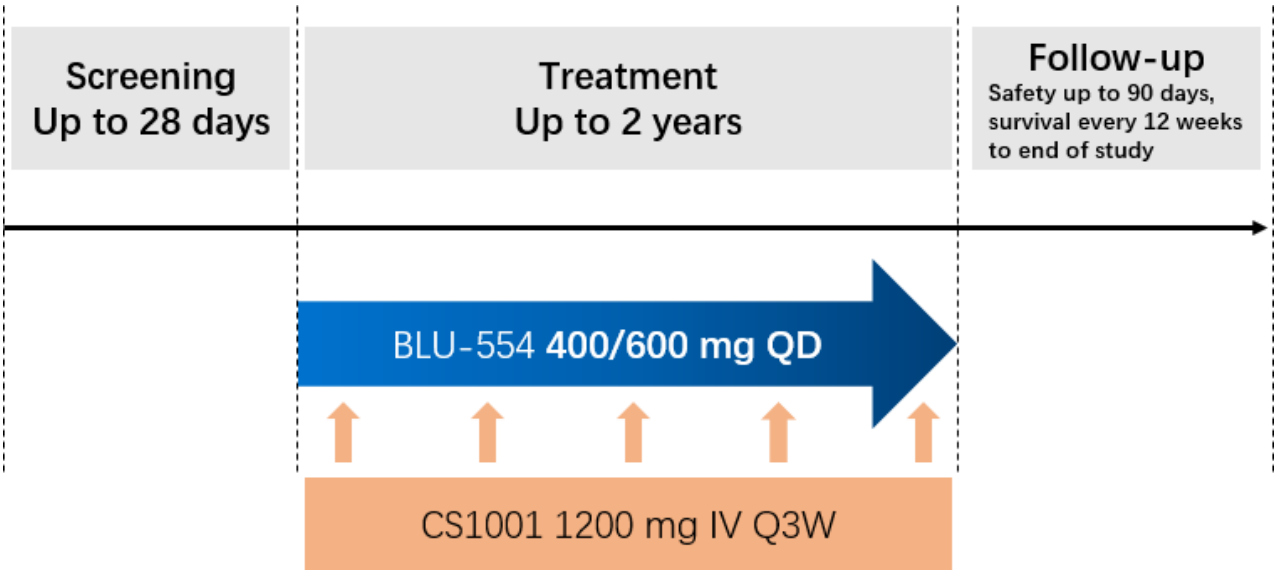
This is a multi-center, open-label, multi-dose and Phase I study for evaluating the safety, tolerance, pharmacokinetic profiles and efficacy profiles of BLU-554 in combination with CS1001 in subjects with advanced HCC.

The study consists of 2 parts, including Phase Ib dose escalation and Phase II dose expansion. Phase Ib is a dose escalation study for determination of the MTD and/or RP2D of BLU-554 in the combination regimen and the primary safety and tolerance of the combination regimen. Phase II is a dose extension study in which preliminary evaluation of the antitumor efficacy and the further evaluation of the safety, tolerance, PK and immunogenicity of combination regimen.

Both Phase Ib and Phase II can be divided into 3 periods, screening period, treatment period and follow-up period (See **Figure 11**)

- The screening period is the 28 days prior to the first dose.
- During the treatment period, the subjects will be administered the study drug once every 21 days (3 cycles). BLU-554 is taken orally (PO) once daily (QD); CS1001 is administered intravenously once every 21 days (Q3W). Subjects with advanced stage solid tumor will be imageologically evaluated every 9 weeks (i.e. every 3 dosing periods) during the 1st year of treatment and every 12 weeks after treatment against Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (See Appendix**错误!未找到引用源。**). The investigator may increase evaluation frequency if clinically indicated. The drug may be administered continually until presence of intolerable adverse reaction, disease progression, withdrawal of consent, loss to follow up, death or study termination. The duration of treatment may be up to 24 months. For subjects suspected of developing a pseudoprogression, if the subjects meet the criteria set forth in the protocol (see Section**错误!未找到引用源。**) it is recommended to continue receiving the study drug before confirmation by imaging. During the period of first documented PD and confirmed PD, subjects will be advised to continue study drug if they meet the following criteria.
- Follow-up period consists of safety follow-up period and survival follow-up period. The safety follow-up period includes 30 days, 60 days and 90 days after the last dose of study drug, or until the initiation of a new anti-tumor treatment, whichever occurs earlier. Survival follow-up will be performed every 12 weeks to collect survival status, subsequent anti-tumor therapy, and study drug-related SAEs until the death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.. See Section **错误!未找到引用源。**

Figure 11:. Study flowchart



During the study period, an SMC consisting of the principle investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representative will be established to review the safety data, PK data, efficacy data from the study and determine the escalation dose level and dosage regimen in dose escalation study so as to determine the MTD, recommend the dose levels selected for the extension study, and determine the RP2D. The SMC will also decide whether or not to include unscheduled dose levels for the study.

Phase Ib: Dose Escalation

The MTD and/or RP2D of two dose levels and preliminary safety evaluation of BLU-554 in the combination regimen will be determined with the starting dose of 400 mg QD (once daily). CS1001 1,200 mg Q3W (every 3 weeks) as the fixed dose will be the RP2D in the monotherapy phase I study CS1001-101. The dose escalation part will use the BOIN design. (See Section **错误!未找到引用源。** for details).

Phase II: Dose Expansion

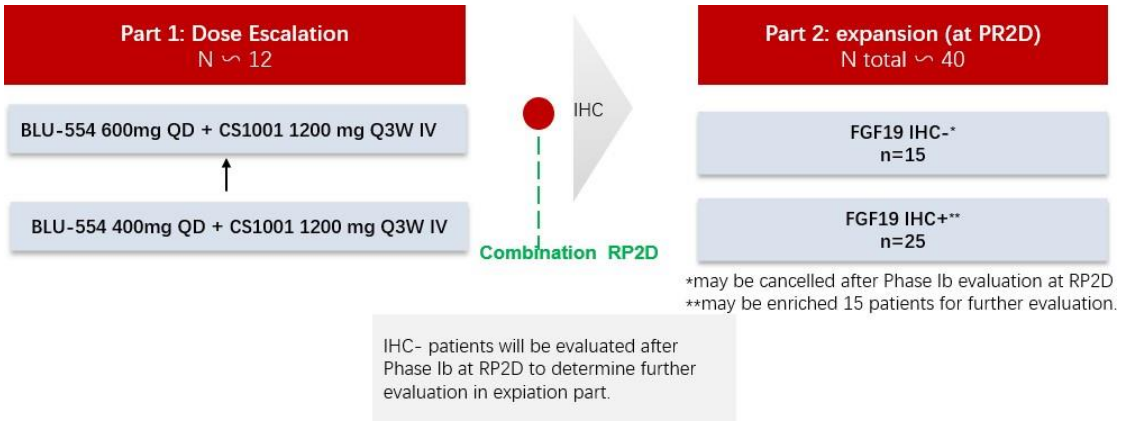
The primary objective of the dose expansion phase is to further evaluate the antitumor efficacy as well as the safety, tolerability, PK and immunogenicity of the combination regimen. Subjects will be enrolled into 2 groups based on FGF19 IHC expression: Group 1 will be HCC subjects with FGF19 IHC-, approximately 15 subjects will be enrolled; Group 2 will be HCC subjects with FGF19 IHC+, approximately 25 subjects will be enrolled, approximately total 40 subjects in expansion part. Data on phase Ib evaluation at RP2D will be used as the basis to determine whether to continue to enroll subjects with FGF19 IHC- in the dose expansion phase. If the statistically pre-specified continuous evaluation range is reached, additional subjects with FGF19 IHC+ may be enrolled for further evaluation. FGF19 IHC test will be performed at central laboratory with FGF19 IHC+ defined as ≥ 1% for inclusion assessment.

Archived or fresh tumor samples must be provided for FGF19 and PD-L1 IHC test which will be performed at central laboratory. (See Section **错误!未找到引用源。**)

The imaging examinations of tumors shall be evaluated in accordance with RECIST v1.1. During the 1st year of the treatment, subjects will receive CT/MRI examination in the screen period and every 9 weeks (at the end of every 3 cycles). After 1 year of study, CT/MRI examinations shall be carried out once every 12 weeks (The investigator may increase the number of tumor evaluations where clinically indicated).

Subjects will be monitored for anti-tumor activity, safety, tolerability, PK profile and host immunogenicity throughout the study from the day of first administration of study drugs up to 90 days after the last administration or up to two-year treatment period of combination regimen.

Figure 12:Study Procedure



4.2. STUDY RATIONALE

4.2.1. Rationale for Study Design and Selection of Subjects

This trial is an open-label study to evaluate the safety, tolerability and PK of the two doses 400 mg, 600 mg QD in a phase Ib BLU-554-1101 study) of BLU-554 in the combination regimen using a dose escalation trial in Phase Ib. Based on the available data, the reasonable dose would be obtained as the recommended dose in the dose extension study (Phase II). In Phase II, a preliminary assessment of the efficacy of the combination regimen will be performed in HCC subjects without prior systemic treatment and further assessment of safety, tolerability, PK and immunogenicity would also be conducted in order to carry out subsequent clinical studies.

4.2.2. Rationale for Dose Selection

The two doses of BLU-554 (400 mg QD, 600 mg QD) and fixed dose of 1,200 mg Q3W of CS1001 (see 错误!未找到引用源。) will be selected as the exploratory dose in the dose escalation phase of this study based on the safety and PK data of BLU-554 (BLU-554-1101) and CS1001 (CS1001-101) monotherapy phase Ib studies. Dose escalation phase data will be used to determine the recommended dose in the dose extension phase. The dose selection of the two study drugs were based on the following:

BLU-554

In Study BLU-554-1101, the MTD/RP2D was determined in the dose escalation phase of the BLU-554 QD and BID dosing regimens, respectively. In the QD dose schedule, a total of 25

subjects received BLU-554 according to the QD dose escalation schedule during Part 1 of the study at doses ranging from 140 mg to 900 mg as outlined in Table 8. No DLTs were observed at doses ranging from 140 to 600 mg QD. Two DLTs were noted at 900 mg QD including 1 subject with Grade 3 abdominal pain and 1 subject with Grade 3 fatigue lasting more than 7 days. Of the 25 subjects in dose escalation, 4 were FGF19 IHC+, 10 were FGF19 IHC-, and 11 were unknown. All 3 responders in Part 1 were FGF19 IHC+, 1 at 280 mg and 2 at 420 mg. Based on the safety profile, PK, and preliminary antitumor activity, 600 mg QD was considered the recommended dose for Part 2 (dose expansion).

Table 8 Dose Escalation Summary for Study BLU-554-1101 (Part 1, QD Dosing Schedule)

Dose	Subjects Treated (N=25)	DLT
140 mg QD	3	0
280 mg QD	3	0
420 mg QD	6	0
600 mg QD（MTD）	6	0
900 mg QD	7	2

Abbreviations: DLT = dose limiting toxicity; MTD = maximum tolerated dose; QD = once daily.

In the BID dose schedule, a total of 9 subjects received BLU-554 at doses of 200 mg or 300 mg. Two (2) DLTs were noted at 200 mg BID, including 1 subject with Grade 3 fatigue lasting greater than 7 days and 1 subject with clinically important AEs (Grade 1 headache, nausea, diarrhea, abdominal pain, and Grade 3 fatigue) that were determined by the Investigator to be a DLT. At 300 mg BID, 1 DLT was noted in 1 subject with Grade 3 pulmonary edema. Pharmacokinetic modeling suggested that 100 mg BID would provide exposure below xenograft efficacy levels as well that of the 280 mg QD dose level. Therefore, further study of the BID schedule is not planned.

As of the data cutoff, a total of 115 subjects were evaluable for the safety analysis evaluation. Most adverse events (AEs) observed in these subjects were Grade 1 or 2. The most common (≥20%) suspected to be related to study drug include diarrhea (N = 87, 76%), nausea (N = 48, 42%), ALT increased (N = 38, 33%), vomiting (N = 42, 37%), AST increased (N = 33, 29%), fatigue (N = 32, 28%) and decreased appetite (N = 22, 19%). Serious adverse events (SAEs) were reported in 49 (43%) subjects, and SAEs considered related to study drug occurred in 18 (16%) subjects, mainly including vomiting, anemia, hyponatremia, and pyrexia, etc.

CS1001:

The CS1001-101 study evaluated the safety and PK profile of CS1001 at 5 dose levels (3 mg/kg, 10 mg/kg, 20 mg/kg, 1,200 mg, 40 mg/kg). As of 08 April 2018, the Safety Monitoring Committee (SMC) completed all 5 dose level assessments for the dose escalation phase CS1001. No DLTs were observed in any dose group, and MTD was not reached. Total of 16 subjects experienced treatment-emergent adverse events (TEAEs), of whom 15 subjects experienced treatment-related TEAEs. No deaths, permanent discontinuations or dose reductions due to TEAEs were reported in the study. The most frequent TEAEs were Grade 1/2 anaemia (n = 7), nausea (n = 6), decreased appetite (n = 5), blood bilirubin increased (n = 4), protein urine present (n = 4), white blood cell count decreased (n = 4) and proteinuria (n = 4). Grade 3 TEAEs were observed in 5 subjects, including bilirubin conjugated increased, gastric haemorrhage, bone pain, ascites and platelet count decreased; 1 of which (platelet count decreased) was considered as treatment-related by investigators. No Grade 4/5 TEAEs were reported. Two (2) serious AEs (SAEs) were reported in

2 subjects, 1 is Grade 3 gastric haemorrhage, the other is Grade 3 ascites. None of them was considered as treatment-related by investigators.

irAEs occurred in 5 subjects, including diarrhea, adrenal insufficiency, hyperthyroidism, hypothyroidism, platelet count decreased, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, thyroxine free decreased, thyroxine free increased, tri-iodothyronine decreased and tri-iodothyronine free increased. All irAEs were Grade 1-3.

Overall, there were no significant toxicity overlap observed from the two investigation products.280 mg QD estimated to be the minimally efficacious dose, to limit the number of subjects treated at subtherapeutic doses, based on the data on tolerance, preliminary anti- tumor efficacy, safety, PK and pharmacodynamics, this study will employ BLU-554 400 mg QD as starting dose in combination with CS1001 1,200 mg Q3W.

4.2.3. Rationale for Biomarker Analysis

The primary biomarkers analyzed in this study are the expression levels of FGF19 and PD-L1 protein. The ORR of BLU-554 mono in the BLU-554-1101 study was 17% in subjects with positive FGF19 protein expression, while the ORR was 0% in the subjects with negative FGF19 protein expression, suggesting that the expression of FGF19 protein is critical to the effect of BLU-554. PD-L1 expression, as predictive biomarkers of PD-(L) 1 antibody, have been demonstrated in multiple tumors (e.g. lung cancer), and preliminary evidence is also shown in liver cancer (e.g. Keynote-224, DOI: *http://dx.doi.org/10.1016/S1470- 2045(18)30351-6)*.

4.3. DOSE ESCALATION

4.3.1. Dose Escalation

The dose escalation part of the study employs a BOIN **[20]** design to determine the MTD and RP2D of BLU-554 in the combination regimen. Two dose levels of BLU-554 will be assessed and the dose of CS1001will be fixed (RP2D in the monotherapy study). See **Table 9** for the details about the dose escalation scheme of combination regimen. Every 21 days (3 weeks) will be considered as one cycle. DLT assessment will be done within 21 days (Cycles1) after the administration.

Table 6:Planned Dose Escalation Scheme

Dose Level	BUL-554	CS1001
1	400 mg QD	1,200 mg Q3W
2	600 mg QD	1,200 mg Q3W

Using BOIN design, the target toxicity probability of the MTD is 0.3 with a maximum sample size of 12. The cohort size included 3 enrolled and treated subjects. See Figure 13 for the study design with the description as below:

1. The starting dose for dose escalation was dose level 1, i.e. BLU-554 400 mg QD in combination with CS1001 1,200 mg Q3W.
2. The dose level for the next cohort was determined according to the dose escalation/decreasing rule in Table 7. Under this rule, the likelihood of a dose dispensing error is lowest. When using Table 7, pay attention to:
    a. "Excluded dose" refers to any current dose and all higher doses that should be excluded from the trial to avoid the treatment for the newly enrolled subjects at these

higher toxic doses.

b. When a dose is excluded, the dose for the next cohort will be decreased by one level. If the minimum dose planned for evaluation is excluded, the trial will be ended for safety reasons and the MTD will be considered as not determinable.

c. In case that all the actions in the table (increase, decrease, exclusion) are not eligible, the current dose will be remained for the next cohort.

d. If the current dose is the lowest dose planned for assessment, and such dose should be reduced according to rule, the current dose will be remained for the next cohort. However, if, based on the number of DLTs, the criteria for excluding dose has met, the trial should be terminated for safety reasons.

e. If the current dose is the highest dose planned for assessment, and such dose should be increased according to rule, the current dose will be remained for the next cohort.

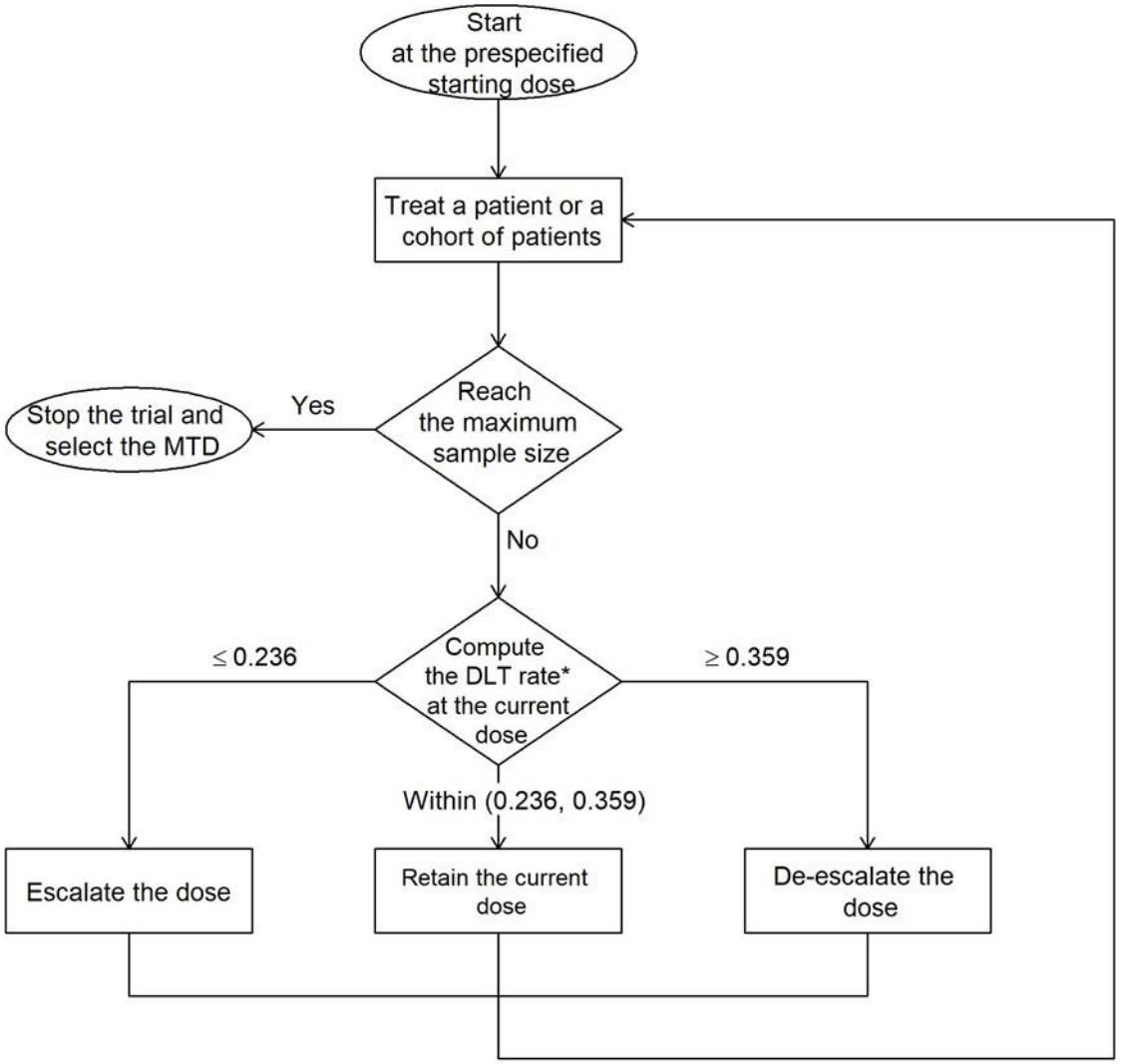
3. Repeat step 2 until a maximum sample size of 12 is reached, the dose escalation is ended.

After the end of the dose escalation, the MTD will be determined using a monotonic regression method: the dose for which the monotonic estimation of the toxicity probability would be the most approximate the target toxicity probability would be selected as the MTD. If the monotonic estimates of toxicity probability for two or more doses are equal and less than the target toxicity probability, the highest dose will be selected as the MTD; if the monotonic estimates of toxicity probability for two or more doses are equal and greater than the target toxicity probability, the lowest dose will be selected as the MTD.

Table 7: BOIN STUDY DESIGN DOSE ESCALATION/DECREASING RULES

Measures	Number of subjects treated at current dose											
	1	2	3	4	5	6	7	8	9	10	11	12
Elevate the dose: if the cases of DLT <=	0	0	0	0	1	1	1	1	2	2	2	2
Decrease the dose: if the cases of DLT>=	1	1	2	2	2	3	3	3	4	4	4	5
Decrease the dose: if the cases of DLT >=	NA	NA	3	3	4	4	5	5	5	6	6	7

Figure 13： Flow Chart of Dose Escalation Phase Ib Study with BOIN Design



MTD = Maximum Tolerated Dose

During the study period, an SMC consisting of the principle investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representative will be established to review the safety data, PK data, efficacy data from the study and determine the escalation dose level and dosage regimen in dose escalation study so as to determine the MTD, recommend dose levels in the extension study, and determine the RP2D. The SMC will also decide whether or not to include unscheduled dose levels for the study.

Once the RP2D is determined in phase Ib, the protocol will be amended to explore the safety and efficacy of the combination regimen in HCC subjects. Currently, Phase Ib study has been completed for subject recruitment on May 20, 2020, and SMC has confirmed the RP2D as

BLU-554 600 mg QD combined with CS1001 1200 mg IV Q3W on June 18, 2020 by reviewing the relevant safety, PK and efficacy data of subjects enrolled in Phase Ib study.

4.3.2. Dose-Limiting Toxicity

Definition of DLT: All toxicity or adverse events (AEs) are graded according to NCI-CTCAE 5.0. Any AE occurring during C1 (21 days) that is not clearly caused by something other than investigational drug:

Hematological toxicity:

- Grade 4 neutropenia that lasts for ＞7 days;
- Grade ≥3 febrile neutropenia (ANC<1,000/mm^3, with a single temperature of ≥38.3℃ or a sustained temperature of ≥38℃ for more than one hour);
- Grade 3 neutropenia with infection;
- Grade 3 thrombocytopenia with clinically significantly bleeding;
- Grade 4 thrombocytopenia;
- Grade ≥4 anemia

Non-hematological toxicity:

- Grade ≥4 toxicity;
- Grade 3 toxicity that fails to be resolved to ≤Grade 2, with the exception of diarrhea, nausea and vomiting;
- Grade ≥3 immune-related adverse event (irAE)
- Any Grade 3 tumor flare reaction (local pain, irritation or rash at known or suspected tumor focus) that lasts for 7 days or above;
- Grade 3 or Grade 4 non-hematological laboratory abnormalities, if meet any of the followings:
  – need medical intervention
  – require hospitalization
  – last for >7 days

and other toxicity of any grade that requires premature termination of the study as determined by the investigator and the sponsor through discussion.

4.3.3. Stopping Criteria For Dose Escalation

To adequately monitor safety of subjects, when subjects reached 12, study enrollment will be held pending data review by SMC. The SMC is established for the determination of dose levels to be administered during dose escalation and dose regimens in this study. The SMC consists of the principal investigator, the CRO's representatives (CRA and other relevant person) and the sponsor's representatives.

In the event that an MTD is not identified, RP2D will be determined by the SMC and the sponsor based on the pharmacokinetics, tolerability and preliminary antitumor activities observed in the dose escalation period, as well as other available data.

4.3.4. MTD Definition

MTD is the highest dose level at which 30% of the subjects experience DLT within Cycle 1 in which at least 6 subjects are available for DLT evaluation. The MTD will be determined using a monotonic regression method: The dose for which the monotonic estimation of the toxicity probability would be the most approximate the target toxicity probability would be selected as the MTD. If the monotonic estimates of toxicity probability for two or more doses are equal and less than the target toxicity probability, the highest dose will be selected as the MTD; if the monotonic estimates of toxicity probability for two or more doses are equal and greater than the target toxicity probability, the lowest dose will be selected as the MTD.

4.3.5. Recommended Phase II Dose (RP2D) Definition

The RP2D will be determined by SMC based on comprehensive data of safety and tolerability, PK, pharmacodynamics, and preliminary anti-tumor efficacy obtained during the dose escalation phase. The RP2D will not exceed the MTD and will be determined at a dose escalation meeting. Additionally, observations related to PK, PD, and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D below the MTD. A minimum of 6 subjects must be treated at the potential RP2D to confirm that it is the RP2D.

4.4. END OF STUDY

Definition of "End of study": all subjects completed the treatment period, EOT, disease progression follow-up and survival follow-up or the Sponsor terminated the study (whichever occurred first). Completion of survival follow-up is defined as at least 80% of subjects died, loss to follow-up or followed up until at least 18 months after the first dose of drug.

4.5. TREATMENT AFTER END OF STUDY

For subjects who are able to benefit from study medication, at the end of the treatment period (up to 2 years), the study drug treatment will be continued after consultation with sponsor.

The therapeutic dose that subjects continue to use is the same as the most recent dose prior to their enrollment into the follow-up period. Different doses are allowed only upon approval of the sponsor and the investigator (based on clinical trial data and subject's conditions at that time).

5. STUDY POPULATION

5.1. GENERAL CONSIDERATIONS

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments, the investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section**错误!未找到引用源。**.

The investigators or their designees must ensure that all subjects who meet the following inclusion and exclusion criteria.

5.2. INCLUSION CRITERIA

To meet the conditions for participation in this clinical study, subjects must:

1. Voluntarily participate in the clinical study. Fully understand and get informed of this

study and sign the Informed Consent Form (ICF).

2. ≥18 years of age on day of signing the informed consent.
3. Unresectable locally advanced or metastatic hepatocellular carcinoma as confirmed by histology or cytology.
4. Stage B or C based on Barcelona Clinic Liver Cancer (BCLC) staging system; In case of Stage B, subject must be ineligible for surgery and/or local therapy, or has progressed after surgery and/or local therapy or refuses surgery and/or local treatment.
5. For Phase Ib, subject has failed after or is unsuitable for the standard systemic therapy against HCC. For Phase II, subject has not previously received systemic therapy [systemic therapies mainly include: chemotherapy, molecular target drugs (e.g. tyrosine kinase inhibitors, TKI), immunotherapy (e.g. anti PD-1/PD-L1, CTLA-4 etc.), biological therapy (e.g. tumor vaccine), cytokines, etc.)].
6. At least one measurable lesion as evaluable by RECIST version 1.1. Target lesions within the field of prior efficacy irradiation or in the area of local treatment (intervention or ablation therapy) are considered measurable in case of confirmation of progression.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-1 point.
8. A-level Child-Pugh score.
9. Expected survival≥3 months.
10. For Phase Ib and II, 9 formalin fixed-paraffin embedded and unstained tumor tissue slides should be provided for FGF19 IHC and PD-L1 analysis in the central laboratory.
    - Patients in the FGF19 IHC+ arm enrolled in the Phase II study must be FGF19 IHC+ as confirmed by the central laboratory
    - Patients in the FGF19 IHC- arm enrolled in the Phase II study must be FGF19 IHC– as confirmed by the central laboratory (whether this arm will be initiated or not will be decided based on Phase Ib data)
11. Clinical laboratory screening criteria:
    - Absolute neutrophil count (ANC)≥1.5×10^9/L
    - Platelet count≥ 75×10^9/L
    - Hemoglobin≥90 g/dL
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × ULN
    - Total bilirubin ≤ 2 ×ULN
    - International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 ×ULN (INR ⩽ 1.5 × ULN and PT ⩽ 1.5 × ULN, if both available)
    - Serum creatinine ≤ 1.5 ×ULN or creatinine clearance (CL)≥60 mL/min (Cockcroft-Gault Formula)

    Female: $\underline{\text{CrCl=(140-age) × weight (Kg) × 0.85}}$

    72× serum creatinine (mg/dL)

    Male: $\underline{\text{CrCl=(140-age) × weight (Kg) × 1.00}}$

    72× serum creatinine (mg/dL)

12. For subjects with hepatitis C virus (HCV) infection, treatment with locally approved and available anti-HCV therapy is required if HCV RNA is detected.
13. For subjects with hepatitis B virus (HBV) infection, HBV DNA ≤2,000 IU/ml at Screening.
    - Subject with HBV DNA (+), treatment with HBV antiviral therapy (as per the local standard of care) is required at least 14 days prior to the initiation of study.
    - Subject with HBsAg (+) and/or HBcAb (+), based on investigator assessment, HBV antiviral therapy may be applied if needed.

14. For female subjects of childbearing potential, serum pregnancy test must be negative within 7 days prior to randomization. Except for female subjects who have been recorded as surgically sterilized or who are postmenopausal, female subjects of childbearing potential or male subjects and their partners must agree to use effective contraception from the signature of the informed consent form (ICF) until at least 6 months after the last dose of study drug. Appendix 6: Effective Contraceptive Methods

5.3. EXCLUSION CRITERIA

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Portal vein tumor thrombosis in the main trunk or contralateral first branch (VP4), involvement of the inferior vena cava or the heart as revealed by imaging at baseline.
2. Prior or current history of hepatic encephalopathy.
3. History of liver surgery and/or local treatment for HCC (intervention, ablation therapy, absolute alcohol injection, etc.) or radiotherapy, etc. within 4 weeks prior to first dose.
4. Active or documented gastrointestinal bleeding within 6 months (e.g. esophageal or gastric varices, ulcer bleeding).
5. Presence of ascites detected by physical examination or clinical symptoms caused by ascites during the screening period, or ascites that need for special treatment, such as repeated drainage, or intraperitoneal drug infusion, etc. (Note: subjects with a small amount of ascites that can only be detected by imaging may be enrolled). Presence of uncontrolled pleural effusion or pericardial effusion (with clinical symptoms, requiring repeated drainage, or intrapleural or pericardial drug infusion, etc.) during the screening period.
6. Presence of meningeal metastasis or central nervous system (CNS) metastatic lesions.
7. According to the New York Heart Association (NYHA) Classification, subject has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure; myocardial infarction or unstable angina (within 6 months), uncontrolled hypertension (systolic blood pressure≥150 mmHg and diastolic blood pressure≥100 mmHg) or clinically significant uncontrolled arrhythmias, including bradycardia that may result in prolonged QT (e.g. Grade II or III heart block). Left ventricular ejection fraction (LVEF) <50%. QTc interval >480 msec (corrected using Fridericia's formula).
8. Subjects who have current interstitial lung disease or noninfectious pneumonitis, and prior history of interstitial lung disease or noninfectious pneumonitis that may affect the assessment or management of study drug-related pulmonary toxicity. Presence of active tuberculosis infection.
9. Any serious acute, chronic infections that require systemic antimicrobial, antifungal or antiviral therapy at screening, excluding viral hepatitis.
10. Malabsorption syndrome or inability to take the study drug orally for other reasons.
11. Had primary malignancies other than HCC within 5 years. The following prior malignancies were excluded: completely excised skin basal cells and squamous cell carcinoma, local prostate cancer responsive to treatment, and carcinoma in situ with complete resection at any site.

12. Subject has had major surgery within 4 weeks prior to first dose (procedures such as central venous cannulation, biopsy, and feeding tube placement are not considered as major surgery).
13. Previously received FGFR4 inhibitor treatment.
14. Blood transfusion, use of hematopoietic stimulating factors [including G-CSF (granulocyte colony stimulating factor), GM-CSF (granulocyte-macrophage colony stimulating factor), EPO (erythropoietin) and TPO (thrombopoietin)] and human albumin preparations within 14 days prior to first dose.
15. Requiring corticosteroids (dose equivalent to > 10 mg/day of Prednisone) or other immunosuppressive drugs within 14 days prior to first dose for systemic therapy.

    Note: For the absence of active autoimmune disease, it is allowed to use inhaled or topical steroids or adrenal hormone replacement therapy with equivalent dose of ≤10 mg/day prednisone. Short-term (≤ 7 days) use of corticosteroids for prophylaxis (e.g., contrast allergy) or for the treatment of non-autoimmune diseases (e.g., delayed hypersensitivity reactions due to contact allergens) is permitted. For subjects requiring hormone therapy, the dose administration should be done at least two days before and after the injection of CS1001.
16. Use of traditional Chinese medicine (elemene, Kanglaite, Cinobufacin, Xiaoaiping, Huaier granule, Ganfule, Jinlong capsule, Aidi, etc.) with anti-liver cancer indication within 14 days prior to the first dose.
17. Subject has received potent CYP3A4 inhibitors and/or inducers within 2 weeks prior to first dose. See Appendix 8: Strong Inhibitors and Inducers of CYP3A4.
18. Concurrent HBV and HCV infection (History of HCV infection, but subjects with HCV RNA(-) can be considered as not being infected with HCV).
19. Subjects with human immunodeficiency virus (HIV) infection.
20. Pregnant or lactating women.
21. Subjects with a history of hypersensitivity or hypersensitivity to any of the components of the investigational drug.
22. Any previous or current clinically significant diseases, medical conditions, history of surgery, signs, or abnormal laboratory parameters that, in the opinion of the investigator, may increase the risks associated with study participation and study drug administration, or affect the subject's ability to receive study drug and reliability of study results; other circumstances that in the opinion of the investigator would preclude participation in the study.
23. Subjects who are unwilling or unable to follow the study procedures as defined. Subjects with no or limited disposing capacity and with psychiatric disorders that may affect study compliance.
24. With the exception of alopecia, all toxicities from prior anticancer therapies and other therapies did not recover to ≤ Grade 1 (per CTCAE v5.0) prior to the first dose of study drug.
25. Subjects who have received prior allogeneic stem cell or solid organ transplantation.

5.4. SUBJECT SUPPLEMENTATION

Phase Ib: Subjects with first cohort of each dose level will be supplemented if meet below criteria, the following cohort subjects of each dose level will depend on SMC decision.

- Subjects receive <75% of the prescribed amount of study drug within 21 days after the first dose, and those without observed DLT will be supplemented.

Phase II: Subjects may be supplemented to have efficacy evaluable subjects (defined as having at least one post-baseline disease response assessment).

5.5. PROCESS OF HANDLING INADEQUATE ENROLLMENT

Subjects who do not meet the inclusion criteria are not permitted to enroll and receive the study drug at any time. No exceptions are allowed under this clause.

If a subject does not meet all inclusion criteria but has accidentally started the study treatment, the investigator should inform the sponsor immediately and discuss with the sponsor regarding continuing or terminating the study drug treatment of that subject. The sponsor must ensure that all decisions are accurately recorded.

5.6. TREATMENT DISCONTINUATION AND STUDY WITHDRAWAL

5.6.1. Criteria for Study Treatment Discontinuation

Subjects will discontinue the study drug treatment if any of the following occurs:

1. Study protocol-specified discontinuation criteria (see Section 错误!未找到引用源。and6.4.4).
2. Any clinical adverse events (AEs) or concurrent diseases that, in the opinion of the investigator, indicate continued participation is not in the best benefit of the subject
3. Disease progression (subjects who meet the criteria for re-challenge after disease progression may continue medication until the progression is confirmed by imaging evaluation)
4. Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
5. Poor compliance from subjects, untimely and quantitative medication, failure of communication by investigators, or may lead to large deviation of test results and can't be remedied, these will result in the discontinuation of study drug after confirmation of investigators and the sponsor.
6. During the study treatment, for any subject who receives any prohibited comedications and/or concomitant treatments that affect the tolerance judgment, the investigators and the sponsor can make subjects withdraw from the study drug treatment after confirmation.
7. Subjects, who are reluctant to continue the clinical trial, can inform to doctor in charge at any time, and can withdraw from it immediately. In accordance with the Helsinki Declaration and other applicable statutes and regulations, subjects are entitled to withdraw from the study at any time for any reason, and the doctor or site can't hold prejudice against his future medical care.

8. Other cases that the investigators consider unsuitable for continued medication.
9. Female subject becomes pregnant
10. Death
11. Follow-up

If a subject fails to complete the study for non-drug related reasons, it will be considered that the subject did not finish the study; if the sponsor considers it is necessary, and then the number of subjects should be supplemented. The decision of subjects should be recorded.

In all cases, all the reasons and primary reason for withdrawal will be recorded in the electronic case report form (eCRF). For the subject who have received at least one dose of the investigational drug, in case that they withdraw from the study with any reason, then the investigators should try their best to persuade subjects to undergo the end-of-study visit and should keep track of subjects with unresolved AE.

5.6.2. Follow-up of Subjects Who Discontinue Treatment

Subjects who discontinue the study drug must continue to be followed, and outcome and/ or survival follow-up data will be collected as required until death, loss to follow-up or end of study.

Subjects who stopped treatment before clearly documented disease progression will continue to undergo imaging examination and tumor evaluation every 9 weeks (±7 days) within 1 year and every 12 weeks (±7 days) after 1 year until presence of any of the followings: (1) disease progression, (2) initiation of new anti-cancer therapy, (3) withdrawal of informed consent, (4) loss to follow-up, (5) death, (6) termination of study, whichever occurs first.

Loss to follow-up is that the contact cannot be established with the subject, and there is insufficient information to determine the status of the subject at that time. Subjects who refuse survival follow-up should be defined as withdrawal of consent instead of loss to follow-up.

For loss to follow-up subjects, the site should contact the subject as much as possible to determine the reasons for loss to follow-up and try to reschedule the visit. The process of attempting to contact the subject should also be documented and the date contacting the subject and the contact information used will be documented in the study file.

5.6.3. Withdrawal From Study

Subjects have the right to withdraw from the study at any time for any reason. If subjects withdraw from the study, they will not be given the study drug or will not be followed up as defined in any protocol.

Subjects may withdraw or be withdrawn from study treatments for any of the following reasons:

- Withdrawal of consent.
- Death;
- Loss to follow-up.

If the subject withdraws consents for the trial and the disclosure of subsequent information, he or she will no longer be treated with the study drug, nor receive visits according to the

protocol schedule, or no subsequent data will be collected. The sponsor will retain the use right of data and information prior to withdrawal of consent by the subject. If the subject withdraws consent for the trial, but does not withdraw consent for disclosure of subsequent information, information related to survival of the subject will continue to be collected and, where possible, until the end of the study.

6. STUDY TREATMENTS

6.1. INVESTIGATIONAL PRODUCT

6.1.1. Investigational Product

- BLU-554 will be provided as capsules for oral administration and be manufactured and provided by Blueprint Medicines.
- CS1001 is an injection, which is manufactured by WuXi AppTec Group.

All study drugs are for investigational use only and should only be used within the context of this study.

6.1.2. Dosage Forms and Strenghts of Investigational Products

See Table 8 for the dosage form and strength of investigational products

Table 8 Dosage Form and Strength of Investigational Products

BLU-554	Dosage Form: Capsule Strength: 100 mg Excipients in the Drug Product: polyvinylpyrrolidone, microcrystalline cellulose, mannitol, croscarmellose sodium, sodium lauryl sulfate. Expiration Date: 36 Months Storage Condition: Stored in the provided container at room temperature (15 to 30 °C, 59 ° – 86 °F), protected from direct sunlight.
CS1001	Dosage Form: Injection. Strength: 600 mg/20 mL/vial. Excipients in the Preparation Formulation: Histidine/ Histidine Hydrochloride, Mannitol, Sodium Chloride, Polysorbate 80 and pH5.5. Expiration Date: 36 months tentatively. Storage Condition: 2 ℃to 8 ℃.

6.1.3. Package and Label

All study drugs will be labeled according to the requirements of Good Clinical Practice (GCP). The label text will be approved in accordance with the procedures of the sponsor agreement, and the site may obtain a copy of the label upon request. All drugs are transported as study-specific main materials.

Drug labels should utilize a unified format, and packaging label contents include: protocol number, clinical trial drug name (marked “specifically used for clinical trial”), strength, storage, batch number, expiration date, sponsor and so on.

The complete records of batch numbers and expiration dates of all study drug and drug labels

will be kept in the sponsor's study folder.

6.2. MANAGEMENT OF INVESTIGATIONAL PRODUCT

The responsibilities for the Management of Investigational Product are in accordance with requirements specified in Appendix 7: Reponsibility For Medication Management

6.2.1. Dispensing and Storage of Investigational Product

The study drug is provided by the sponsor and distributed to the sites as planned. A designated person of the clinical trial unit is responsible for management and distribution, and investigational product should be stored in a medicine cabinet with locks.

A designated person of the site is responsible for the unified preservation, management and distribution of the study drug. The responsible person of the site will confirm that the study drug has been received in writing and that the study drug is used within the framework of the clinical study as requested by the protocol. The receipt, distribution and return of the study drug will be documented.

The study drug will be distributed by a member of the study group. The member shall ensure and record that the subjects receive the dispensed drugs as planned and record the number and date of drug dispensing and recovery in the original medical record

6.2.2. Preparation and Administration of Investigational Product

When BLU-554 and CS1001 are administered on the same day, BLU-554 is administered first, followed by intravenous CS1001. The subject should be given with CS1001 through intravenous infusion as soon as possible after BLU-554 administration.

- BLU-554

BLU-554 doses should be administered with a glass of water in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Each dose should be administered at approximately the same time each day. Subjects should take BLU-554 in the morning. Subjects should be instructed to swallow capsules whole and to not chew the capsules.

If the subject forgets to take a dose, he/she should take BLU-554 until 4 pm that day (the BLU-554 dose should be administered with a glass of water in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration). If the dose has not been taken by 4 pm, then that dose should be omitted and the subject should resume treatment with the next scheduled dose.

If a subject vomits during or after taking BLU-554, re-dosing is not permitted until the next scheduled dose.

A temporary discontinuation (up to 3 weeks) in BLU-554 dosing is allowed for subjects who require an interruption (e.g., for surgery or another procedure) during the treatment period.BLU-554 should be discontinued 48 hours before the procedure and resumed 48 hours after the procedure is completed.

- CS1001

The route of administration for CS1001 is intravenous infusion, the infusion process shall be in accordance with local clinical practices (recommend to use infusion set fitted with a 0.2 micron embedded or additional filter). Specific drug preparation and other unique requirements can be found in the drug manual.

As a routine precautionary measure, the subject should be observed for 2 hours in the area with resuscitation equipment and first aid medicines after receiving the first two doses of test drug infusion.

Drug Dilution Methods:

- Use 250 mL of sterile physiological saline (0.9% sodium chloride solution) to dilute the total dose of the drug to be administered.

Drug Use Instructions:

- CS1001 is administered by intravenous infusion rather than IV bolus.
- Ensure that the study drug solution is clear, transparent, and free of visible particles.
- Draw the study drug injection with a syringe. The volume of the injection is 40 mL (3 mL/bottle: 13.33 bottles, or 20 mL/bottle: 2 bottles; do not mix the two strengths of injections during one infusion configuration). Inject it into a 250 mL saline intravenous infusion bag.
- Turn upside-down **gently** when mixing, and prohibit shaking.
- Visually inspect the prepared solution. If it is not clear or has precipitation, the solution should be discarded and be recorded in the responsibility log of drug management.
- Record the time and the corresponding dose (in mg) of CS1001 on the intravenous infusion bag label.
- The infusion of the study drug should be completed within **60 - 120 minutes.** According to Section**错误!未找到引用源。**, if the infusion reaction occurs, the infusion time can be prolonged. Do not use the same infusion intravenous catheter while administering other drugs.
- At the end of infusion, the infusion tube should be rinsed with a sufficient amount of saline.
- It is recommended that the study drug should be given to the subject immediately after preparation to avoid exposure of the prepared drug to room temperature over the recommended **6-hour limit**. Among them, the 6-hour time limit includes storage time of DP bottles at room temperature, storage time of infusion solution in the intravenous infusion bag and infusion duration. If you need to delay the use of prepared drugs, you can place it in a refrigerator (2-8 ℃), but not more than **24 hours.**

6.2.3. Return and Destruction of Study Drugs

In this study, the study drug will be recovered. All unused and/or partially used study drugs will be returned to the sponsor-designated third party for destruction upon completion of

complete accountability records at the study site (please refer to the drug manual and corresponding instructions for specific instructions on drug distribution, accountability and recovery). Relevant personnel of the trial shall ensure that the disposal of study drug is reasonably arranged, appropriate handling procedures are formulated according to applicable regulations, guidelines and rules and regulations, and relevant records are made. Study drugs will be destroyed after approval of the sponsor.

6.3. COMPLIANCE TO STUDY TREATMENT

- BLU-554

Subjects will be dispensed the appropriate number of study drug bottles to allow for dosing for a full cycle, or until the next scheduled visit. Subjects are to bring back all unused capsules (or the empty bottles) on D1 of each treatment cycle or at the next scheduled visit. Compliance with the dosing regimen will be assessed based on brought back of unused drug (or empty bottles).

- CS1001

In order to ensure the treatment compliance, the dosage will be monitored by the primary investigator or his/her designees. Accurate medication (at the initiation and end of the infusion) time and dosage should be recorded. If the infusion is interrupted, the cause of the interruption must also be recorded in the eCRF.

- Overdose

An overdose is defined as: the subject (intentionally or accidentally) takes a drug dose that exceeds 20% of the protocol specified dose. Subjects who are suspected to have an overdose must receive appropriate supportive care as determined by the investigator and medical monitor after consultation. Any adverse event resulting from an overdose should be reported to the medical monitor and included in the standard adverse event report.

6.4. STUDY TREATMRNT ADJUSTMENT

These guidelines should be followed by clinical Investigators, however, for an individual subject, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines must be documented and communicated with the sponsor. Adverse events are to be graded according to NCI CTCAE version 5.0.

- For the Phase Ib dose escalation, dose reductions for BLU-554 during the evaluation period of DLTs are only allowed if a DLT is observed.
- Dose reduction is not permitted for CS1001. If a subject experience a CS1001 related toxicities, then the subject must suspend or permanently discontinue CS1001 treatment.
- During the study treatment, if Investigator can judge AE is associated with one of the investigation products, the IP can be suspended, another IP could continue to be administrate. If cannot judge, both of the IPs should be suspended.
- If the study treatment is delayed according to the scheduled administration time for any reason (BLU-554 interrupted 2 weeks, CS1001 interrupted 9 weeks), the study treatment will no longer continue to be given (if the investigator considers that the subject is still benefiting, the subject may continue to receive the treatment with the consent of the medical monitor, i.e. the sponsor).
- Two administration delays are allowed due to toxicity. If the need for third delayed

administration of toxicity occurs, after consultation with the sponsor, the study treatment will be permanently terminated.

6.4.1. BLU-554 Dose Modifications

- Any Grade 1 or Grade 2 BLU-554-related AE no dose modification required
- Any Grade 3 or Grade 4 BLU-554-related AE, suspend (for at most 2 weeks) until event is ≤ Grade 1, or has returned to baseline, then resume by reducing 1 dose level. (if returned to ≤ Grade 1 or baseline within 14 days, and Investigator believes that it is in the subject's best interest, treatment may resume without dose reduction, with the written approval of the sponsor). If not resolved or returned to ≤ Grade 1 or baseline within 14 days, subjects should discontinue the treatment with BLU-554.
- After reducing the dose of BLU-554 due to BLU-554-related adverse events, subjects should maintain such reduced dose during the subsequent treatment. The dose can be reduced as low as 300 mg.

* In case immune mediated etiology cannot be excluded; consider following the guidelines in Section 14.3.

6.4.2. CS1001 Dose Suspension

CS1001 will be **suspended** for any of the following CS1001-related adverse reactions:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
  - Grade 2 drug-related hypothyroidism/hyperthyroidism do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require dose delay
  - For a subject who has Grade ≥ 2 drug-related AST, ALT, or total bilirubin elevation, dose delay is required
  - Any Grade ≥3 drug-related amylase or lipase abnormalities not associated with symptoms or manifestations of pancreatitis do not require dose delay. If such Grade ≥ 3 amylase or lipase abnormalities occur, the sponsor's medical monitor should be consulted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of CS1001.

6.4.3. CS1001 Dose Resumption

Subjects may resume treatment with CS1001 when the CS1001-related AE(s) resolve to Grade ≤ 1 or baseline within 9 weeks from the scheduled dosing, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume

treatment if the event recovers to Grade ≤ 2 skin toxicity.

- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must be completely resolved to baseline level before treatment is resumed. For patients with Grade 1 pneumonitis despite steroid tapering for at least 1 month, treatment may be resumed after discussion with and approval by the sponsor's medical monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the sponsor medical monitor.

Two dose delays are allowed due to toxicity. If the need for third delayed administration of toxicity occurs, after consultation with the sponsor, the study treatment will be permanently terminated.

6.4.4. CS1001 Permanent Discontinuation

Subjects will be required to permanently discontinued CS1001 for the following drug relatedadverse events:

- Any Grade 2 CS1001-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- ≥ Grade 3 infusion-related reaction during or after CS1001 infusion see Section 错误!未找到引用源。
- Grade 3-4 severe pneumonitis
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or serious uncontrollable bleeding event requires discontinuation;
    - any drug-related liver function test (LFT) abnormalities that meet the following criteria requires discontinuation:
      - AST or ALT > 5-10 × ULN for 2 weeks
      - AST or ALT > 10 × ULN
      - Total bilirubin > 5 × ULN
      - Concurrent AST or ALT > 3× ULN and total bilirubin > 2 × ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grad4 neutropenia ≤ 7 days

  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the sponsor Medical Monitor.

- Any event that leads to delay in dosing lasting > 9 weeks from the scheduled dosing requires discontinuation, with the following exceptions:
  - Dose delays to allow for prolonged steroid tapers to manage drug-related adverse events may be allowed if approved by the sponsor medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 9 weeks from the scheduled dosing, the sponsor medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue, more frequently study visit should take if clinically indicated during such dosing delays.
  - Dosing delays lasting > 9 weeks from the scheduled dosing that occur for non-drug-related reasons may be allowed if approved by the sponsor medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 9 weeks, the sponsor medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue, more frequently study visit should take if clinically indicated during such dosing delays.

6.5. CONCOMTANT TREATMENT

All concomitant medication used throughout the treatment period and safety follow-up period (30, 60 and 90 days after the last dose of the study drug) should be recorded starting from the signature of the ICF by the subjects, which should include the dose, regimen, route, indications, starting date and end date of the concomitant drug.

6.5.1. Prohibited Medications/Vaccines

The following medications and procedures are prohibited during the study:

- use of strong CYP3A4 inhibitors and inducers is prohibited during the study (Please refer to Section **错误!未找到引用源。**
- Do not use any anti-tumor drugs other than the study drug (irrespective of those approved by the Health Authority or investigational treatment), including but not limited to chemotherapy, radiotherapy, immunotherapy, bio-targeted therapy, hepatic intervention, local therapy and traditional Chinese medicines with anti-hepatocellular carcinoma indication.
  - Palliative local therapy (including surgery and radiation therapy) to extra-hepatic non-target lesions may be allowed.

- Immunosuppressive agents, including but not limited to systemic corticosteroids, etc. (the dose higher than 10 mg/day prednisone or equivalent dose), with the exception of special circumstances requiring such agents for the treatment of an AE, in which the investigator must discuss with the sponsor's medical monitor.
- The use of live vaccines should be prohibited during the study period.
- For Phase Ib, prophylactic medications, such as prophylactic anti-emetic, prophylactic colony-stimulating factor, erythropoietin etc., are not permitted during the DLT observation period (D1 to D21 of Cl). Drugs or treatments that correct hematologic toxicity are not allowed.

6.5.2. Permitted Treatment

The permitted treatments for this study include:

- After discussion and consultation with the medical monitor, the investigator can perform supportive treatment (e.g. local radiotherapy against pain (extra-hepatic non-target lesions only)), or thoracic puncture and drainage to relieve the subject's symptoms).
- Bisphosphonates indicated for bone metastases are permitted during the study period.
- Local, ocular, intraarticular, intranasal and inhaled glucocorticoids therapies (with extremely low systemic absorption) in subjects are also acceptable; ≤ 10 mg/day of prednisone or equivalent dose of the similar drugs as the adrenal alternative therapy are also acceptable; short-term (＜3 weeks) use of glucocorticoids for prophylactic treatment (e.g. to prevent allergy to contrast medium) or for the treatment of non-autoimmune diseases (e.g., delayed type hypersensitivity caused by contact with allergen) is also allowable.

6.6. SPECIAL PRECAUTIONS

Subjects should be closely observed and monitored during the administration of CS1001 up to 30 minutes after completion of the infusion.

If a grade 2 or higher hypersensitivity reaction, inflammatory reaction or infusion-related reaction occurs, the CS1001 infusion will be discontinued. Recommendations for treatment of infusion-related reactions and severe hypersensitivity reactions according to NCI are presented in sections错误!未找到引用源。 and错误!未找到引用源。 respectively.

6.6.1. Infusion-Related Reaction

Infusion-related reaction symptoms include fever, chills, nausea, itching, angioedema,

hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or high blood pressure. Severe reactions include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation and cardiogenic shock. The subjects should be closely monitored for such reactions. Please refer to Table 9 for treatment adjustments for infusion-related reactions caused by administration of CS1001.

The site must have conditions for the treatment of serious infusion-related reactions, such as immediate access to the intensive care unit (ICU) or the equal environment and availability of appropriate treatment (including adrenaline, corticosteroids, intravenous antihistamines, bronchodilators and oxygen). In the event of an infusion-related allergic reaction or an allergic

reaction of ≥ 2 level, the CS1001 infusion will be stopped.

In the event of hypersensitive reactions, the best available medical treatment must be taken for these subjects. Based on the guidelines for emergency treatment of allergic reactions published by Resuscitation Association Working Group (UK), it is recommended that subjects should immediately report any delayed response to the investigator.

Table 9:Treatment adjustments for infusion-related reaction symptoms after administration of CS1001

NCI-CTCAE Classification	Treatment Adjustment for CS1001
Level 1 - Mild Mild and transient reactions; no need to interrupt infusion; and no intervention required.	When the infusion rate of CS1001 decreases by 50%, it is necessary to closely monitor any worsening reaction until the reaction disappears. Medical treatment can be given on demand.
Level 2 - Moderate The need of treatment or infusion interruption, and timely relief after symptomatic treatment (e.g., antihistamines, NSAIDs, anesthetics, intravenous fluids, etc.); and the need of prophylactic treatment with treatment time ≤ 24 hours.	CS1001 infusion should be suspended. Once the infusion-related reaction disappears or the severity drops to level 1 or below, the infusion may be restarted at a rate reduced to 50% of the previous rate, and any worsening reaction should be closely monitored. Appropriate medical management strategies should be established based on the following text.
Level 3 or Level 4 - Severe or life-threatening Level 3: The delay of symptom relief (e.g., symptomatic administration and/or the failure of timely relief after transient interruption of the infusion); the symptomatic relapse after initial improvement; and hospitalization or clinical consequences (e.g., kidney damage, pulmonary infiltration, etc.) due to clinical sequelae. Level 4: life-threatening; and the need of emergency intervention (e.g., the need of ventilator support, etc.).	The CS1001 infusion should be discontinued immediately and the infusion tube connected to the subject should be disconnected. Whether to continue the study treatment will be determined by the investigator. Appropriate medical management strategies should be established, as described below; The subject should immediately withdraw from CS1001 treatment group and should not receive additional CS1001 treatment. Appropriate medical management strategies should be established based on the following text.

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs.

Once the infusion rate of CS1001 is reduced by 50% or the infusion is suspended due to infusion-related reactions, the reduced infusion rate must be maintained at all subsequent infusions. If the subject occurs the infusion-related reaction (≥ level 2) for the second time at a slower infusion rate, the infusion should be discontinued, and the subject should withdraw from CS1001 treatment group.

Infusion Reactions of CTCAE Level 1 or Level 2: Appropriate medical treatment strategies should be established according to the reaction type. It includes but is not limited to antihistamines (e.g., diphenhydramine or equivalent drugs), antipyretic agents (e.g., paracetamol or equivalent drugs), oral or intravenous corticosteroids on demand, epinephrine, bronchodilators and oxygen. Bedside monitoring must be continued until symptom relief is achieved. In the subsequent dosing period, the subject will receive prophylactic oral antihistamines (e.g., diphenhydramine or

equivalent drugs) and antipyretic agents (e.g., paracetamol or equivalent drugs) at least 30 minutes prior to infusion and will be closely monitored for infusion-related clinical signs and symptoms.

Infusion Reactions of CTCAE Level 3 or 4: The infusion should be discontinued immediately. Appropriate medical management strategies should be established immediately according to severity and type of the reaction. It includes but is not limited to oral or intravenous antihistamines, antipyretic agents, corticosteroids, epinephrine, bronchodilators and oxygen.

Whenever the subject occurs an infusion-related reaction of Level 4, CS1001 must be discontinued.

If an infusion-related reaction of Level 3 occurs, whether to continue the study treatment will be determined by the investigator after consulting with the sponsor. If it is decided to continue the treatment, the infusion time of CS1001 should be at least 1 hour for **the next dosing period**. Prophylactic antihistamines (e.g., diphenhydramine 50 mg or equivalent drugs) and antipyretic agents (e.g., paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) or equivalent drugs) will be given within 30 to 60 minutes prior to infusion. The subject will be closely monitored for infusion-related clinical signs and symptoms.

6.6.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

In the event of hypersensitive reactions, the best available medical treatment must be taken for these subjects. It is recommended that subjects should immediately report any delayed response to the investigator.

In the event of generalized allergic reactions/anaphylactoid reactions (typical manifestations occur within a few minutes after dosing and are characterized by respiratory distress, laryngeal edema and/or intense bronchial spasm; subsequent vascular collapse or shock in general but without previous dyspnea; skin manifestations such as itching and urticaria, with/without edema; and gastrointestinal symptoms such as nausea, vomiting, abdominal cramps and diarrhea), **the infusion must be discontinued and the subject should discontinue study drug administration.**

In the event of hypersensitive reactions, the subject will be given infusions of adrenaline and dexamethasone, followed by immediate monitoring, and the ICU should be prepared for a ready-to-use state when needing to be transferred to the ICU.

If the subject appears the above reactions after receiving the treatment for the first time, it is advisable to administer prophylactic 25 mg indomethacin or a similar dose of NSAIDs (NSAIDs) (e.g., 600 mg ibuprofen and 500 mg naproxen sodium) within 30 to 60 minutes prior to each **subsequent** CS1001 infusion. Or according to the investigator's judgment, other fever treatment may be given to the subject (e.g., paracetamol).

6.6.3. Immune-Related Adverse Events

If an immune-mediated AE is suspected, the investigator should ensure that the evidence of etiology is conclusive or other causes may be excluded.

For any irAE of ≥ Grade 3 or irAE of Grade 2 with the requirement of drug suspension or permanent withdrawal, the investigator should inform the sponsor as soon as possible and consult with the sponsor if necessary.

Based on the severity of AE, CS1001 will be suspended and corresponding treatment will be given. For subjects who use corticosteroids, corticosteroid dose will be gradually reduced within at least 1 month after the adverse reaction is improved to grade 1 or better. Short-term immunosuppressive agents such as tumor necrosis factor antagonists, mycophenolate mofetil or other drugs may be used if needed. If the severity of AE is maintained at grade 1 or better, CS1001 treatment can be restarted. In the event of an immune-mediated persistent, worsening or recurrent adverse event of Grade 3, or an immune- mediated event of Grade 4, CS1001 treatment should be discontinued permanently. For the identification, diagnosis, management and dose adjustment of irAE, please refer to APPENDIX 3: GUIDANCE FOR IMMUNE-RELATED ADVERSE REACTIONS MANAGEMEMT

6.6.4. Other Specific Adverse Events or Adverse Drug Reactions

The light absorption characteristics of BLU-554 suggest the possibility that BLU-554 treatment will be associated with phototoxicity. Therefore, subjects should use clothing and sunscreen to avoid direct sun exposure.

7. STUDY ASSESSMENT AND PROCEDURES

7.1. SAFETY ASSESSMENTS

Throughout the study, safety assessments should be performed at all study site visits. The severity, time, and correlation with study treatment will be assessed.

Subjects' vital signs, physical examination, ECOG performance status score, ECG, and safety laboratory tests will be measured and assessed at specified intervals throughout the study. Subjects' medical histories are collected during the screening period to understand the underlying diseases. Special attention should be paid to immune-related adverse reactions (e.g. gastrointestinal tract, skin, lung, liver, kidney, endocrine organs, etc.).

Adverse events and laboratory test results will be graded according to NCI-CTCAE v5.0 throughout the study. The characteristics of toxicity events include severity, duration, and onset time. Safety endpoints included all types of adverse events, safety laboratory assessments, ECG, and vital signs, etc.

Subjects will continue to be evaluated for safety. Subjects will be evaluated for safety if they take any study medication.

7.1.1. Vital Signs

Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure. Additional vital sign assessment monitoring may be performed at the discretion of the investigator based on clinical needs.

7.1.2. Physical Examination and ECOG Performance

A comprehensive physical examination includes the examination of the head, eyes, ears, nose, throat, skin, thyroid, nervous system, respiratory, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight should be measured and recorded.

Brief physical examination includes examination of the skin, respiratory, cardiovascular system, and abdomen (liver and spleen).

The investigator must assess the abnormal changes in ECOG scores.

7.1.3. Electrocardiogram (ECG)

A 12-lead ECG will be collected at the scheduled time in the SoA. Whenever possible, the same electrocardiograph should be used throughout the study. The subject should rest for at least 10 minutes for collection of 12 lead ECGs at a supine position. All ECG safety must be assessed by a qualified physician. In case of any abnormalities, ECG must be repeated.

7.1.4. Echocardiography

Left ventricular ejection fraction and ventricular function will be assessed byechocardiography at the time points described in the SOA.

7.1.5. Laboratory Tests

The blood and urine samples used for clinical laboratory assessment will be collected as specified by the protocol. The specific collection time points are described in the SOA. Details of sample preparation and analysis will be provided by local laboratories. The reference ranges for all safety parameters will be provided by local laboratories.

This study will detect the following parameters;

Blood test	Platelet Count	*RBC Indices:*	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Serum Chemistry	BUN/Urea[1]	Potassium	AST	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
				Total cholesterol
				Triglyceride
CK-MB	CK-MB			
HBV、HCV[1]、HIV	HCV antibody, HBsAg and HIV antibody			
AFP	AFP			
Coagulation	PT, INR and aPTT			
Routine Urine Test	pH, Specific gravity, Glucose, ketones, WBC, protein			
Thyroid Function	FT3, FT4 and TSH			
immunogenicity	ADA level			
FGF19、PD-L1 expression	FGF19 IHC、PD-L1			
Pregnancy test[2]	β-hCG			

1. The detection of this test item for the same patient in the same study site should be consistent throughout the study.
2. Subjects with HBsAg positive will further assess HBV DNA test, subject with HCV antibodypositive will further assess HCV RNA test.
3. A serum pregnancy test should be performed for female subjects at Screening; thereafter, a serum or urine pregnancytest should be performed on every odd cycle (e.g. C3, C5).

As for unexpected clinical laboratory detection values or values with unknown cause, if the investigator judges them as clinically significant, they should be repeatedly detected within 24h and continuously followed up until the detection results return to their normal value range and/or a rational explanation is found for such abnormality. The clinical laboratory will clearly mark the detection values beyond the normal value range, and the principal investigator needs to judge whether these abnormal values are clinically significant one by one, record those clinically significant ones as AEs and elaborate their relationship with treatment.

7.1.6. Immunogenicity

Immunogenicity involves the immune response to CS1001 itself, and is characterized through CS1001-related antibodies which may appear in subjects. These antibodies may cause CS1001 to be more quickly eliminated from the blood, or cause subjects receiving CS1001 treatment again at a later point of time to show infusion-related reactions. Blood samples used for immunogenicity analysis are respectively collected at the points of time provided in Table 4 and Table 5. The samples collected will be used to assess the anti-drug antibody (ADA) level of subjects (including assessment of neutralizing antibody Nab levels).

7.2. EFFICACY ASSESSMENTS

Efficacy assessments will be performed by the investigator and BICR, respectively, according to RECIST v1.1.

Radiographic (CT or MRI) assessments will be performed within 28 days prior to the first dose (baseline assessment), every 9 weeks during the first year of the study and every 12 weeks thereafter, according to RECIST v1.1 (APPENDIX 2: THE LATEST REVISED RECIST GUIDANCE (VERSION 1.1))) until 1) disease progression, 2) initiation of new anti-cancer therapy, 3) withdrawal of informed consent, 4) loss of follow-up, 5) death, 6) termination of study, whichever occurs first. In addition to subjects who discontinue treatment due to disease progression as determined by radiographic assessment, additional subjects should continue to undergo radiographic assessments at the scheduled time. Baseline tumor assessment should include brain (phase II study only), chest, abdomen, pelvis and other sites suspected of tumor lesions, and subsequent evaluations should include all sites evaluated at baseline (phase II study: subjects who have no brain metastases confirmed by imaging at screening will not be required to undergo regular brain imaging at subsequent visits, which may be scheduled by the investigator as clinically indicated), and should be performed using the same imaging method used at baseline.. If a subject has undergone a bone scan within three months of baseline assessment and was determined to be negative, the bone scan was not required for the baseline assessment. For subjects with bone metastases at screening, bone lesions should be followed up at subsequent visits. For subjects without bone metastases at baseline, follow-up with bone lesions is not required, unless the subject develops symptoms. The same detection technique as the baseline was used throughout the study. If an unscheduled tumor assessment occurs and the subject does not experience disease progression, subsequent tumor assessments should also be performed as scheduled.

All radiographic results in this study will be interpreted by the sites or radiologists. The subjects will be clinically managed (including continuation or discontinuation of study treatment) based on the investigator's assessment of tumor imaging and the investigator's clinical judgment during the study.

7.3. PHARMACOKINETIC EVALUATION AND IMMUNOGENICITY ASSESSMENTS

Blood for the pharmacokinetic profile of CS1001 and BLU-554 will be collected by venipuncture. According to the time points specified in Table 4 and Table 5, venous cannulation will be performed to collect plasma for detection of blu-554 and serum for detection of CS1001 respectively. PK samples shall not be sampled from the ipsilateral arm that has been injected with the drug. The actual sampling time (to the exact minute) of each sample will be recorded in the eCRF and in the

database.

See the central laboratory manual for the handling of PK samples, including labeling and shipment. The corresponding labeling provided by the Sponsor must be applied on the collection tubes and sample storage tubes prior to sampling. For ease of reading, the label must be applied longitudinally along the tube. Labeling shall use high quality materials to ensure that it will not fall off the tube under extreme conditions.

During shipping, the samples must be kept frozen in a freezer at -80 °C and placed in a box with dry ice. The samples were shipped to a bioanalytical laboratory, and the serum concentration of CS1001 was analyzed by the validated ELISA method, and the plasma concentration of BLU-554 was analyzed by the validated LC-MS/MS method.

7.4. BIOMARKER EVALUATION

Biomarkers related to this study include FGF19 and PD-L1.

Where permitted by the Ethics Committee, all subjects who sign the informed consent form are required to provide 9 formalin fixed-paraffin embedded and unstained tumor tissue slides for the FGF19 and PD-L1 protein expression test during screening. Biomarker test (may include different methods for detecting FGF19 protein expression) will be applied in central lab. Detailed instructions for the collection, handling, and shipping of biomarker samples will be described in the applicable study laboratory manual.

7.5. STUDY PROCEDURES

7.5.1. Screening Phase

Written informed consent for the subject's signature must be obtained prior to the start of the screening period assessments and prior to the start of any study-related assessments.

Screening will be Days -28 to -1, and all subjects will undergo screening procedures to determine eligibility. All subjects should provide archived or fresh tumor samples for an ICH assessment prior to enrollment.

Required tumor tissue samples:

Subjects must provide 9 formalin fixed-paraffin embedded and unstained tumor tissue slides for FGF19 and PD-L1 assessment at central laboratory.

The following procedures will also be performed at the Screening visit:

- Obtain demographic data, including gender, date of birth/age, race, and ethnicity;
- Complete medical history, including a history of HCC and other malignancies, concurrent illnesses, prior treatments and the response to each treatment if available. The medical history obtained at C1D1 will be focused on disease-related symptoms and changes from the previous visit;
- Complete physical examination, including ECOG PS;
- AFP;
- Tumor imaging (MRI or CT);
- Vital signs including weight, temperature, pulse, and systolic/diastolic blood pressure. Height and weight will also be measured at Screening;
- 12-lead ECG;

- Echocardiogram;
- Clinical laboratory assessment (blood test, coagulation, serum chemistry, CK-MB, urinalysis);
- HBV, HCV, HIV;
- Thyroid Function;
- Serum pregnancy test within 7 days prior to dosing on C1D1 (women of childbearing potential only);
- AE, SAE (only collect AEs and SAEs as specified in the electronic case report completion guidelines (eCCI))
- Concomitant medication.

Re-screening is permitted for one time, but need to decide by investigator and sponsor assessment. Central laboratory-confirmed FGF19 IHC results obtained at screening # 1 may be used in the assessment of FGF19 IHC status at re-screening without recollecting tumor samples for testing.

7.5.2. Treatment Phase

For treatment phase of the study, all tests are performed at the time points specified in the dosing cycles. Subjects eligible for enrollment receive every 21 days (every 3 weeks) of BLU-554 in combination with CS1001 treatment as a cycle.

The items to be completed during the treatment phase are as follows:

C1D1:

- Checking inclusion/exclusion criteria
- Check/collect medical history
- Body weight, vital sign examination: body temperature, pulse, systolic and diastolic blood pressures are measured before and after infusion
- ECOG performance status score (prior to infusion)
- Physical examination
- 12-lead ECG
- Echocardiogram
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis (when laboratory tests and study drug administration are scheduled on the same day, the results should be available before administration can be scheduled. Clinical laboratory tests do not need to be repeated on C1D1 if the screening visit tests are performed within 7 days prior to first dose (C1D1) (i.e., there is a -7 day window for laboratory tests on C1D1).)
- AFP
- Thyroid function (when thyroid function tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled. If the thyroid function test in the screening period is performed within 7 days prior to the first dose, it does not need to be repeated before the first dose (i.e., there is a -7 day window for thyroid function tests on C1D1).)
- PK blood, immunogenicity blood samples

- Study drug administration, medication compliance
- DLT evaluation (Phase Ib only)
- AE，SAE, concomitant medications

C1D2:

- 12-lead ECG
- Echocardiogram (if clinically indicated)
- PK blood, immunogenicity blood samples
- BLU-554 administration, medication compliance
- DLT evaluation (Phase Ib only)
- AE, SAE, concomitant medications

C1D8 (Phase Ib only):

- Body weight, vital sign examination: body temperature, pulse, systolic and diastolic blood pressure are measured before and after infusion
- Physical examination
- Echocardiogram (if clinically indicated)
- Blood test, blood biochemistry and CK-MB (The laboratory tests should be completed within 3 days pre-dosing. When the laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- PK blood, immunogenicity blood samples
- BLU-554 administration, medication compliance
- DLT evaluation (Phase Ib only)
- AE，SAE, concomitant medications

C1D15:

- Body weight, vital sign examination: body temperature, pulse, systolic and diastolic

blood pressure are measured before and after infusion

- Physical examination
- Echocardiogram (if clinically indicated)
- Blood test, blood biochemistry and CK-MB (The laboratory tests should be completed within 3 days pre-dosing. When the laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- PK blood, immunogenicity blood samples
- BLU-554 administration, medication compliance
- DLT evaluation (Phase Ib only)
- AE，SAE, concomitant medications

C2D1:

- Body weight, vital sign examination
- ECOG performance status score (before infusion)
- Physical examination
- 12-lead ECG
- Echocardiogram (if clinically indicated)
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis (The laboratory tests should be completed within 3 days pre-dosing. When laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- Thyroid function (It should be completed within 3 days pre-dosing. When thyroid function tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- AE, SAE, concomitant medications
- PK blood, immunogenicity blood samples
- Study drug administration, medication compliance

C3D1:

- Body weight, vital sign examination

- ECOG performance status score (before infusion)
- Serum/urine pregnancy test (It is performed on D1 (± 4 days) of each odd cycle thereafter for women of childbearing potential)
- Physical examination
- 12-lead ECG
- Echocardiogram (if clinically indicated)
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis (The laboratory tests should be completed within 3 days pre-dosing. When laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- AE, SAE, concomitant medications
- PK blood, immunogenicity blood samples
- Study drug administration, medication compliance

C4D1:

- Body weight, vital sign examination
- ECOG performance status score (before infusion)
- Physical examination
- Tumor imaging examination
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis (The laboratory tests should be completed within 3 days pre-dosing. When laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- Thyroid function (It should be completed within 3 days pre-dosing. When thyroid function tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- AE, SAE, concomitant medications
- PK blood, immunogenicity blood samples
- Study drug administration, medication compliance

C5D1 and D1 of subsequent cycles:

- Body weight, vital sign examination
- ECOG performance status score (before infusion)
- Serum/urine pregnancy test (It is performed on D1 (± 4 days) of each odd-numbered cycle thereafter for women of childbearing potential)
- Physical examination
- Tumor imaging examination (Imaging (CT or MRI) assessments are performed per RECIST v1.1 for Cycle 5 as clinically required, and every 9 weeks during year 1 and every 12 weeks thereafter for subsequent cycles)
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis (The laboratory

tests should be completed within 3 days pre-dosing. When laboratory tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)

- Thyroid function (The test is not required in Cycle 5, and thyroid function test is performed before dosing every 2 cycles in subsequent cycles (C6, C8, C10 …). It should be completed within 3 days pre-dosing. When thyroid function tests and study drug administration are scheduled on the same day, the results should be available before the administration can be scheduled.)
- HBV, HCV (HBV DNA should be retested every 12 weeks for subjects with HBsAg positive, HCV RNA should be retested every 12 weeks for subjects with HCV antibody positive, i.e. C5, C9, C13 …)
- AFP (every 12 weeks, i.e. C5, C9, C13…)
- AE, SAE, concomitant medications
- PK blood, immunogenicity blood samples
- Study drug administration, medication compliance

For subjects suspected of developing a pseudoprogression, if the subjects meet the following criteria, it is recommended to continue receiving the study drug before confirmation by imaging. Subjects will sign the informed consent for subsequent treatments of disease progression.

a) Have clinical benefits as assessed by the investigator, e.g., no clinical signs and symptoms of significant disease progression (including worsening laboratory findings);

b) Tolerance to study drug;

c) Sable Eastern Cooperative Oncology Group (ECOG) performance status score;

d) No rapid disease or tumor progression requiring urgent alternative medical intervention at critical anatomical sites (such as spinal cord compression).

It is the responsibility of the investigator to determine if the subject may benefit from the subsequent treatment. Decisions should be made carefully to maximize the availability of further treatment for subjects who potentially benefit from it and to avoid long-term use of ineffective therapy.

In rare cases, if the investigator considers subjects can benefit from the treatment, subjects may continue the treatment after disease progression determined by the confirmatory tumor imaging assessment, and subjects must sign the informed consent again. In that case, it's necessary to consult with the sponsor first.

7.5.3. End of Treatment (EOT) Visit

The date of EOT visit is defined as the date when the investigator decides to discontinue the administration. The EOT visit should be performed 0-7 days after the EOT date. If the EOT visit and a treatment visit occur within 7 days, the repeat items do not need to be conducted. If the EOT visit occurs within the safety follow-up window, repeat items do not need to be conducted. If an alternate treatment is started within 7 days of the EOT date, the EOT visit should be conducted prior to the first dose of alternate therapy. The last administration date is calculated as the later last administration date of the two study drugs. It should be noted that the date on which the investigator decided to stop dosing may not coincide with the date of last dose.

The following items to be completed for the EOT visit are as follows:

- Body weight, vital signs

- ECOG score, physical examination
- Blood test, coagulation, blood biochemistry, CK-MB and urinalysis
- Thyroid function
- 12-lead ECG
- Echocardiogram
- Tumor imaging (if the subject discontinue treatment due to disease progression (excluding pseudoprogression), it is not necessary to repeat the imaging assessment at last visit. If the subject has completed tumor imaging assessment within 28 days prior to EOT visit or safety visit, it is not required to repeat such examinations at the two visits.)
- Serum/urine pregnancy test (It is performed for women of childbearing potential)
- HBV、HCV
- AFP
- PK blood samples, immunogenicity blood samples
- AE, SAE, concomitant medications

7.5.4. Follow-up Phase

The follow-up phase includes safety follow-up phase and survival follow-up phase.

Safety follow-up phase consists of 30 days, 60 days and 90 days after the last dose of study drug or until the start of a new antineoplastic treatment, whichever occurs first.

Safety follow-up phase consists of 3 visits:

(Note: safety visit 2 and safety visit 3 may be conducted by telephone follow-up)

Safety Visit 1 (30 ± 7 days after last dose):

- 12-lead ECG
- Serum/urine pregnancy test (It is performed for women of childbearing potential)
- Examination of vital signs
- Physical Examination
- ECOG performance status score
- Tumor imaging examination (if applicable)
- HBV, HCV tests
- Clinical laboratory tests (blood test, blood biochemistry, urinalysis, coagulation, CK-MB)
- Thyroid function test
- Concomitant medications
- AE, SAE
- Subsequent anti-tumor therapy (if any)

Safety Visit 2 (60 ± 7 days after last dose)

- AE, SAE, concomitant medications
- Subsequent antineoplastic therapies (if any)

Safety Visit 3 (90 ± 7 days after last dose)

- AE, SAE, concomitant medications
- Subsequent antineoplastic therapies (if any)

Survival follow-up:

From the last dose of study drug, subjects will be contacted by telephone or face-to-face every 12 weeks, to collect subject survival status, subsequent anti-tumor therapy and study drug-related SAEs until the death, loss of follow-up, withdrawal from the study, or study termination, whichever occurs first.

8. ADVERSE EVENT AND SERIOUS ADVERSE EVENT

It is the principal investigator's responsibility to ensure that all participants are familiar with the content of this section.

8.1. DEFINITION OF AN ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence after clinical study subjects receive a drug, which need not necessarily have a causal relationship with the treatment. AEs include any unfavorable and abnormal sign (e.g., abnormal laboratory tests), symptom, or disease temporally associated with the use of a (investigational) drug, whether or not related with the (investigational) drug (as defined by ICH).

It includes new events, exacerbation of underlying conditions, or increased frequency, and abnormal diagnostic results including abnormal laboratory values.

Examples of AEs include, but not limited to:

- Abnormal laboratory test results;
- Clinically relevant symptoms and signs;
- Physical examination result change;
- Hypersensitivity reactions.

In addition, symptoms or signs attributable to the following events are also included

- Overdosage;
- Drug discontinuation;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependence
- Drug leakage;

- Pregnancy

AEs include serious adverse events (SAEs) and non-serious AEs.

8.2. ABNORMAL LAB RESULTS

The following criteria should be used to determine whether laboratory results should be reported as adverse events:

- Accompanied by symptoms, and (or);
- Require further diagnostic examination or pharmacological/surgical intervention, and (or);
- Lead to study treatment modifications (out of protocol-specified dose modification) or;
- Considered to be an adverse event by the Investigator or Sponsor.

If any of the above criteria is not met, only the repeat test for abnormal findings is needed and it does not constitute an adverse event. Reporting error test results does not need to be reported as an adverse event.

8.3. DEFINATION OF A SERIOUS ADVERSE EVENT

An SAE is any event that meets any of the following criteria as per the ICH definition:

- Death.
- Life-threatening ("life-threatening" means that the subjects are exposed to the risk of death in the event rather than the case it may theoretical lead to death in more serious event.)
- Inpatient hospitalization or prolongation of existing hospitalization (the reason for this condition is due to adverse events rather than the elective surgery, non-medical reasons, etc., as described below).
- Persistent or significant disability/incapacity.
- Causing congenital malformations or birth defects in offspring (congenital malformations or birth defects in the offspring of the subject);
- Significant medical events.

Important medical events that may not necessarily result in death, be life-threatening or require hospitalization may be considered as an SAE when, based upon appropriate medical and scientific judgment, they may jeopardize the subject and may require intervention measures to prevent one of the outcomes listed in this definition.

Examples of such events are: Intensive treatment in an emergency room or at home for allergic bronchospasm; Blood abnormalities or convulsions that do not result in inpatienthospitalization; Development of drug dependency or drug abuse. If the investigator considers that clinical symptoms and signs of an adverse event have a clinically significant impact, the AE is classified as a serious adverse event. Important medical events assessed by medical data and clinical experience of the investigator should be handled with reference to expedited reporting of serious adverse events. In addition, any suspected transmission of an infectious substance potentially via a medicinal product is also considered as an important medical event.

Unlisted (Unexpected) Adverse Event

Unlisted adverse events refer to those whose nature or severity does not correspond to the reference safety information of the respective medicinal product. For investigational medicinal products, the expectedness of an adverse event will be judged on the basis of whether they are listed in the Investigator's Brochure. For comparator products approved for marketing, the expectedness of an adverse event will be judged based on whether it is listed in the package leaflet.

Hospitalization

Adverse events leading to hospitalization or prolonged hospitalization during the study are classified as serious adverse events. Any new hospitalization in medical institutions (even if the hospital stay is less than 24 hours) meets the criteria. Hospitalization also includes intra-hospital transfer to an urgent/intensive care unit (e.g., from pediatrics to the medicine, medicine to the intensive care unit for coronary heart disease, and from neurology department to the TB ward, etc.).

The hospitalization in following institutions is not included:

- Rehabilitation;
- Hospice care;
- Short-term care (e.g. nursing care);
- Professional nursing;
- Home care;
- Admission to the general emergency department;
- Surgery on the same day (outpatient/ day surgery/ day-to-day operation).

Hospitalization or prolonged hospitalization due to following reasons is not a serious adverse event:

- Hospitalization that is not associated with a new onset of an adverse event or exacerbation of a pre-existing AE (e.g., an examination of pre-existing ongoing laboratory abnormalities);
- Hospitalization for a non-medical reason (e.g., the subject is homeless);
- Transactional hospitalizations (e.g., annual physical examinations);
- Study protocol-specified hospitalization (e.g., for procedures required by the study protocol);
- Voluntary hospitalization not leading to clinical adverse events (e.g. for elective cosmetic surgery);
- Pre-scheduled hospitalizations or procedures (Entire study protocol and (or) pre-planned treatments or procedures by subjects should be documented in the baseline files);
- Hospitalization only for the use of study medication.

Diagnosis and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the disease treated by such procedures should be reported as an adverse event if it meets the definition of an adverse event. For example, acute appendicitis that occurs during the adverse event reporting period should be reported as an adverse event and the appendectomy procedure to treat this disease should be recorded as the treatment of the adverse event.

8.4. DOCUMENTATION OF ADVERSE EVENTS

All AEs spontaneously reported by subjects or answered by them after an open-label question "Do you have any health problem from the last visit/asking a question to the present?" by the investigator, or AEs observed should be collected and recorded. When collecting AE data, it is preferable to record the diagnosis (if possible) rather than to record a series of signs and symptoms. However, if a diagnosis is known, and the subject still has other signs or symptoms not belonging to the diagnosis, each symptom or sign should be recorded separately.

8.4.1. Time of AE Collection

AEs and SAEs will be collected from time of signature of main informed consent, throughout the treatment period and including the follow-up period.

Documentation of AEs and SAEs from time of signature of informed consent through the first dose of study drug is described in the electronic case report completion guidelines (eCCI).

Note: If the investigator gets known of any SAEs (including deaths) after the subjects have completed the safety follow-up or withdrawn from the study, the investigator should inform the sponsor's Pharmacovigilance team or representatives if, in his/her discretion, there is a reasonable possibility that such event is possibly correlated with the investigational drug.

8.4.2. Follow-up of Unresolved Adverse Events

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to follow up until all events are resolved, even though the event still exists after the discontinuation of treatment or termination of the study. As indicated medically, the investigator should follow up any AE that is not resolved at last visit by investigator.

The sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3. Events that Occur after Subject Withdraws from Study

After the subject has been permanently discontinued from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring after the safety follow-up period. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently discontinued from study, and he/she considers there is a reasonable possibility that the event is related to the investigational product, the investigator should notify the sponsor PV group or its representative.

8.4.4. Variables collected

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Change of CTCAE grade
- Whether the AE is serious or not
- Investigator causality attribution against the Investigational Product
- Action taken with regard to investigational product
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of SAE
- AE is serious due to
- Date of discharge (if applicable)
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of SAE

8.4.5. Severity Analysis

It is important to distinguish between serious and severe AEs. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mile stroke but would be a SAE.

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 5.0.

8.4.6. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event.

If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

For SAEs causal relationship will also be assessed for other medication and study procedures. This includes non-treatment-emergent SAEs (e.g., SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the

subject's medical record.

- Not protocol related: The event is related to an etiology other than the procedure/intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

8.4.7. Disease Progression

Disease progression can be considered as a worsening of subject's condition attributable to the disease for which the investigational product is being studied. Symptomsand/or signs associated with disease progression should neither be documented as an AE nor be reported as a SAE in an expedited fashion. But according to CTCAE 5.0, death due to disease progression needs to be reported as SAE in an expedited fashion.

8.4.8. New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the investigational product and have been identified after the subject's inclusion in this study.

8.5. REPORTING OF ADVERSE EVENTS

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.5.1. Requirements for Serious Adverse Event Reporting

All serious adverse events occurring during clinical study must be reported to the sponsor or its designated representative by investigational staff immediately ***within 24 hours*** of when he/she becomes aware of it. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of pregnancy cases.

The sponsor representative works with the investigator to ensure that all the necessary information is provided within above timeline.

For all serious adverse events, the investigator is obligated to pursue and provide information to the sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided.

In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated sponsor representative.

In case EDC is down, facsimile transmission/encrypted email of the filled paper Adverse Event Report form is the preferred backup method to transmit this information to the project contact

for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a hardcopy of the Adverse Event Report form sent by encrypted mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the paper Adverse Event Report form within 24 hours when he/she aware of the event.

The contact information for assistance with SAE reporting, specific to the site, are listed in the investigator folder provided to each site. The original copy of the Adverse Event Report form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

For details, please refer to the study specific Safety Management Plan (SMP).

The sponsor representative will advise the investigator/study site personnel how to proceed.

The sponsor has a legal responsibility to notify, as appropriate, both the local Health Authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB) /Independent Ethics Committee (IEC).

Abnormal Liver Function Tests

Abnormal liver function that meets the following conditions will be considered as SAE, which shall be reported by the investigator according to the SAE reporting process. If no other criteria are applicable, the important medical serious event criterion could be used for judgment.

- For subjects with normal baseline of AST and ALT and total bilirubin: Treatment-emergent AST or ALT $\geq$3 × ULN, total bilirubin $\geq$2 × ULN, ALP < 2 × ULN (or not available) with no evidence of hemolysis;
- For subjects with abnormal baseline ALT or AST or total bilirubin: Treatment-emergent AST or ALT $\geq$2 ×baseline values and $\geq$3 × ULN, or $\geq$8 × ULN (whichever is smaller) with total bilirubin level increased by at least 1 × ULN from baseline or if the value reaches $\geq$ 3 × ULN (whichever is smaller).

Disease progression

Death due to disease progression requires expedited reporting as an SAE per CTCAE 5.0.

New onset of tumors

New onset of tumors should be classified as SAEs. New primary tumor is defined as a tumor found after study enrollment that is not primarily attributable to the use of study drug.

8.5.2. Requirements for Non-serious Adverse Event Reporting

All adverse events will be reported on the adverse event page(s)/module of the eCRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse

event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.6. OVERDOSE

Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. Subjects with a suspected overdose should be managed with symptomatic treatment or appropriate supportive therapy.

For any drug overdose (whether or not it causes an AE), the investigator should complete a paper Adverse Event Report form within 24 hours of being informed and report it to the sponsor's pharmacovigilance representative. For drug overdoses with AE, AE information shall be recorded and reported together with drug overdose information in accordance with the requirement of Section 8.5.

8.7. PREGNANCY

To ensure subject safety, each pregnancy during study must be reported by the investigator or other site personnel to the sponsor’s representatives within 24 hours after being aware of its occurrence. The Sponsor's representatives together with the investigator will ensure that all relevant information is reported to the Sponsor's Pharmacovigilance Representative and the pregnancies and the outcome of each pregnancy in subjects who have been treated with the investigational drug should be reported. Abnormal pregnancy outcomes should be considered as SAEs, which should be reported in the Serious Adverse Event Reporting Form within the appropriate reporting timelimit for SAE.

8.7.1. Maternal Exposure

A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or after discontinuing and/or being directly exposed to the investigational product.

If a subject is found to be pregnant during the study, the study drug should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate sponsor representatives within 24 hours of when he/she becomes aware of it.

The same timelines apply when outcome information is available.

The Pregnancy report module in the CRF is used to report the pregnancy (in case of failure of EDC system, the Pregnancy Report Form of sponsor could be filled out for reporting before accessing into the EDC system for supplementation when the EDC system has recovered) and

the Pregnancy Outcome Report is used to report the outcome of the pregnancy.

Pregnancies occurring up to 180 days after the completion of study medication must also be reported to the investigator.

8.7.2. Paternal Exposure

A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during his partners' pregnancy.

Information on the pregnancy of a subject's partner must be obtained directly from the subject's partner. Therefore, prior to obtaining information on the pregnancy, the investigator must obtain the consent of the subject's partner.

Male subjects should refrain from fathering a child or donating sperm during the study and for 180 days following the last dose.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 180 days after the last dose should be followed up and documented.

9. QUALITY CONTROL ,QUALITY ASSURANCE AND DATA MANAGEMENT

9.1. QUALITY CONTROL AND QUALITY ASSRANCE

During trial conduct, CStone or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow CStone monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. The trial site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to Quality Assurance audits performed by CStone, and/or to inspection by appropriate regulatory authorities. Such audits/inspections can occur at any time during or after completion of the study.

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.

9.2. DATA MANAGEMENT AND CODING

Data Management will be performed by the sponsor delegated Data Management Vendor.

An electronic data capture (EDC) system will be used for this study. All eCRF data will be entered in electronic forms at the site. Data collection, including all entries, corrections and alterations are to be made by investigator or authorized site personnel designated by the investigator. The eCRF

records will be automatically appended with the identification of the creator, by means of their unique User ID. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. All entries to the study database and changes will be fully recorded in a protected audit trail.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. The monitor will review the eCRFs and evaluate them for completeness and consistency by source document verification.

The data will be validated as defined in the Data Management Plan. Data queries will be raised for inconsistent, impossible or missing data. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Adverse events and medical/ surgical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). All coding will be performed by the vendor.

10. QUALITY CONTROL AND QUALITY ASSRANCE

10.1. SAMPLE SIZE DETERMINATION

It is planned to enroll not more than 12 subjects in the phase-Ib dose-escalation study. The observed toxicity will decide the actual sample size.

According to efficacy result of BLU-554-1101 study (data cut-off date: 16 Jun 2018), ORR was 17% (11/63) for FGF19 IHC+ subjects (1st line and above) and 0 (0/38) for FGF19 IHC-subjects. ORR of PD-1/PD-L1 monotherapy was reported around 10~20% for 1st line and 2nd line HCC subjects. Based on the data above, BLU-554 in combination with CS1001 is targeting 40% ORR for FGF19 IHC+ subjects and 30% ORR for FGF19 IHC- subjects. Combining the subjects treated at RP2D in Phase Ib and those in Phase II, gating criteria in Bayesian framework are developed as the following:

Gating based on 25 FGF19 IHC+ subjects

- A non-informative ORR prior is assumed at Beta (0.45, 0.55).
- Timing - when all 25 subjects finish at least two post-baseline tumor assessments
- Go - 12 responses or more, corresponding ORR 48%, the probability of combo ORR> 40% is 0.788.
- No go - 8 (32%) responses or fewer, the probability of combo ORR<40% is 0.797.
- Evaluate - 9 (36%) to 11 (44%) responses, evaluate other endpoints, DOR, DCR, safety, etc., and additional 15 FGF19 IHC+ subjects may be enrolled for further evaluation.

Gating based on 40 FGF19 IHC+ subjects (if enrichment of 15 FGF19 IHC+ subjects as decided)

- A non-informative ORR prior is assumed at Beta (0.45, 0.55).
- Timing - when all 40 subjects finish at least two post-baseline tumor assessments
- Go - 18 responses or more, corresponding ORR 45%, the probability ofcombo ORR > 40% is 0.737.
- No go - 14 (35%) responses or fewer, the probability of combo ORR<40% is 0.744.
- Evaluate - 15 (37.5%) to 17 (42.5%) responses, evaluate other endpoints, DOR, DCR, etc.

Gating based on FGF19 IHC- subjects treated at RP2D in Phase Ib

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - only conducted if at least 6 FGF19 IHC- subjects are treated at RP2D in Phase Ib, when they finish at least two post-baseline tumor assessments
- No go - 0 response, the probability of combo ORR<30% is greater than 0.99, Phase II will only include the FGF IHC+ cohort
- Evaluate - 1 response or more, the cohort of FGF IHC- subjects will be included in Phase II

Gating based on 15 FGF19 IHC- subjects

- A non-informative ORR prior is assumed at Beta (0.2, 0.8).
- Timing - when all 15 subjects finish at least two post-baseline tumor assessments
- Go - 6 responses or more, corresponding ORR 40%, the probability of combo ORR > 30% is 0.757. If the final decision for FGF19 IHC+ subjects is "go", FGF19 IHC- subjects

  may also be included in the target population of future development.

- No go - 3 (20%) responses or fewer, the probability of combo ORR<30% is 0.845. future development will not include FGF19 IHC- subjects in the target population.
- Evaluate - 4 (26.7%) to 5 (33.3%) responses, evaluate other endpoints, DOR, DCR, etc.

The sample sizes of 25 or 40 FGF19 IHC+ subjects and 15 FGF19 IHC- subjects are selected to have reasonably high probability of ORR exceeding the target when the go criteria are met or ORR being lower than the mono therapies when no-go criteria are met.

The go and no-go criteria are set up to guide future development of the combination. **They are not binding** decision-**making rules**.

If the actual numbers of evaluable subjects are different from those planned above, the same method will be used to calculate the posteriori probability that ORR will reach the predefined target for reference in subsequent development.

10.2. UMMERIES OF CONDUCT OF STUDY

10.2.1. Analysis Populations

Safety analysis set: consists of all subjects receiving at least one dose of investigational product.

Efficacy analysis set: consists of all subjects with measurable baseline disease who received at least one dose of investigational product. It will be the primary analysis set for efficacy in this study.

Note: Subjects who were screened but never started treatment will be listed, but not included in any efficacy analysis set. Therefore, these subjects will not be included in any of the summary tables.

Dose-determining set: consists of all subjects from the safety analysis set who, in Cycle 1, meet the minimum exposure criterion and complete the follow-up on Cycle 1 Day 21 or discontinue the treatment due to DLT.

A subject is considered to have met the minimum exposure criterion if in Cycle 1 the subject

has received ≥75% of the treatment (not necessarily consecutively). Subjects who do not meet these minimum safety evaluation requirements are considered to be ineligible for the dose-determining set. Determination of the MTD uses subjects eligible for the dose- determining set.

Pharmacokinetic analysis set: consists of all subjects who received at least one dose of investigational product and had at least one post-baseline pharmacokinetic assessment.

Immunogenicity analysis set: consists of all subjects receiving at least one dose of investigational product and having available ADA data.

Biomarker analysis set: consists of all subjects receiving at least one dose of investigational product and having available biomarker data.

All analysis sets will be determined before the database is locked.

10.2.2 Demographics and Baseline

Demographics and baseline profiles will be summarized in the safety analysis set, e.g. age,

gender, baseline disease characteristics, ECOG status and prior anti-tumor therapeutic regimens. Baseline values refer to data obtained in the last measurement prior to administration of the first dose of the investigational product.

Continuous data will be summarized using descriptive statistics (mean, median, standard deviation and range), and frequencies and percentages will be described for categorical data.

10.3. SAFETY ANALYSIS

Adverse events and toxicities will be evaluated according to NCI-CTCAE v5.0. Safety assessment will be conducted through medical review of adverse events and laboratory values. The incidence of DLT in the DLT population will be evaluated by dose group.

Treatment emergent adverse events (TEAE) will be summarized by preferred term, system organ class, NCI-CTCAE severity grade and causality with investigational product.

TEAE is defined as (regardless of severity)

- Any adverse event following initiation of treatment
- Adverse event that exists at the time of initiation of treatment but begins to worsen following initiation of treatment
- Adverse event that has occurred and remitted prior to treatment but recurs following initiation of treatment

Vital signs (including weight changes) and clinical laboratory values will be descriptively summarized by dose. ECG data will be evaluated and any abnormality will be listed. A tabular listing and summary of subjects in whom treatment with the investigational product is discontinued due to AE will be provided. A listing of death data will be provided.

10.4. EFFICACY ANALYSIS

Response based on investigators' assessment will be collected while on study every 9 weeks within 1 year, and every 12 weeks thereafter according to RECIST v1.1.

- **Objective Response:** The number and proportion of subjects who achieve objective tumor response (CR or PR) will be summarized. Objective response rate will be determined along with 95% confidence interval.
- **Progression Free Survival (PFS):** PFS is defined as the time from the date of first study dose to disease progression or death (whichever occurs first). Subjects without event (no disease progression or death) will be censored at the date of "last tumor assessment". Kaplan-Meier methodology will be used to estimate median PFS, PFS rate at various time points, and their 95% confidence intervals. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.
- **Duration of Response:** Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). For subjects who are alive without progression following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment or last follow-up for progression of disease.
- **Time to Progression (TTP):** TTP is defined as the time from the date of first study dose to disease progression. Subjects without event (no disease progression) will be censored at the date of "last tumor assessment". Kaplan-Meier methodology will be used to estimate median TTP and 95% confidence interval.
- **Disease Control Rate:** Disease control rate (DCR) is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v1.1.
- **Overall Survival:** Overall survival is defined as the time interval between the date of the first investigational product dose to the date of death from any cause.

  Kaplan-Meier methodology will be used to estimate median OS, OS rate at various time points, and their 95% confidence intervals.

10.5. PHARMACOKINETIC ANALYSES

Pharmacokinetic parameters will be analyzed by standard non-compartmental methods with Phoenix WinNonlin (Version 6.3 or higher). Actual sampling times will be used in the final PK parameter calculations.

PK parameters will include but not limited to:

Single dose: peak concentration ($C_{max, single}$), time to maximum serum concentration (T_{max}), area under the concentration-time curve after drug administration ($AUC_{0-\tau}$);

Repeated dose: peak concentration ($C_{max, ss}$) at steady state, trough concentration ($C_{trough, ss}$) at steady state, area under the concentration-time curve ($AUC_{\tau, ss}$), clearance rate at steady state (CL_{ss}/F (BLU-554), CL_{ss} (CS1001)).

In order to evaluate the extent of accumulation after repeated doses, accumulation ratio will be calculated as below formulas:

Accumulation coefficient of AUC = $AUC_{\tau, ss}/AUC_{0-\tau}$

Accumulation coefficient of C_{max} = $C_{max, ss}/C_{max, single}$

Where, $ALU_{0-\tau}$ for BLU-554 and CS1001 refers to $AUC_{0-24h,\ single}$ and $AUC_{0-21d,\ single}$ respectively, $AUC_{\tau,\ ss}$ refers to $AUC_{0-24h,\ ss}$ and $AUC_{0-21d,\ ss}$ respectively. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Summary statistics including number, arithmetic mean, SD, geometric mean and coefficient of variation will be calculated for all PK parameters (for $T_{max,}$ only median and range will be calculated).

10.6. IMMUNOGENICITY ANALYSES

Immunogenicity assessment data will be summarized by dose level, including:

Number and percentage of subjects with positive ADA assays at baseline

Number and percentage of subjects with at least one positive ADA assay at any time point following administration of the first dose

The relationship between CS1001 concentrations and ADA assessment results will be explored.

10.7. BIOMARKER ANALYSES

Measurement of biomarkers, such as the expression of FGF19 and PD-L1 in tumor cells and tumor-infiltrating immune cells prior to treatment, will be presented based on available data. The correlation between measurement of the above indicators and clinical outcomes (e.g., antineoplastic efficacy) will be described in graphical and tabular forms.

11. ETHICAL, REGULATORY AND OTHER REQUIREMENT

11.1. HEALTH AUTHORITY APPROVAL

The Sponsor will obtain approval from the appropriate regulatory authorities prior to initiating the study at study sites of this country, in accordance with the applicable country- specific regulatory requirements.

11.2. ETHICAL CONDUCT OF THE STUDY AND ETHICAL APPROVAL

This study will be conducted in accordance with (ICH)/ GCP and all applicable regulatory requirements, including, where applicable, the current Declaration of Helsinki. The investigator (or sponsor, if applicable) is responsible for obtaining the review and approval of the study protocol, informed consent form of site, and any other information provided to the potential subjects (e.g., advertisements or information supporting or supplementing the informed consent form). The investigator agrees that the Ethics Committee can obtain all relevant documents directly. The composition of the Ethics Committee must comply with all applicable regulatory requirements. The Sponsor will provide the investigator with relevant documents/ materials necessary for the review and approval of the study by the Ethics Committee.

If the study protocol, informed consent form or any other information that have been available for potential subjects after approval of the Ethics Committee, is revised during the study, the investigator will be responsible for ensuring the approval of the Ethics Committee for these amendments (if applicable). The investigator must comply with all applicable regulatory requirements regarding the use of the revised informed consent form, including access to prior

approval of the revised informed consent form by the Ethics Committee before a new subject uses a new form to agree to participate in the study. The approval for revised ICF/ other information from the Ethics Committee and copies for approved revised ICF/

other information must be sent to the applicant in a timely manner.

11.3. INFORMED CONSENT PROCESS

The principal investigator at each site will:

- Ensure that each subject is provided with complete and adequate oral or written information about the nature, purpose, possible risks and benefits of the study.
- Ensure that each subject knows he/she can voluntarily discontinue the study at any time.
- Ensure that each subject is given an opportunity to ask questions and given the appropriate explanation by the investigator, and given sufficient time to consider the information provided.
- Ensure that each subject provides signed and dated informed consent forms prior to performing any study-related procedure.
- Ensure that the original signed informed consent form is maintained in the investigator's study file.
- Ensure that a copy of the signed informed consent form is provided to the subject.

11.4. CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

The study procedures may be modified only after the principal investigator is in consultation with the sponsor.

If there are any significant changes to the study protocol, these changes must be documented in the amendment of the latest clinical study protocol if needed. The amendment should be approved by the appropriate Ethics Committee and national regulatory authorities (if applicable) prior to implementation. The protocol amendment should comply with local requirements. The sponsor will issue the latest version of the protocol and any amendment to each principal investigator.

If a modification to the site's Informed Consent is required for the protocol amendment, the sponsor and the Ethics Committee of the site will approve the informed consent amendment prior to using it. If requested by local authorities, any administrative change should be informed to and approved by each ethics committee.

11.5. PROTOCOL ADHERENCE AND DEVIATION

Please read the protocol completely and follow the instructions. Exceptions can be made, however, in emergency situations where the investigator or trained study personnel believe there is a need for immediate intervention for the protection, safety and well-being of the subject.

In case of major protocol deviations due to emergency, accident or negligence, the investigator or designee must contact the medical monitor by telephone at earliest convenience. This makes a decision on whether or not the subject should continue the study as early as possible. The investigator, sponsor, and medical monitor will document the decision.

11.6. STUDY CLOSURE

At the end of the study, the monitor will perform the following activities with the investigator or study site personnel (if applicable):

- Return all study data to the sponsor.
- Data queries.
- Count, verification and disposition of study drugs not used.
- Check the integrity of the study records.
- Return all treatment numbers to the sponsor.
- Sending PK samples to the testing laboratory.

In addition, the sponsor will reserve the right to suspend or permanently discontinue clinical trials at a study site or all sites at any time, including, but not limited to, for the reason of safety, ethical issues, or serious non-compliance. If the sponsor decides to take this action, the sponsor will fully discuss with the investigator (including the reason for action). If feasible, the sponsor will inform the investigator in advance of the measures taken.

In the event of suspension or termination of the study for safety reasons, the sponsor will promptly inform all other participating investigators and/ or the study sites and will inform the regulatory authorities of the suspension or termination of the study and reasons for this action. If required by applicable regulations, the investigator must inform the Ethics Committee in a timely manner and provide reasons for suspension or termination.

All study data must be returned to the sponsor if the study is terminated prematurely. In addition, all unused study drugs will be disposed of according to the sponsor's study-related procedures.

Corresponding financial compensation will be provided to the investigator and/or site according to the agreement between the investigator and the sponsor.

11.7. RECORDS RETENTION

Following closure of the study, the investigator must maintain all study records in a safe and secure location. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site, as dictated by any site requirements or local laws or regulations, or the sponsor’s standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the

records in the event that the investigator leaves the site.

11.8. CLINICAL STUDY REPORT

At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to Health Authority concerned and to Investigators.

11.9. CONFIDENTIAL AND PRIVACY

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their treatments. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All study activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IEC/IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC/IRB, institutional policies, or sponsor requirements.

11.10. PUBLICATION PRIVACY

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide the sponsor with a copy of the proposed publication and allow the sponsor a period of at least 30 days (or, for abstracts, at least 5 working days) to review the proposed publication. Proposed publications shall not include any sponsor information or any personal data on any subject other than the study results, such as name or initials.

At the sponsor's request, the submission or other disclosure of a proposed publication will be delayed a sufficient time to allow the sponsor to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply

rather than this statement.

11.11. INSURANCE, REIMBURSEMENT AND COMPENSATION

CStone holds and will maintain an adequate insurance policy covering damages arising out of CStone's sponsored clinical studies.

CStone will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.

The Investigator must notify CStone immediately in case of any claims or lawsuits.

11.12. *(PREMATURE)* TERMINATION OF THE STUDY

- Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.
- Premature termination of this study may occur as the result of a Health Authority decision, change in opinion of the IRB/EC, or investigational product safety problems. In addition, CStone retains the right to discontinue development of this investigational product at any time.

If a study is prematurely terminated, CStone will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within (a time period set by CStone). As directed by CStone, all study materials must be collected and all eCRFs completed to the greatest extent possible.

12. ABBREVIATIONS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Disease
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ATP	Adenosine triphosphate
AST	Aspartate aminotransferase
AUC	Area under the serum concentration
BCLC	Barcelona clinic liver cancer
β-hCG	Beta - human chorionic gonadotropin
BID	Bis in die
BSC	Best supportive care
C	Cycle
CBC	Complete blood count
CL	Clearance
CNS	Central nervous system
C_{max}	Maximum observed serum concentration
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
C_{trough}	Minimum observed serum concentration
CYP3A4	Cytochrome P450 3A4
CYP7A1	Cholesterol 7-alpha hydroxy-lase
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
EASL	European Association for the Study of the Liver
EC_{50}	Effective concentration for 50% of maximal activity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCCI	Electronic case report form completion guidelines
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
ERK	Extracellular signal-regulated kinase
FGF	Fibroblast growth factor
FGFR4	Fibroblast growth factor receptor 4
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure

Abbreviation	**Definition**
ICC	Intrahepatic cholangiocarcinoma
ICF	Informed consent form
IHC	Immunohistochemistry
INR	International normalized ratio
irAE	Immune-related adverse event
MTD	Maximum tolerated dose
Nab	Neutralizing antibody
NCI-CTCAE	NCI Common Terminology Criteria for Adverse Event
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death factor ligand-1
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Peros
PR	Partial response
PS	Performance status
PT	Prothrombin time
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SMC	Safety monitoring committee
t½	Half-life
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
UNL	Upper normal limit
V_{ss}	Apparent volume of distribution at steady state

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14. APPENDIX

14.1. [redacted]

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14.2. APPENDIX 2: THE LATEST REVISED RECIST GUIDANCE (VERSION 1.1)

The following text is from: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1).

Definition

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable lesion

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Unmeasurable lesion

All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subject to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

- During the assessment at baseline, all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and be recorded and measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that are subject to reproducible repeated measurements.

- Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

- 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 diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record

multiple non-target lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph node” or “multiple liver metastases”).

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are above the upper normal limit at baseline, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has

developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be

present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the subject also has measurable disease: In this setting, for the determination of "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease: This circumstance arises in some Phase III trials when it is not one of the inclusion criteria to have measurable disease. The same general concept as noted above applies here, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen,

the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some evaluations of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal

  FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the investigational product treatment until the end of treatment taking into account any requirement for confirmation. On occasion that a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings

of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the subject is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered unevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-	No	PR
CR	PD Not	No	PR
PR	evaluated Non-	No	PR
	PD or not all evaluated		
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
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; and PD = progressive disease.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment

without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and in-evaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure that the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized clinical trials (phase II or III) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of review by the sites to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of subjects achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

14.3. APPENDIX 3: GUIDANCE FOR IMMUNE-RELATED ADVERSE REACTIONS MANAGEMEMT

Identification, diagnosis, management of immune-related adverse events and dose adjustment method are listed in detail as following:

irAE	**Potential signs and symptoms**	**Diagnosis and differential diagnosis**	**Recommended management**	**Dose modification**
Pneumonitis	Symptomatic: dyspnea, cough, pleuritic chest pain, hypoxia Asymptomatic: lung infiltrates that mimic severe bacterial pneumonia	• Radiographic imaging of chest • Observe the specimen of tissues and lavage fluids used in bronchoscopy to investigate infectious pathogens and perform a pathologic evaluations on them	Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold the administration of CS10[redacted] until resolved to ≤ Grade 1
			Severe (≥ Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; in-patient hospitalization; consultation with a respiratory physician; additional immunosuppression with infliximab can be considered	Permanent discontinuation from the study
Colitis	Watery diarrhea, mucus or blood in stool, abdominal pain, nausea/vomiting, dehydration, peritoneal signs, bowel perforation	• Stool cultures • Endoscopy or colonoscopy to rule out infection • Biopsy to rule out alternative etiology	Moderate (≤Grade 2) diarrhea: antidiarrheal medication, oral hydration, electrolyte supplement	Continue dosing
			Persistent Moderate (Grade 2) diarrhea: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold the administration of CS1001 until resolved to ≤ Grade 1
			Severe (Grade 3) diarrhea: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be	Withhold the administration of CS1001 until resolved to ≤ Grade 1

			considered for steroid refractory diarrhea	
			Recurrent severe (Grade 3) or life-threatening (Grade 4): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics;	Permanent discontinuation from the study

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			infliximab can be considered for steroid refractory diarrhea; in-patient hospitalization	
			If bowel perforation is suspected, steroid should be withheld, and surgical opinion should be explored; in-patient hospitalization; Infliximab should not be administered	Permanent discontinuation from the study
Hepatitis	Symptomatic: fever, fatigue, nausea, abdominal pain, hepatomegaly, Asymptomatic: elevation of liver function tests (hepatic transaminases, bilirubin)	• Chemistry: elevated levels of hepatic transaminases • Serologic testing: should be performed to rule out viral hepatitis (including hepatitis A and B), cytomegalovirus, and Epstein-Barr virus • Ultrasonograms of the liver • Biopsy or radiologic	• Grade 2: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents • For subjects with liver metastasis or HCC who entered the study with Grade 2 elevation of AST/ALT, investigational drug will be withheld if AST/ALT increase ≥ 50% relative to baseline.	Withhold the administration of CS1001 until resolved to ≤ Grade 1

		imaging to distinguish from other etiologies of hepatic injury, such as neoplastic disease progression in the liver, infections, and effects of other medications or alcohol intake	• Severe (≥ Grade 3): administration of high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); if not improved after 48-72 hours, alternative immunosuppression agents (mycophenolate mofetil) should be considered; in-patient hospitalization; consultation with a hepatologist • For subjects with liver metastasis or HCC who entered	Permanent discontinuation from the study

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			the study with Grade 2 elevation of AST/ALT, investigational drug will be permanently discontinued if AST/ALT increase ≥ 50% relative to baseline and lasting ≥1 week • Total serum bilirubin >3 times upper limit of normal	
Hypophysitis	Headache refractory to nonsteroidal anti-inflammatory drugs or other analgesics; weakness; fatigue, weight gain or weight loss; changes in mood or behavior; hypotension; electrolyte disturbances; abdominal pain; loss of libido; adrenal crisis; hypogonadism	• Clinical chemistry tests • Endocrinologic laboratory test, ACTH, thyroid function test, • Magnetic resonance imaging (MRI) of the brain: enlargement of the pituitary with variable contrast enhancement characteristics	Grade 2 without adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); initiate appropriate hormone replacement therapy; consultation with an endocrinologist	Withhold the administration of CS1001 until resolved to ≤ Grade 1
			Severe (≥ Grade 3) or adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); consultation with an endocrinologist	Permanent discontinuation from the study
Nephritis	Hematuria, peripheral edema, elevated serum creatinine	• Clinical chemistry tests • Urine test • Biopsy if necessary	Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold the administration of CS1001 until resolved to ≤ Grade 1

			Severe (≥ Grade 3): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Permanent discontinuation from the study
Hypothyroidism /hyperthyroidism	Typically asymptomatic and is identified by lab tests	T3, T4, TSH test results	Asymptomatic Moderate (≤ Grade 2) hypothyroidism: thyroxine replacement therapy	Continue dosing
			Asymptomatic Moderate (≤ Grade 2)	Continue dosing

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			hyperthyroidism: consider beta blockade	
			Severe (≥ Grade 3) hypothyroidism: replacement therapy	Withhold the administration of CS1001 until resolved to asymptomatic Grade 2 or ≤ Grade 1 or baseline
			Severe (Grade 3) hyperthyroidism lasting ≥ 6 weeks despite active management: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold the administration of CS1001 until resolved to asymptomatic Grade 2 or < Grade 1 or baseline
			Life-threatening (Grade 4) hyperthyroidism	Permanent discontinuation from the study
Dermatitis	Maculopapular rash or erythroderma, pruritus, skin ulceration, bullous dermatitis, Stevens-Johnson syndrome	• Unless an alternative etiology is identified, it should be considered immune-related • Pathologic evaluation of skin biopsy can be performed to rule out alternative etiology	Moderate (≤ Grade 2, up to 30% of body surface area): topical corticosteroids and oral over-the-counter antihistamines and systemic corticosteroids if no improvement within 7 days	Continue dosing
			Severe (Grade 3, > 30% of body surface area): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold the administration of CS1001 until resolved to ≤ Grade 2

			Life-threatening (Grade 4, Stevens-Johnson syndrome, toxic epidermal necrosis, full-thickness dermal ulceration, necrosis or hemorrhage): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); in-patient hospitalization; consultation with a dermatologist	Permanent discontinuation from the study
Neuromuscular toxicity	Peripheral sensory	• Physical exam	Moderate (≤ Grade 2): administration of	Withhold the administration of

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
	neuropathy, muscle weakness, Guilliain-Barre syndrome, transverse myelitis, myasthenia gravis	of sensory change, loss of deep-tendon reflexes • Neuroimaging, nerve conduction exam, • Nerve/muscle biopsy	corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	CS1001 until resolved to ≤ Grade 1
			Severe (≥ Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study
Ocular toxicity	Photosensitivity, pain or dryness of the eyes, blurred vision, uveitis, iritis, episcleritis	• ophthalmic exam	Moderate (≤ Grade 2): topical steroids (1% prednisolone)	Withhold the administration of CS1001 until resolved to ≤ Grade 1; if not resolved ≤ Grade 1 within 14 days with topical steroids or initiation of systemic treatment, permanent discontinuation from the study
			Severe (≥ Grade 3): high dose systemic corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study
Other irAEs, such as arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis			Moderate (Grade 2)	Withhold the administration of CS1001 until resolved to ≤ Grade 1
			Severe (≥ Grade 3)	Permanent discontinuation from the study

14.4. APPENDIX 4: ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5:649-655.

14.5. PPENDIX 5: NEW YORK HEART ASSOCIATION (NYHA)

When there is a reasonable uncertainty that the symptoms or signs are not of cardiac origin, the diagnosis should be *No heart disease.*

Functional Capacity	**Objective Assessment**
Class I. Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A. No objective evidence of cardiovascular disease.**
Class II. Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B. Objective evidence of mild cardiovascular disease.**
Class III. Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C. Objective evidence of moderate cardiovascular disease.**
Class IV. Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D. Objective evidence of severe cardiovascular disease.**

*The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

14.6. APPENDIX 6: Effective Controception Methods

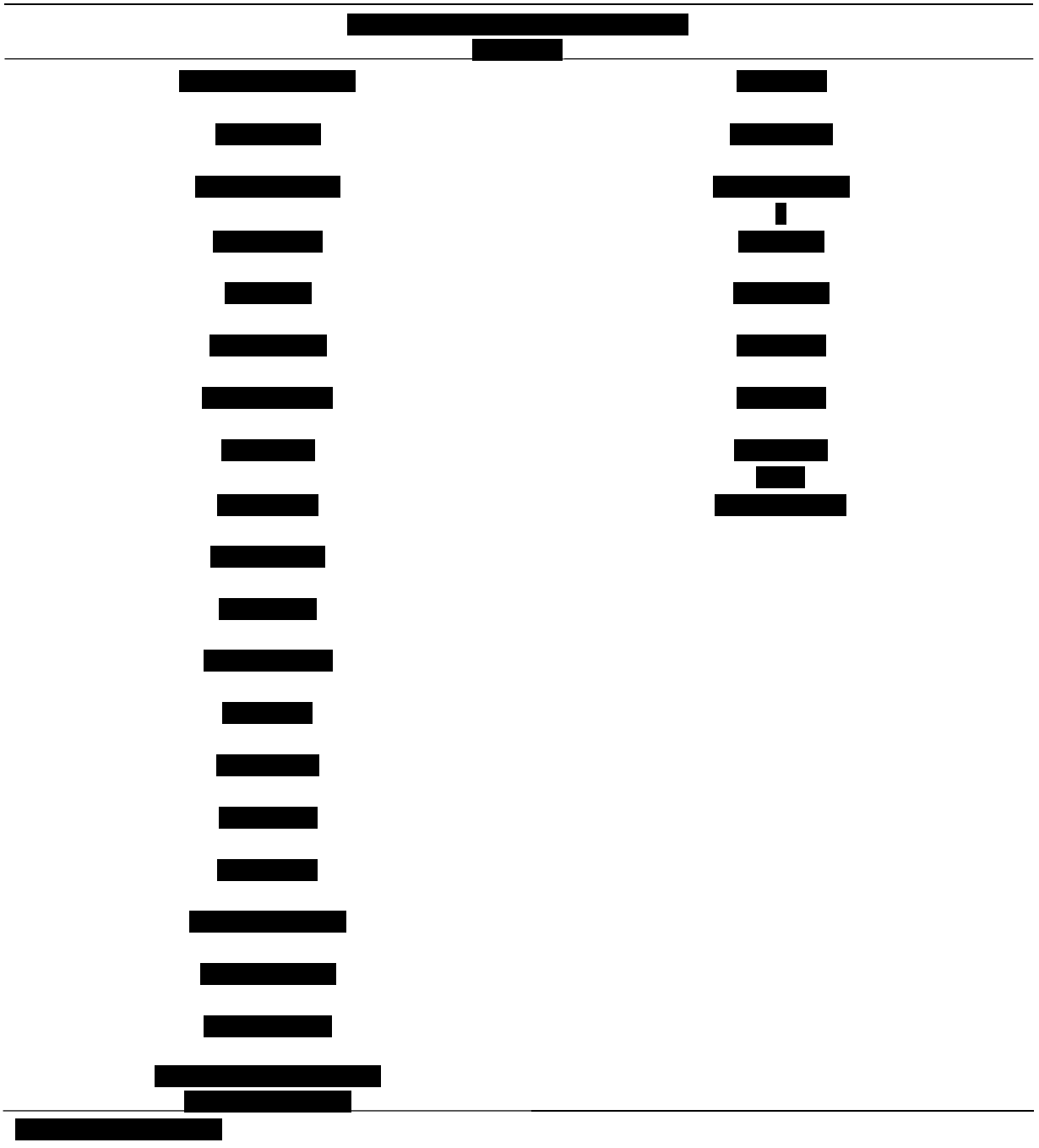
The following measures are considered to be effective conception methods:

- Diaphragm
- Intrauterine device
- Cervical cap
- Female condom
- Condom
- Spermicide

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]



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		data)	
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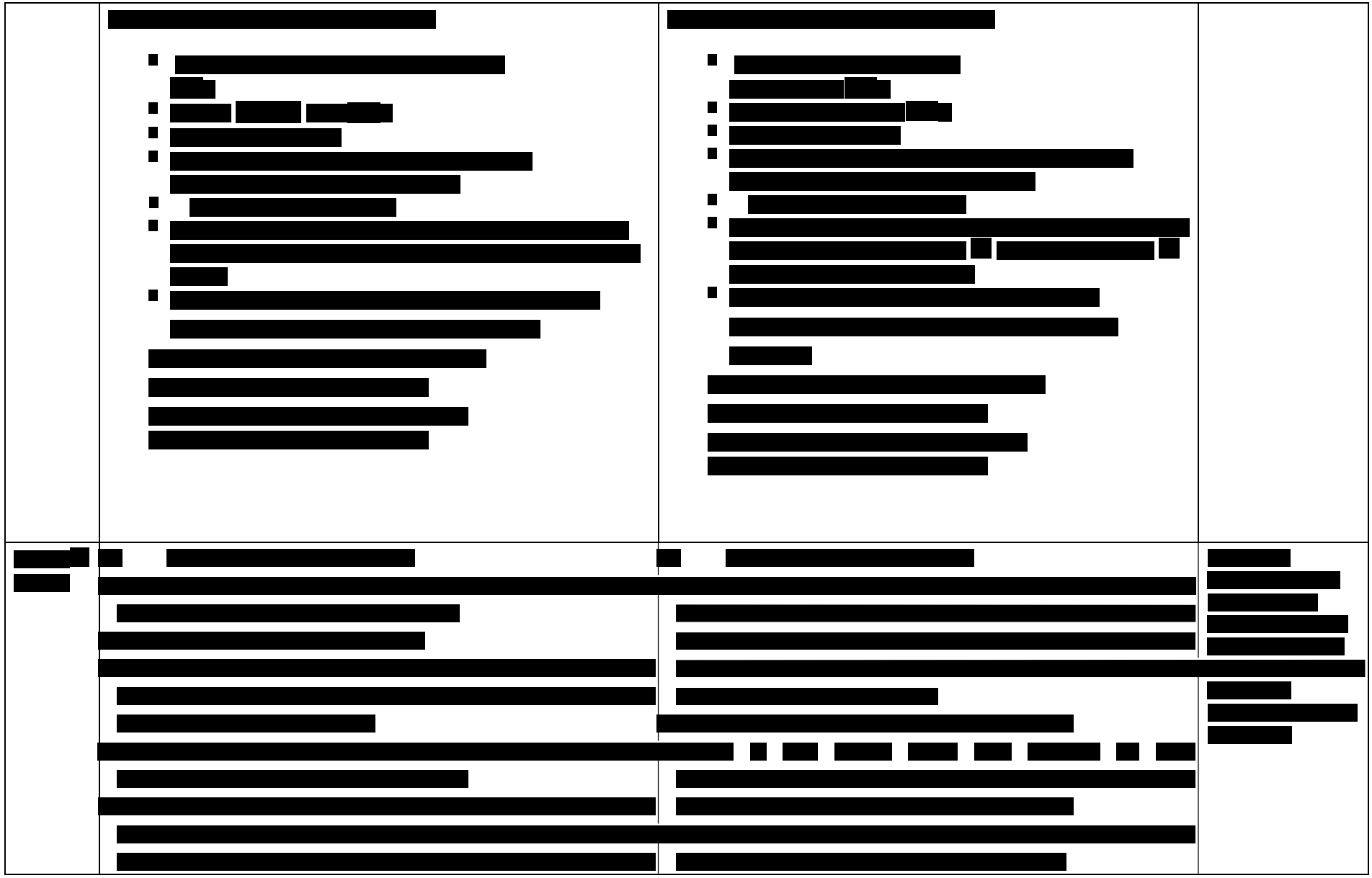

	[redacted]	[redacted]	
[redacted]	[redacted] [redacted] [redacted] | [redacted]	[redacted] [redacted] [redacted] | [redacted]	[redacted] study.

	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted] Immunogenicity Blood Sample [redacted] X AE Monitoring X	[redacted] Immunogenicity Blood Sample [redacted] X Subsequent anti-tumor therapy [redacted] X X X X AE Monitoring X	[redacted]
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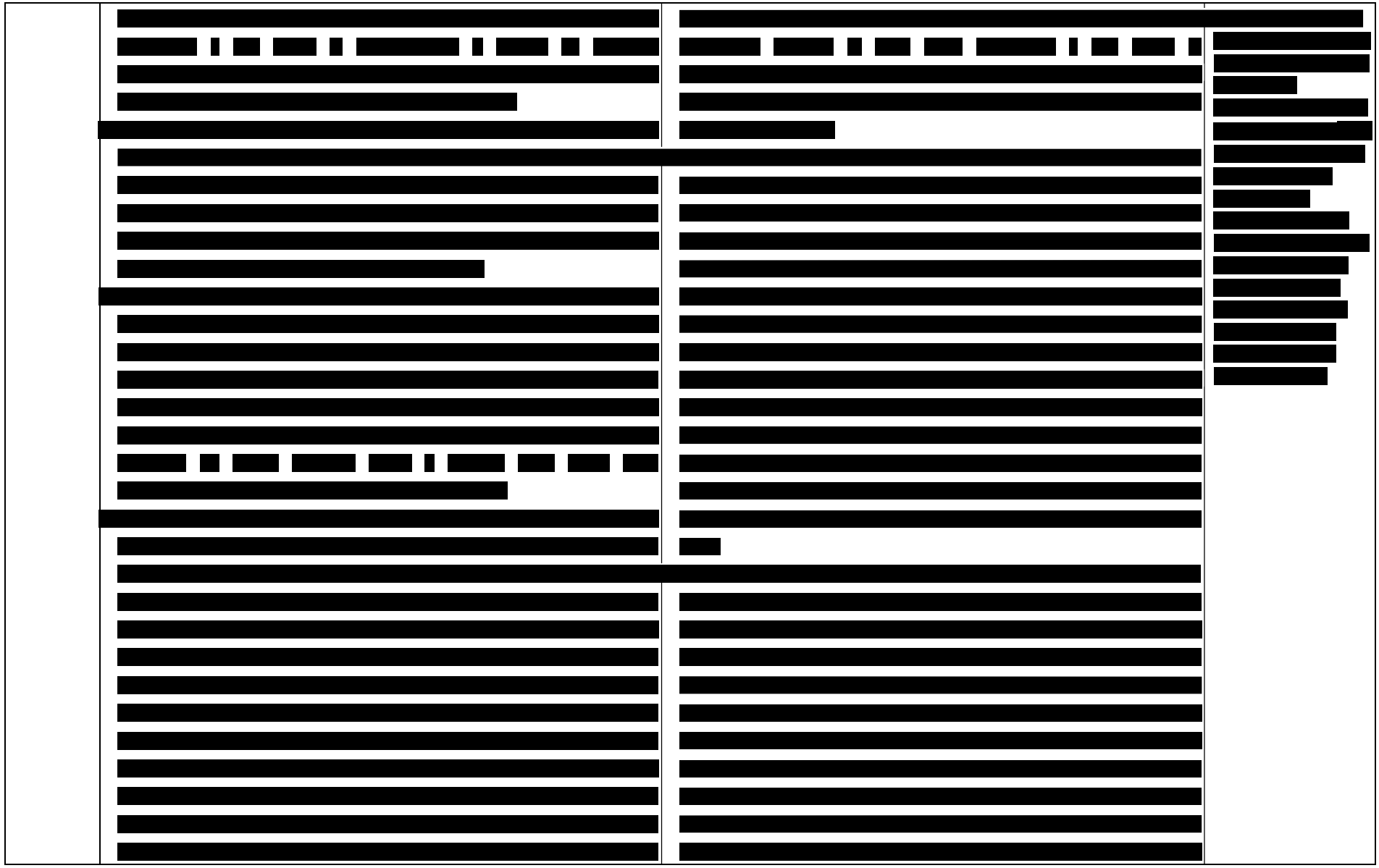

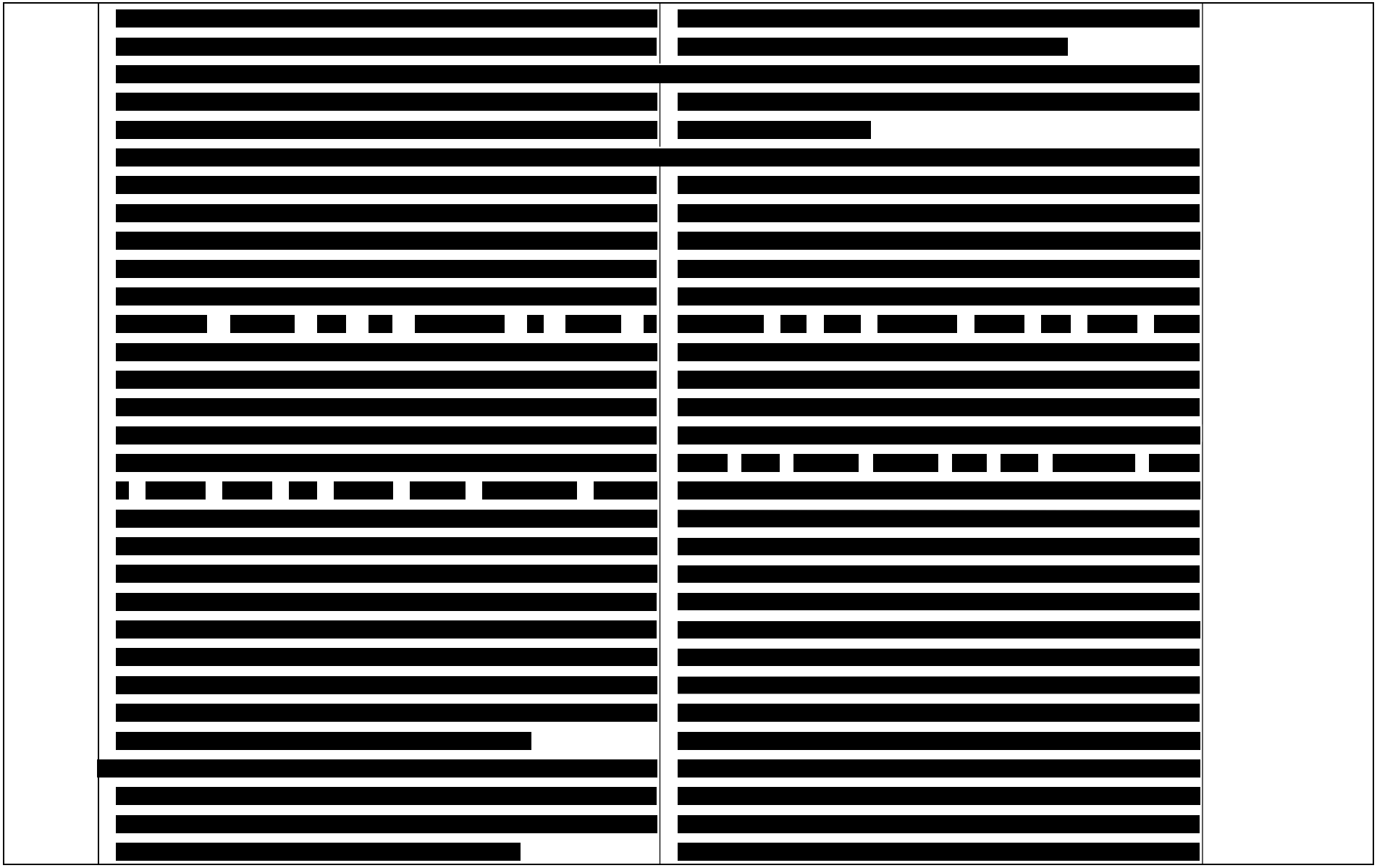

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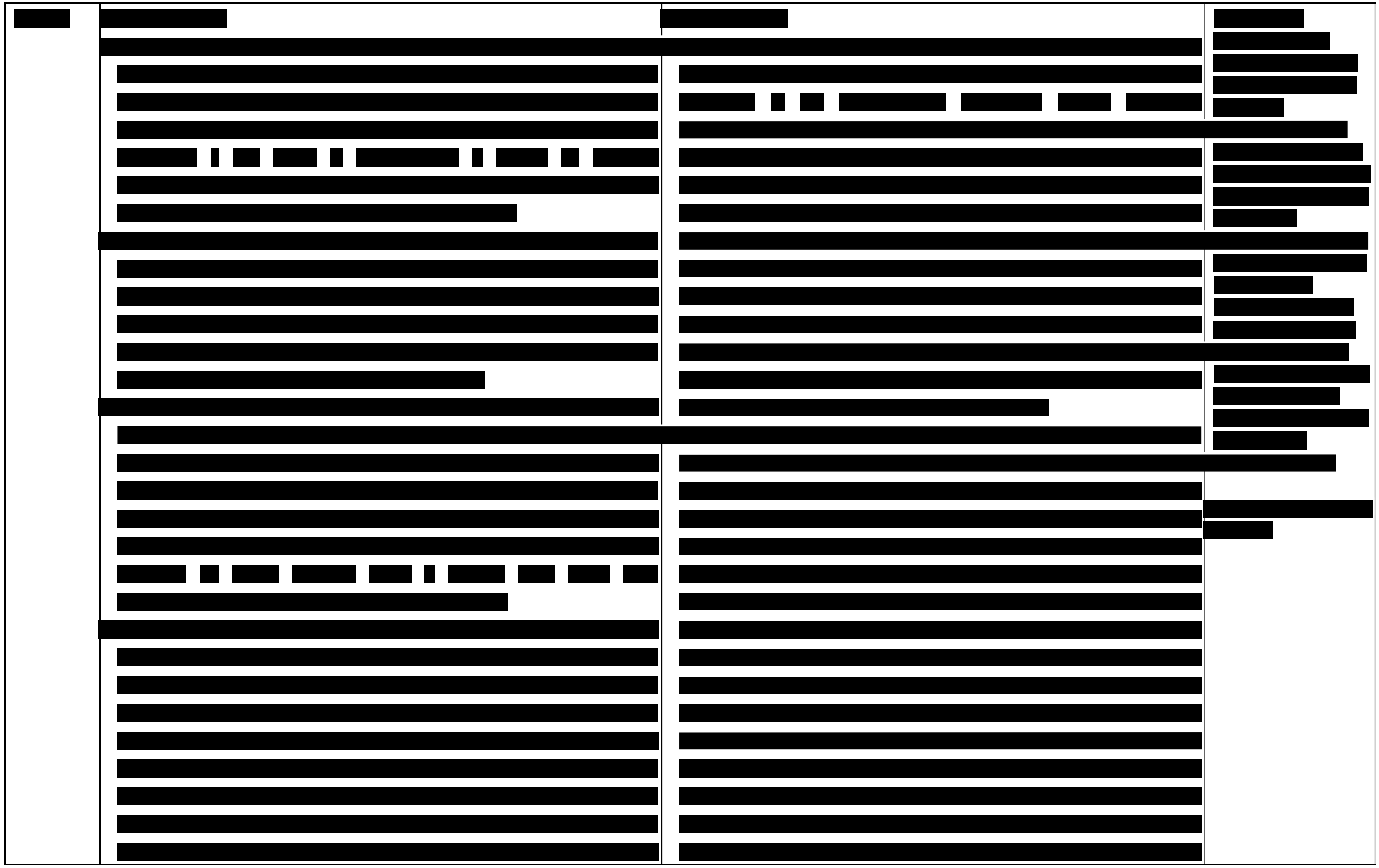

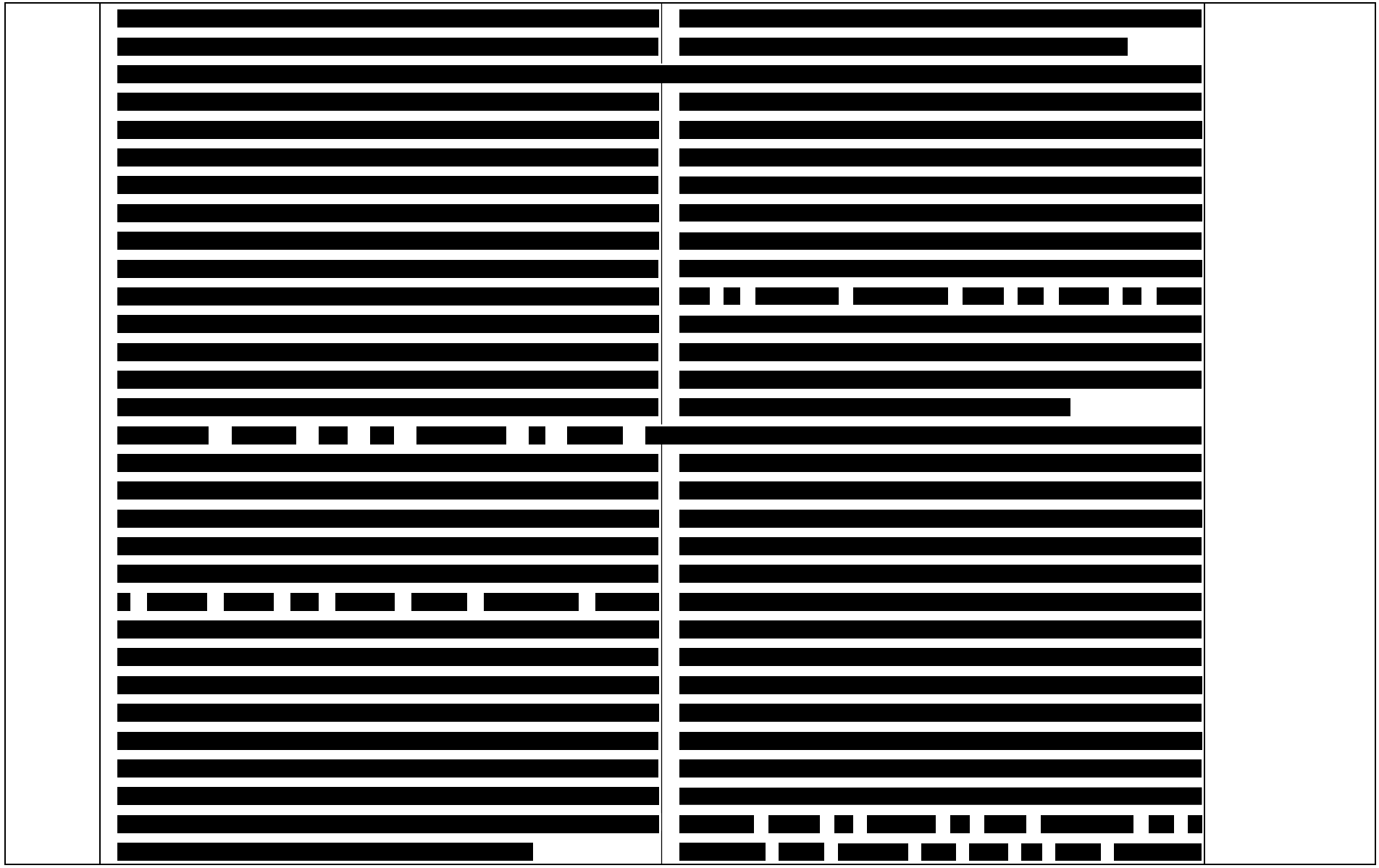

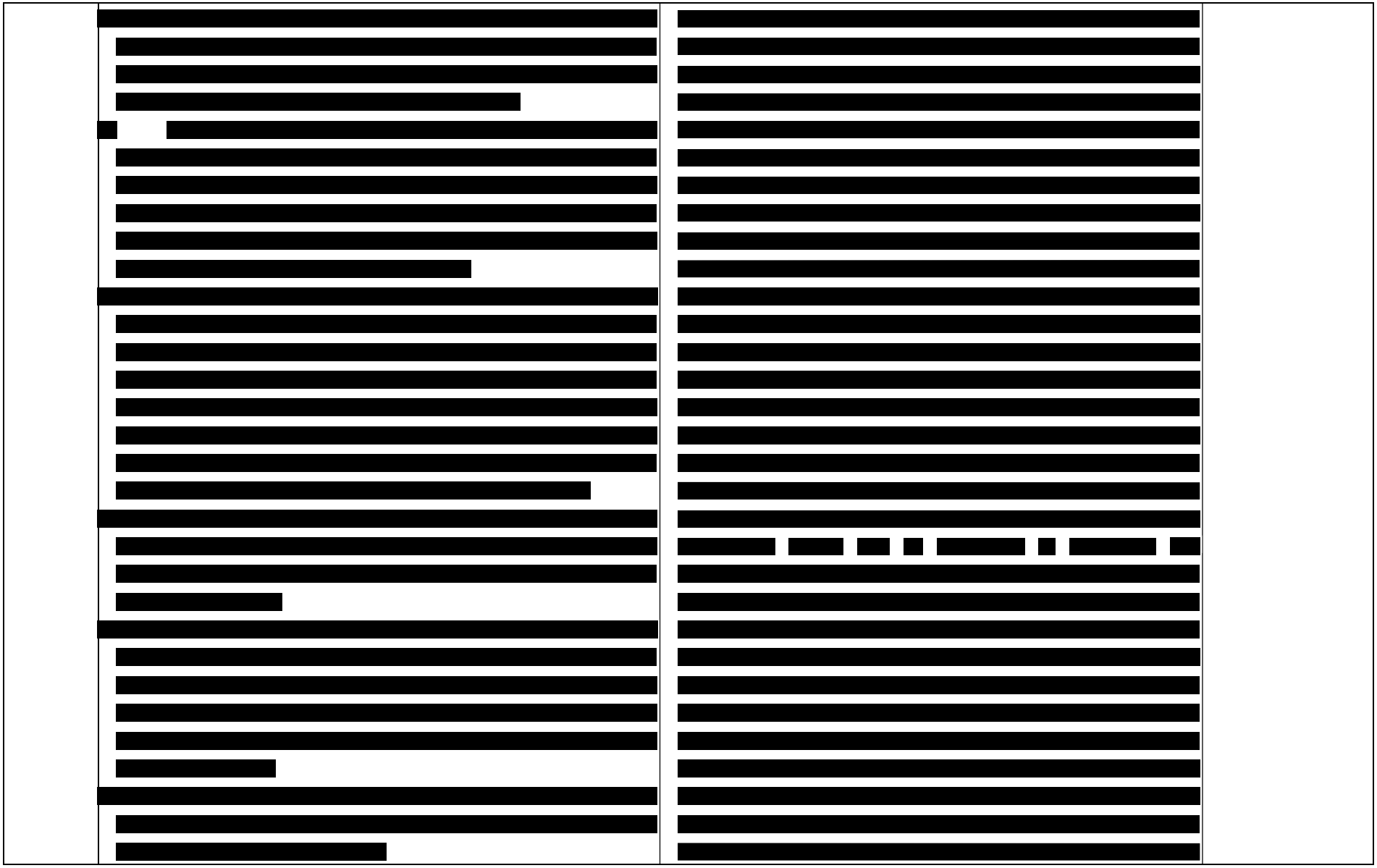

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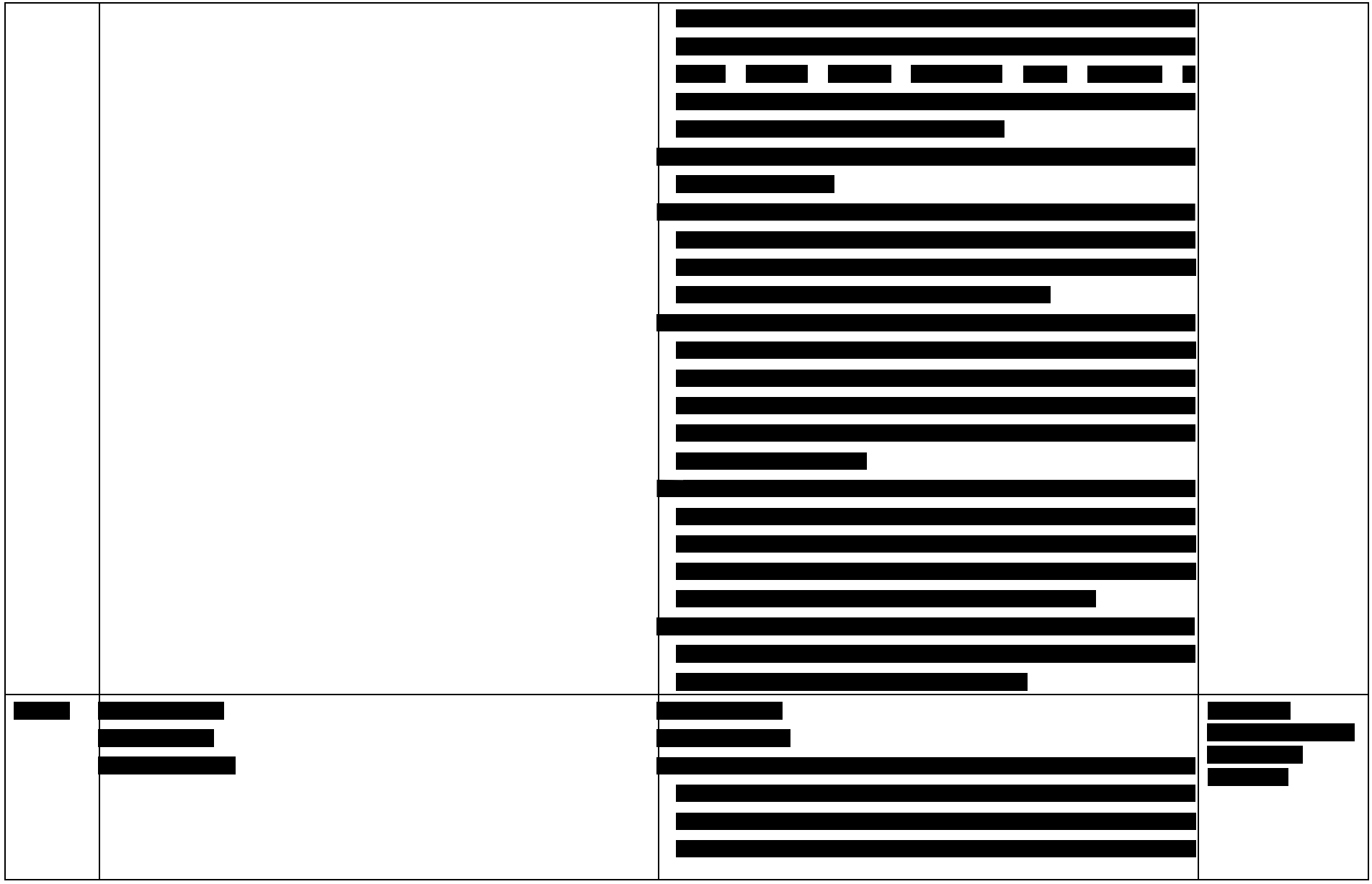

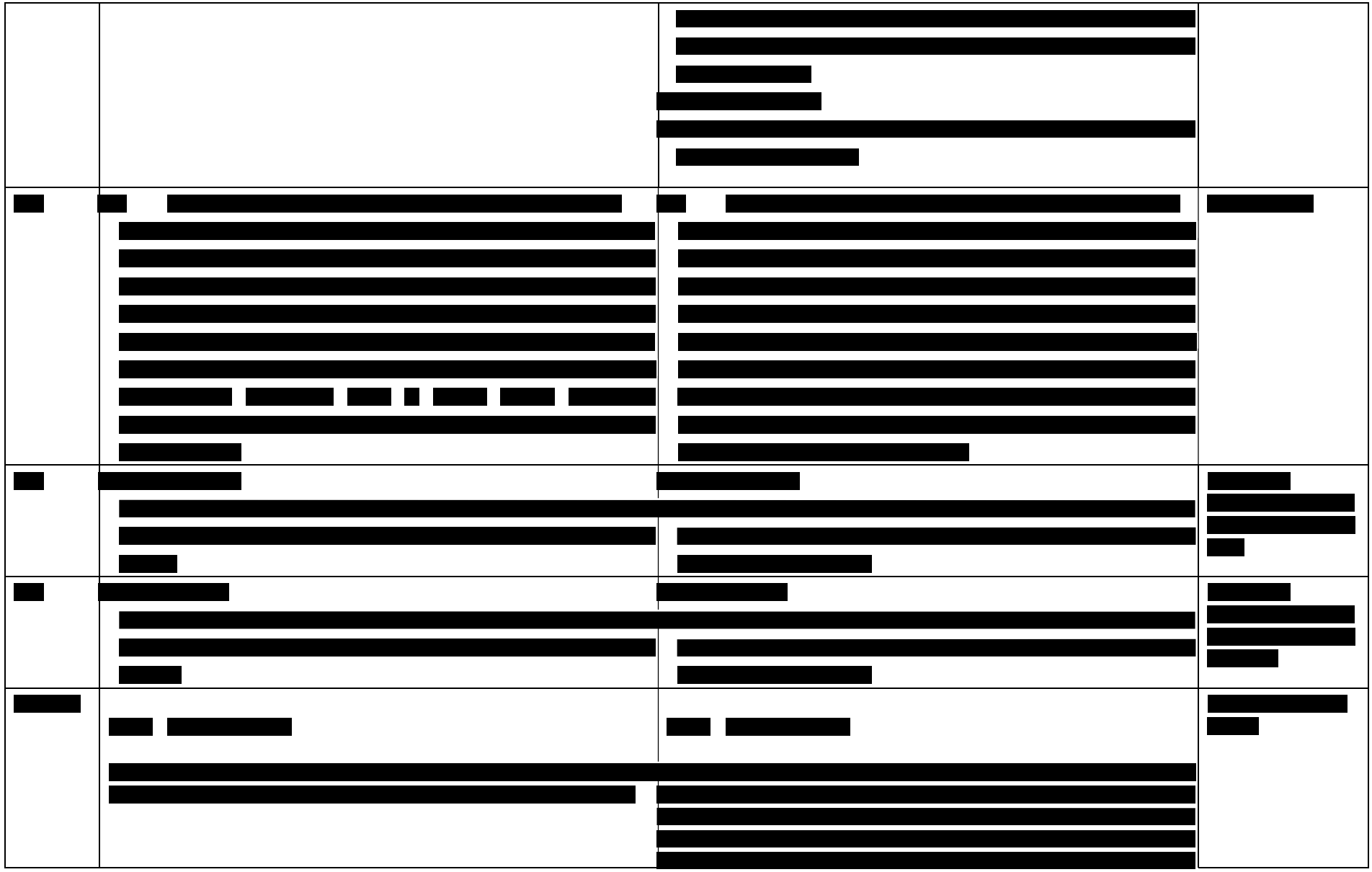

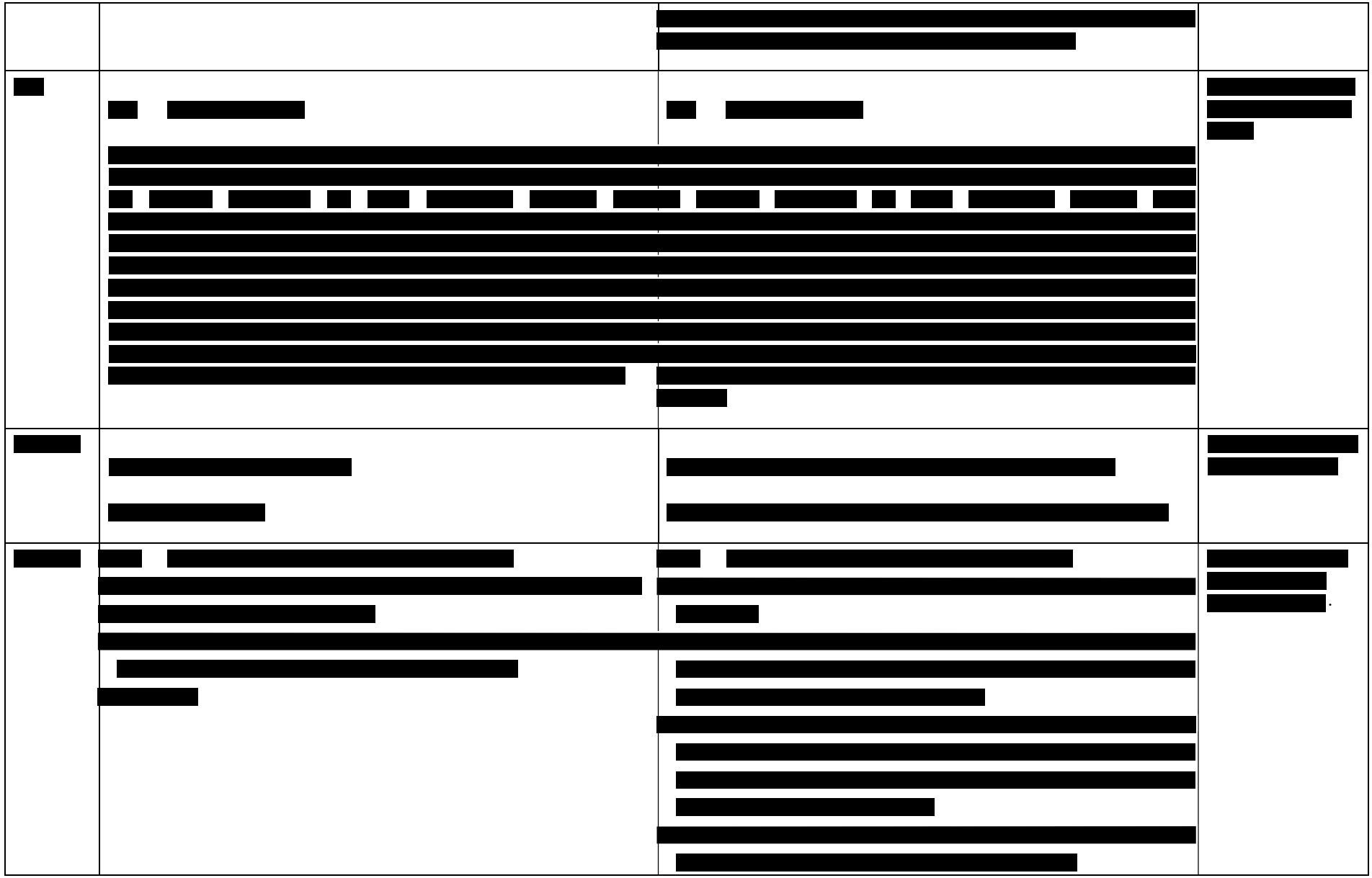

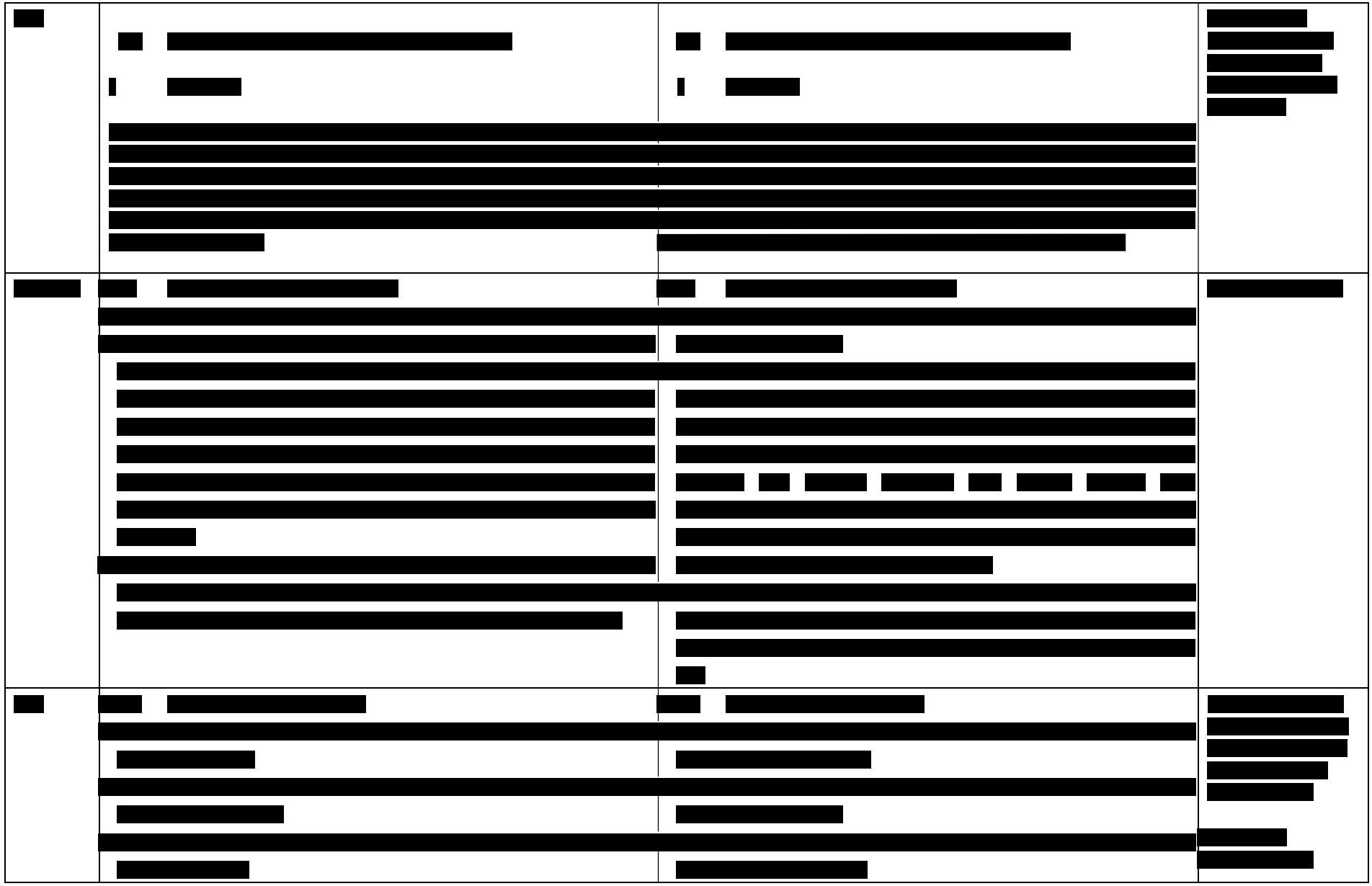

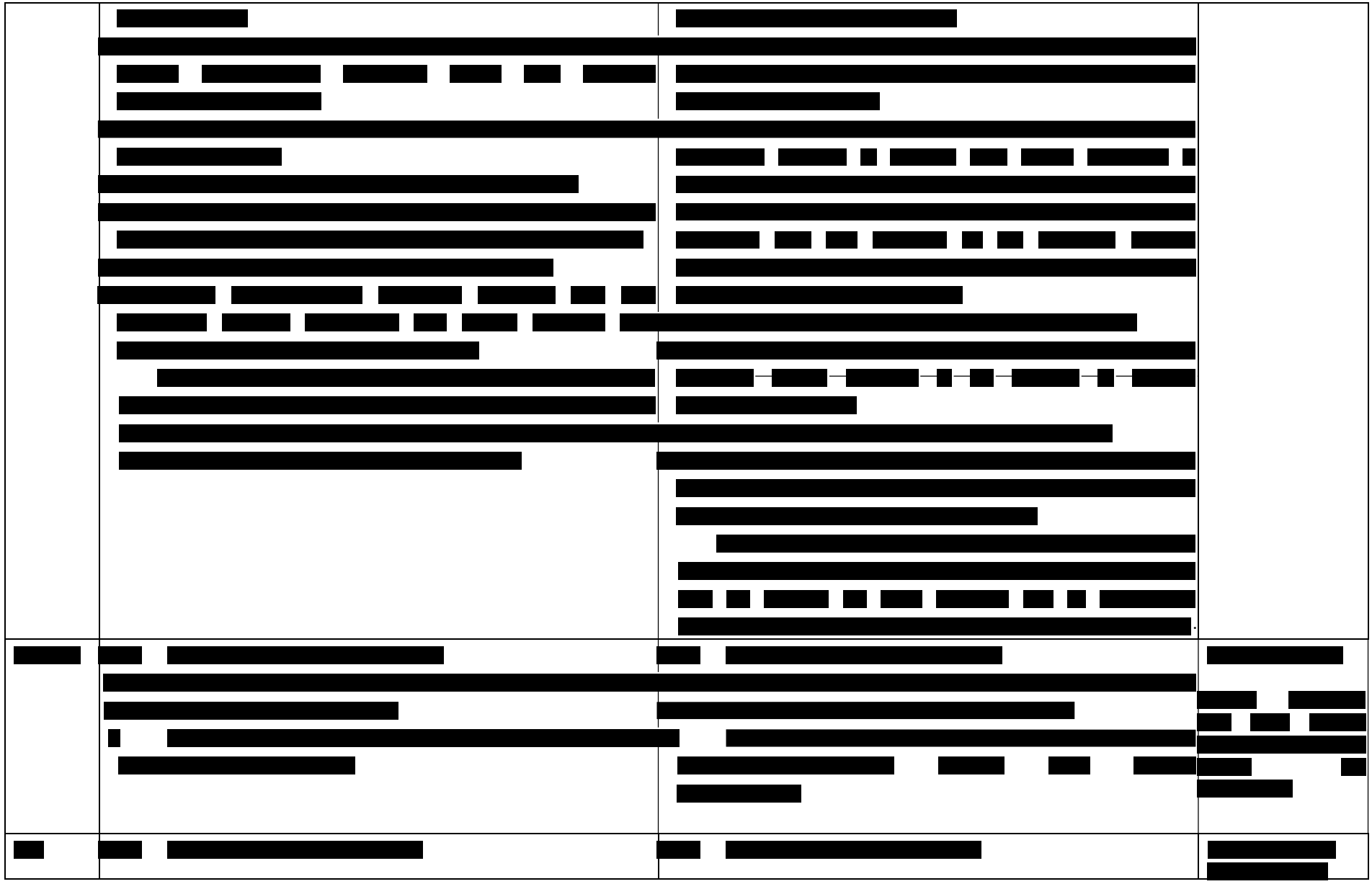

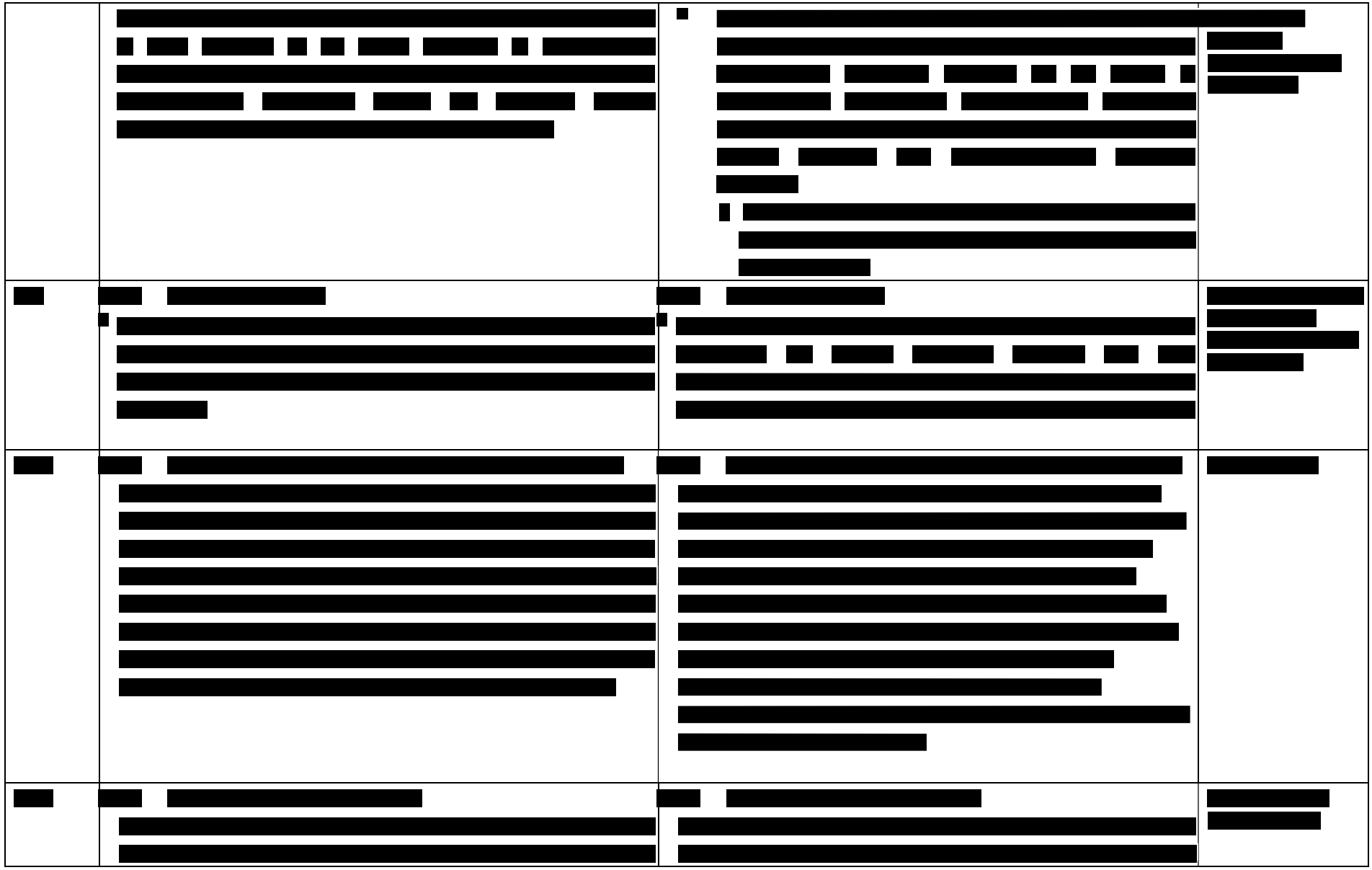

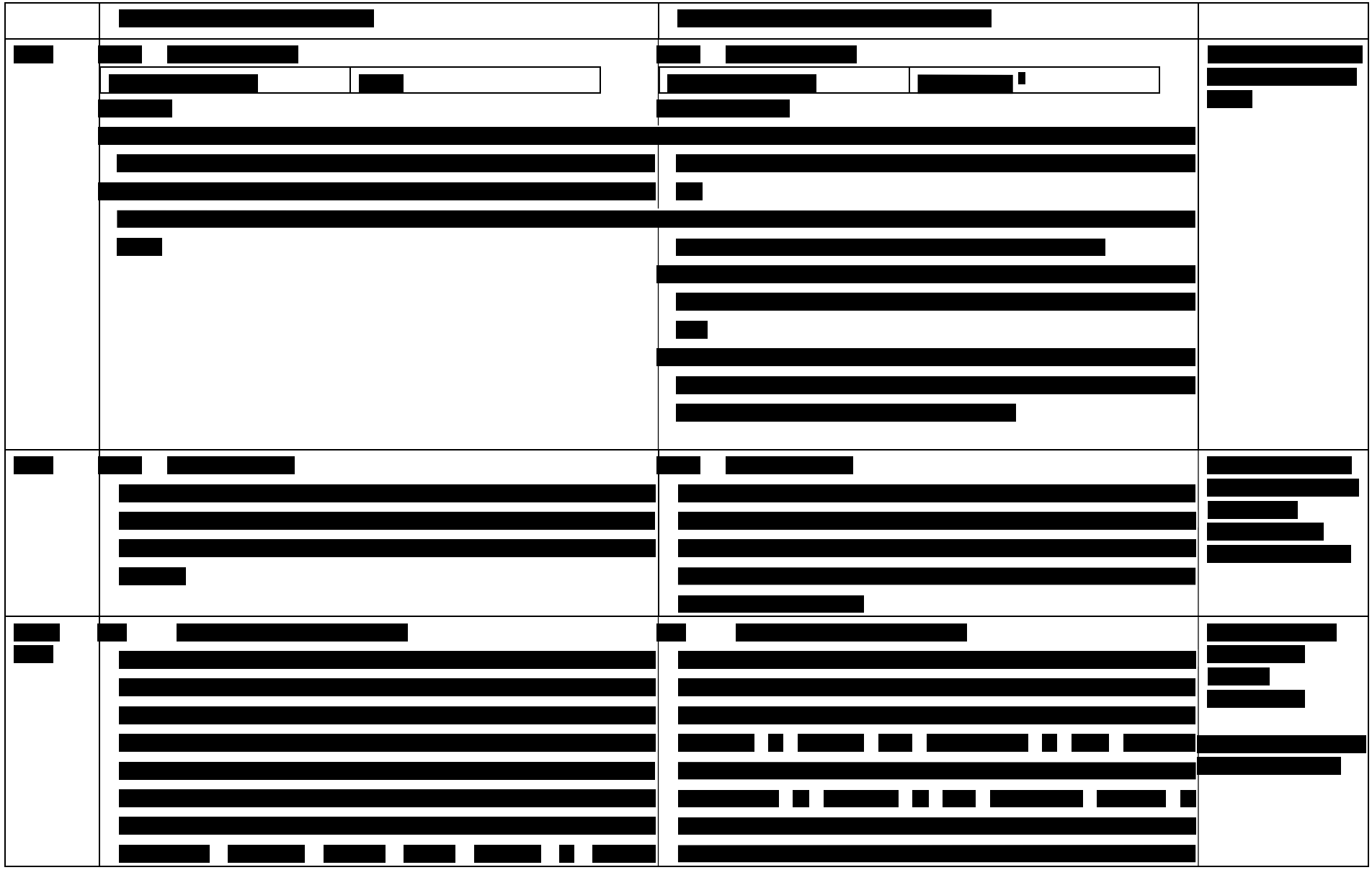

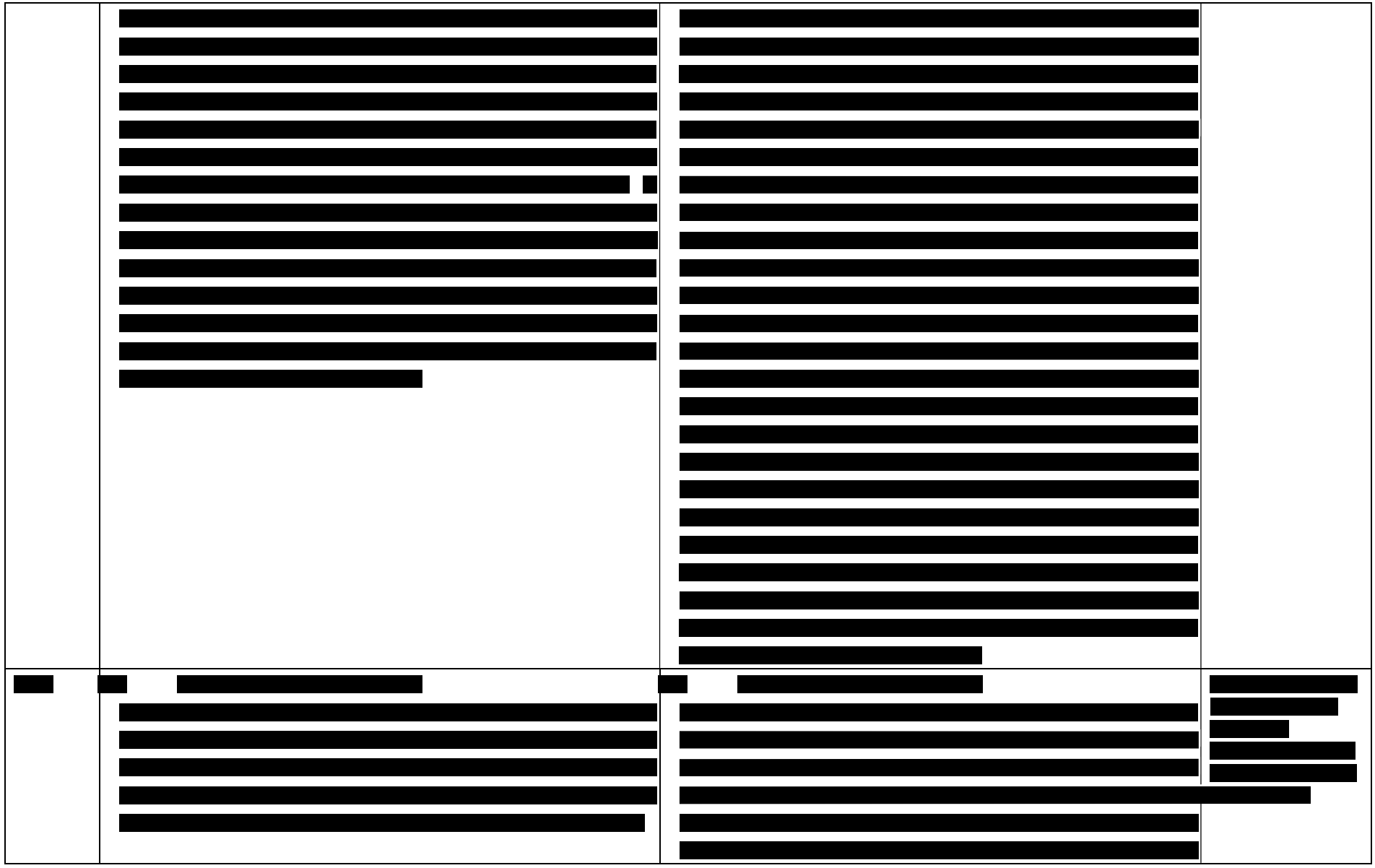

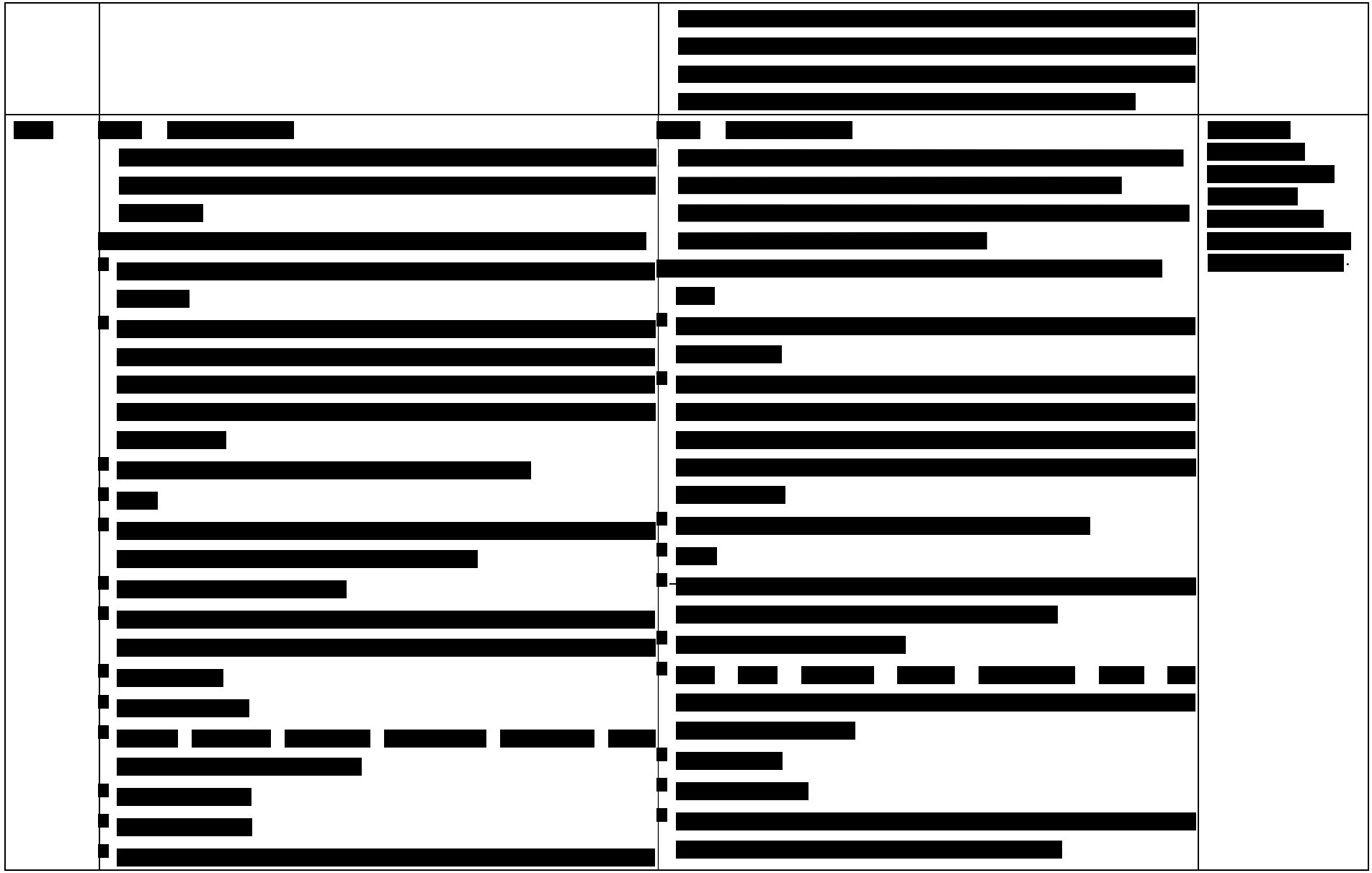

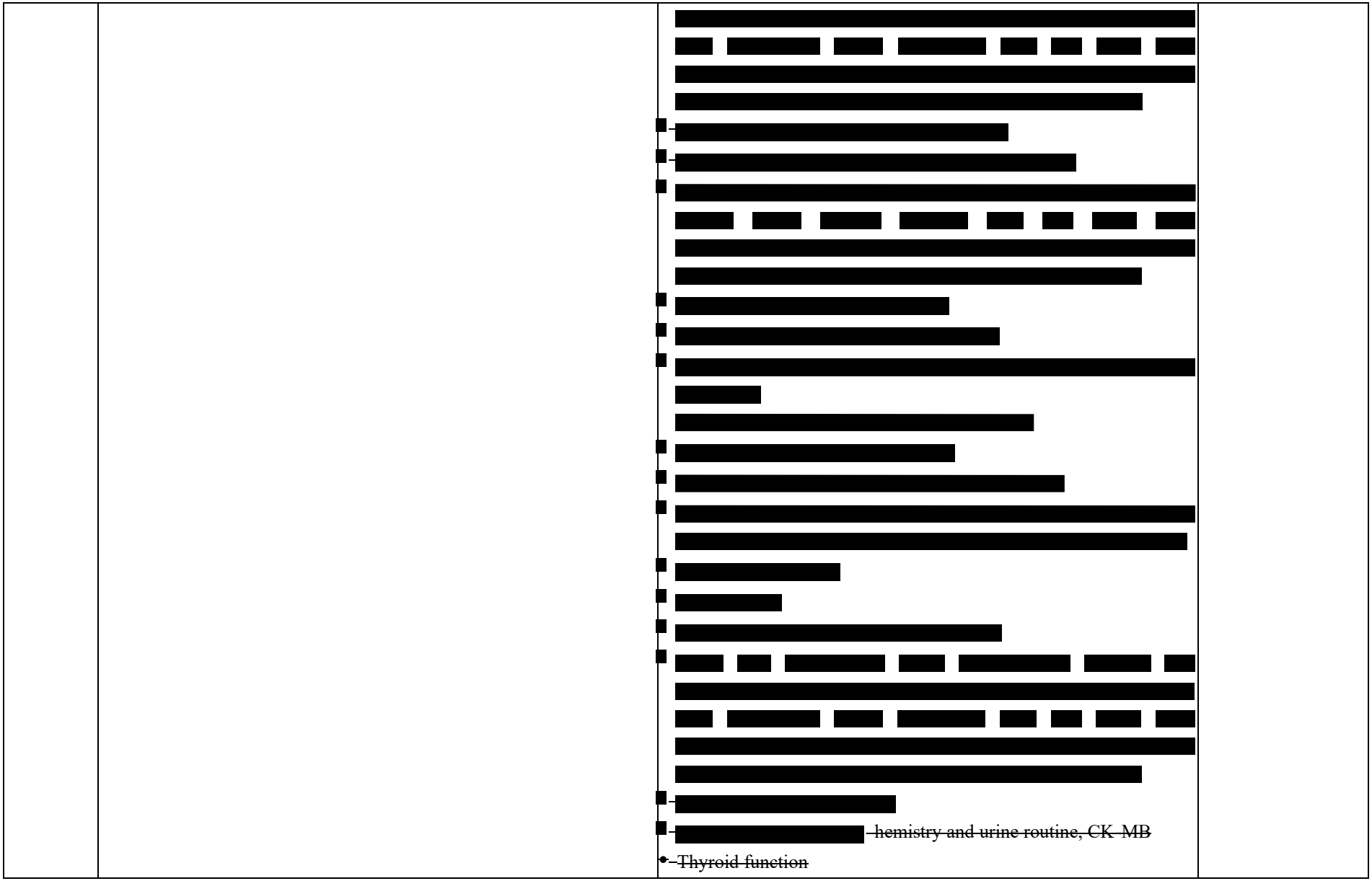
~~hemistry and urine routine, CK-MB~~
~~Thyroid function~~


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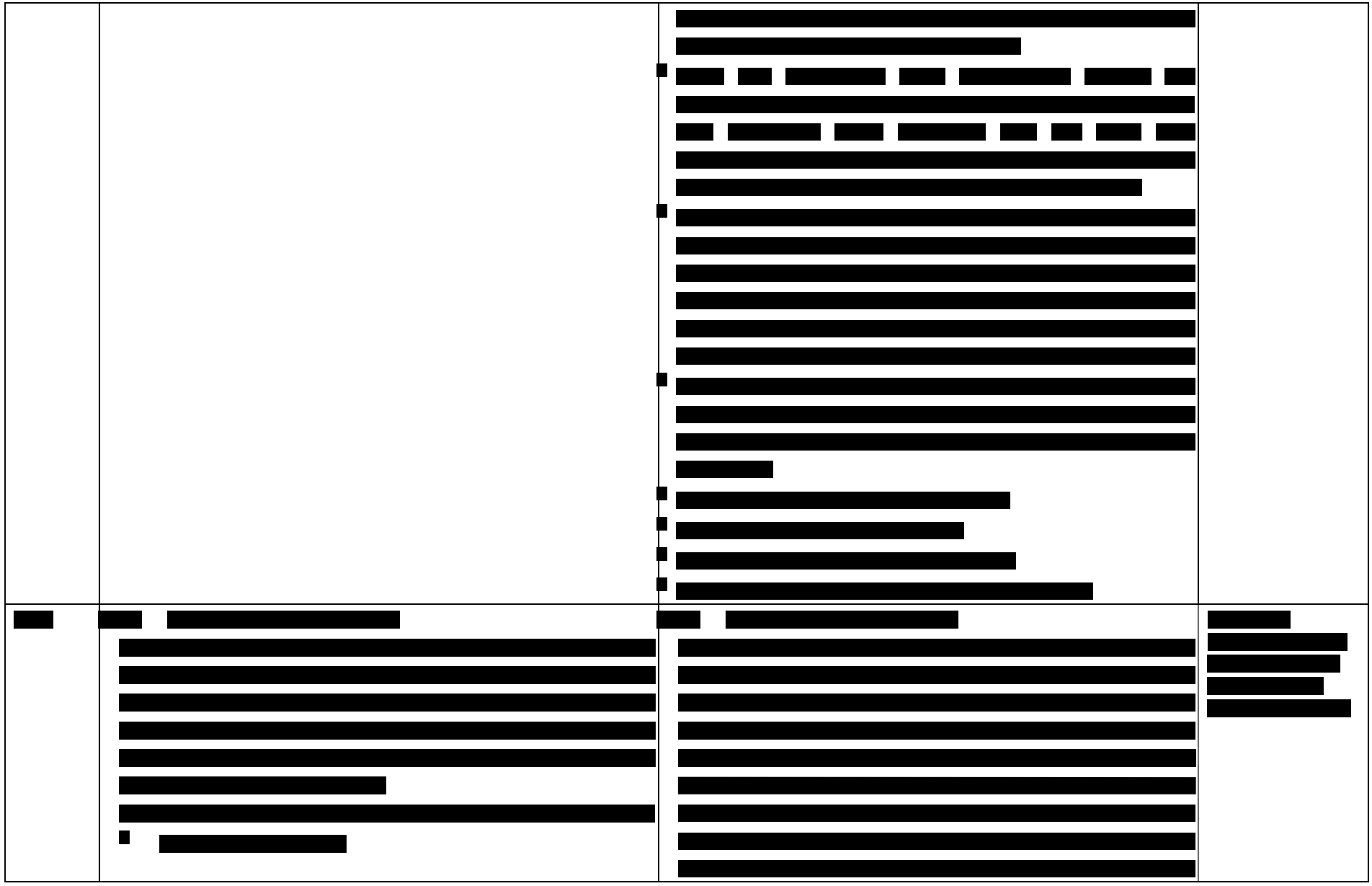

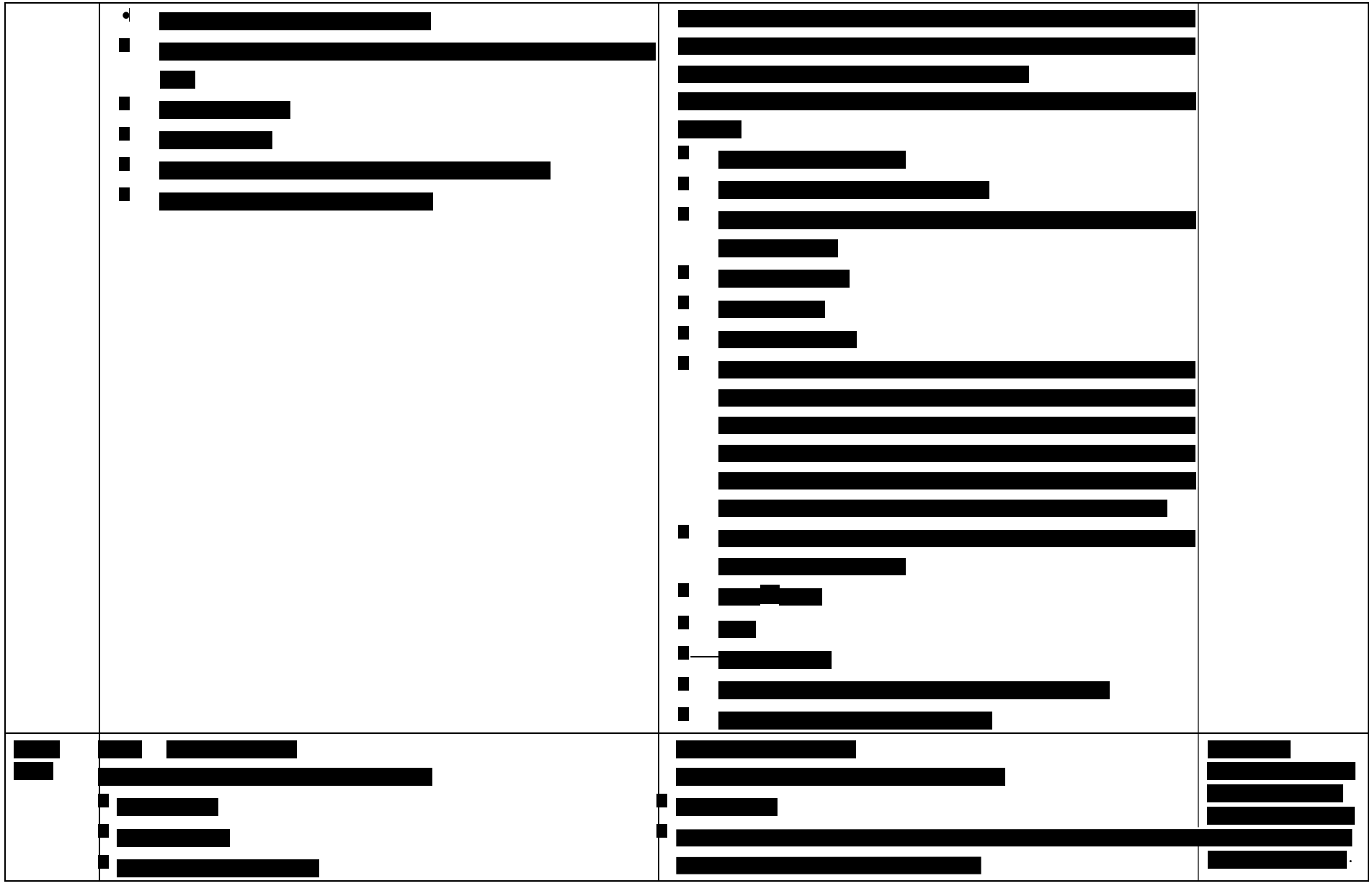

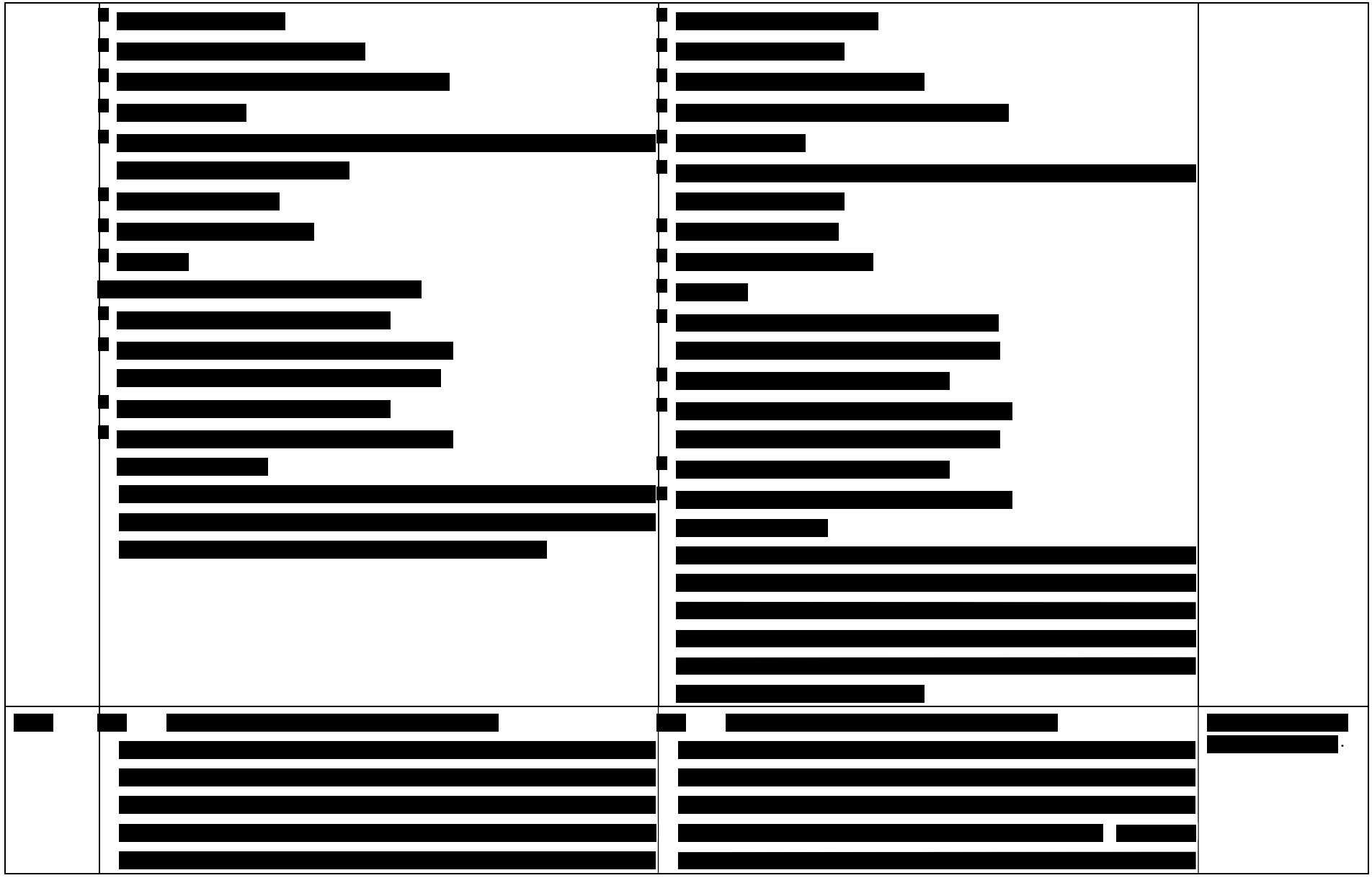

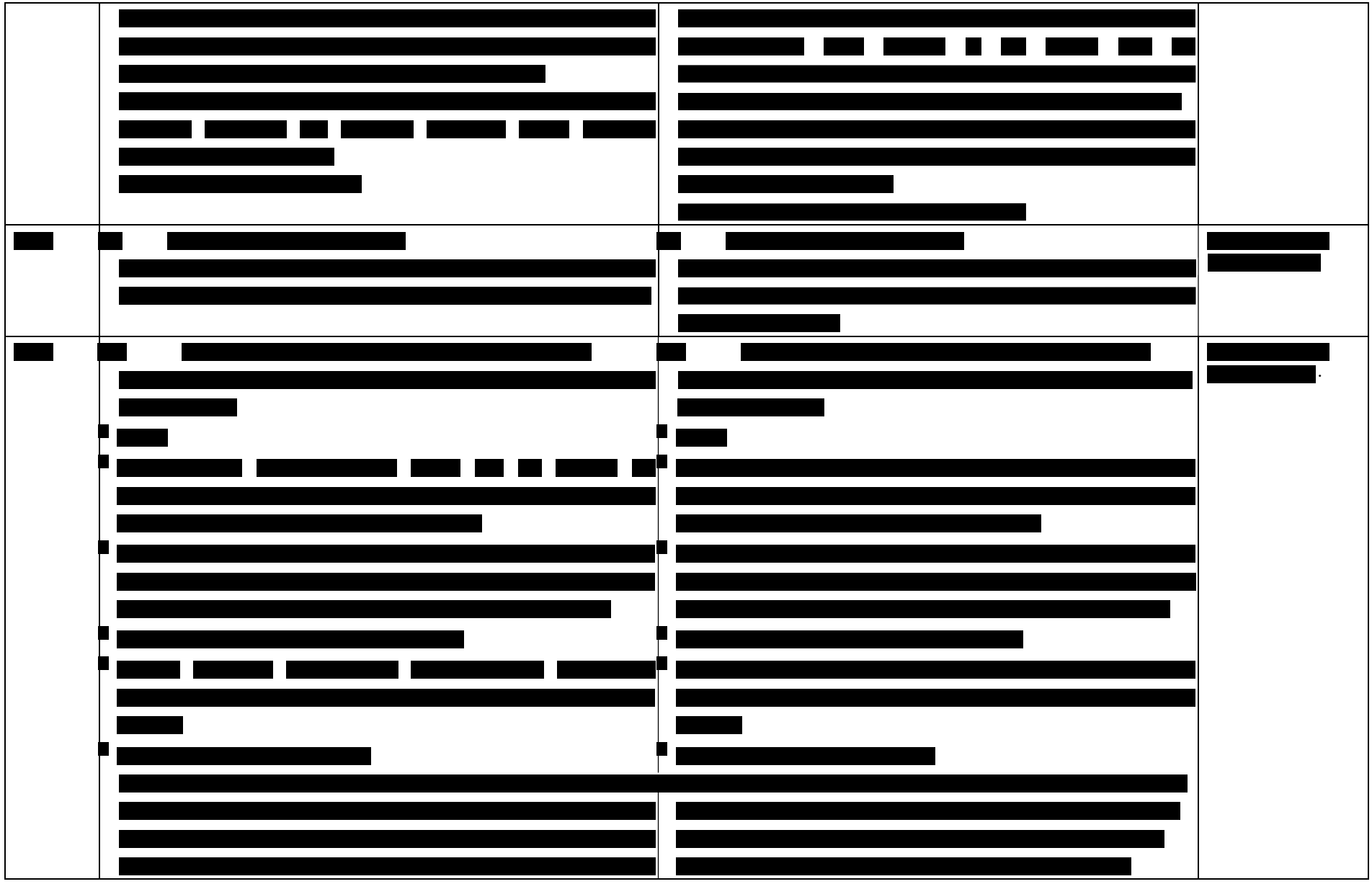

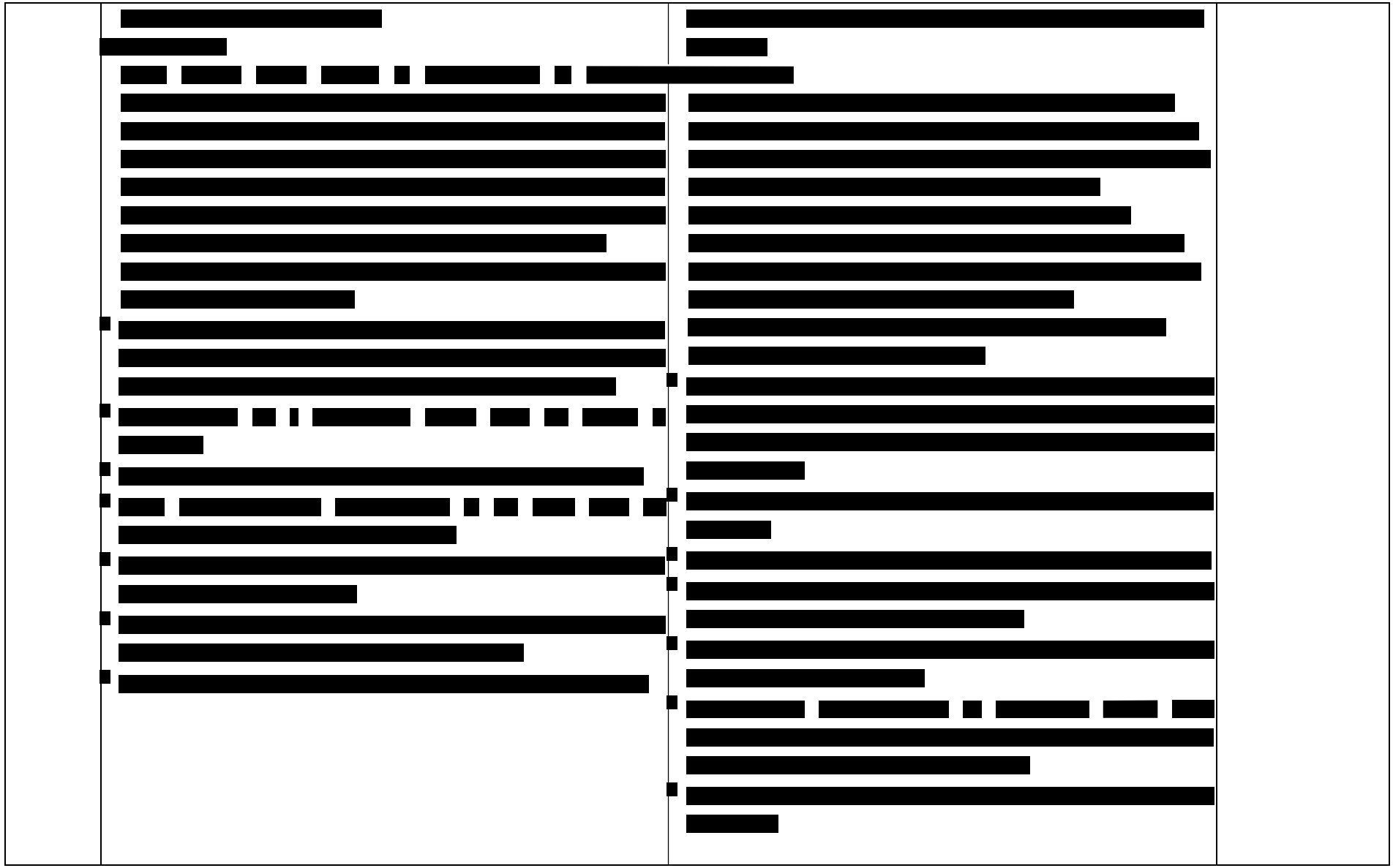

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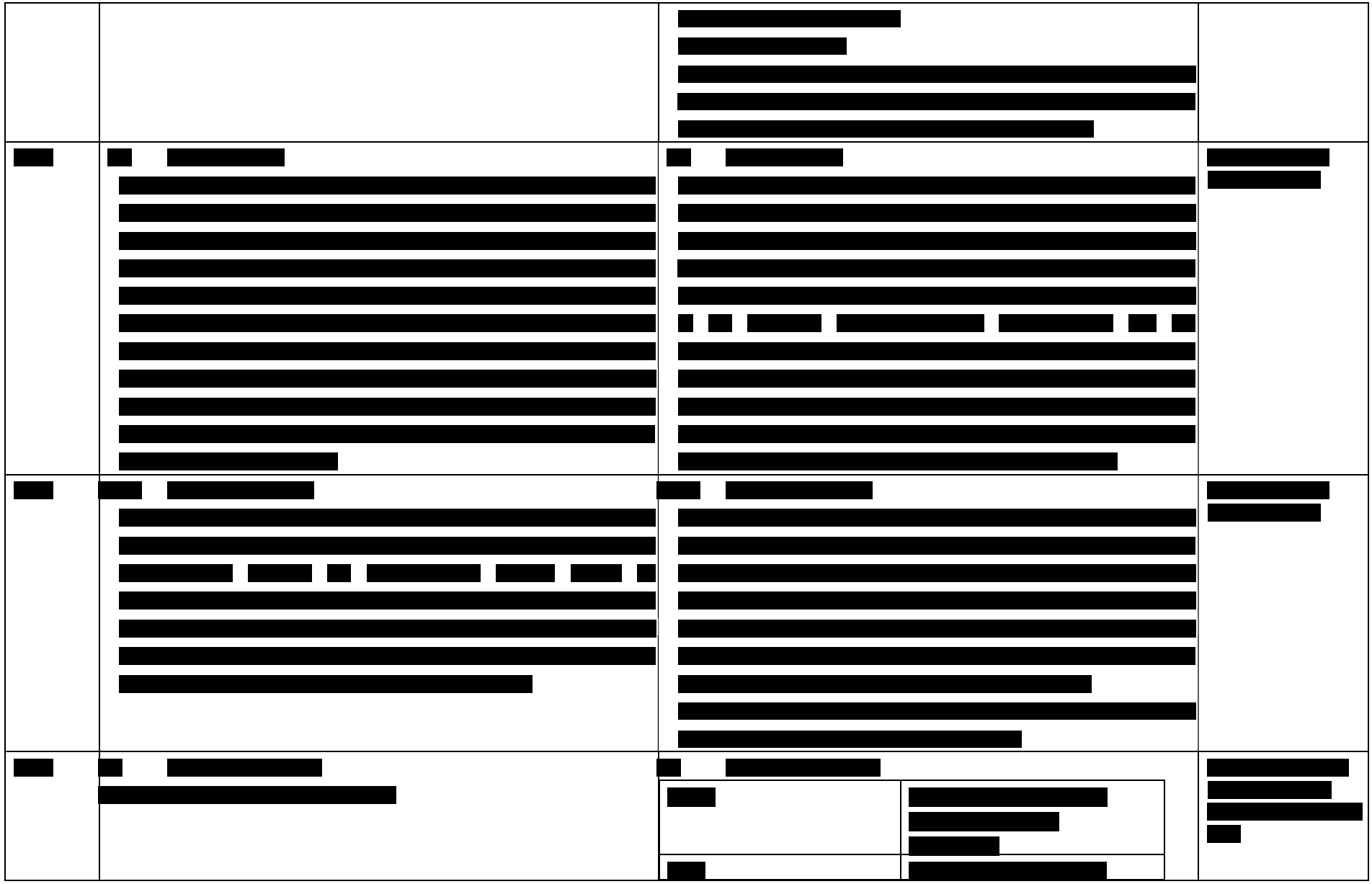

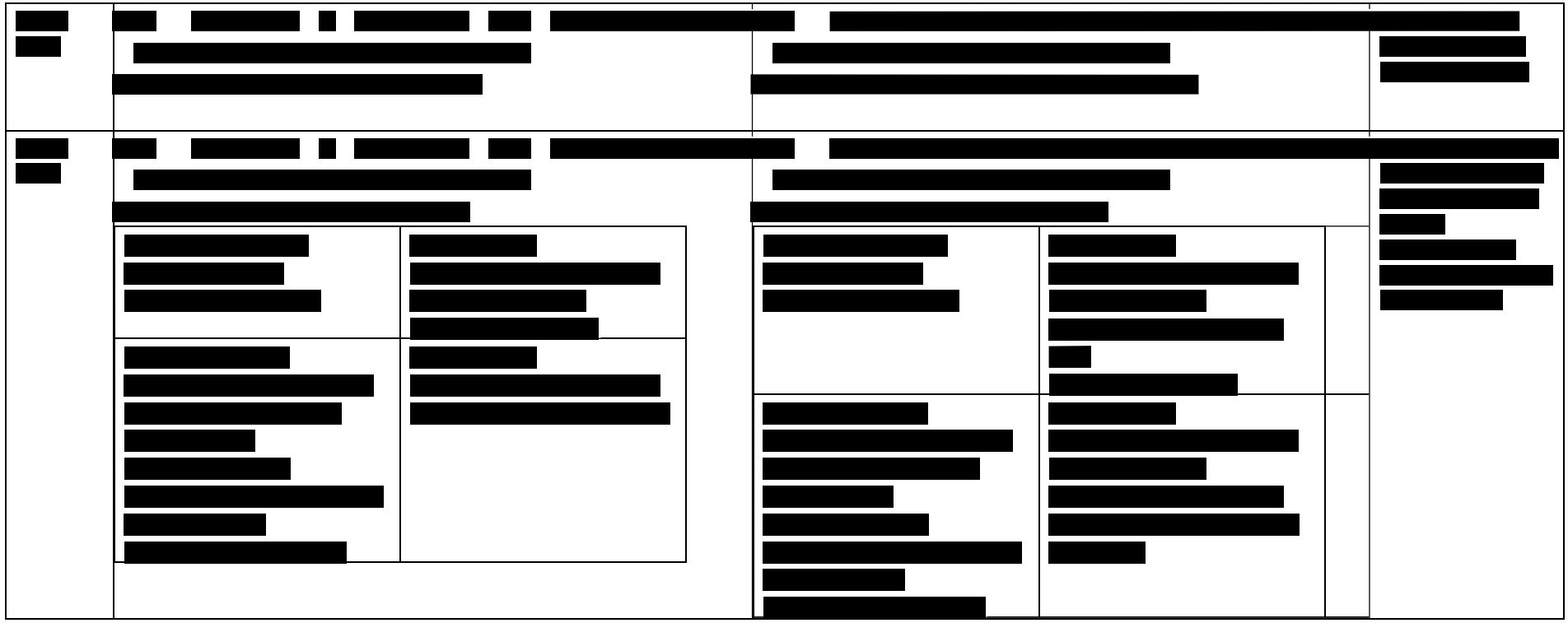

	2019 **After revision: Version No.: 2.0; Version Date: Jun 26, 2019**

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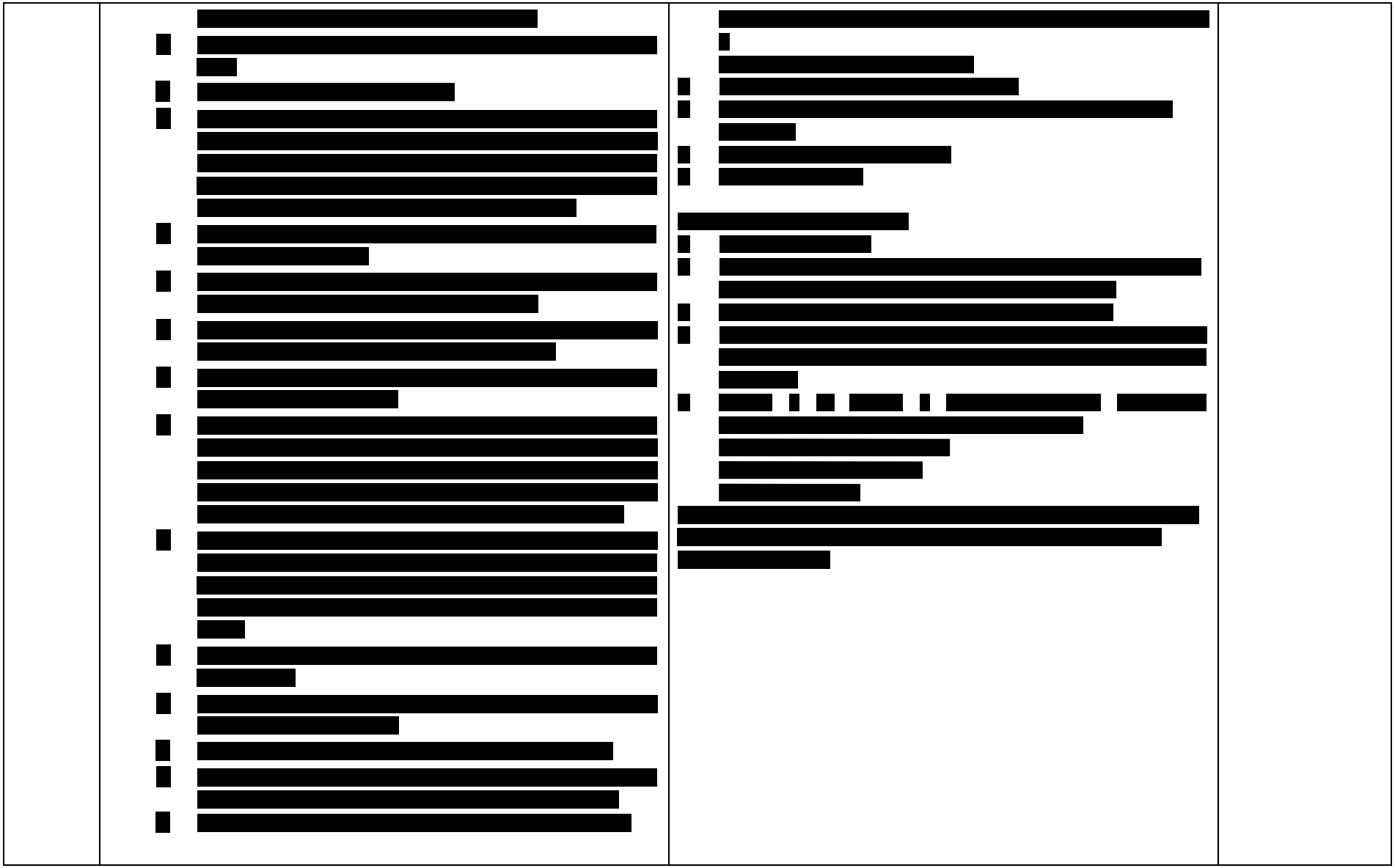

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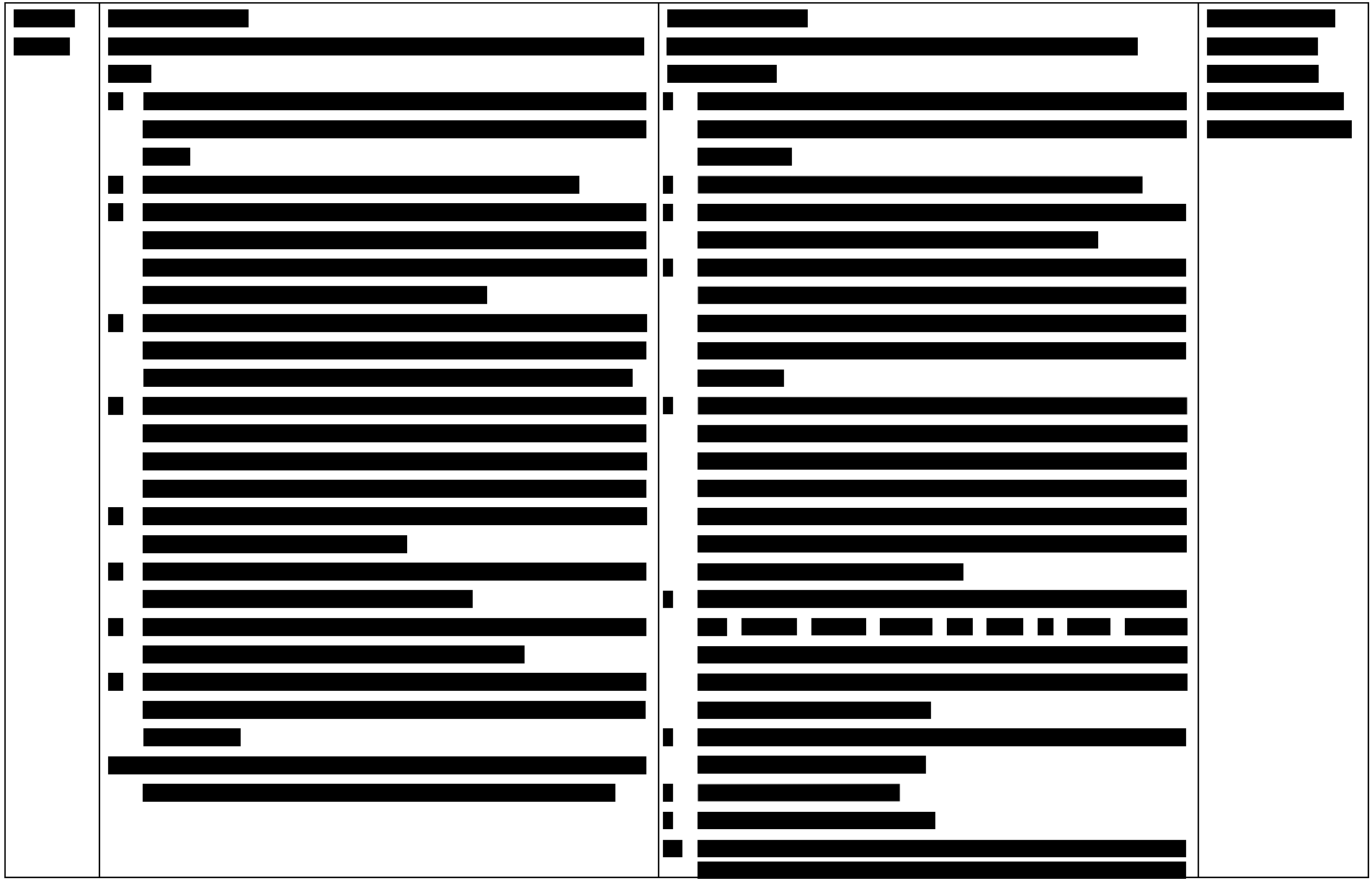

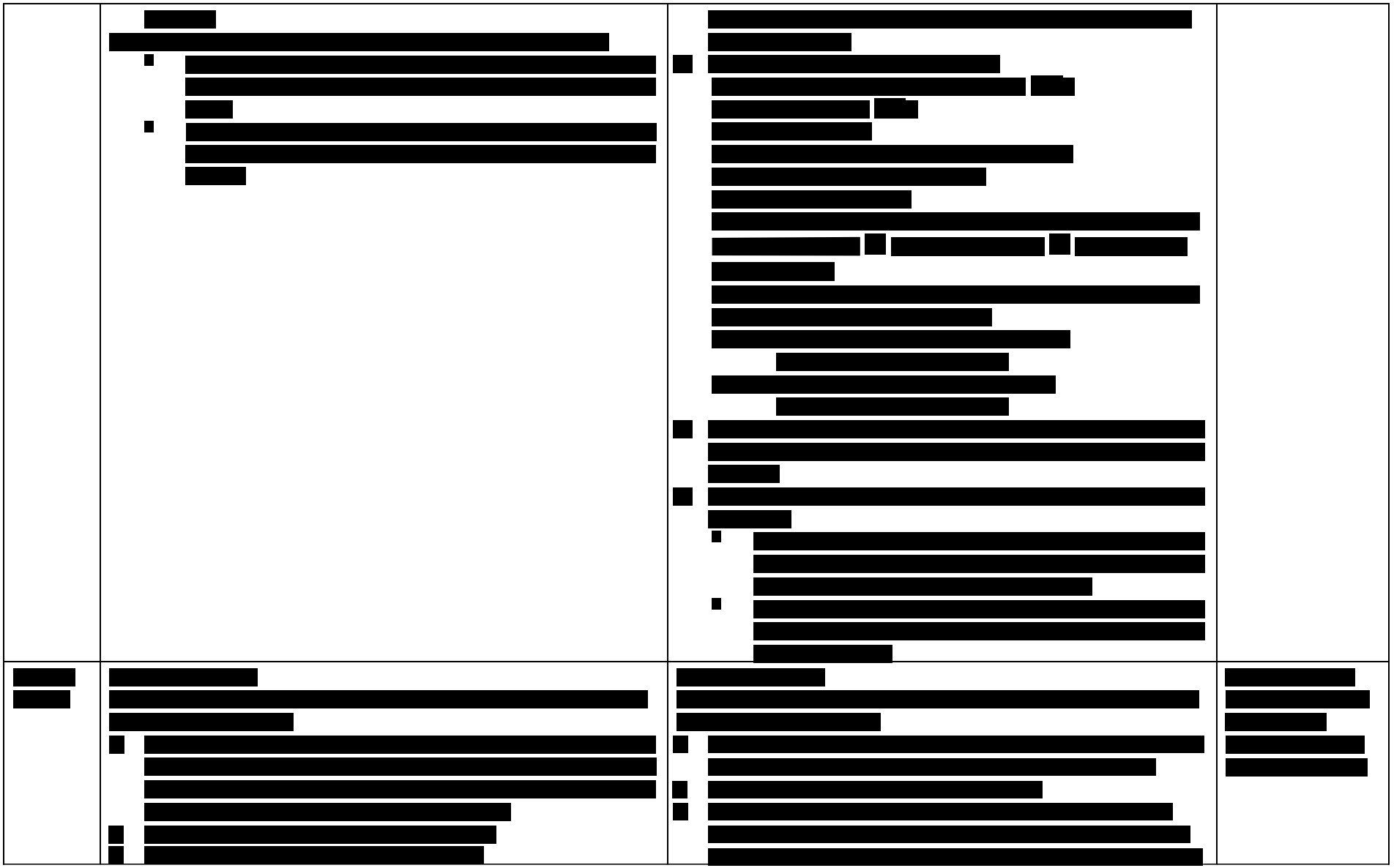

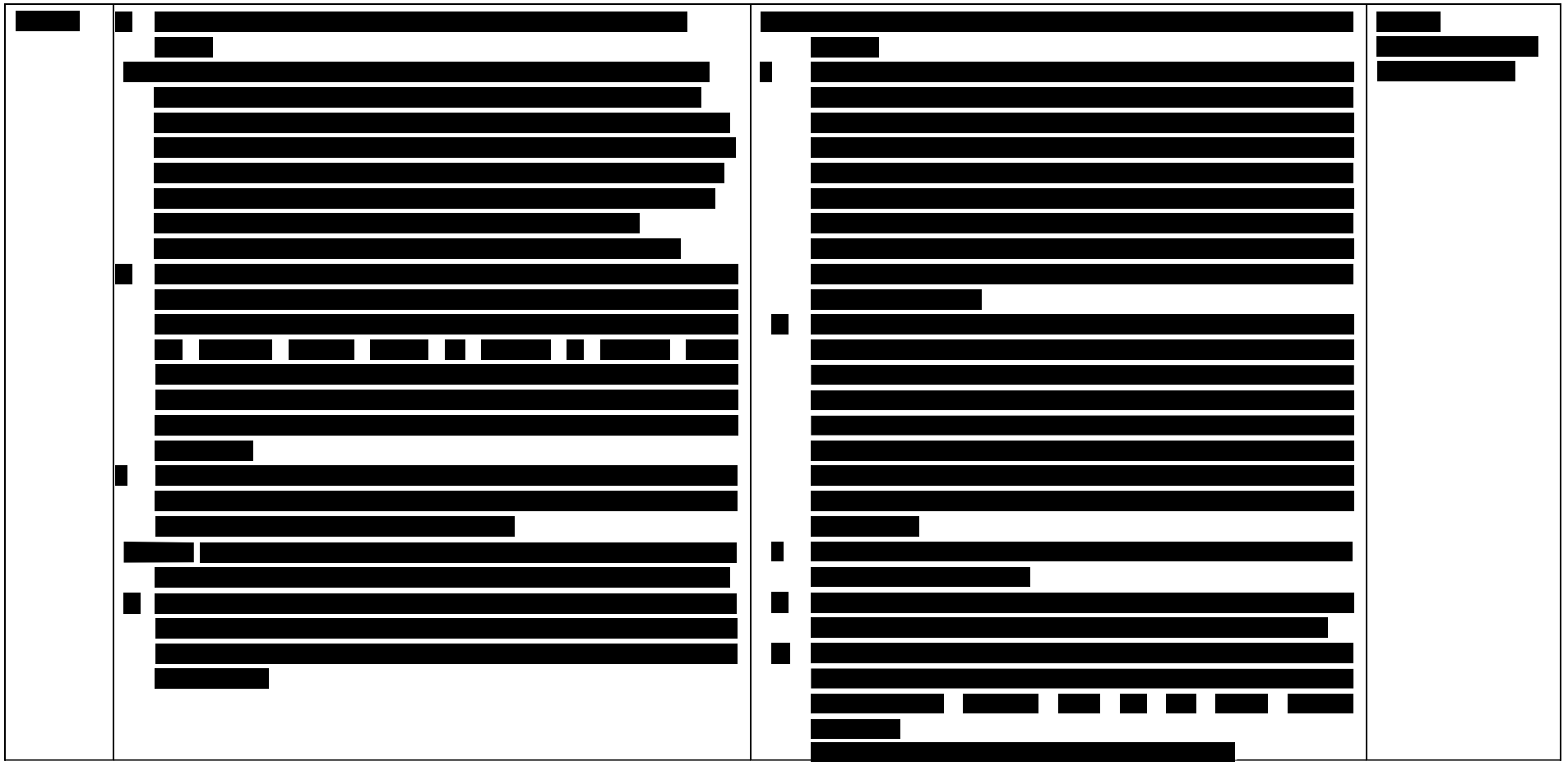

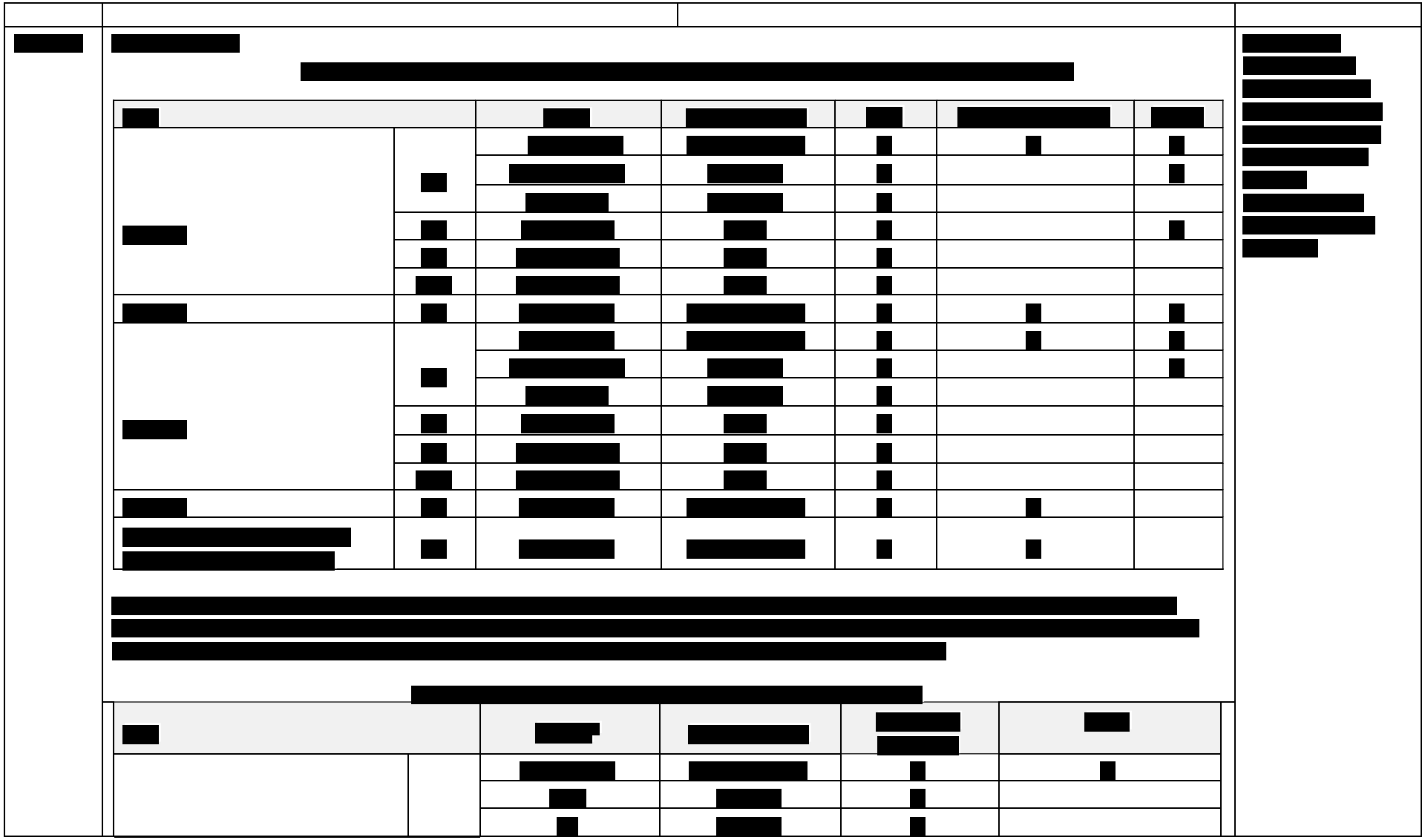

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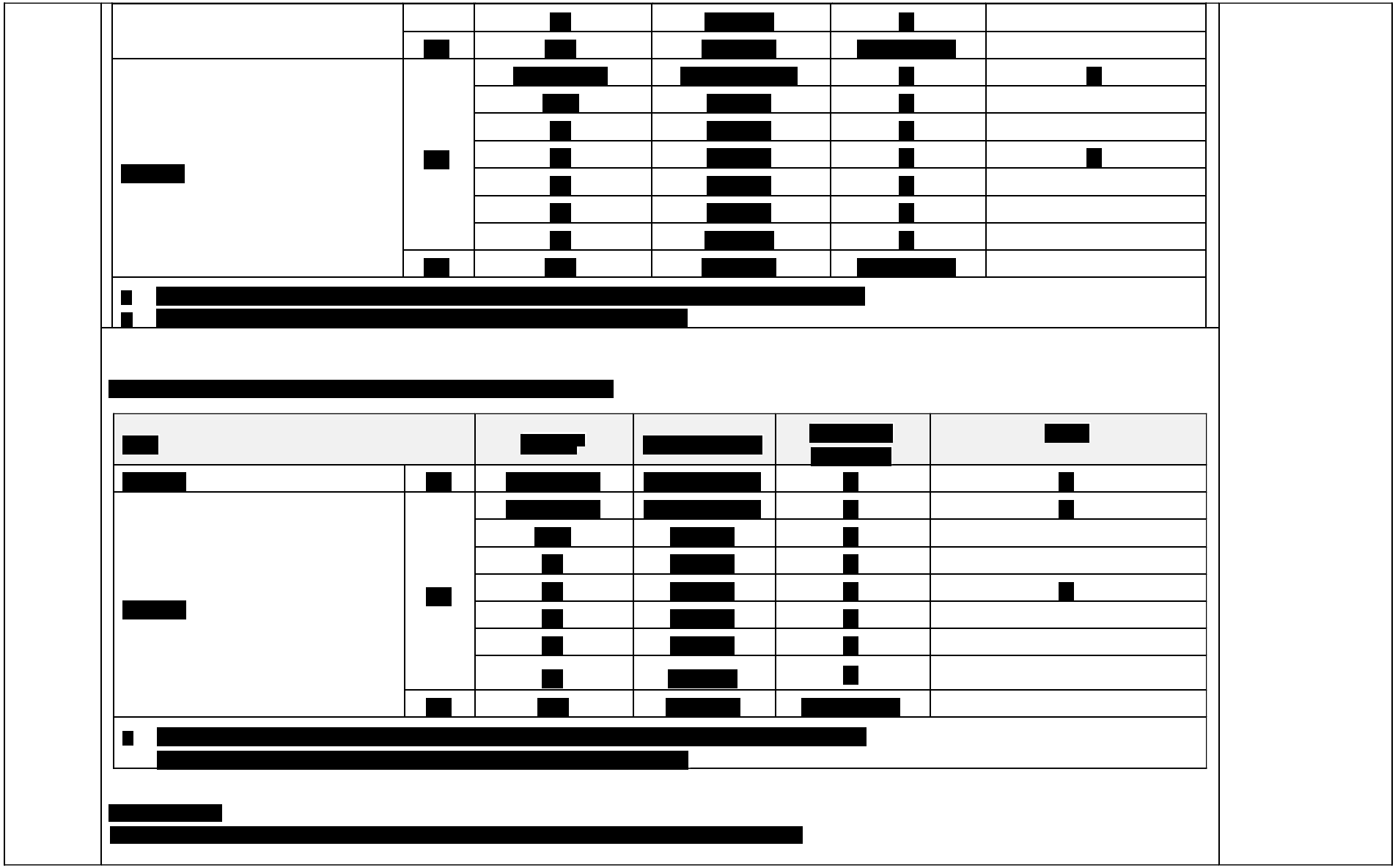

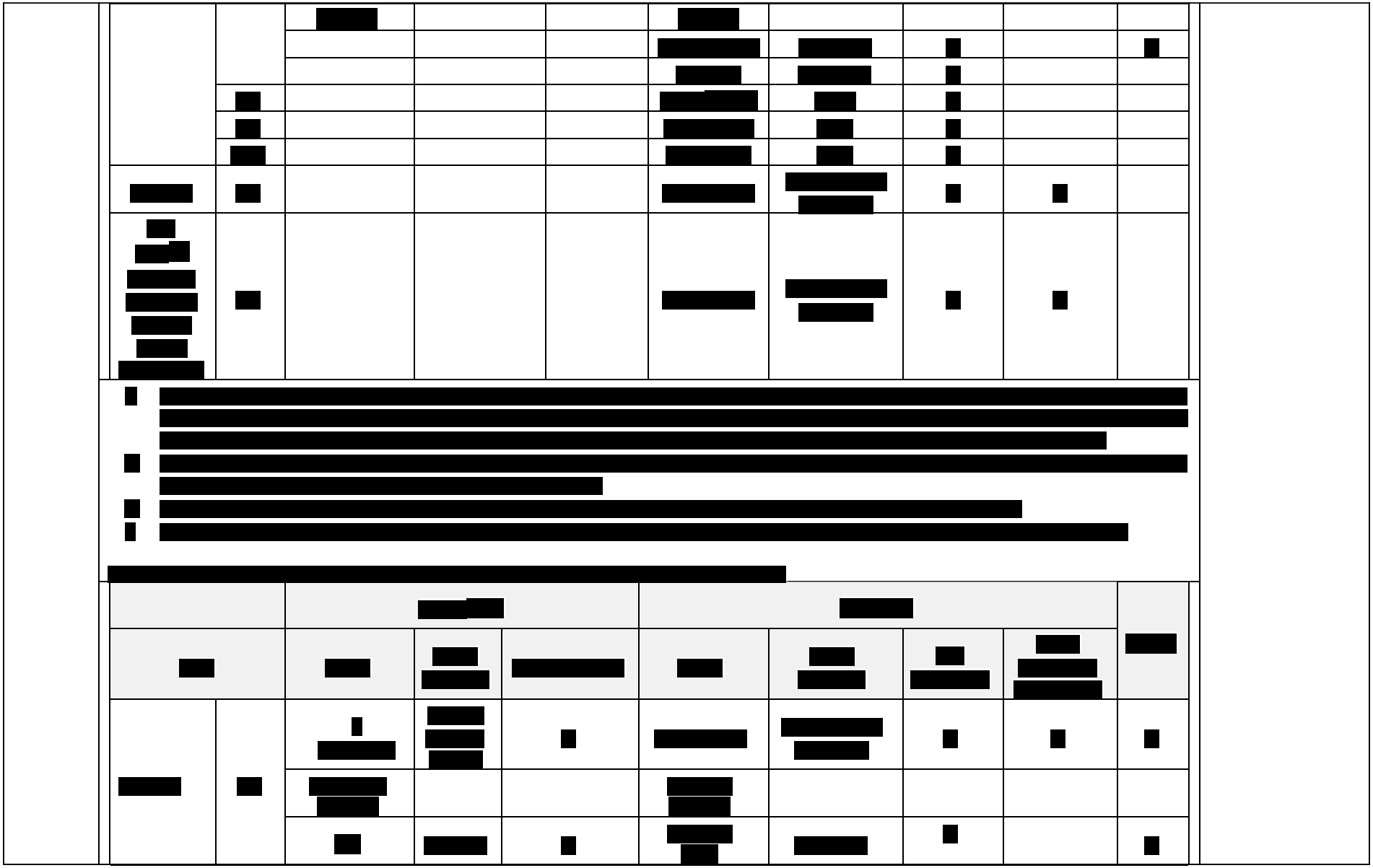

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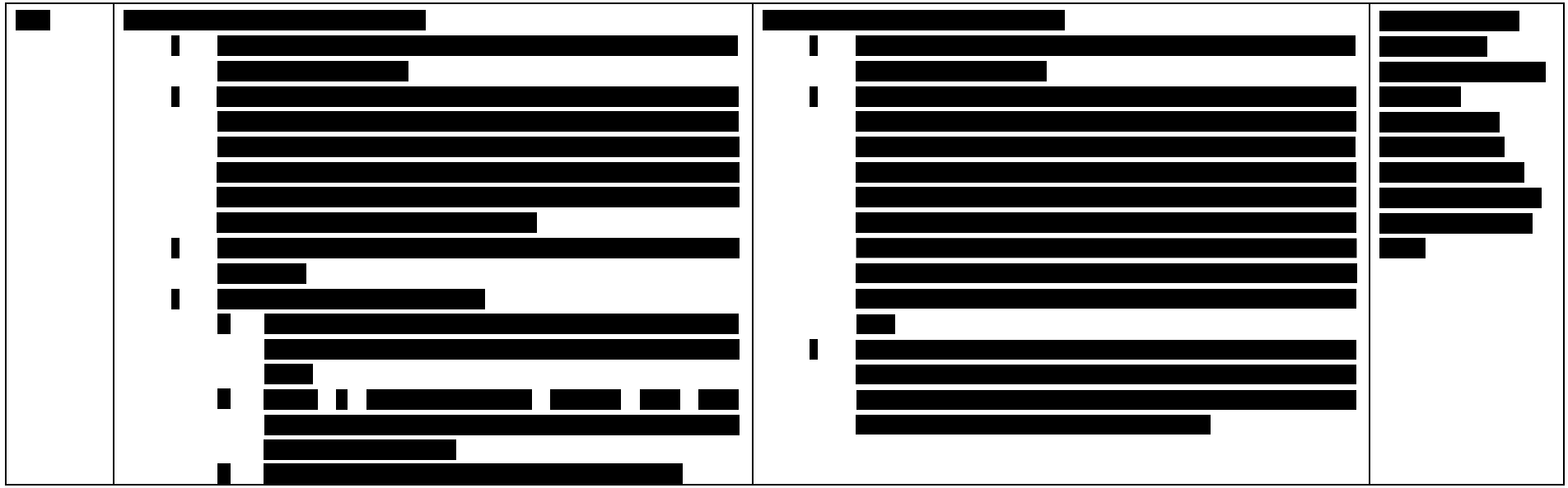

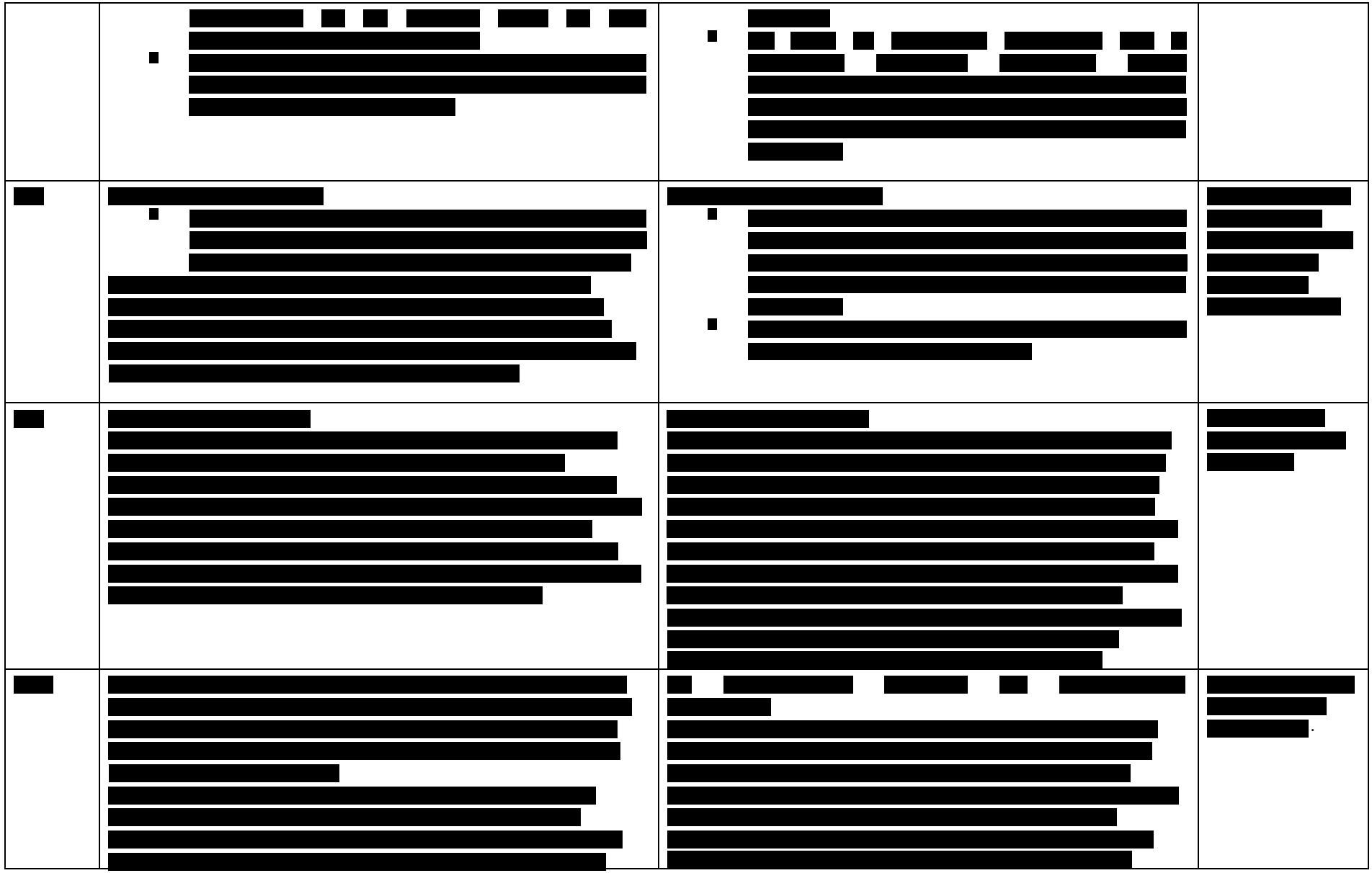

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